## Season 1, Episode #03

# Sickle Cell Disease

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**Sickle cell disease (SCD)** affects between 70,000 and 100,000 people in the United States. SCD is associated with major morbidity and mortality especially if children do not receive appropriate medical care. Even with treatment, life expectancy is still reduced by 20-30 years. Fortunately, all newborns in the US are screened for SCD so most cases are detected early.

### Sickle cell basics

Remember that hemoglobin consists of four protein subunits. Typically, two subunits called alpha-globulin and two subunits called beta-globulin combine with heme to form normal hemoglobin (Hgb A). Patients with sickle cell disease are unable to make normal beta-globulin and instead form abnormal sickle hemoglobin (Hgb S). Hemoglobin S is due to a substitution of the amino acid valine for glutamic acid in the 6$^{th}$ position of the beta globin chain. Patients with SCD have at least one beta-globulin gene sickle mutation and are unable to produce normal amounts of hemoglobin A. The severity of SCD worsens with increased hemoglobin S and decreased hemoglobin A production. Below is a chart of the common genotypes included in SCD.

**Exhibit 1a. Typical Laboratory Findings in Sickle Cell Disease**

| Genotype | Hb* (g/dL)† | HbS (%) | HbA (%) | HbA2 (%) | HbF (%) | HbC (%) |
|---|---|---|---|---|---|---|
| SS | 6–9 | >90 | 0 | <3.5 | <10 | 0 |
| Sβ$^0$-thalassemia | 7–9 | >80 | 0 | >3.5 | <20 | 0 |
| Sβ$^+$-thalassemia | 9–12 | >60 | 10–30 | >3.5 | <20 | 0 |
| SC | 9–14 | 50 | 0 | <3.5 | ≤1.0 | 45 |

* Definitions for abbreviations are as follows: Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; $HbA_2$ = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

† The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).

The term **sickle cell anemia (SCA)** is reserved for **Hgb SS** and **Hgb Sβ0-thalassemia** as these are the most severe genotypes of sickle cell disease that are unable to produce any normal Hgb A. They also have greater than 80% Hgb S.

Patients only have "**sickle cell trait**" if they have one Hgb S and one normal beta-globulin gene. These patients are mostly unaffected and have normal hemoglobin levels and >60% normal Hgb A. They are not considered to have SCD.

**Exhibit 1b. Typical Laboratory Findings in Sickle Cell Trait (Provided for Comparison)**

| Genotype | Hb* (g/dL)† | HbS (%) | HbA (%) | HbA2 (%) | HbF (%) | HbC (%) |
|---|---|---|---|---|---|---|
| AS | normal | ≤40 | >60 | <3.5 | ≤1.0 | 0 |

In 2014, the NHLBI (National Heart Lung and Blood Institute) produced an expert panel report on the management of sickle cell disease. Let's have a look at some highlights of this guideline to learn more about prevention and the acute care of children suffering with SCD.

**Prevention of Invasive Bacterial Infection**

Young children with SCA (Hgb SS and Hgb Sβ0-thalassemia) are at very high risk for pneumococcal and other encapsulated bacteremia and meningitis. These patients have defective or absent splenic function within the first year of life. Children with Hgb SC and Hgb Sβ+ thalassemia have a lower incidence of infection but are still treated as high risk. Below are the recommendations from the NHLBI guidelines about penicillin prophylaxis. Note also that these patients should seek medical care for any fever greater than 38.5C due to the risk of severe bacterial infections.

| Recommendations |
|---|
| 1. Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 in all children with HbSS. ***(Strong Recommendation, Moderate-Quality Evidence)*** |
| 2. Discontinue prophylactic penicillin in children with HbSS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the recommended pneumococcal vaccination series, and if not, complete the series immediately. ***(Weak Recommendation, Moderate-Quality Evidence)*** |
| 3. Consider withholding penicillin prophylaxis from children with HbSC disease and HbSβ⁺-thalassemia unless they have had a splenectomy ***(Weak Recommendation, Low-Quality Evidence)*** |
| 4. Assure that people of all ages with SCD have been vaccinated against *Streptococcus pneumoniae*.* ***(Strong Recommendation, Moderate-Quality Evidence)*** |
| 5. Remind people with SCD, their families, and caregivers to seek immediate medical attention whenever fever (temperature greater than 101.3°F or 38.5°C) occurs, due to the risk for severe bacterial infections. ***(Consensus–Panel Expertise)*** |

Children with SCD should receive all routine and additional pneumococcal and meningococcal vaccines. The 23-valent pneumococcal polysaccharide vaccine should be given at age 2 and booster at 5 years. Infants should receive additional meningococcal vaccines at 2, 4, 6 and 12-15 months with boosters every 3-5 years thereafter.

