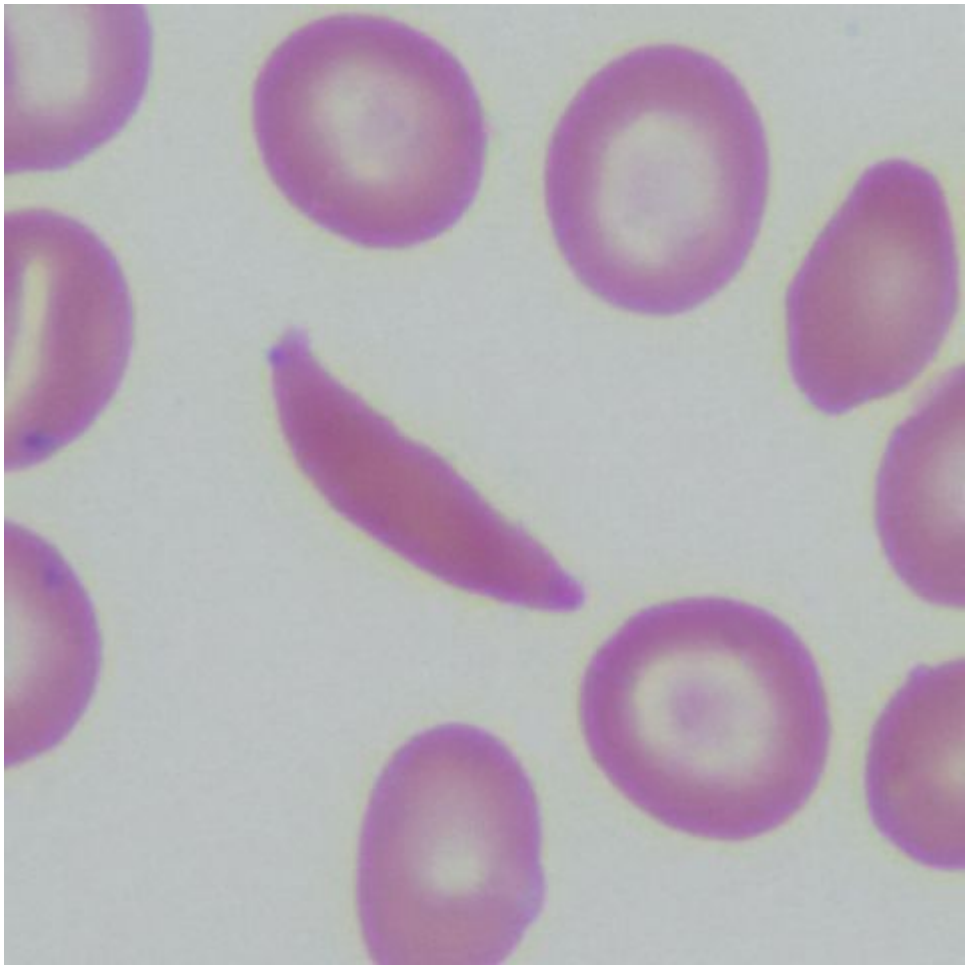
Sickle Cell Anemia in Children — Symptoms and Treatment

See online here

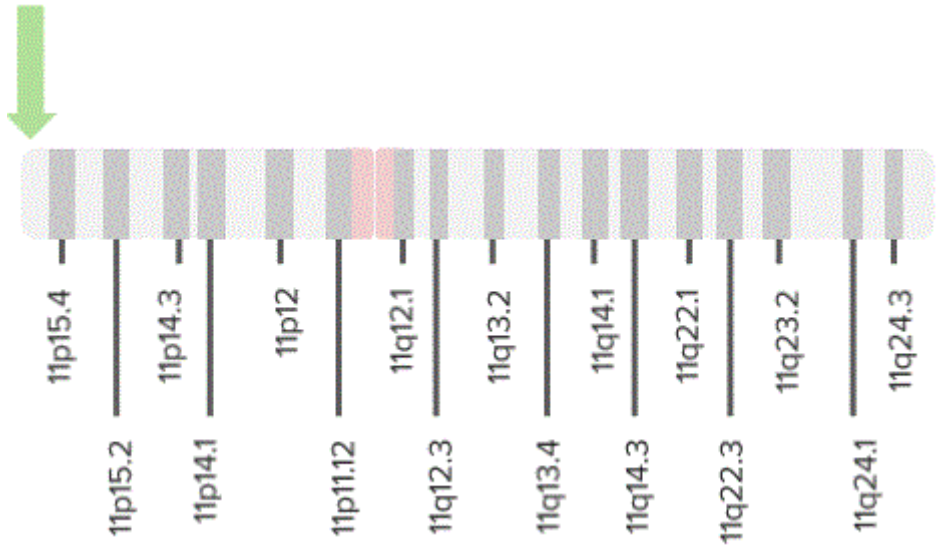
Sickle cell disease is a genetic blood disease that is characterized by abnormal hemoglobin that can undergo polymerization in certain conditions, such as hypoxia, acidosis or dehydration. This process of polymerization is responsible for the distortion of the red blood cell shape and the hemolysis of red blood cells. Children can present with symptoms and signs suggestive of chronic hemolytic anemia, acute splenic sequestration syndrome, acute vaso-occlusive syndromes, acute chest syndrome, or proliferative sickle retinopathy.



