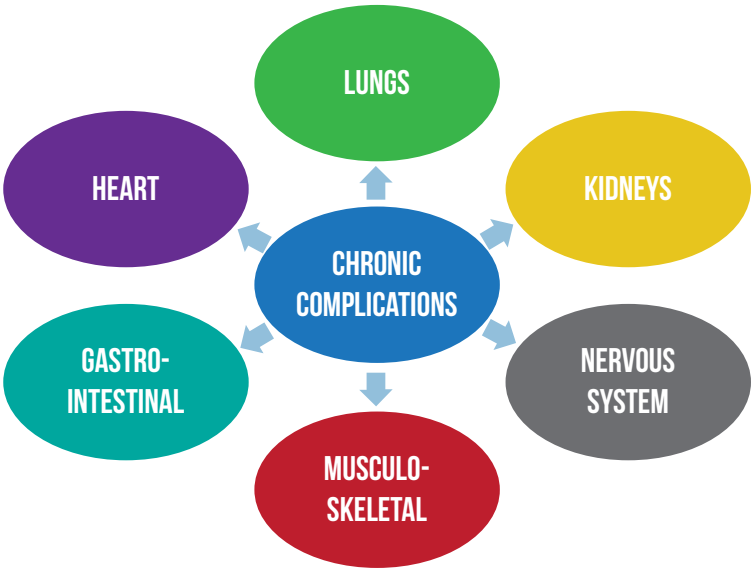
## CLINICAL INSIGHT

### 1. Epidemiology

Sickle cell disease (SCD) is the most common inherited disorder in the United States, with approximately 1400 children born each year in the US with the disease. Once considered a disease affecting only children, the median survival is 48 years in individuals with Hb SS/S 0 and 55 years with Hb SC/S +. Consequently, chronic complications experienced by adults account for substantial morbidity and mortality. Among the numerous organ systems that can be affected by complications, the heart, lungs, and kidneys account for about 50% of identifiable causes of death. Hospital admissions make up the bulk of healthcare services, with the age group 18 to 34 years accounting for about 50% of admissions.



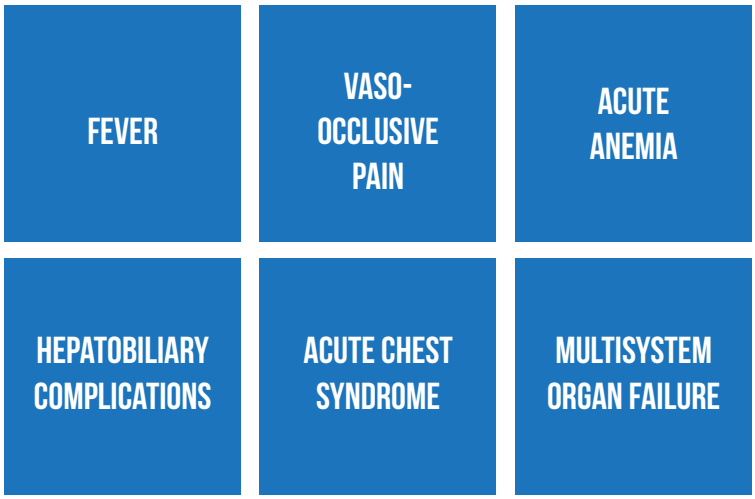

### 2. Comprehensive Care

There are 4 components to comprehensive care for individuals with SCD: health maintenance, treatment of acute complications, prevention and treatment of chronic complications, and, for selected individuals, curative therapy. Health maintenance that includes providing age-appropriate preventive services is especially important. Impaired mental health is a key focus of care as depression and anxiety are common in individuals with SCD, and contributes to pain disorders, poor quality of life, and increased healthcare utilization. In addition to lack of access to comprehensive care, patient mistrust of the healthcare system and stigma are common barriers to care.