**Approach to fever**

Fever may be the presenting symptom of an acute life-threatening infection in children with sickle cell disease and should be carefully evaluated in coordination with hematology consultation. Here are some key points that may help when caring for these patients:

- Every patient with SCD who has a temperature of 38.5C or higher should present to medical care for history, physical exam, laboratory assessment (CBC w/differential, reticulocyte count, blood culture at a minimum) and

empiric IV antibiotics targeting Streptococcus pneumoniae and gram-negative enteric organisms (ceftriaxone is a reasonable choice in many healthcare settings).

- Patients that are ill-appearing or febrile to 39.5C or greater are at higher risk of infection and will likely require close observation and continued IV antibiotic therapy until bacterial infection is reasonably excluded.
- Children with associated shortness of breath, tachypnea, cough or crackles should receive a chest x-ray to evaluate for acute chest syndrome.
- Osteomyelitis should be considered if there is localized or multifocal bone tenderness, especially when accompanied by erythema and swelling.

**Acute anemia**

There is wide variability of baseline hemoglobin levels for patients with sickle cell disease. The more severe genotypes such as Hgb SS and Hgb Sβ0-thalassemia have baseline values between 6-8 g/dL. Children with less severe phenotypes like Hgb SC and Hgb Sβ+ thalassemia may have hemoglobin levels 9-12 g/dL. Patients or their families commonly know their individual baseline hemoglobin and this is an important part of your history. **Acute anemia** is defined as a decline in hemoglobin by 2.0 g/dL or more below the patient's baseline value. There are many causes of acute anemia in patients with SCD and these include aplastic episode, splenic sequestration, and acute chest syndrome which we will introduce below.

**Aplastic episode**

An aplastic episode or "crisis" is a common cause of acute anemia in children with SCD especially Hgb SS. These children typically have a gradual onset of fatigue, shortness of breath and possibly syncope. An aplastic episode commonly occurs in the context of a febrile illness. The diagnosis can be inferred by labs which commonly are notable for an acute anemia (3-6 g/dL) and **low reticulocyte count** (maybe even 0%). Etiology is likely secondary to a viral infection. Parvovirus B19 is a virus known to destroy erythroid precursors and cause an aplastic episode. Remember that children with SCD rely on robust erythrocytosis to maintain their baseline hemoglobin level. RBCs have a shortened life span due to repeated sickling. Daily hemoglobin and reticulocyte measurement should be performed monitoring for marrow recovery. RBC transfusion should be provided if there are signs of hemodynamic instability to maintain hemoglobin to an acceptable level. There is no need to "normalize" or return the hemoglobin level to the patient's baseline value.

**Splenic sequestration**

Splenic sequestration is defined as sudden enlargement of the spleen and reduction in hemoglobin concentration by at least 2 g/dL below the baseline value. **Reticulocyte count is usually elevated** and the **platelet count is decreased** as red blood cells and platelets are trapped in the spleen. This occurs most commonly in children between 1 to 4 years of age. Severe genotypes (Hgb SS and Hgb Sβ0-thalassemia) will typically lose splenic function due to autoinfarction and involution by age 5 making splenic sequestration much less likely after this time. Patients with milder disease (Hgb SC and Hgb Sβ+ thalassemia) or those on hydroxyurea or chronic transfusions may retain splenic function into adulthood. In these cases, splenic sequestration may occur at any age.

Infants with splenic sequestration may become acutely ill and present as hypovolemic shock. These patients require hematology consultation and should receive small aliquots of pRBCs to maintain hemodynamic stability, but excessive transfusion (Hgb >8 g/dL) should be avoided. Over the next several days sequestered

erythrocytes in the enlarged spleen may reenter the circulation and lead to hyperviscosity symptoms due to a high hemoglobin concentration.

**Acute chest syndrome**

Acute chest syndrome (ACS) is the most common cause of death in children with SCD. ACS is defined as signs and symptoms of lower respiratory disease (cough, shortness of breath, crackles) and a new pulmonary infiltrate on chest radiograph. This closely resembles pneumonia and ACS should be assumed in patients with the above presentation. ACS is commonly secondary to infection but may also be secondary to bone marrow fat embolism, pulmonary edema, post-operative, or vaso-occlusive crisis. It is also associated with acute anemia. These patients are at risk for progression of disease and development of multisystem organ failure. These patients require expert consultation and early transfer to tertiary center with pediatric ICU capability. Treatment centers around respiratory support, bronchodilators, blood transfusion and broad-spectrum antibiotics including atypical coverage (ceftriaxone and azithromycin is reasonable for most patients). If respiratory failure progresses despite initial management, exchange transfusion is likely indicated.

Resources for further reading and references from the podcast episode:

- Rincon-Lopez et al. Low-risk factors for severe bacterial infection and acute chest syndrome in children with sickle cell disease. *Pediatric Blood Cancer*. June 2019. https://www.ncbi.nlm.nih.gov/pubmed/30740900
- Eisenbrown et al. Practice Variation in Emergency Department Management of Children with Sickle Cell Disease Who Present with Fever. *Pediatric Emergency Care*. August 2018. https://www.ncbi.nlm.nih.gov/pubmed/30020250
- Here is a direct link to the NHLBI guideline:

https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf