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# Sickle Cell Disease

MA Bender, MD, PhD[1] and Katie Carlberg, MD[1]

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## Summary

### Clinical characteristics

Sickle cell disease (SCD) is characterized by intermittent vaso-occlusive events and chronic hemolytic anemia. Vaso-occlusive events result in tissue ischemia leading to acute and chronic pain as well as organ damage that can affect any organ system, including the bones, spleen, liver, brain, lungs, kidneys, and joints. Dactylitis (pain and/or swelling of the hands or feet) is often the earliest manifestation of SCD. In children, the spleen can become engorged with blood cells in a "splenic sequestration." The spleen is particularly vulnerable to infarction and the majority of individuals with SCD who are not on hydroxyurea or transfusion therapy become functionally asplenic in early childhood, increasing their risk for certain types of bacterial infections, primarily encapsulated organisms. Acute chest syndrome (ACS) is a major cause of mortality in SCD. Chronic hemolysis can result in varying degrees of anemia, jaundice, cholelithiasis, and delayed growth and sexual maturation as well as activating pathways that contribute to the pathophysiology directly. Individuals with the highest rates of hemolysis are at higher risk for pulmonary artery hypertension, priapism, and leg ulcers and may be relatively protected from vaso-occlusive pain.

### Diagnosis/testing

SCD encompasses a group of disorders characterized by the presence of at least one hemoglobin S allele (HbS; p.Glu6Val in *HBB*) and a second *HBB* pathogenic variant resulting in abnormal hemoglobin polymerization. Hb S/S (homozygous p.Glu6Val in *HBB)* accounts for the majority of SCD. Other forms of SCD result from compound heterozygosity for HbS with other specific pathogenic beta globin chain variants (e.g., sickle-hemoglobin C disease [Hb S/C], sickle beta-thalassemia [Hb S/$\beta^+$-thalassemia and Hb S/$\beta^0$-thalassemia], Hb S/D, Hb S/$O_{Arab}$, Hb S/E).

The diagnosis of SCD is established by identification of significant quantities of HbS with or without an additional abnormal beta globin chain variant by hemoglobin assay or by identification of biallelic *HBB* pathogenic variants including at least one p.Glu6Val allele (e.g., homozygous p.Glu6Val; p.Glu6Val and a second *HBB* pathogenic variant) on molecular genetic testing.

**Author Affiliation:** 1 Department of Pediatrics, University of Washington, Seattle, Washington; Email: mbender@fredhutch.org; Email: katie.carlberg@seattlechildrens.org.

Newborn screening for SCD began in the United States in 1975 in New York and expanded to include all 50 states by 2006. Newborn screening programs perform isoelectric focusing and/or high-performance liquid chromatography (HPLC) of an eluate of dried blood spots. Some newborn screening programs confirm results with molecular testing.

## Management

*Targeted therapies:* Disease-modulating pharmacotherapies (hydroxyurea, L-glutamine, voxelotor, and crizanlizumab); hematopoietic stem cell transplantation; gene therapy.

*Supportive care:* Education of parents, caregivers, and affected individuals on avoidance of potential triggers of vaso-occlusion (dehydration, climate extremes, overexertion, and, when possible, trauma and infection), health maintenance, prophylactic medications, early interventions, warning signs of acute illness, pain management options, and urgent care plan; antibiotic prophylaxis for *Streptococcus pneumoniæ*; immunizations including those for asplenic individuals; folic acid supplementation; red blood cell (RBC) transfusion therapy and treatment for iron overload. Management of pain episodes includes reversal of inciting triggers, hydration, anti-inflammatory agents, and pain medication. Pain episodes are additionally managed with a multimodal approach (e.g., warmth, massage, distraction, acupuncture, biofeedback, self-hypnosis). RBC transfusion as needed for splenic sequestration; splenectomy may be necessary. Fever and suspected infection are treated with appropriate antibiotics. Life-threatening or severe complications (e.g., severe ACS, stroke, aplastic crisis, chronic kidney failure) are often treated with RBC transfusion or RBC exchange. Treatment of pulmonary hypertension generally includes treating inciting factors and optimizing SCD therapy to stop progression; severe priapism may require aspiration and irrigation. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for those with kidney disease with kidney transplant for end-stage kidney disease; mental health therapy and community resources.

*Surveillance:* Periodic comprehensive medical and social evaluation, mental health and neurocognitive assessment, and routine dental care. Annual complete blood count with differential and reticulocyte count; annual transcranial Doppler to determine risk of stroke in all children with Hb S/S and Hb S/$\beta^0$-thalassemia; annual developmental assessment throughout childhood; neurocognitive assessment prior to school entry and as needed; brain MRI in childhood when examination can be tolerated without anesthesia and repeated as needed; annual assessment of vitamin D level and renal function (blood urea nitrogen, serum creatinine, urinalysis, and urine microalbumin or urine protein-to-creatinine ratio); ophthalmologic evaluation annually beginning at age ten years. Because of the high frequency and severity of cardiopulmonary complications there should be a particularly low threshold to obtain an echocardiogram, pulmonary function tests, six-minute walk test, N-terminal pro-brain natriuretic peptide (NT-proBNP), and sleep study in individuals of any age with cardiac or pulmonary concerns; EKG in those on medications that may alter corrected QT interval; growth assessments throughout childhood; annual assessment of iron status and liver function; MRI as needed to evaluate for iron overload; assessment of mental health and social needs at least annually.

*Agents/circumstances to avoid:* Dehydration, extremes of temperature, physical exhaustion, extremely high altitude, trauma, infection, recreational drugs with vasoconstrictive or cardiac stimulation effects, and meperidine.

*Evaluation of relatives at risk:* Early diagnosis of at-risk family members allows for genetic counseling as well as education and intervention before symptoms or end-organ damage are present.

*Pregnancy management:* Women with SCD who become pregnant require close follow up and monitoring by a hematologist and obstetrician. Increased risk for preterm labor, thrombosis, preeclampsia, infectious complications, ACS, and acute painful episodes have been reported during pregnancy. Hydroxyurea should be discontinued during pregnancy.

## Genetic counseling

SCD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *HBB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic beta globin chain variants and being affected, a 50% chance of inheriting one beta globin chain variant and being heterozygous, and a 25% chance of inheriting neither of the familial beta globin chain variants. If the SCD-related *HBB* pathogenic variants in a family are known, molecular genetic testing can be used to identify which at-risk family members are heterozygous; if only one (or neither) SCD-related *HBB* pathogenic variant in a family is known, HPLC can be used to detect common qualitative abnormalities (i.e., abnormal hemoglobins). Molecular genetic prenatal testing and preimplantation genetic testing for SCD are possible when both *HBB* pathogenic variants have been identified in an affected family member and the genetic status of the parents is known.

# *GeneReview* Scope

| Sickle Cell Disease: Included Disorders |
| --- |
| • Homozygous p.Glu6Val (Hb S/S)<br>  ◦ Sickle cell disease due to Hb S/S<br>• Compound heterozygosity for p.Glu6Val (HbS) and a second *HBB* pathogenic variant<br>  ◦ Sickle-hemoglobin C disease (Hb S/C)<br>  ◦ Sickle beta-thalassemia (Hb S/$\beta^+$-thalassemia and Hb S/$\beta^0$-thalassemia)<br>  ◦ HbS and another pathogenic beta globin chain variant (e.g., Hb S/D, Hb S/$O_{Arab}$, Hb S/E) |

For synonyms and outdated names see Nomenclature.

# Diagnosis

The term "sickle cell disease" (SCD) encompasses a group of disorders characterized by the presence of at least one hemoglobin S allele (HbS; p.Glu6Val in *HBB*) and a second *HBB* pathogenic variant resulting in abnormal hemoglobin polymerization. **SCD (Hb S/S)** caused by the homozygous *HBB* variant p.Glu6Val is the most common cause of SCD. SCD caused by compound heterozygous *HBB* pathogenic variants includes **sickle-hemoglobin C disease (Hb S/C)** and two types of **sickle beta-thalassemia (Hb S/$\beta^+$-thalassemia and Hb S/$\beta^0$-thalassemia)**. Other *HBB* variants such as HbD and $HbO_{Arab}$ result in severe forms of SCD when inherited with HbS, while HbE can lead to a milder form. Another common variant that leads to less severe and possibly even asymptomatic phenotypes when inherited is hereditary persistence of fetal hemoglobin (HPFH). Many other *HBB* variants in combination with HbS result in a phenotype similar to sickle cell trait.

## Suggestive Findings

### Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for SCD identifies the relative quantification of hemoglobins (e.g., fetal hemoglobin [HbF], adult hemoglobin [HbA], sickle hemoglobin [HbS]) using isoelectric focusing and/or high-performance liquid chromatography (HPLC) on an eluate of dried blood spots. Hemoglobins identified by NBS are reported in order of quantity.

- The normal newborn screening result is "FA" (i.e., HbF > HbA)
- Infants with HbS identified on NBS require additional confirmatory testing of a separate blood sample within four weeks (see Table 1 and Hemoglobinopathies: Current Practices for Screening, Confirmation and Follow-up).

### Scenario 2: Symptomatic Individual

A symptomatic individual who was not previously followed for SCD may present with findings of SCD if NBS was not performed or caregivers did not follow through with recommended NBS follow up. NBS technology is highly sensitive, but false negative NBS can occur when S/$\beta^+$-thalassemia is reported as sickle cell trait, or as a result of labeling or handling errors.

Suggestive clinical, laboratory, and family history features can include the following.

**Clinical features**

- Infants with spontaneous painful swelling of the hands and feet
- Recurrent episodes of severe pain with no other identified etiology
- Pallor
- Jaundice
- Pneumococcal sepsis or meningitis
- Severe anemia with splenic enlargement
- Stroke, especially in a child

Note: Most individuals with SCD are healthy at birth and become symptomatic later in infancy or childhood after fetal hemoglobin levels decrease.

**Laboratory features**

- Normocytic anemia (though some forms of SCD cause microcytic anemia)
- Sickle cells, nucleated red blood cells (RBCs), target cells, and other abnormal RBCs on peripheral blood smear; Howell-Jolly bodies indicate hyposplenism.
- Presence of HbS on a hemoglobin assay (e.g., HPLC, isoelectric focusing, cellulose acetate electrophoresis, citrate agar electrophoresis) with an absence or diminished amount of HbA (For information about advantages and disadvantages of various hemoglobin assays, click here.)

**Family history** of SCD, sickle cell trait, or any of the preceding suggestive features of SCD (particularly in a person of sub-Saharan African, Indian, or Central American descent) is suggestive of the diagnosis. Absence of a known family history does not preclude the diagnosis. SCD can be present in an individual of any ethnic background.

## Establishing the Diagnosis

The diagnosis of SCD **is established** in a proband by identification of significant quantities of HbS with or without an additional abnormal and pathogenic beta globin chain variant by **hemoglobin assay**, and/or by identification of biallelic *HBB* pathogenic variants including at least one p.Glu6Val allele (e.g., homozygous p.Glu6Val; p.Glu6Val and a second *HBB* pathogenic variant) on **molecular genetic testing**.

### Hemoglobin Assay

Hemoglobin assay identifies adult hemoglobins (HbA, HbS, and other beta globin variants [e.g., HbC, HbE]) in addition to fetal hemoglobin (HbF), which is normally the predominant hemoglobin in newborns but decreases over the first year of life.

- Identification of HbS as the sole adult beta chain on Hb assay indicates either Hb S/S or Hb S/$\beta^0$-thalassemia (see Table 1). These can be distinguished by molecular genetic testing, a combination of hemoglobin testing and other clinical studies, or in combination with family history.

- Hb S/$\beta^0$-thalassemia and Hb S/$\beta^+$-thalassemia are distinguished by the presence of HbA in individuals with S/$\beta^+$-thalassemia, but HbA is below that observed in sickle cell trait. Findings on NBS in those with S/$\beta^+$-thalassemia are easily confused with S/$\beta^0$-thalassemia and sickle cell trait.
- Identification of HbS and an additional beta chain variant (e.g., HbC, HbD, HbO, HbE) on Hb assay can establish the diagnosis in individuals who are compound heterozygous for specific *HBB* pathogenic variants (e.g., Hb S/C, Hb S/D, Hb S/O, Hb S/E).

**Table 1.** Sickle Cell Disease: Diagnostic Test Results

| Abnormal Globin Beta Chain Variants [1] | Hemoglobins Identified by Age Six Weeks [2] | Phenotype | Hematologic Studies by Age Two Years | |
|---|---|---|---|---|
| | | | MCV [3, 4] | $HbA_2$ [5] |
| S/S ($\beta^S\beta^S$) | HbF, HbS | Hemolysis & anemia by age 6-12 mos | N | <3.6% |
| S/$\beta^0$-thal ($\beta^S\beta^0$) | | | ↓ | >3.6% |
| S/$\beta^+$-thal ($\beta^S\beta^+$) | HbF, HbS, HbA | Milder hemolysis & anemia | ↓ | >3.6% |
| S/C ($\beta^S\beta^C$) | HbF, HbS, HbC | | N or ↓ | <3.6% |

Table shows typical results; exceptions occur. Less common genotypes (e.g., Hb S/D, Hb S/O, Hb S/E) are not included.
↑ = increased; ↓ = decreased; β = beta; HbA = adult hemoglobin; HbC = hemoglobin C; HbF = fetal hemoglobin; HbS = sickle hemoglobin; MCV = mean corpuscular volume; N = normal; thal = thalassemia
*1.* The beta-thalassemias are divided into $\beta^+$-thalassemia, in which reduced levels of normal beta globin chains are produced, and $\beta^0$-thalassemia, in which there is no beta globin chain synthesis.
*2.* Hemoglobins are reported in order of quantity (e.g., HbF, HbS, HbA = HbF > HbS> HbA).
*3.* Normal mean corpuscular volume: ≥70 fL at age six to 12 months; ≥72 fL at age one to two years; ≥81 fL in adults
*4.* Interpretation can be difficult as coexisting iron deficiency and alpha-thalassemia are common in individuals with SCD and can also reduce the mean corpuscular volume.
*5.* $HbA_2$ results vary somewhat depending on laboratory method. The $HbA_2$ percentages stated are not absolutes, and $HbA_2$ percentage can be lower in individuals with Hb S/$\beta^0$-thalassemia due to an *HBB* deletion.

## Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing, targeted analysis,** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *HBB* may be considered first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **Targeted analysis** (e.g., allele-specific PCR) can be performed to detect *HBB* pathogenic variant p.Glu6Val and to distinguish individuals with Hb S/S from those with sickle cell trait (Hb A/S) [Toye et al 2018]. Additional allele-specific assays are required to identify other *HBB* variants (e.g., HbC, HbD, HbO, HbE).
- **A multigene panel** that includes *HBB* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

**Table 2.** Molecular Genetic Testing Used in Sickle Cell Disease

| Gene [1] | Method | Proportion of Pathogenic Variants [2] Detectable by Method |
|---|---|---|
| *HBB* | Sequence analysis [3, 4] | 100% |
| | Gene-targeted deletion/duplication analysis [5] | See footnote 6. |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Note: All affected individuals have at least one copy of the p.Glu6Val allele. Targeted assays for p.Glu6Val (HbS), p.Glu6Lys (HbC), p.Glu121Gln (HbD), p.Glu26Lys (HbE), and p.Glu121Lys ($HbO_{Arab}$) may be available (see Molecular Genetics).
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*6. HBB* deletions or duplications will not result in a sickle pathogenic variant; however, *HBB* deletions are causative of beta-thalassemia, and *HBB* variant p.Glu6Val in *trans* with an *HBB* deletion leads to Hb S/$\beta^0$-thalassemia.

# Clinical Characteristics

## Clinical Description

The clinical manifestations of sickle cell disease (SCD) result from intermittent episodes of microvascular occlusion leading to tissue ischemia/reperfusion injury and chronic hemolysis, both of which contribute to multiorgan dysfunction. The severity of disease manifestations varies, even in individuals with the same *HBB* pathogenic variants.

**Vaso-occlusive events** are associated with ischemia/reperfusion damage to tissues that lead to pain and acute or chronic injury affecting any organ system. The bones/marrow, spleen, liver, brain, lungs, kidneys, eyes, and joints are often affected. The biologic markers associated with the "vaso-occlusive phenotype" include the following [Darbari et al 2012, Wood et al 2012, Kato et al 2018]:

- A higher white blood cell count
- A lower fetal hemoglobin level
- Coexisting alpha-thalassemia trait
- Vessel flow resistance related to deoxygenation

**Chronic hemolysis** is associated with chronic anemia as well as vascular dysfunction [Sundd et al 2019]. Individuals with the highest rates of hemolysis are at increased risk of developing pulmonary artery hypertension, priapism, gallstones, leg ulcers, and nephropathy [Kato et al 2018]. Biologic markers for the "hemolytic phenotype" include the following:

- Elevated plasma levels of lactate dehydrogenase (LDH)
- A low hemoglobin level
- A high reticulocyte count

Conversely, coexisting alpha-thalassemia trait is protective against this phenotype [Romana et al 2021].

**Complications related to vaso-occlusive events**

- **Vaso-occlusive pain episodes** are the most frequent cause of recurrent morbidity in individuals with SCD and account for most SCD-related hospital admissions as well as school and work absences [Bou-Maroun et al 2018, Fingar et al 2019]. Pain can be acute, recurrent, or chronic, and is complicated by coexisting chronic disease [Martinez at al 2020]. Racial prejudice and suspicion of drug seeking frequently prevent sufficient treatment for excruciating pain in individuals with SCD. Vaso-occlusion results from multicellular aggregates that block blood flow in small blood vessels, depriving downstream tissues of nutrients and oxygen, followed by re-perfusion injury resulting in tissue ischemia, inflammation, and tissue death in the affected vascular beds. Vaso-occlusion and ischemic tissue damage cause excruciating pain. Young children more often report pain in their extremities, whereas older individuals more commonly experience pain in the head, chest, abdomen, and back [Brandow & DeBaun 2018]. Recurrent episodes of acute pain ultimately contribute to the development of chronic pain, likely driven by nervous system sensitization. Diagnostic criteria for chronic pain syndrome in individuals with SCD have been established [Dampier et al 2017]. It is imperative for providers to recognize the complex role of various psychosocial factors in an individual's experience of pain [Brandow & DeBaun 2018].
- **Dactylitis** (pain and/or swelling of the hands or feet) is often the earliest manifestation of SCD and occurs in infants and children. The dorsa of the extremities are most often involved; one or all four extremities can be involved. Although immediate sequelæ are rare, dactylitis has been implicated as a risk factor for severe disease [Silva et al 2015].
- **Splenic sequestration and infarction.** Splenic sequestration occurs in 10%-30% of children with SCD, most commonly between age six months and three years, and may follow a febrile illness. Splenic sequestration is characterized by an acutely enlarging spleen with hemoglobin more than 2 g/dL below the affected individual's baseline value. Mild-to-moderate thrombocytopenia may also be present. Children with splenic sequestration may experience abdominal pain, nausea, vomiting, lethargy, or irritability. Blood transfusion may be required, as severe splenic sequestration may progress rapidly to shock and death. Recurrent episodes (or difficult-to-manage acute episodes) may require splenectomy. Historically most children with sickle cell disease due to Hb S/S or Hb S/$\beta^0$-thalassemia have a dysfunctional spleen within the first year of life and complete auto-infarction and atrophy resulting from ischemia of the spleen by age five years, although this natural history may be altered by hydroxyurea and chronic transfusion therapy [Gale et al 2016, Pereda et al 2019]. Splenic dysfunction contributes to the increased risk of sepsis and infection.
- **Infection.** Young children with SCD and splenic dysfunction are at high risk for septicemia and meningitis caused by encapsulated bacteria including *Streptococcus pneumoniæ*, *Neisseria meningiditis*, and *Hæmophilus influenzæ*. Vaccination programs and prophylactic penicillin have significantly decreased the incidence of these infections [Adamkiewicz et al 2003, Oligbu et al 2019].

  Individuals with SCD are also at increased risk for other infections such as osteomyelitis caused by *Staphylococcus aureus* or other organisms such as *Salmonella* species. Infectious agents implicated in acute chest syndrome include *Mycoplasma pneumoniæ*, *Chlamydia pneumoniæ*, and *Streptococcus pneumoniæ*, as well as viruses. Parvovirus remains an important cause of aplastic crisis. Indwelling central venous catheters confer a high risk of bacteremia in individuals with SCD [Chulamokha et al 2006, Zarrouk et al 2006, Ordóñez et al 2021].
- **Acute chest syndrome (ACS)** is a complex process that can arise from multiple diverse etiologies. ACS is a major cause of mortality [Klings & Steinberg 2022]. While the definition of ACS varies in the literature, the diagnosis is typically established by identification of a new pulmonary infiltrate on chest radiograph in a person with SCD, often in the presence of respiratory tract symptoms, chest pain, hypoxemia, and/or fever. ACS often develops in the setting of a vaso-occlusive episode or with other acute manifestations of

SCD, frequently after two to three days of severe vaso-occlusive pain. ACS can progress rapidly (over several hours to days) to requiring intubation and mechanical ventilatory support. A high index of suspicion is indicated; the presenting signs and symptoms of ACS can be highly variable, and affected individuals may initially have a normal physical examination [Morris et al 1999]. Multiple etiologies, often occurring simultaneously, can contribute to ACS (e.g., fat emboli from bone marrow infarcts, pneumonia, pulmonary infarction, pulmonary embolus, asthma) [Mekontso Dessap et al 2011, Klings & Steinberg 2022].

**Neurologic complications** in SCD include stroke, silent cerebral infarcts, cerebral hemorrhage, cerebral blood flow abnormalities including moyamoya disease, and cerebral microvascular disease. Up to 50% of individuals with SCD will manifest some degree of cerebrovascular disease by age 14 years [Bernaudin et al 2011].

- **Ischemic strokes**, most often seen in children and older adults, are among the most catastrophic manifestations of SCD. Common presenting signs and symptoms include hemiparesis, monoparesis, seizures, aphasia or dysphasia, cranial nerve palsies, and mental status changes. Prior to routine screening with transcranial Doppler (TCD), overt strokes occurred in as many as 11% of children with SCD in the United States, with the peak occurrence between ages two and nine years. Without therapy, strokes recur in 50%-70% of affected individuals within three years after the first event. Transfusion therapy instituted after an initial stroke has significantly reduced this risk [Serjeant 2013]. Narrowing of cerebral vessels is a risk factor for stroke, and elevated flow velocity on TCD identifies most children at high risk [Adams et al 1998], allowing intervention prior to the development of stroke [DeBaun & Kirkham 2016]. A proportion of children with normal velocities on initial TCD convert to higher-risk velocities over time.
- **Silent cerebral infarcts (SCI)** occur in approximately 39% of children with SCD by age 18 years [Bernaudin et al 2015] and greater than 50% of adults with SCD by age 30 years [Kassim et al 2016]. SCI are lesions identified on cerebral imaging studies without known focal neurologic symptoms; however, such lesions are associated with neurocognitive deficits [Prussien et al 2019] and an increased risk for overt stroke [Miller et al 2001, Jordan et al 2018]. Thus, despite a normal physical exam, SCI should not be considered clinically insignificant. Cerebral arterial stenosis is noted to be a risk factor for SCI but is not always reflected by increased TCD velocities. Thus, TCDs are used to screen for intracranial stenosis and risk of overt stroke, while MRI/MRA are used to identify SCI [DeBaun et al 2020].

**Complications related to hemolysis.** A hemolysis syndrome marked by an elevated LDH, low hemoglobin level, and high reticulocyte count is associated with leg ulcers, priapism, pulmonary artery hypertension, systemic hypertension, and platelet activation [Hebbel 2011]. Other consequences of hemolysis include chronic anemia, jaundice, predisposition to aplastic crisis, and cholelithiasis. While those with the highest rates of hemolysis may experience fewer pain episodes, the overall mortality rate for this group of individuals may be higher [Hebbel 2011, Kato et al 2017].

**Aplastic crisis** is the temporary interruption of red blood cell (RBC) production, typically caused by human parvovirus B19 infection in children, resulting in an acute and potentially life-threatening anemia. Sickle RBCs survive for about seven to 12 days, compared to 100-120 days for normal RBCs. Thus, infection with parvovirus B19, which has tropism to erythroid precursors, can interrupt RBC production for eight to ten days, resulting in a drop in hemoglobin level of 1 g/dL per day, leading to life-threatening anemia in individuals with SCD that may require RBC transfusion. Other infections such as *Streptococcus pneumoniæ*, *Salmonella*, and Epstein-Barr virus (EBV) have also been associated with transient RBC aplasia.

**Pulmonary artery hypertension (PAH)** affects approximately 6%-35% of adults with SCD and can have profound consequences [Parent et al 2011]. Although a similar proportion of children with SCD have PAH as diagnosed by echocardiography, PAH in children does not appear to be associated with the same dire outcomes as in adults [Lee et al 2009, Liem et al 2009, Hebson et al 2015].

While many have defined PAH in SCD based on elevated tricuspid regurgitant jet velocity (TRV) on transthoracic echocardiography (TTE), subsequent studies using direct measurement of pulmonary arterial pressure (PAP) by right heart catheterization indicate that this may overdiagnose PAH [Parent et al 2011]. PAH in adults is associated with markedly increased mortality [De Castro et al 2008] and significant morbidity, including exercise intolerance [Sachdev et al 2011]. Risk factors for PAH include markers of increased hemolysis such as elevated LDH [Kato et al 2006], markers of cardiac strain such as elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) [Machado et al 2006], and the presence of obstructive sleep apnea [Hebson et al 2015]. Some individuals are relatively asymptomatic in the early stages of PAH. The relevance of these factors in children is less clear.

**Priapism** is very common among males with SCD. Upward of 35% of adult males with SCD have experienced this complication, with a mean age of onset of 15 years [Adeyoju et al 2002]. These painful, unwanted erections occur spontaneously, with nocturnal erections, or with fever and dehydration. Males may have episodes of stuttering (intermittent) priapism lasting less than two to four hours that are often recurrent and may precede a more severe and persistent episode. Severe priapism episodes are persistent; those lasting more than two to four hours need rapid intervention because prolonged priapism may result in permanent erectile tissue damage and impotence [Rogers 2005].

**Kidney disease.** Various renal manifestations are seen in SCD. The term sickle nephropathy is used to describe the accumulation of multiple renal insults. The acidity, hypoxia, and hypertonicity characteristic of the renal medulla, in combination with slow capillary transit, makes this location particularly inciting of HbS polymerization and RBC sickling. The vasculopathy associated with both occlusion and hemolysis leads to glomerular and tubular dysfunction correlating to the clinical manifestations of volume depletion, nocturia, and polyuria. Although work is ongoing [Lemes et al 2021, Ataga et al 2022], there are no widely accepted early biomarkers of kidney damage; elevated creatinine is evident only in later stages of disease progression. Hyperfiltration, however, begins early and leads to microalbuminuria and proteinuria, which should be monitored. Greater than 50% of infants with SCD (ages 9-12 months) were shown to have elevated glomerular filtration rates [Ware et al 2010]. Improvement can be seen with hydroxyurea therapy [Aygun et al 2013].

Other renal complications include acute kidney injury, hematuria, urinary tract infection and pyelonephritis, renal medullary carcinoma, and blood pressure abnormalities [Ataga et al 2022].

**Other complications** of SCD include avascular necrosis (most commonly involving the femoral head or humerus), restrictive lung disease, cholelithiasis, retinopathy, cardiomyopathy, and delayed growth and sexual maturation. Individuals with sickle-hemoglobin C disease (Hb S/C) are at particularly high risk for retinopathy and avascular necrosis [Powars et al 2002]. Cardiopulmonary complications represent a major mortality risk in adults [Fitzhugh et al 2010].

Individuals who receive frequent RBC transfusion can have complications of iron overload resulting from tissue iron deposition damaging the liver, lungs, and heart [Kushner et al 2001], and alloimmunization that may interfere with the ability to obtain fully matched units of blood for transfusion [Vichinsky et al 1990].

**Mental health manifestations.** Both children and adults with SCD are at increased risk for mental health disorders including depression, anxiety, social withdrawal, and suicidal ideations [Levenson et al 2008, Connolly et al 2019].

**Life expectancy and quality of life.** While there has been a significant decrease in childhood death rates to as low as 0.47 in 100,000 between 2015 and 2017 [Payne et al 2020], overall survival has not varied much, and quality of life is greatly diminished [Kato et al 2018]. The median survival in the US for those with SCD is difficult to determine but was estimated at age 43 years as of 2017 [Payne et al 2020]. The main causes of death are infection, ACS, PAH, and cerebrovascular events [Bakanay et al 2005]. Causes of death in children tend to differ from those in adults. Children have higher rates of death from infection and sequestration crises, whereas

adult mortality is secondary to chronic end-organ dysfunction, thrombotic disease, and treatment-related complications [Manci et al 2003].

Systemic and institutional racism are major contributors to decreased quality of life and increased mortality in those with SCD [Power-Hays & McGann 2020]. Individuals with SCD are often stigmatized and marginalized. Access to quality, respectful care is decreased, and research and funding are significantly lower for SCD than other less common conditions in the US.

**Heterozygotes for HbS** (i.e., Hb A/S or **sickle cell trait**) have hemoglobins A (adult) and S (sickle). Heterozygous individuals are not anemic and have normal RBC indices, with HbS percentages typically near 40%. Hb A/S confers a survival advantage in children who contract malaria; this is thought to be a major selective pressure for persistence of the HbS pathogenic variant (p.Glu6Val) in regions of the world where malaria is endemic.

The amount of HbS present in heterozygotes is insufficient to produce sickling manifestations under most circumstances and, thus, these individuals are usually asymptomatic. However, they are at risk for several complications [Key & Derebail 2010]:

- Extremes of physical exertion, dehydration, and/or altitude can induce sickle cell vaso-occlusive events in some individuals with Hb A/S [Mitchell 2007]. Individuals with Hb A/S should maintain aggressive hydration during extreme physical exertion, with no formal activity restrictions recommended. There is increased awareness of the low but significant risks for pulmonary emboli, exertional rhabdomyolysis, and sudden death with extreme exertion in individuals with Hb A/S. This has led to the mandatory offering of testing to all NCAA Division I college athletes [Bonham et al 2010]. The full implications of this policy are unclear, and the role of genetic counseling in this setting is complex, as there is debate about the impact and consequences of testing [Tarini et al 2012, Thompson 2013, Buchanan et al 2020].
- Splenic infarct at high altitudes can occur in some individuals with Hb A/S.
- Renal medullary carcinoma is an extremely rare form of kidney cancer occurring almost exclusively in individuals with Hb A/S [Goldsmith et al 2012]; investigation for renal medullary carcinoma should be considered in individuals with Hb A/S who present with hematuria. Recent population studies have identified an increased incidence of renal manifestations in individuals with Hb A/S including rhabdomyolysis, end-stage kidney disease, chronic kidney disease, and renal papillary necrosis [Hulsizer et al 2022].
- HB A/S may be associated with an increased risk for venous thromboembolism [Kato 2019, Hulsizer et al 2022].
- Individuals with Hb A/S are at increased risk for serious complications following traumatic hyphema [Gharaibeh et al 2019].
- Hb A/S has not been associated with avascular necrosis, stroke, leg ulcers, or cholelithiasis [Goldsmith et al 2012, Naik et al 2017].