Overview

Sickle cell disease, also known as sickle cell anemia, is a **genetic blood disorder that is caused by the substitution of thymine for adenine in the 6th codon of the beta-globin gene**. This single-point substitution mutation results in the production of

the amino acid valine in place of glutamic acid. The resulting hemoglobin is abnormal and different from the wild-type hemoglobin in being more rigid and can undergo polymerization when the patient is exposed to oxidative stress.



“Sickle Cell Disease. Point mutation” Image created by Lecturio

The diagnosis of sickle cell disease is usually made at the time of birth in the United States because of the mandatory testing for sickle cell disease in all newborns in the United States. Prevention of acute chest pain syndrome, the management of the different sickle cell disease clinical sequelae, and the prevention of infectious complications are the mainstay treatment approaches for the condition in children.

The key features of sickle cell disease is chronic hemolytic anemia and microvascular obstruction termed asvaso-occlusion.

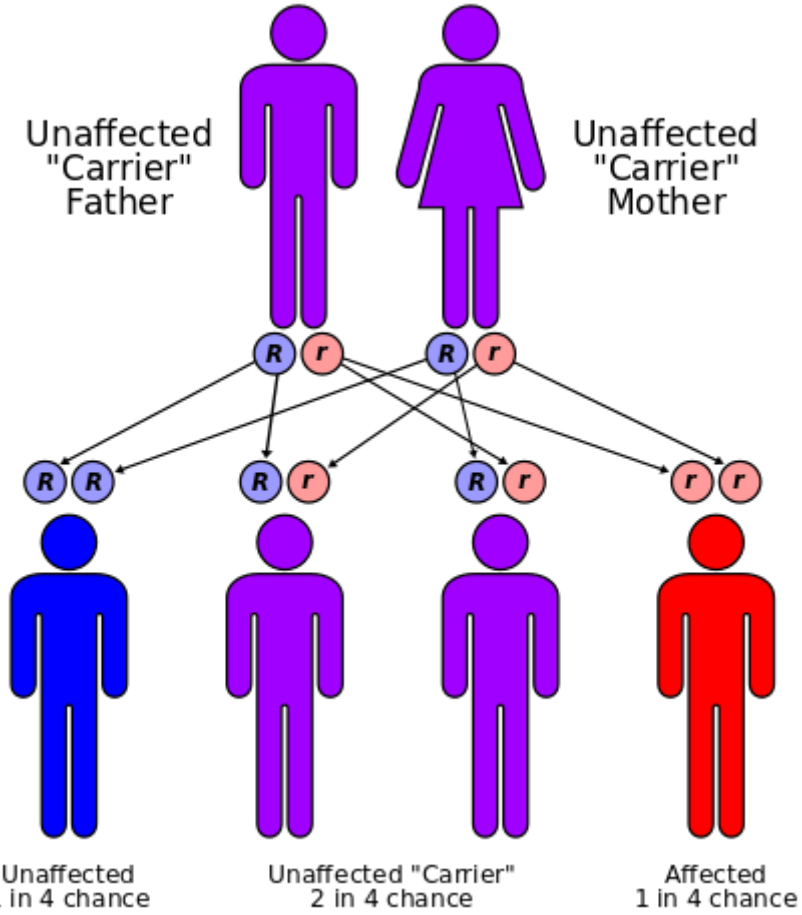


Image: “Sickle-cell disease is inherited in the autosomal recessive pattern.” by Cburnett.
License: CC BY-SA 3.0

Epidemiology of Sickle Cell Disease in Children

Sickle cell disease is more commonly seen in children who come from **families of African or Mediterranean descent**. This observation has been explained by the possible protective role of the disorder in people who live in areas with malaria epidemics as it shortens the half-life of the red blood cell, making it more difficult for the malarial parasite to thrive and survive.

