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Overview of the clinical manifestations of sickle cell disease

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INTRODUCTION — Vaso-occlusive phenomena and hemolysis are the clinical hallmarks of sickle cell disease (SCD), an inherited disorder due to homozygosity for the abnormal hemoglobin, hemoglobin S (HbS). Vasoocclusion results in recurrent painful episodes (previously called sickle cell crisis) and a variety of serious organ system complications that can lead to life-long disabilities and/or early death.

Hemoglobin S (HbS), results from the substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain, which produces a hemoglobin tetramer (alpha2/beta S2) that is poorly soluble when deoxygenated [1]. The polymerization of deoxy HbS is essential to vaso-occlusive phenomena [1]. The polymer assumes the form of an elongated rope-like fiber, which usually aligns with other fibers, resulting in distortion into the classic crescent or sickle shape (image 1) and a marked decrease in red cell deformability. (See "Sickle hemoglobin polymer: Structure and functional properties".)

This polymerization process is altered by several factors. Fetal hemoglobin (HbF) is a major modulator of polymerization in that the higher the HbF levels, the more benign the clinical and hematologic features of sickle cell anemia [2]. However, polymerization alone does not account for the pathophysiology of SCD. Subsequent changes in red cell membrane structure and function, disordered cell volume control, and increased adherence to vascular endothelium also play an important role [1,3].

An overview of the clinical manifestations of homozygous SCD will be presented here, with more complete discussions of the major clinical manifestations presented separately (eg, pulmonary, renal, bone and joint, cerebrovascular disease) [4]. The diagnosis and treatment of SCD and the management of pregnancy in SCD are also discussed separately. (See "Diagnosis of sickle cell disorders" and "Overview of the management and prognosis of sickle cell disease" and "Hydroxyurea and other disease-modifying therapies in sickle cell disease" and "Pregnancy in women with sickle cell disease".)

GENERAL OVERVIEW — The clinical manifestations of sickle cell disease vary markedly among the major genotypes. The following general principles apply to the major sickle cell subtypes. However, within each subtype, there can be a marked variability in disease severity. (See "Variant sickle cell syndromes".)

- The term sickle cell disease (SCD) is generally used to describe all of the conditions associated with the phenomenon of sickling, whereas the term sickle cell anemia is generally used to describe homozygosity for hemoglobin S (ie, Hb SS).
- The disorder is most severe in patients with homozygosity for HbS, of intermediate severity in hemoglobin SC disease (HbSC, combined heterozygosity for hemoglobins S and C), and generally benign in those with sickle cell trait (heterozygosity for HbS). (See "Variant sickle cell syndromes".)
- Among patients with sickle cell-beta thalassemia, the disease varies with the quantity of hemoglobin A, often being quite severe in patients with sickle cell-beta (0) thalassemia and less severe in patients with sickle cell-beta (+) thalassemia. This difference may not apply to cerebrovascular disease. In one series of 3647 patients from the Cooperative Study of Sickle Cell Disease, for example, the age-adjusted incidence of cerebrovascular accident per 100 patient years was 0.61 in SCD, 0.15 in HbSC disease, and 0.09 and 0.08 in sickle cell-beta (+) thalassemia and sickle cell-beta (0) thalassemia, respectively (figure 1) [5].

- Among patients with coexisting alpha thalassemia, the anemia is less severe (because of a lower cellular hemoglobin concentration) but the effects on the clinical manifestations are variable.

Patients with homozygous Hb S are typically anemic and often lead a life punctuated by recurrent painful vasoocclusive episodes [6]. Clinical signs and symptoms typically develop at an early age. This was illustrated in a study of 305 children diagnosed at birth in whom the prevalence of symptoms according to age was as follows [7]:

- Six months of age — 6 percent
- Twelve months of age — 32 percent
- Two years of age — 61 percent
- Six years of age — 92 percent
- Eight years of age — 96 percent

Dactylitis (acute pain in the hands and/or feet) was the most common initial symptom, occurring in 40 percent overall and 50 percent of children who became symptomatic before age two. An acute episode of pain was the initial symptom in more than 25 percent and was the most frequent initial symptom after the age of two. The third major presenting symptom was splenic sequestration, occurring in 20 percent overall and one-third before age two. Over time, vaso-occlusion can occur in virtually every organ system, accounting for the characteristic acute and chronic multisystem failure associated with this disease. Progressive vaso-occlusion resulting in multiorgan dysfunction often occurs without any overt clinical manifestations.