## Genotype-Phenotype Correlations

Although a tremendous amount of individual variability occurs, individuals with Hb S/S and S/$\beta^0$-thalassemia are generally more severely affected than individuals with Hb S/C or S/$\beta^+$-thalassemia. Genetic factors that are responsible for this variability are being investigated [Steinberg & Adewoye 2006].

Individuals with Hb S/C have longer RBC life span and higher hemoglobin concentration associated with fewer vaso-occlusive pain episodes. Splenomegaly and the associated risk for splenic sequestration can persist well beyond early childhood. Proliferative retinopathy and avascular necrosis are more likely to develop than in those with other sickle hemoglobinopathies.

The presence of alpha-thalassemia may modify SCD severity (see Differential Diagnosis). In general, alpha-thalassemia improves RBC survival and decreases hemolysis in SCD. However, the clinical effect on SCD is unclear and can be variable, including possible decreased complications arising from hemolysis and potentially increased complications from vaso-occlusive events [Steinberg 2005].

### Nomenclature

Historically in the US the term sickle cell anemia has been used to describe persons homozygous for p.Glu6Val (i.e., Hb S/S) or, at times, persons with Hb S/$\beta^0$-thalassemia. With increased awareness of the broad spectrum of clinically significant sickle hemoglobinopathies with varying degrees of anemia, the trend has been to use the umbrella term "sickle cell disease" (SCD). The term SCD should be followed by a detailed genotypic description for the individual (e.g., Hb S/S, Hb S/C, Hb S/$\beta^0$-thalassemia). It is important to avoid dehumanizing terms such as "sickler" when referring to individuals with SCD.

### Prevalence

The HbS allele is common in persons of African, Mediterranean, Middle Eastern, and Indian ancestry and in persons from the Caribbean and parts of Central and South America but can be present in individuals of any ethnic background.

Among African Americans, the prevalence of sickle cell trait (Hb A/S) is about 10%, resulting in the birth of approximately 1,100 infants with SCD (Hb S/S) annually in the US. Approximately one in 300-500 African Americans born in the US has SCD; more than 100,000 individuals are estimated to have SCD (Hb S/S) [Hassell 2010].

The prevalence of *HBB* alleles associated with SCD is higher in other parts of the world. In many regions of Africa, the prevalence of the HbS pathogenic variant (p.Glu6Val) is as high as 25%-35%, with an estimated 15 million Africans affected by SCD and 300,000-400,000 affected births per year worldwide [Kato et al 2018]. SCD accounts for as many as 16% of deaths of children younger than age five years in western Africa [Neville & Panepinto 2011].

## Genetically Related (Allelic) Disorders

**Beta-thalassemia** is defined by an imbalance of alpha and beta globin synthesis. Most commonly this imbalance is caused by *HBB* pathogenic variants that result in decreased or absent production of beta globin (hemoglobin A), although it can also occur with excessive alpha chain production (see Differential Diagnosis), as with the presence of triplicated alpha globin genes. More than 200 different beta-thalassemia pathogenic variants have been described.

## Differential Diagnosis

The following diagnoses may be considered in an individual presenting with clinical features of sickle cell disease (SCD) who did not have access to newborn screening. Each of these conditions would be easily distinguished from SCD by the absence of hemoglobin S on hemoglobin assay.

- Acute or chronic anemia
- Hemolytic anemia
- Legg-Calve-Perthes disease
- Osteomyelitis
- Septic arthritis

# Management

Management guidelines for sickle cell disease (SCD) have been published [National Heart, Lung, and Blood Institute 2014, Yawn et al 2014, Sickle Cell Society 2018, Liem et al 2019, National Health Service 2019, Brandow et al 2020, Chou et al 2020, DeBaun et al 2020, Kanter et al 2021]; see also the American College of Emergency Physicians guideline available online.

## Evaluations Following Initial Diagnosis

To establish the extent of end-organ damage and needs in an individual diagnosed with SCD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with Sickle Cell Disease

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Hematology** | Hematologist consultation | |
| | • CBC & reticulocyte count<br>• Measurement of HbF (%)<br>• Thalassemia testing: hemoglobin electrophoresis or HPLC & inclusion body prep<br>• RBC genotyping so that antigen-matched blood may be given if transfusion is urgently needed | • Baseline laboratory studies should be done in infants ≥12 mos<br>• During childhood HLA typing should be offered to affected person & all full sibs that are unaffected or carry a hemoglobin trait. |
| **Renal** | • Serum vitamin D level<br>• Renal function tests (BUN, serum creatinine, urinalysis, urine microalbumin) | |
| **Liver** | • Assessment of iron status (ferritin, TIBC, % saturation)<br>• Liver function tests (ALT, direct & indirect bilirubin, LDH) | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & families re nature, MOI, & implications of SCD or other hemoglobinopathy they are at risk for to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. | |

ALT = alanine aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; HbF = fetal hemoglobin; HLA = Human leukocyte antigen; HPLC = high-performance liquid chromatography; LDH = lactate dehydrogenase; MOI = mode of inheritance; RBC = red blood cell; SCD = sickle cell disease; TIBC = total iron-binding capacity

*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

# Treatment of Manifestations

## Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

**Table 4.** Sickle Cell Disease: Targeted Therapies

| Treatment Class | Specific Therapy | Mechanism of Action | Dose | Comments |
|---|---|---|---|---|
| **Disease-modulating pharmacotherapy** | Hydroxyurea | • Induction of HbF synthesis<br>• Metabolized into nitric oxide, a potent vasodilator | 20 mg/kg, titrated to maximum tolerated dose | • Results in ↓ sickling & ↑ RBC survival<br>• ↓ WBC, reticulocyte, & platelet counts<br>• ↓ cell adhesion & overall improvement in blood flow<br>• ↓ vascular inflammation |
| | L-glutamine | Antioxidant | Oral (Note: Dose is weight-dependent; see medication package insert.) | |
| | Voxelotor | Binds hemoglobin & ↑ its affinity for oxygen | Oral (Note: Dose is weight-dependent; see medication package insert.) | |
| | Crizanlizumab | Antibody to P-selectin; ↓ cell adherence to endothelium, which ↑ microvascular blood flow | 5 mg/kg IV infusion once per month | |
| **Transplantation** | HSCT | Replace SCD-producing marrow w/compatible marrow from a donor w/o SCD or a donor with sickle cell trait | | |
| **Gene therapy** | Exagamglogene autotemcel (exa-cel) (autologous ex vivo CRISPR/Cas9 gene editing) | Activation of HbF by inhibiting Bcl11a activity in erythroid cells [1] | | |
| | Lovotibeglogene autotemcel (lovo-cel) (autologous ex vivo lentiviral vector gene therapy) | Production of anti-sickling hemoglobin ($HbA^{T87Q}$) [2] | | |

HbF = fetal hemoglobin; HSCT = hematopoietic stem cell transplantation; RBC = red blood cell; SCD = sickle cell disease; WBC = white blood cell

*1.* Frangoul et al [2021]

*2.* Kanter et al [2023]

**Disease-modulating therapies** are discussed in several reviews [Ware et al 2017, Rai & Ataga 2020, Salinas Cisneros & Thein 2020, Pace et al 2021, Brandow & Liem 2022]. There are now four FDA-approved medications for SCD in addition to chronic transfusion and curative therapies.

**Hydroxycarbamide (hydroxyurea).** Hydroxyurea benefits individuals with SCD via several mechanisms [Ware et al 2010, McGann & Ware 2015, Ware 2015, Qureshi et al 2018]. The reported benefits of hydroxyurea treatment continue to increase. Hydroxyurea has been primarily studied in individuals with Hb S/S and Hb S/$\beta^0$-thalassemia; less information is available regarding benefits in individuals with Hb S/C. Benefits include:

- Decreased pain;
- Decreased hospitalizations;
- Decreased episodes of acute chest syndrome;
- Decreased need for transfusion;
- Primary stroke prevention;
- Increased life span.

Oral hydroxyurea is safe to use in children as young as age six months [Wang et al 2011] and is recommended in individuals with Hb S/S and Hb S/$\beta^0$-thalassemia age nine months or older [Yawn et al 2014, Qureshi et al 2018].

While even low-dose hydroxyurea has clinical benefits, increasing evidence suggests that its benefits increase with higher dosing. Hydroxyurea can lead to myelosuppression. While relative myelosuppression has clinical benefit, with higher hydroxyurea dosing, complete blood counts (CBC) and reticulocyte counts must be monitored to avoid toxicity. To balance the benefits and risks of hydroxyurea, many suggest titration of the drug to determine the dose in each person that provides a reduction in WBC count into a target range without toxicity [Strouse & Heeney 2012, Yawn et al 2014, Ware 2015, Qureshi et al 2018]. Pharmacokinetics have been used to predict an optimal starting dose of hydroxyurea to more rapidly reach an optimal dose and maximal clinical benefits [Quinn et al 2021].

**L-glutamine** is an oral amino acid approved for the prevention of acute complications in individuals age five years and older with SCD, whether on hydroxyurea or not [Niihara et al 2018]. Glutamine is involved in many pathways that may affect SCD and levels are decreased in SCD. Because of its antioxidant properties, it was thought to benefit RBCs directly, but while decreasing acute events by 25%, there was no impact on hemoglobin levels.

**Voxelotor** is an oral agent approved in individuals age four years and older that binds hemoglobin and increases its affinity for oxygen, thus decreasing crystallization, and it has been shown to increase hemoglobin levels and decrease hemolysis whether on hydroxyurea or not [Vichinsky et al 2019]. While voxelotor has been approved on the basis of improving lab values, its impact on pain, stroke, quality of life, and other complications are being investigated.

**Crizanlizumab** is a chimeric antibody to P-selectin, a key cell surface adherence protein, given as a once-monthly IV infusion that has been shown to decrease acute crises by 45% in individuals age 16 years and older whether on hydroxyurea or not [Ataga et al 2017]. The antibody decreases cell adherence to the endothelium to an extent where microvascular blood flow is improved, yet infections are not increased.