Ethnicity	Frequency of HbAS (Sickle trait)
African-Americans	7.3 %
Hispanic Americans	0.7 %
Sub-Saharan Africa	30 %
India	13 %
Middle East	0.2 – 27 %
Greece	1.5 – 7.5 %
Caribbean	4 – 10 %

The estimated incidence of sickle cell disease in African American children is 1 per 500. Approximately, 100,000 patients with sickle cell disease live nowadays in the United States.

The most important risk factors for increased mortality and morbidity in children with sickle cell disease include the **presence of dactylitis before 1 year of age**,

a **baseline hemoglobin level below 7 g/Dl in the second year of life,** and the **presence of leukocytosis in the second year of life**. Higher levels of red blood cells with fetal hemoglobin correlate with less severe disease with a lower mortality rate. After 10 years of age, rates of painful crises decrease with an increase in complication rates. The median age of death in patients with the disease is 27 years.

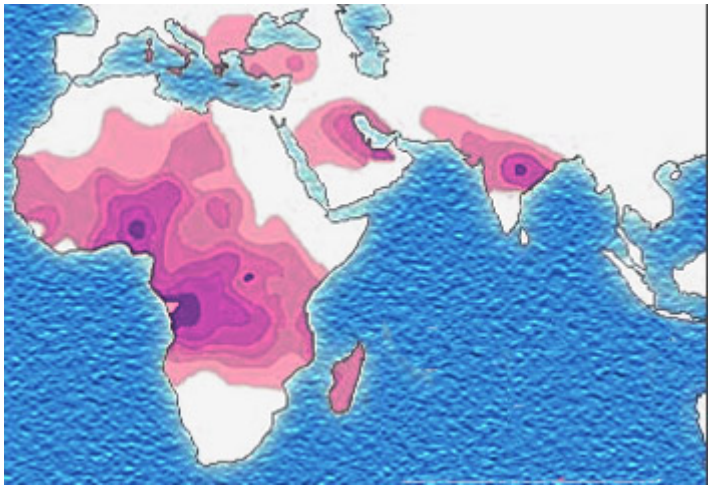


Image: “Distribution of the sickle-cell trait shown in pink and purple.” by Muntuwandi. License: CC BY-SA 3.0

Pathophysiology of Sickle Cell Disease

The red blood cells in patients with sickle cell disease undergo **chronic hemolysis and polymerization of the abnormal hemoglobin known as HbS**. The polymerization of HbS results in vaso-occlusion, which is responsible for the different symptoms of sickle cell disease in children, such as acute chest syndrome.

The most common triggers of polymerization are hypoxia, the development of fever due to an infectious illness, dehydration, or the presence of acidosis such as in diabetic ketoacidosis. When HbS undergoes polymerization, elongated linear fibers from inside the red blood cell. These fibers distort the shape of red blood cells to a sickle shape and make them more prone to destruction and hemolysis and cannot regain its original shape. They become stiff and sticky and cannot move easily through blood vessels. They either stick to each other or macrophages to form clusters that lead to blockage of small arteries and capillaries resulting in vaso-occlusion causing pain and other symptoms. This, in turn, results in hemolysis. This micro infracts may accumulate in major organs causing multi-organ damage as a complication.

The red blood cells in children with sickle cell disease survive for approximately 12 to 16 days, instead of the normal lifespan of normal red blood cells which range between 120 and 160 days.