MAJOR CLINICAL MANIFESTATIONS

Acute painful episodes — Episodes of acute pain, previously called sickle cell crisis, are the most common type of vasoocclusive event. (See "Vasoocclusion in sickle cell disease".)

Acute pain is the first symptom of disease in more than 25 percent of patients and is the most frequent symptom after the age of two years [7]. Acute pain is also the complication for which patients with sickle cell disease commonly seek medical attention [8,9], although some of these episodes are short-lived and are managed at home [10,11]. The frequency of pain peaks between the ages of 19 and 39; more frequent pain is associated with a higher mortality rate in patients over age 19 [6].

There is considerable variability in the severity and frequency of acute painful episodes experienced by patients [11,12]. In one large study, one-third of patients rarely had pain, one-third were hospitalized for pain approximately two to six times per year, and one-third had more than six pain-related hospitalizations per year [13].

Similar results were noted in a prospective evaluation of 3578 patients (ranging from newborns to age 66) by the Cooperative Study of Sickle Cell Disease [6]. Over a five-year period, the mean number of pain episodes per year was 0.8 in SCD, 1.0 in sickle cell-beta (0) thalassemia, and 0.4 in HbSC disease and sickle cell-beta (+) thalassemia. Among the patients with SCD, 40 percent had no painful episodes, while 1 percent had 3 to 10 episodes per year. Among patients with SCD over age 20, those with high rates of pain episodes tend to die earlier [6,14].

Pain frequency in this report correlated with high hemoglobin levels [6]. A similar observation has been made in another study in which a hemoglobin concentration >8.5 g/dL was a major risk factor [15]. Low fetal hemoglobin levels also appear to be a risk factor [6]

Most pain frequency studies have focused on emergency department or hospital visits. However, the increasing use of comprehensive long-term diary studies describe a different spectrum of painful events. One group studied pain by using a daily assessment diary in adults with sickle cell disease [11]. Pain was reported in 55 percent of analyzed patient days, while 29 percent of patients reported pain almost daily. In this study, a painful event without utilization of hospital care was the norm rather than the exception. A similar discrepancy between home-managed pain and hospital treatment has been observed in pediatric patients [10].

Pain may be precipitated by events such as weather conditions (eg, high wind speed, low humidity, atmospheric

pollutants) [16-18], dehydration, infection, stress, menses, alcohol consumption, nocturnal hypoxemia [19,20], and rarely obstructive sleep apnea [21]. However, the majority of painful episodes have no identifiable cause. The episodes can affect any area of the body, with the back, chest, extremities, and abdomen being most commonly affected; the pain severity can range from trivial to excruciating. Approximately one-half of episodes are accompanied by objective clinical signs such as fever, swelling, tenderness, tachypnea, hypertension, nausea, and vomiting. (See "Bone and joint complications in sickle cell disease" and "Differential diagnosis of abdominal pain in adults", section on 'Sickle cell disease'.)

There are often premonitory symptoms and, in most instances, the episode lasts for two to seven days [22]. Frequent pain may generate feelings of despair, depression, and apathy that interfere with daily life and promote an existence that revolves around pain. A comprehensive approach to pain with an understanding of each patient's management plan is indicated. Many variables affect therapy such as opioid clearance, hyperalgesia, and pseudoaddiction [23]. (See "Acute pain management in adults with sickle cell disease".)

Laboratory studies — There is no test to diagnose a vaso-occlusive event. Standard laboratory tests cannot be used to distinguish pain crisis from the baseline condition. The peripheral blood smear typically reveals that 5 to 50 percent of the red cells are irreversibly sickled cells (picture 1), although the presence of sickled forms on the peripheral smear is not diagnostic of an acute pain episode.