**Hematopoietic stem cell transplantation (HSCT)** from a healthy donor with no *HBB* pathogenic variant or a donor with sickle cell trait can be curative in individuals with SCD. Children with SCD receiving HSCT using a matched-sib donor can expect greater than 90% chance of cure with an overall survival of 93% [Gluckman et al 2017]. The chance of cure must be weighed against potential long-term consequences of HSCT, including chronic graft-versus-host disease, cardiac abnormalities, and infertility. In addition, it is estimated that fewer than 30% of individuals with SCD have suitable matched-sib donors. There are strategies using alternative

donors (e.g., unrelated donors, haploidentical donors such as a parent, cord blood), as well as less intensive conditioning regimes. Outcomes in those treated with HSCT and those receiving routine medical care are improving, leading to debate as to who should be transplanted, how, and when. Comparative analyses have identified risk factors and the development of risk scores to guide decision making [Eapen et al 2019, Brazauskas et al 2020]. The first large consensus-based recommendations for HSCT in SCD have been released [Kanter et al 2021]. In general, myeloablative conditioning in younger children with a matched-sib donor yields the best outcomes, and in adults a non-ablative regime is suggested. In addition, with the high long-term risk to those with neurovascular events receiving routine therapy, options for HSCT should be addressed. The criteria, risks, and benefits of transplantation are changing rapidly; thus, it is important for families and providers to discuss the risks and benefits with specialists at a transplantation center with expertise in SCD.

**Gene therapy.** There are many active gene therapy trials using multiple strategies, and individuals with SCD have been cured [Abraham & Tisdale 2021]. Strategies include the addition of a non-sickling beta globin gene, disruption of Bcl11a activity by gene mutation or mRNA inactivation, and genome editing to correct or alter the *HBB* pathogenic variant. While initial results have been very promising, with two types of therapy approved by the FDA (see Table 4), questions about long-term risks, durability, and outcomes compared to medicinal therapy continue to be investigated. An increased risk of myeloid malignancy has been noted, likely related to the state of the bone marrow in individuals with SCD, conditioning regime, stem cell manipulation, and expansion demands, but not to mutagenesis by the viral vectors used. These promising approaches should be considered for individuals with severe sequelae of SCD who do not have a matched-sib donor, as should the potential for a haploidentical transplant. These options should be discussed with an expert who is up to date in this rapidly evolving field.

## Supportive Care

**Lifelong comprehensive care** is necessary to minimize morbidity, reduce early mortality, and maximize quality of life. Management of SCD includes routine primary care and dental care, review of potential disease-modifying and curative therapies, and joint decision making on a care plan (see Published Guidelines / Consensus Statements).

**Ongoing education** of parents, caregivers, and affected individuals is essential to help minimize morbidity and mortality. Education comprises a regular review of interventions, including the following:

- Maintaining hydration and avoiding extremes of climate
- Learning to live a full life with modifications to avoid triggering complications
- The importance of routine health maintenance visits, prophylactic medications, early intervention for both acute and chronic complications, and community support and resources
- Warning signs of acute illness such as fever, respiratory symptoms, pallor, lethargy, splenic enlargement, priapism, and neurologic changes, including education for the affected individual, as developmentally appropriate
- A systematic approach to pain management including identifying and reversing common triggers for SCD pain (and distinguishing it from other etiologies of pain), hydration, warmth, ambulation, distraction, and other comfort maneuvers, as well as initiation of NSAIDs and appropriate use of opiates
- All families should:
    - Have a plan in place for 24-hour access to a medical facility that can provide urgent evaluation and treatment of acute illnesses such as fever, acute chest syndrome (ACS), splenic sequestration, priapism, and stroke;
    - Be informed of the affected family member's baseline (steady state) laboratory values for purposes of comparison, as values often change during acute illness.

**Penicillin prophylaxis** prevents 84% of life-threatening episodes of childhood *Streptococcus pneumoniæ* sepsis [Gaston et al 1986]:

- By age two months, all infants with SCD should receive penicillin V potassium prophylaxis (125 mg orally twice a day).
- At age three years, the dose is increased to 250 mg orally, twice a day, and then continued until at least age five years.

**Prophylaxis for those allergic to penicillin** can include erythromycin or azithromycin, but care should be taken to avoid medications that alter metabolism and increase the risk of prolonged QTc syndrome [Anah et al 2021].

**Immunizations.** Timely administration of vaccines is essential. Clinicians should follow the recommended vaccine schedule for functionally asplenic individuals, which includes additional vaccines such as the 23-valent pneumococcal polysaccharide vaccine, and an altered schedule for meningococcal vaccines. Persons with SCD are considered high priority for annual influenza vaccine and COVID-19 immunization [Yawn et al 2014].

**Folic acid supplementation** should be considered to support increased red blood cell (RBC) synthesis required as a result of high RBC turnover in individuals with SCD. Despite this long-standing practice, the clinical implications of folic acid supplementation and increasing the serum folate remain unclear [Dixit et al 2018], and there are ongoing studies to assess its utility in children with SCD [Williams et al 2020].

**Chronic RBC transfusion therapy** can decrease the number of RBCs at risk to sickle, significantly reducing the risk of pain, stroke, acute chest syndrome, and other complications. The initial goal of chronic RBC transfusion therapy varies depending on indication but typically is to maintain the percentage of HbS at less than 30% and suppress reticulocytosis. Unfortunately, with the risks related to iron overload, high rates of alloimmunization related in part to minor antigen mismatches with donors primarily of northern European ancestry, and potential reactions, RBC transfusion should be reserved for very specific situations. Chronic RBC transfusion therapy may be warranted for the following [Yawn et al 2014, Howard 2016, Ware et al 2017]:

- Primary prevention of stroke in individuals with an abnormal transcranial Doppler (TCD), treatment of silent infarcts, and prevention of stroke recurrence
- Prevention of stroke recurrence
- Treatment of chronic pain refractory to other therapies
- Pulmonary hypertension
- Chronic kidney failure
- Recurrent episodes of ACS
- Severe end-organ damage

Complications of chronic RBC transfusion therapy include iron overload, alloimmunization, hyperhemolysis, and (rarely) infection. Transfusion is not indicated for isolated pain episodes. To limit alloimmunization and transfusion reactions, extended matching of RBC antigens should be performed, and blood products should be leuko-reduced (i.e., removal of white blood cells from the transfusion product). RBCs antigen matched at the full Rh locus (D, C, E) and Kell have been suggested to decrease alloimmunization rates, as well as other alleles when possible [Lasalle-Williams et al 2011]. To decrease alloimmunization, extended RBC antigen profile by genotype should be obtained for all individuals with SCD at the earliest opportunity (optimally before first transfusion) [Chou et al 2020]. If not available or needed acutely, serology can be used. Defining antigens molecularly has multiple benefits, including the ability to type cells when serologic reagents are not available [Yazdanbakhsh et al 2012, Matteocci & Pierelli 2014].

**Iron overload.** Individuals receiving prophylactic as well as chronic transfusions are at risk for iron overload; the amount of blood transfused and serum ferritin concentration should be monitored. Those with high exposures or documented iron overload should have an assessment of organ iron accumulation. With increasing

availability, radiographic assessment of iron in multiple organs by $T_2$*-weighted MRI is replacing biopsy [Wood 2007]. The noninvasive nature of monitoring iron overload via MRI or SQUID (superconducting quantum interference device) has led to significant improvements in the outcome of individuals with iron overload [Coates 2014]. Oral or subcutaneous iron chelation therapy are recommended for those with documented excessive tissue iron deposition; acceptance and use of medications is the main limiting factor in affected individuals [Coates & Wood 2017].

## Management of Specific Complications

Brousse et al [2014], Yawn et al [2014], Sickle Cell Society [2018], Liem et al [2019], Brandow et al [2020], DeBaun et al [2020], and the American College of Emergency Physicians include suggestions for management of specific complications of SCD.

**Vaso-occlusive pain episodes** (including dactylitis)

- The initial focus should include the reversal of inciting triggers (e.g., cold, dehydration, acute infection).
- Pain episodes are managed using a multimodal approach that may include warmth, hydration, massage, distraction, acupuncture, biofeedback, self-hypnosis, and pharmaceuticals.
- Uncomplicated pain episodes may be managed at home with oral hydration and oral analgesics including NSAIDs and opiates.
- More severe pain episodes require hospitalization and administration of parenteral fluids and analgesics in addition to adjunctive treatments such as massage and physical therapy.
- Optimal analgesia is generally achieved with morphine (or other opiate) given around the clock by a patient-controlled analgesia device or by continuous infusion.
- NSAIDs (e.g., ketorolac, ibuprofen, naproxen) may be used to augment the analgesic effect of opiates and decrease inflammation. Additional pharmaceuticals to consider include ketamine for both adults and children as well as serotonin and norepinephrine reuptake inhibitors in adults with chronic pain [Brandow et al 2020].
- Adequate but not excessive IV hydration should be provided to maintain euvolemia, and individuals should be monitored closely for the development of other complications such as ACS, splenic sequestration, or opiate-induced constipation and pruritis.
- A thorough evaluation for infection including blood culture, urine culture, and chest radiograph should be considered based on the clinical scenario.

Note: Transfusion and hydroxyurea are not useful treatments for acute pain episodes (see Prevention of Primary Manifestations).

**Splenic sequestration.** Severe episodes of splenic sequestration may progress rapidly to cardiovascular collapse and death; thus, emergency RBC transfusion is indicated when signs of cardiovascular instability are present. Parents should be taught how to monitor for splenic enlargement and recognize symptoms of sequestration, and when to seek medical attention. Individuals who experience multiple severe episodes of splenic sequestration may require splenectomy.

**Fever/suspected infection.** Individuals with temperature greater than 38.3 °C or persistent temperature elevation above baseline require:

- Rapid triage and physical assessment;
- Urgent complete blood count (CBC) with differential and reticulocyte count;
- Blood culture (and other cultures as clinically indicated) and a low threshold for chest radiograph when respiratory symptoms are present, as ACS can often present with a normal physical examination;
- Parenteral broad-spectrum empiric antibiotics such as ceftriaxone pending culture results. If ceftriaxone is used, an observation period should be required after administration given the risk of severe drug-induced

hemolysis [Neuman et al 2014]. A macrolide antibiotic should be added if pneumonia/ACS is a concern. Additional antibiotics should be added only for proven or suspected meningitis or other severe illness.

Note: With the changing natural history of fever and sepsis in individuals with SCD in the US there is increasing evidence that empiric treatment with parenteral antibiotics without obtaining cultures may be appropriate for well-appearing, fully immunized children with fever <39 °C; however, this work has not yet been replicated [Baskin et al 2013, Ellison et al 2015] nor has it become widely accepted practice. There are additional published clinical pathways that outline outpatient management [Ellison et al 2018, Erno et al 2022].