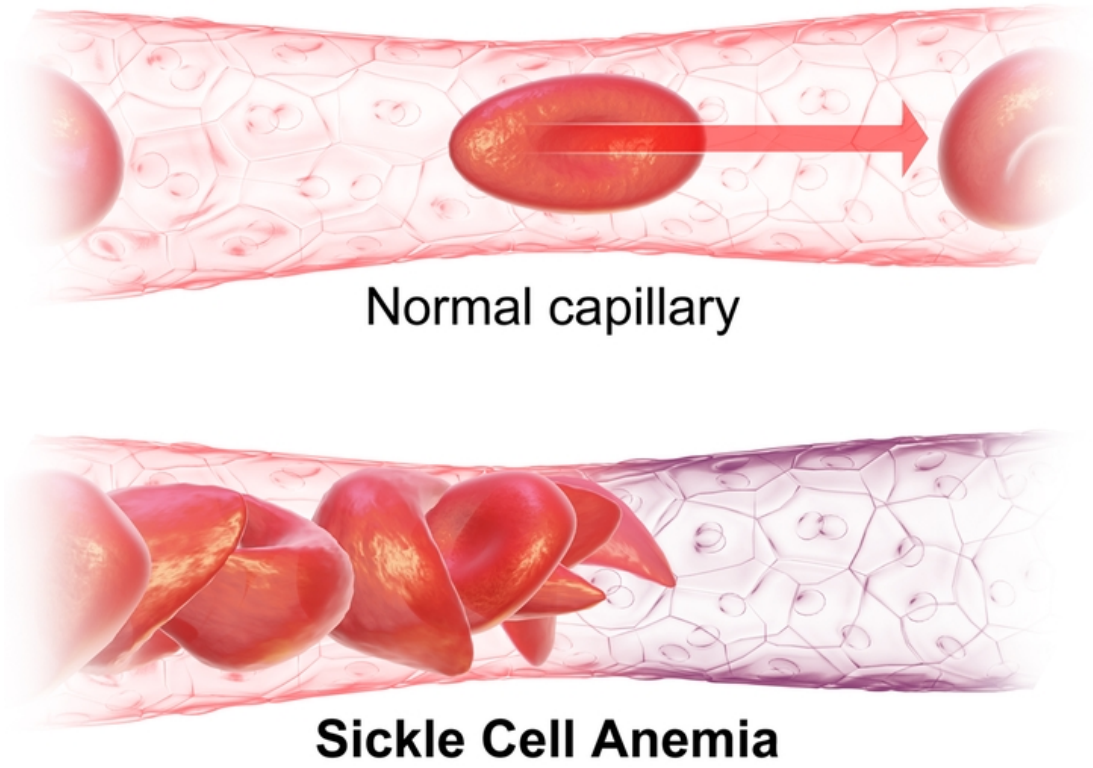


Image: “Sickle Cell Anemia” by BruceBlaus. License: CC BY-SA 4.0 The picture is cropped.

The most important factor in decreasing mortality in children with sickle cell disease is the percentage of fetal hemoglobin in red blood cells. Red blood cells with fetal hemoglobin usually survive much longer than those with HbS and do not undergo polymerization.

Patients with a sickle cell disease are at an **increased risk of developing infectious complications,** such as osteomyelitis due to the vaso-occlusive nature of the disorder. Fortunately, the risk of death due to infectious complications in this cohort of patients decreased significantly in the last decades after the introduction of penicillin prophylaxis.