### 3. Management of Complications

The American Society of Hematology released several guidelines in 2019-2020 to guide the management of patients with selected acute and chronic complications. Strokes, many of which are silent, are the most common debilitating complication in children, while vaso-occlusive pain is common in all individuals with SCD. The management of complications in every individual with SCD requires a multidisciplinary care team across the lifespan that includes the hematologist, mental health specialist, neurologist, pulmonologist, nephrologist, and orthopedic surgeon, as well as ongoing involvement of the primary care clinician and social worker.

**Acute Complications:**




**4. Pharmacotherapy Overview**

Four medications have been approved for use in individuals with SCD: hydroxyurea, L-glutamine, voxelotor, and crizanlizumab. There are numerous differences among these medications, including mechanism of action, indication, age group, dosing, and precautions for use. Hydroxyurea is recommended for most individuals with SCD, beginning at the age of 9 months.

**5. Pharmacotherapy**

Key benefits of hydroxyurea are that it decreases the risk of stroke and improves survival. In addition, it reduces by 50% the frequency of severe acute pain, acute chest syndrome, and blood transfusion. Embryo-fetal toxicity and cutaneous vasculitic toxicities are limitations to the use of hydroxyurea.

L-glutamine reduces the number and time to acute pain episodes with low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain occurring more frequently than with placebo.

Voxelotor raises the hemoglobin level ~1 g/dL and improves markers of hemolysis, but offers no significant benefit for acute vaso-occlusive pain. It is well tolerated, although diarrhea, nausea, abdominal pain, and fever are more common with voxelotor than placebo.

Crizanlizumab 5 mg/kg reduces the number of and time to first and second acute pain episodes, as well as hospitalization rate. Nausea, fever, diarrhea, and arthralgia are more common with crizanlizumab than placebo.

| Medication | Advantages | Warnings & Precautions |
|---|---|---|
| Hydroxyurea (Siklos) | Improves life expectancy;<br>reduces rate of pain ~50%;<br>reduces rate of acute chest syndrome ~50%;<br>reduces rate of transfusion ~50%;<br>reduces risk of ischemic stroke | Embryo-fetal toxicity; cutaneous vasculitic toxicities; drug interaction with antiretrovirals, live virus vaccine |
| L-glutamine (Endari) | Reduces risk of pain events | – |
| Voxelotor (Oxbryta) | Increases Hgb level (mean 1.1 g/dL) | Hypersensitivity reactions; perform quantification of Hgb species when not receiving voxelotor |
| Crizanlizumab (Adakveo) | Reduces rate of pain ~50% | Infusion-related reactions; interference with automated platelet counts |

## 6. Curative Therapy

Hematopoietic stem cell transplant is the only curative therapy currently available for SCD and is generally reserved for individuals who have suffered a stroke. Myeloablative matched related donor transplant has been the mainstay of therapy for children over the past 25 years, particularly for children where the quality of life has been dramatically impaired by repetitive pain episodes associated with SCD. Nonmyeloablative stem cell transplantation is preferred for adults, particularly those with heart, lung, or kidney complications. Haploidentical transplant with post-transplant cyclophosphamide is a promising alternative on the horizon. Transplant complications can be more serious than the disease itself, requiring careful consideration with the patient/family.

Gene therapy and gene editing options are under investigation. LentiGlobin, a viral vector that delivers a modified but functional copy of the hemoglobin subunit β gene, is being investigated for the treatment of severe vaso-occlusive pain and acute chest syndrome. The safety and efficacy of BIVV003, a gene-edited red blood cell therapy to boost the production of fetal hemoglobin, are being investigated in patients with SCD undergoing autologous hematopoietic stem cell transplantation.

## 7. Coordinated Care

The complex needs of the individual with SCD are best met by a multidisciplinary care team. Individuals in the age group 18 to 21 years, where care is transitioned from pediatric to adult care, are particularly vulnerable to fragmented care. The primary care clinician plays a critical role, particularly related to preventing chronic complications and holistic management, while the social worker is integrally involved in working with the patient to identify and resolve barriers to care. Ongoing patient education and collaboration are instrumental in optimizing health outcomes.