**Acute chest syndrome (ACS).** The index of suspicion for ACS should be high when individuals with SCD have fever, chest pain, or signs or symptoms of respiratory compromise. Given the high mortality associated with ACS, an aggressive multimodal treatment strategy should be initiated [Miller 2011]:

- Perform chest radiograph examination.
- Provide aggressive treatment with oxygen, analgesics, and antibiotics (including a macrolide).
- Incentive spirometry should be encouraged.
- Hypoxemia can progress to need for intubation and mechanical ventilatory support.
- Simple RBC transfusion may be required for those who are critically ill, have multilobar disease, or have progressive disease despite conservative therapy.
- Emergent RBC exchange should be considered in certain severe cases in which the hemoglobin is greater than 10 g/dL and/or the HbS is greater than 30%; however, the quality of evidence in this area is still low [NHLBI 2014, Dolatkhah & Dastgiri 2020].

**Stroke.** Any history of an acute neurologic symptom or event warrants emergent evaluation including a CBC with reticulocyte count and a noncontrast brain CT examination. Cerebral hemorrhage requires immediate neurosurgical consultation. An MRI/MRA to define injury should be obtained as soon as available, but definitive treatment with exchange transfusion should never be delayed for these results.

Treatment for children with acute ischemic stroke includes the following:

- Neurologic status should be monitored and increased intracranial pressure and seizures aggressively treated if present.
- Exchange transfusion with the goal of decreasing HbS percentage to less than 30% of the total hemoglobin followed by a chronic transfusion program can significantly decrease risk for recurrent stroke [Wang et al 2000]. Without continued therapy, as many as 60%-90% of individuals who have had a stroke have a second stroke within three years. Thus, in most individuals a preventive chronic transfusion protocol is initiated after a central nervous system event and continued indefinitely [Adams & Brambilla 2005, DeBaun et al 2020] (see Prevention of Primary Manifestations).
- Hydroxyurea has been studied as an alternative to transfusion therapy [Ware et al 2012]. While it does not provide the same protection as transfusion therapy, it may be an alternative for affected individuals who are unable to receive transfusion therapy (e.g., individuals with limited access to medical care) or are difficult to transfuse because of alloimmunization [de Montalembert 2012].

**Silent cerebral infarcts.** Chronic transfusion has been shown to reduce silent infarcts. Given the high prevalence of silent infarcts, it has been recommended that a one-time screening MRI be obtained without sedation in early-school-age children as well as in adults with SCD. Once a lesion is identified, the American Society of Hematology 2020 consensus guidelines [DeBaun et al 2020] recommend:

- Neurologic evaluation to assure that infarcts are classified as a silent cerebral infarct rather than overt stroke;
- Discussion regarding secondary prevention options including regular blood transfusions and stem cell transplantation;

- Discussion regarding cognitive screening assessment;
- MRI surveillance every 12 to 24 months to assess for progression.

**Aplastic crisis.** Monitoring of hematocrit (both absolute and compared with the individual's baseline), reticulocyte count, and cardiovascular status are required. Blood transfusion may be necessary. Aplastic crisis caused by parvovirus B19 will often spontaneously resolve; however, if the reticulocyte count does not improve, intravenous gamma globulin can be considered to assist in viral clearance. Any sibs or other close contacts with SCD should be monitored for RBC aplasia because parvovirus is easily transmissible. Also of note, feto-maternal transmission of parvovirus can lead to fetal hydrops and demise, particularly before the 20th week of gestation.

**Pulmonary hypertension.** Diagnostic criteria, as well as when and how to intervene, are becoming increasingly controversial [Hassell et al 2014, Klings et al 2014a, Klings et al 2014b, Hebson et al 2015, Liem et al 2019, Chan et al 2023]. Existing consensus guidelines are not fully accepted by experts in the field. Thus, discussion with local sickle cell and pulmonary hypertension experts should be used to guide care. The following general approach is reasonable:

- Aggressive evaluation and treatment of additional etiologies contributing to pulmonary hypertension (e.g., thrombotic disease, obstructive sleep apnea)
- Optimization of SCD-related therapy to stop progression (e.g., chronic transfusions, hydroxyurea, oxygen therapy if hypoxemic)

**Priapism.** Episodes of severe priapism require urgent evaluation and treatment, including hydration and analgesia, and may require aspiration and irrigation [Ateyah et al 2005] by a urologist. For refractory cases, sympathomimetic drugs [Canguven et al 2013] and surgical interventions may be indicated [Ahuja et al 2021]. Although prophylactic measures such as alpha-adrenergics, PDE5 inhibitors, antiandrogens, and luteinizing hormone-releasing hormone analogs have been used for those with refractory or recurring priapism [Olujohungbe & Burnett 2013], no randomized control trials support their use [Chinegwundoh et al 2020].

**Kidney disease.** For children and adult with proteinuria, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers have been recommended. Affected individuals with end-stage kidney disease should be referred for kidney transplant [Liem et al 2019].

**Mental health.** Identify and provide assistance in accessing medical and community resources. This includes involvement with community groups as well licensed professionals.

## Surveillance

Affected individuals should be seen routinely for evaluation of SCD-related comorbidities. Surveillance should be tailored to an individual's specific genotype and clinical history. Routine age-dependent screening allows for early detection and treatment of end-organ damage. While the National Heart, Lung, and Blood Institute in the US released guidelines for surveillance, the recommendations are not complete, and some have been modified since publication. The American Society of Hematology has been developing multiple sets of guidelines, but gaps remain, especially for genotypes other than Hb S/S and Hb S/$\beta^0$-thalassemia. The following are general guidelines compiled from several sources (see also Published Guidelines / Consensus Statements).

**Table 5.** Recommended Surveillance for Individuals with Sickle Cell Disease

| System/Concern | Evaluation [1] | Frequency |
|---|---|---|
| **Hematology** | CBC w/differential & reticulocyte count | Annually & as needed |
| | RBC genotyping (or phenotyping if needed urgently) so that antigen-matched blood may be given if transfusion is needed | In 1st yr of life & always prior to 1st transfusion to guide extended RBC antigen matching, thus ↓ risk of alloimmunization w/ transfusions |

*Table 5. continued from previous page.*

| System/Concern | Evaluation [1] | Frequency |
|---|---|---|
| **Stroke & silent cerebral infarcts** | Transcranial Doppler | • Annually from age 2-16 yrs in all children w/Hb S/S & Hb S/$\beta^0$-thalassemia<br>• Children w/normal velocities require ongoing annual eval. |
| | Developmental assessment | Annually throughout childhood |
| | Neurocognitive assessment to identify learning difficulties | • Prior to school entry & repeated every 2-3 yrs<br>• Immediately if concerns of decline |
| | Brain MRI exam | • Initial MRI when child can tolerate w/o sedation<br>• Repeat MRI in those w/new neurocognitive deficits or concerns |
| **Renal** | • Serum vitamin D level [2]<br>• Assessment of renal function (BUN, serum creatinine, urinalysis, & urine microalbumin or urine protein-to-creatinine ratio) | Annually |
| **Restrictive lung disease** | PFTs | In those w/history of ACS or clinical manifestations of pulmonary disease [3] |
| **Retinopathy** | Ophthalmologist exam for proliferative retinopathy | Annually beginning at age 10 yrs |
| **Cardiomyopathy / Other cardiac manifestations** | • Echocardiogram to determine tricuspid regurgitant jet w/consideration of right heart catheterization<br>• EKG in those on medications that may alter QTc | • When indicated by signs/symptoms of cardiac manifestations<br>• NT-proBNP, 6MWT, EKG, PFTs, & sleep study depending on clinical manifestations<br>• Screening for end-organ manifestations vary. [4] |
| **Growth deficiency** | Assessment of growth | At each visit throughout childhood |
| **Liver** | • Assessment of iron status (ferritin, TIBC, % saturation)<br>• Liver function tests (ALT, direct & indirect bilirubin, alk phos, LDH) | Annually |
| | MRI to assess iron overload | Recommendations vary. [5] |
| **Psychiatric** | Mental health screening for signs of depression, anxiety, & isolation | |

*Table 5. continued from previous page.*

| System/Concern | Evaluation [1] | Frequency |
|---|---|---|
| **Family/ Community** | • Assess social determinants of health.<br>• Social work assessment w/emphasis on medical & concrete needs & effect of SCD on lifestyle | At least annually |

6MWT = six-minute walk test; ACS = acute chest syndrome; ALT = alanine aminotransferase; alk phos = alkaline phosphatase; BUN = blood urea nitrogen; CBC = complete blood count; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-brain natriuretic peptide; PFTs = pulmonary function tests; QTc = corrected QT interval; RBC = red blood cell; SCD = sickle cell disease; TIBC = total iron-binding capacity

*1.* Lab values should be provided to parents/caregivers and affected adults to allow long-term monitoring and comparison during times of illness.

*2.* Vitamin D level is indicated because of the high prevalence of vitamin D deficiency in individuals with SCD and the potential role in fetal hemoglobin expression.

*3.* See Liem et al [2019] for additional information.

*4.* See Liem et al [2019] and Published Guidelines / Consensus Statements for additional information.

*5.* See Published Guidelines / Consensus Statements.

## Agents/Circumstances to Avoid

Education for individuals with SCD involves learning how to control one's environment to minimize the chance of exacerbations. Environmental controls include avoiding the following:

- Dehydration
- Extremes of temperature (e.g., swimming in cold water, which can trigger a pain episode)
- Physical exhaustion
- Extremely high altitude without oxygen supplementation
- Trauma
- Infection
- Cocaine. While alcohol and illegal drugs are never endorsed, cocaine and its derivatives, with their vasoconstrictive and cardiac stimulation effects, are particularly dangerous drugs in the setting of SCD.
- The analgesic meperidine, which should be avoided as first-line therapy because of potential central nervous system toxicity

## Evaluation of Relatives at Risk

Early diagnosis of at-risk family members may allow for intervention before symptoms are present.

If born in the US, sibs with SCD are diagnosed by universal newborn screening soon after birth (at which time referral to a pediatric hematologist is appropriate). Many states also identify sickle cell trait on newborn screening.

If newborn screening data are not available for at-risk sibs, several diagnostic approaches can be considered:

- If the *HBB* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, the gold standard is a combination of high-performance liquid chromatography or isoelectric focusing combined with a CBC and reticulocyte count. As microcytosis helps guide interpretation of results, a measure of iron status such as a zinc protoporphyrin test or serum iron and total iron-binding capacity is of benefit.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Pregnancy complications in SCD can be minimized with close follow up and collaboration between hematologic and obstetric teams [Asare et al 2017]. Pregnancy in women with SCD involves increased risk for thrombosis, infectious complications, acute painful episodes, acute chest syndrome, preeclampsia, and maternal death [Oteng-Ntim et al 2015a, Kuo & Caughey 2016, Lewis et al 2021]. For the fetus, there is increased risk of preterm birth, intrauterine growth restriction, stillbirth, and perinatal mortality [Oteng-Ntim et al 2015b, Boafor et al 2016, Kuo & Caughey 2016]. The risk of pregnancy complications increases when access to prenatal care is limited, reinforcing the importance of close hematologic and obstetric follow up [Asare et al 2017]. The benefits of a chronic transfusion program versus the use of "as-needed" transfusions has not been established [Okusanya & Oladapo 2016], but expert consensus has identified individuals for whom prophylactic transfusions at regular intervals should be considered at the onset of pregnancy. These include women with a history of severe SCD-related complications before the current pregnancy, additional features of high-risk pregnancy (e.g., additional comorbidities including nephropathy) [Chou et al 2020], and those who develop SCD-related complications during the current pregnancy.

Current guidelines recommend discontinuing hydroxyurea treatment during pregnancy. While reports of human infants exposed prenatally to hydroxyurea have not identified an increased risk of malformations, hydroxyurea has been noted to increase congenital anomalies in experimental animal models.

The role of chronic transfusions in lieu of hydroxyurea needs to be addressed. Chelation during pregnancy remains controversial and is generally not advised; both deferasirox and deferoxamine are category C medications in pregnancy, while deferiprone is category D. However, given the deleterious long-term effects of discontinuing iron chelation for nine months, many providers recommend resuming chelation therapy in the second and third trimesters, specifically with deferoxamine due to its larger molecular size, prohibiting it from crossing the placenta [Diamantidis et al 2016, Sorrentino et al 2020, Taher et al 2020].

More than 99% of births to women with SCD occurring after 28 weeks' gestation are live births of infants with normal Apgar scores [Smith et al 1996]. Attention to postnatal opiate withdrawal in infants of mothers treated with high-dose opiates during pregnancy is warranted.

## Therapies Under Investigation

Increased understanding of SCD pathophysiology has led to the development of drugs that target different pathways as well as attempts to improve medications currently in use. While not comprehensive, several promising agents targeting different pathways are presented here, with emphasis on those that are in Phase II/III clinical trials [Kato et al 2018, Carden & Little 2019, Osunkwo et al 2020, Rai & Ataga 2020].

**Allosteric changes in hemoglobin to decrease HbS polymerization.** HbS polymerizes in the T (tense) conformation associated with deoxygenation, but not the R (relaxed) conformation associated with oxygenation. The FDA-approved drug voxelotor binds a subpopulation of hemoglobin leading to a conformational change stabilizing the R state, decreasing polymerization, increasing hemoglobin, and decreasing hemolysis. However, a more efficacious version is in trials. Erythrocyte pyruvate kinase activators lower 2,3-DPG, increasing oxygen affinity homogeneously, thus decreasing crystallization, while also increasing RBC ATP, which may provide additional benefits. Multiple versions are in trials with promising results.

**Decreasing the consequences of hemolysis.** Hemolysis leads to multiple consequences, including both decreased synthesis and increased destruction of nitric oxide (NO). Arginine, the precursor of NO, has been studied in several contexts in the US and Africa and has shown benefit in hospitalized people with SCD pain as well as with other complications. Notably, the FDA-approved amino acid L-glutamine is a precursor to arginine. In addition, multiple agents such as soluble guanylate cycle stimulators and phosphodiesterase inhibitors are in

trials to improve NO metabolism. Free heme leads to multiple negative downstream events, thus hemopexin and other agents to "detoxify" heme are being investigated.

**Decreasing adhesion to the endothelium.** Adhesion of WBC to the endothelium of the microcirculation slows blood flow through the microcirculation, increasing HbS polymerization and worsening SCD. While the FDA-approved chimeric anti-P-selectin antibody crizanlizumab decreases pain and acute events, multiple trials with fully humanized antibodies and antibodies to other adherence receptors are yielding promising results.

**Induction of fetal hemoglobin.** Though induction of fetal hemoglobin (HbF) is the oldest approach to drug therapy for SCD, hydroxyurea remains the only FDA-approved HbF inducer. Multiple pathways and factors associated with the high-level expression of the HbF genes (*HBG1* and *HBG2*) have been identified and continue to be investigated. Multiple agents aimed at inhibiting epigenetic modifications known to repress gamma globin production are being investigated with the goal of "reactivating" expression and inducing HbF (e.g., DNA methyltransferase [DNMT1], histone deacetylase and lysine-specific demethylase [LSD-1] inhibitors). While progress on these agents has been slow, there has been explosive progress in activating HbF by inhibiting Bcl11a activity, a natural inhibitor of gamma gene expression. While pharmaceutical agents are being sought, multiple gene therapy trials designed to disrupt Bcl11a expression using a variety of approaches are ongoing. (One gene therapy approach to disrupt Bcl11a expression was recently approved by the FDA; see Targeted Therapies.)

**Anti-inflammatory pathways.** Multiple approaches are being pursued, including the use of omega-3 fatty acids and adenosine A2A receptor agonists.

**Anticoagulants and antiplatelet agents.** Hypercoagulability and platelet activation are major contributors to vaso-occlusion. While many agents have been investigated, one promising agent is tinzaparin, which may act both through anticoagulation activity and by decreasing platelet adherence and activation.

Due to the rapid development of therapies for SCD, it is important to search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe to access information on clinical studies and to discuss available studies with an expert in SCD.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Sickle cell disease (SCD) is inherited in an autosomal recessive manner.

## Risk to Family Members

**Parents of a proband**

- The parents of an individual with SCD are typically heterozygous for one *HBB* pathogenic variant; that is, one parent is heterozygous for hemoglobin S (HbS; *HBB* variant p.Glu6Val) and one parent is heterozygous for HbS or a different beta globin chain variant (e.g., HbC, HbD, HbO, or HbE).

  Alternatively, it is possible that one or both parents have biallelic beta globin chain variants (e.g., Hb S/S or compound heterozygous *HBB* pathogenic variants [e.g., Hb S/$\beta^0$-thalassemia]) and are affected.

  Typical parental alleles are described in Table 6.

- Evaluation of the parents is recommended to determine their genetic status and to allow reliable recurrence risk assessment.
    - If both SCD-related *HBB* pathogenic variants have been identified in the proband, molecular genetic testing can be used to determine the genetic status of the parents.
    - If only one (or neither) SCD-related *HBB* pathogenic variant has been identified in the proband, high-performance liquid chromatography (HPLC) can be used to detect common abnormal hemoglobins.

      Note: HPLC can be used to detect common qualitative abnormalities (i.e., abnormal hemoglobins). However, HPLC cannot definitively distinguish Hb S/$\beta^0$-thalassemia from Hb S/S (this differentiation requires molecular genetic testing or integration with other laboratory studies).
- If one parent is found to have an HbS allele, a beta globin chain variant is not identified in the other parent, and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the beta globin chain variants identified in the proband occurred as the result of a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband has Hb S/S (i.e., two HbS alleles), additional possibilities to consider include:
    - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
    - Uniparental isodisomy for the parental chromosome with the HbS allele that resulted in homozygosity for the p.Glu6Val pathogenic variant in the proband [Swensen et al 2010].
- Heterozygotes for HbS have hemoglobins A and S (i.e., Hb A/S or sickle cell trait). The amount of HbS present in individuals with sickle cell trait is insufficient to produce sickling manifestations under most circumstances; thus, such individuals are usually asymptomatic, but are at risk for several complications (see Clinical Description, **Heterozygotes for HbS**).

**Table 6.** Sickle Cell Disease: Typical Proband and Parent Hemoglobin Alleles

| Hemoglobin Beta Chain Variants in Proband | Typical Parental Hemoglobin Alleles [1] | |
|---|---|---|
| | One Parent | Other Parent |
| Hb S/S | A/S | A/S |
| Hb S/$\beta^0$-thal [2] | | A (w/additional laboratory features of $\beta^0$-thal or $\beta^+$-thal carrier: ↓ MCV, normal or ↑ $HbA_2$, normal or ↑ HbF) |
| Hb S/$\beta^+$-thal [2] | | |
| Hb S/C | | A/C |

Table shows typical results; exceptions occur. Some rare beta globin chain variants (e.g., Hb S/D, Hb S/E, Hb S/O) are not included.
Hb = hemoglobin; HbA = adult hemoglobin; HbF = fetal hemoglobin; Hb S/C = sickle-hemoglobin C disease; Hb S/S = homozygous for *HBB* variant p.Glu6Val; MCV = mean corpuscular volume; thal = thalassemia; ↑ = increased; ↓ = decreased
*1.* Assumes that uniparental disomy is absent and that both parents are heterozygous. Some parents may be homozygous or compound heterozygous.
*2.* HbA is detectable in individuals with Hb S/$\beta^+$-thalassemia but not Hb S/$\beta^0$-thalassemia or Hb S/C.

### Sibs of a proband

- If both parents are known to be heterozygous for an *HBB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic beta globin chain variants and being affected, a 50% chance of inheriting one beta globin chain variant and being heterozygous, and a 25% chance of inheriting neither of the familial beta globin chain variants.
- If one parent is known to be heterozygous for a beta globin chain variant and the other parent is affected with SCD, each sib of an affected individual has a 50% chance of inheriting biallelic beta globin chain

variants and being affected and a 50% chance of inheriting one beta globin chain variant and being heterozygous.
- If both parents have biallelic beta globin chain variants (i.e., both parents have homozygous or compound heterozygous *HBB* pathogenic variants), all sibs of an affected individual will inherit biallelic beta globin chain variants and be affected.
- Because a tremendous amount of individual variability occurs in SCD, the severity of disease manifestations in a sib who inherits biallelic beta globin chain variants cannot be predicted on the basis of the clinical course observed in the proband (see Genotype-Phenotype Correlations).
- Heterozygotes for HbS have hemoglobins A (adult) and S (sickle) (i.e., Hb A/S or sickle cell trait). The concentration of HbS present in individuals with sickle cell trait is insufficient to produce sickling manifestations under most circumstances; thus, these individuals are usually asymptomatic but are at risk for several complications (see Clinical Description, **Heterozygotes for HbS**).

**Offspring of a proband.** If the reproductive partner of an individual with SCD:

- Does not have a beta globin chain variant (or variants), offspring will be heterozygous for a beta globin chain variant (i.e., heterozygous for an *HBB* pathogenic variant);
- Is heterozygous for a beta globin chain variant, offspring will have a 50% chance of having SCD and a 50% chance of being heterozygous for a beta globin chain variant;
- Is also affected with SCD, all offspring will have biallelic beta globin chain variants (i.e., biallelic *HBB* pathogenic variants) and be affected.

Note: Because a tremendous amount of individual variability occurs in SCD, the severity of disease manifestations in offspring who inherit biallelic beta chain variants cannot be predicted on the basis of the clinical course observed in other affected family members (see Genotype-Phenotype Correlations).

**Other family members**. Each sib of the proband's parents is at a 50% or greater risk of being heterozygous for a beta globin chain variant (i.e., an *HBB* pathogenic variant).

## Heterozygote Detection

**Molecular genetic testing.** If the SCD-related *HBB* pathogenic variants in a family are known, molecular genetic testing can be used to identify which at-risk family members are heterozygous.

**HPLC.** If only one (or neither) SCD-related *HBB* pathogenic variant in a family is known, HPLC can be used to detect common qualitative abnormalities (i.e., abnormal hemoglobins). Note that HPLC may not always detect quantitative abnormalities such as thalassemias, which, when inherited with an HbS allele, result in a significant hemoglobinopathy; see Beta-Thalassemia for information on how to diagnose a coexisting thalassemia.

## Related Genetic Counseling Issues

See **Management**, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- It must be kept in mind that non-sickle hemoglobin disorders (e.g., beta-thalassemia) can interact with the SCD-causing variant to cause clinically significant disease. As a result, family members without HbS can still have a child with a significant sickle hemoglobinopathy, which makes counseling difficult and leads to misconceptions in the community and, on occasion, allegations of infidelity. For example, if one parent has sickle cell trait and the other is a carrier of beta-thalassemia, it would be correct to state that, although one parent is not a SCD carrier, there is still a 25% chance that each pregnancy would have a significant hemoglobinopathy. Therefore, partners of individuals who are known to be heterozygous for HbS should

be offered a thalassemia screening panel that includes hemoglobin electrophoresis, complete blood count and reticulocyte count, and a measure of iron status (e.g., zinc protoporphyrin, ferritin, and total iron-binding capacity) to screen for carrier status for sickle cell trait and other beta globin disorders.
- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

**Early testing.** Increasing community awareness of SCD in populations at high risk (see Prevalence) is important in facilitating genetic counseling and early testing.

**Cord blood banking.** Given the increasing safety and availability of stem cell transplantation in SCD and the limited number of immunologically matched donors available for individuals with SCD, it is appropriate to discuss sib cord blood banking with the parents of an affected individual.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic prenatal testing and preimplantation genetic testing for SCD are possible when:

- Both *HBB* pathogenic variants have been identified in an affected family member; and
- The genetic status of the parents is known. Because one parent may have a non-HbS *HBB* pathogenic variant (or biallelic *HBB* pathogenic variants) that can interact with HbS to cause a sickle hemoglobinopathy (e.g., sickle-hemoglobin C disease or sickle beta-thalassemia), the genetic status of the parents must be defined before prenatal testing can be performed.

Because of the extreme variation in clinical course, it is not currently possible to accurately predict the severity of SCD based on the prenatal finding of biallelic SCD-related *HBB* pathogenic variants.

When the mother is known to be heterozygous and the father is unknown and/or unavailable for testing, options for prenatal testing can be explored in the context of formal genetic counseling.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **American Sickle Cell Anemia Association**

  **Phone:** 216-229-8600

  **Fax:** 216-229-4500

  **Email:** irabragg@ascaa.org

  www.ascaa.org

- **California Sickle Cell Resources**
  www.casicklecell.org
- **Medical Home Portal**
  Sickle Cell Disease
- **MedlinePlus**
  Sickle Cell Disease
- **Parent and Caregiver Handbook for Sickle Cell**
  California Department of Public Health
  cdph.ca.gov/Programs/CFH/DGDS
- **Sickle Cell Disease Association of America, Inc.**
  **Phone:** 800-421-8453 (toll-free); 410-528-1555
  **Fax:** 410-528-1495
  **Email:** info@sicklecelldisease.org
  www.sicklecelldisease.org
- **Sickle Cell Disease Foundation**
  **Phone:** 877-288-CURE (2873); 909-743-5226
  **Email:** info@scdfc.org
  www.scdfc.org
- **Sickle Cell Disease National Resource Directory**
  stacks.cdc.gov
- **Sickle Cell Information Center**
  www.scinfo.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state
- **National Haemoglobinopathy Registry**
  United Kingdom
  **Phone:** 0161 277 7917
  **Email:** support@mdsas.com
  www.nhr.nhs.uk

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Sickle Cell Disease: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|

*Table A. continued from previous page.*

| | | | | | |
|---|---|---|---|---|---|
| *HBB* | 11p15.4 | Hemoglobin subunit beta | HBB @ LOVD<br>HbVar: A Database of Human Hemoglobin Variants and Thalassemias (HBB) | HBB | HBB |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Sickle Cell Disease (View All in OMIM)

| | |
|---|---|
| 141900 | HEMOGLOBIN--BETA LOCUS; HBB |
| 603903 | SICKLE CELL DISEASE |

## Molecular Pathogenesis

*HBB* encodes the hemoglobin beta chain. The normal heterotetrameric protein hemoglobin A (HbA) comprises two hemoglobin alpha chains, two hemoglobin beta chains, and four heme moieties. Sickle hemoglobin (HbS) results specifically from the p.Glu6Val variant. In deoxygenated sickle hemoglobin, an interaction between p.Val6 and the complementary regions on adjacent molecules results in the formation of highly ordered, insoluble molecular polymers that aggregate and distort the shape of red blood cells (RBCs), making them brittle and poorly deformable, increasing adherence to the endothelium. This can lead to veno-occlusion, decreased tissue perfusion, and ischemia. While this is thought to be the proximate defect leading to several aspects of clinical disease, multiple pathophysiologic pathways are involved in SCD [Zhang et al 2016, Kato et al 2017].

Polymerized hemoglobin is also injurious to the RBC membrane, resulting in cellular dehydration, oxidative damage, and increased adherence to endothelial cells [Gladwin & Rodgers 2000, Hebbel 2000, Nagel 2001] and chronic hemolysis. Other factors contributing to the pathophysiology of SCD include leukocytosis (resulting in increased production of injurious cytokines and altered blood flow), coagulation abnormalities, and abnormal vascular regulation. The net result of these abnormalities is shortened RBC life span or hemolysis and intermittent vascular occlusion and a state of chronic inflammation.

**Mechanism of disease causation.** The variant p.Glu6Val leads to a gain of function due to a change in protein conformation that exposes a hydrophobic patch allowing for polymerization under certain conditions [Valastyan & Lindquist 2014, Kato et al 2018].

***HBB*-specific laboratory technical considerations.** The variant p.Glu6Val is detectable by targeted molecular genetic testing or sequence analysis. If sickle beta-thalassemia disease is suspected, consider *HBB* sequence analysis and deletion analysis as deletions, frameshift, nonsense, and missense variants have been reported, including in the 5'UTR, 3'UTR, and deep intronic regions.

**Table 7.** Notable *HBB* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change [1] | Predicted Protein Change [2] | Hb Variant |
|---|---|---|---|
| NM_000518.4<br>NP_000509.1 | c.20A>T | p.Glu6Val<br>(p.Glu7Val) | HbS |
| | c.19G>A | p.Glu6Lys<br>(p.Glu7Lys) | HbC |
| | c.79G>A | p.Glu26Lys<br>(p.Glu27Lys) | HbE |
| | c.364G>C | p.Glu121Gln<br>(p.Glu122Gln) | HbD |
| | c.364G>A | p.Glu121Lys<br>(p.Glu122Lys) | $HbO_{Arab}$ |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

*1.* DNA nucleotide changes follow current nomenclature guidelines, where the number 1 corresponds to the first nucleotide of the initiating methionine.

*2.* In this column and throughout the text of the *GeneReview*, the protein changes (e.g., p.Glu6Val) follow the long-standing convention in the hemoglobin literature of beginning the numbering of amino acids at the second amino acid residue (Val) rather than the initiating Met. This convention was adopted many years ago because the initiating methionine is not part of the mature beta globin protein. The standard nomenclature for protein changes is given in parentheses. The Globin Gene Server (globin.bx.psu.edu) lists variants using both numbering conventions.

# Chapter Notes

## Author Notes

Dr Bender formally ran the Odessa Brown Children's Clinic Sickle Cell Program associated Seattle Children's and the University of Washington, and a basic science lab at the Fred Hutchinson Cancer Research Center focused on the regulation of the chromatin structure and gene expression using the beta globin locus as a model, gene therapy, and novel agents to treat sickle cell disease and thalassemia. Clinically, Dr Bender has a long-standing commitment to hemoglobinopathies with particular interest in patient and provider education, immigrant populations, community outreach, and optimizing access to health care, and he has a special admiration of and interest in understanding the diverse array of cultural beliefs about sickle cell disease and how to use this to optimize care. He has a special interest in newborn screening; he consults for the Washington Newborn Screening Program, works with the Association of Public Health Laboratories Hemoglobinopathy group, and contributes to the ACMG ACT sheets. Dr Bender has received the American Society of Hematology's Champion for Advocacy award, was a member of the NIH Sickle Cell Disease Advisory Committee, and worked with the Puget Sound Blood Center's Rare Blood Groups Task Force. He is honored to have the ability to work with patients and families affected by sickle cell disease. Email: mbender@fredhutch.org

Dr Carlberg is a pediatric hematologist with a clinical focus on patients affected by hemoglobinopathies and other red blood cell disorders. She has a particular interest in simplifying and demystifying the process of transitioning from the pediatric to adult heath care system for those with chronic health care needs. Her research during fellowship focused on the development of a noninvasive prenatal test for hemoglobinopathies. Email: katie.carlberg@seattlechildrens.org

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## Author History

MA Bender, MD, PhD (2006-present)
Katie Carlberg, MD (2022-present)
Gabrielle Douthitt Seibel, MN, MPH, ARNP; Seattle Children's Hospital (2014-2017)
William Hobbs, MD, PhD; Puget Sound Blood Center (2009-2014)
Krysta Schlis, MD; Children's Hospital Oakland (2003-2006)
Elliott Vichinsky, MD; Children's Hospital Oakland (2003-2006)

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- 17 November 2022 (sw) Comprehensive update posted live
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- 9 February 2012 (me) Comprehensive update posted live
- 6 August 2009 (me) Comprehensive update posted live
- 7 March 2006 (me) Comprehensive update posted live
- 15 September 2003 (me) Review posted live
- 21 April 2003 (ev) Original submission

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