Clinical Presentation of Sickle Cell Disease in Children

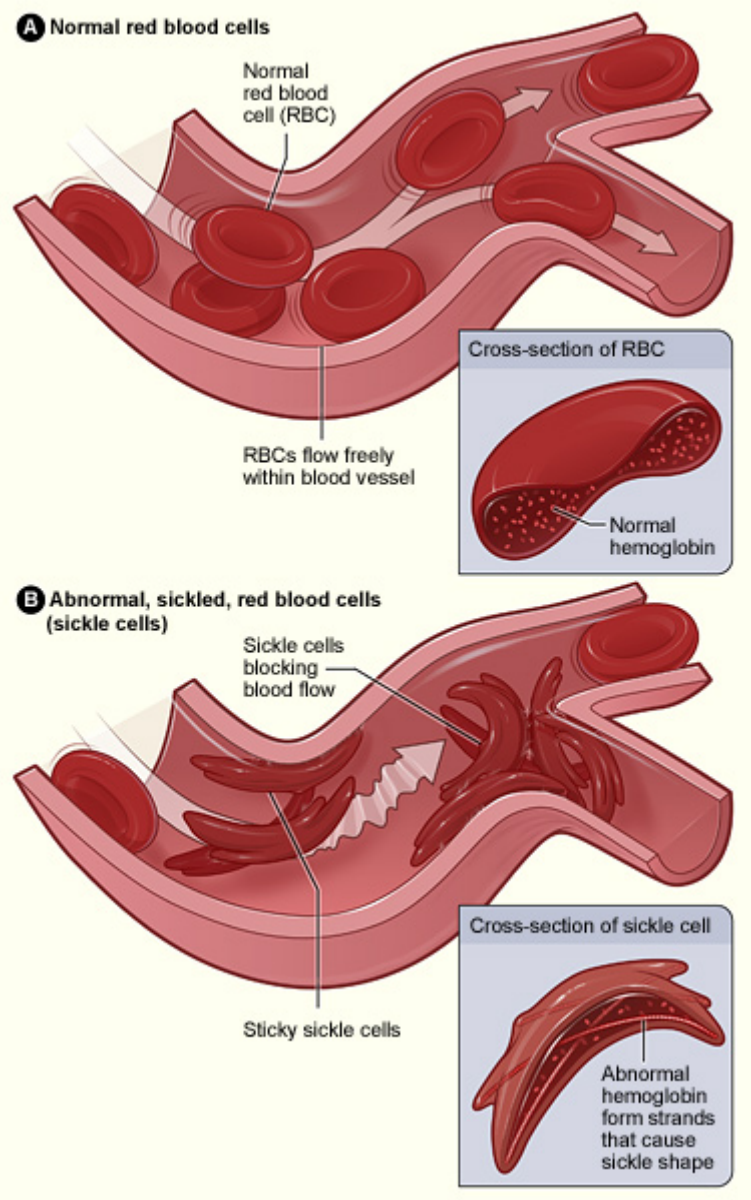


Image: “Figure A shows normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin. Figure B shows abnormal, sickled red blood cells blocking blood flow in a blood vessel. The inset image shows a cross-section of a sickle cell with abnormal (sickle) hemoglobin forming abnormal strands.” by The National Heart, Lung, and Blood Institute. License: Public Domain

Acute and chronic pain is a common feature of sickle cell disease caused due to vaso-occulsion. Pain crisis is the most prominent feature of the disease. While infants are less likely to develop acute pain syndrome due to the higher level of fetal hemoglobin in their blood, older children can present with acute chest pain, bone pain, and other painful crisis because of sickle cell disease. The severity of sickle cell disease can be rated upon the number of painful episodes per year.

Hemolytic Anemia is present in all patients with sickle cell disease.

Growth retardation is one of the main features of sickle cell disease with delayed sexual function and being underweight.

Splenic sequestration can happen in one-third of the patients with sickle cell disease. The risk appears to be higher in children younger than 6 years of age. When rapid enlargement of the spleen occurs, and especially if associated with significant circulatory

collapse, the mortality rate becomes high.

Milder forms of splenic sequestration are more common and are **characterized by an absolute hemoglobin level that is above 6 g/dL**. The early detection of acute splenic sequestration in children with sickle cell disease contributed to an increased incidence of the clinical manifestation, but a significantly reduced mortality rate.

Because of splenic sequestration in sickle cell disease, patients are at an **increased risk of impaired splenic function** and are predisposed to recurrent bacterial infections, especially with encapsulated organisms. Splenic sequestration is quite uncommon in adulthood.

Acute chest syndrome is characterized by **severe chest pain, fever, wheezing, tachypnea and possible pulmonary pathology**. The most common pulmonary pathologies associated with acute chest pain in children with sickle cell disease are pulmonary fat embolism, lung infection or atelectasis. Pulmonary hypertension is one of a serious complication. In some patients, the acute chest crisis is caused by the sickling phenomenon and the vaso-occlusive nature of the disease itself.

Stroke risk is also higher in children with sickle cell disease. The current risk of stroke in children with sickle cell disease is estimated to be around 1% before 20 years of age. Large vessels are more commonly involved in stroke in children with sickle cell disease, compared to small vessels and medium-sized vessels.

Small cell disease is responsible for silent cerebral infarcts and silent cerebral ischemic lesions. These so-called silent lesions have been consistently correlated with worse school achievement and developmental delay.

In contrast to adults, nephropathy is relatively rare in children with sickle cell disease. Children who develop sickle cell disease can present with edema and frothy urine. End-Stage renal disease is very rare in children with sickle cell disease.

Children aged between 10 and 20 years are at an **increased risk of developing proliferative sickle retinopathy,** a condition that is associated with an increased risk of decreased visual acuity and visual impairment.

Avascular necrosis of the femoral head or other bony structures, while being common in adults, is very rare in children may result in leg ulcers.

Diagnostic Workup for Sickle Cell Disease in Children

Routine screening for sickle cell disease at birth is currently mandatory for all children born in the United States. Once the diagnosis is confirmed, different blood tests can be carried out to assess the severity of the condition.

Hemoglobin electrophoresis can establish the diagnosis of HbS. Patients **usually have a hemoglobin level that is between 5 and 9 g/dL, a decreased hematocrit, an elevated leukocyte count, a low erythrocyte sedimentation rate and an elevated reticulocyte count.** Peripheral blood smears show target cells, elongated cells and red blood cells with nuclear remnants known as Howell-Jolly bodies. The presence of Howell-Jolly bodies in red blood cells indicates that the patient has developed auto-infarction of the spleen.

The level of fetal hemoglobin should be determined as it has been shown to correlate with prognosis.

Children who present with abdominal pain and abdominal distension should undergo an ultrasonography examination to assess the size of the spleen.

Patients who present with acute chest pain should undergo a **chest x-ray which usually shows diffuse lung infiltrates**. The picture might resemble that of acute respiratory distress syndrome. Atelectasis can also be excluded by a chest x-ray.

Transcranial Doppler studies have been shown to be life-saving when it comes to the prediction of the risk of stroke in children with sickle cell disease.

A magnetic resonance imaging in a child with sickle cell disease, who shows a progressive decline in his or her school performance, might reveal silent cerebral infarcts or deep white matter lesions. The presence of deep white matter lesions indicates silent cerebral ischemia.

Patients presenting with edema and frothy urine should undergo a **urinalysis which might reveal proteinuria**, the earliest sign of kidney involvement in sickle cell disease. Albuminuria is very sensitive for sickle cell disease induced nephropathy. Serum creatinine levels are usually not elevated in the early stages of sickle cell disease nephropathy, and should not be relied upon for the evaluation of kidney function in this cohort of patients.

After 10 years of age, **ophthalmic funduscopy should be used to assess the retina** in children with sickle cell disease and to exclude proliferative sickle retinopathy. This is especially useful in children with progressive visual impairment in the second decade of life.

Treatment of Sickle Cell Disease in Children

The treatment of sickle cell disease is based on the complete evaluation of the case through laboratory tests and age of the patient to prevent the complications and reduce mortality rates. This can be explained by the following points:

Sickle cell disease patients, who develop an episode of acute splenic sequestration, should be evaluated for splenectomy. Whenever possible, **splenectomy should be delayed until the age of 3 to 5 years**. Children who are younger than 3 years of age, and who develop multiple episodes of splenic sequestration, should receive routine monthly blood transfusions which are known to delay splenectomy.

Children who are confirmed to have HbS should **receive penicillin prophylaxis**. Penicillin prophylaxis should be started at the age of 2 months with an oral dose of 125 mg twice a day. When the child reaches the age of 3 years, the dose should be increased to 250 mg twice daily.

Children with sickle cell disease should receive the 23-valent pneumococcal vaccine and the **protein-conjugated pneumococcal vaccine** to lower the risk of Streptococcus pneumoniae infections.

Patients with acute vaso-occlusive crisis might develop acute chest syndrome due to the limited depth of inspiration and the need for chest and back splinting. To lower the risk of acute chest syndrome, standardized doses of pain medication and the use of patient-controlled analgesia is recommended. Over-sedation increases the risk of impaired

respiratory effort and atelectasis, which again increases the risk of acute chest syndrome.

Patients who develop acute chest syndrome should receive a cephalosporin plus a macrolide to cover pneumonia, and adequate intravenous fluid replacement therapy. It is recommended to use the least possible amount of intravenous fluid replacement to prevent the development of fluid overload and pulmonary edema. Patients who do not respond to this empirical therapy should receive blood transfusions. Exchange transfusions might be needed.

Patients who receive routine blood transfusions should receive an iron chelator to prevent iron overload. Deferasirox is the first oral medication that can be used in this cohort of children. The use of hydroxyurea in children should be limited to those who develop one of the previously mentioned clinical sequelae of sickle cell disease. When hydroxyurea is used, close monitoring of the different blood cell lines should be carried out to detect myelosuppression.

Gene-based therapies for sickle cell disease are under extensive research with very promising early results.

References

Meier ER, Miller JL. Sickle Cell Disease in Children. Drugs. 2012;72(7):895-906. doi:10.2165/11632890-000000000-00000.

Notes