The most promising laboratory indicators of acute vaso-occlusion are changes in the density distribution of sickle cell subpopulations and the rheologic properties of the blood [24-26]. There is often an increase in the fraction of dense cells and a decrease in the maximum deformability of sickle cells one to three days prior to the onset of pain; this is followed by a decrease in the number of dense cells, and an increase in red cell deformability to values higher than those seen in the steady state [25]. These observations suggest that the first phase of the crisis may be characterized by preferential trapping of deformable cells in the microcirculation [25]; these deformable cells may be more likely to adhere to vascular endothelium [24].

The evolution of pain is also associated with changes in the levels of acute phase reactants (eg, C-reactive protein, fibrinogen) [26,27], serum lactate dehydrogenase [28], interleukin-1, tumor necrosis factor, and serum viscosity [29].

Neurologic complications — The Cooperative Study of Sickle Cell Disease found that 24 percent of individuals with sickle cell anemia experienced a clinical overt stroke by age 45. In childhood, 25 percent of children with sickle cell anemia have silent ischemic lesions that may impair neurocognitive function and predict for progressive disease. Transcranial Doppler Screening (TCD) of children detects increased blood flow in the Circle of Willis which strongly predicts stroke risk. These findings have resulted in all children with sickle cell anemia being screened for ischemic injury. Patients with elevated flow on TCD screening are placed on permanent transfusion therapy. (See "Cerebrovascular complications of sickle cell disease".)

As patients with sickle cell anemia age, they are also at risk for neurocognitive decline and intracranial hemorrhage. These findings have led to increased surveillance of adult patients for ischemic brain injury. One study evaluated neurocognitive function in neurologically asymptomatic adults with sickle cell anemia. Compared with healthy controls, neurologically intact adults with sickle cell anemia had poorer cognitive performance, which appears to correlate with age and hemoglobin [30].

Chronic transfusion therapy is the mainstay therapy for patients with overt central nervous system injury as well as those with abnormal TCD screening. Hydroxyurea has been evaluated as an alternative option in selected patients. The "SWiTCH" trial randomly assigned stable patients with a history of a stroke to receive either transfusion or hydroxyurea. The study was stopped early because of the increased rate of stroke in the hydroxyurea treatment group [31]. This subject is discussed in depth separately. (See "Cerebrovascular complications of sickle cell disease", section on 'Cerebral infarction'.)

Bone marrow transplantation is often considered in those children with these complications and sibling matches [30]. The success of sibling-matched transplantation for children with sickle cell disease has led to trials evaluating

unrelated, matched cord blood transplantation in sickle cell patients [32]. These experimental trials are ongoing. (See "Hematopoietic cell transplantation in sickle cell disease".)

Epilepsy in individuals with sickle cell disease is two to three times more common than in non-sickle populations and is associated with increased all-cause mortality. This was shown in an examination of all records of the 543 persons in the Jamaica sickle cell cohort, in which the five-year cumulative incidence of febrile convulsions was 2.2 percent and the incidence rate of epilepsy was 100 per 100,000 person-years [33]. Male gender (OR 4.0; 95% CI 1.03-20) and dactylitis in childhood (OR 17; 95% CI 4.8-63) were associated with an increased risk of developing epilepsy. The hazard ratios for all-cause mortality were 3.6, 2.3, and 3.4 for those with acute symptomatic seizures, a single seizure, or epilepsy, respectively. That both acute symptomatic seizures and stroke occurred during the same period of life (ie, before the 11th birthday) suggests a shared pathologic process.

Multiorgan failure — The potentially fatal acute multiorgan failure syndrome is most often seen during severe pain episodes in patients with SCD [34]. The pathogenesis of this syndrome in SCD is uncertain but may be reversed by prompt and aggressive exchange transfusion therapy [34,35]. (See "Sepsis and the systemic inflammatory response syndrome: Definitions, epidemiology, and prognosis".)

Psychosocial issues — Most patients with sickle cell disease are well adjusted [36]. However, there are issues involving low self esteem, social isolation, poor family relationships, and withdrawal from normal daily living [36-38]. Specific problem areas may include inappropriate pain coping strategies, reduced quality of life, anxiety, depression, and neurocognitive impairment [30,39-41].

Well-adjusted patients have active coping strategies, family support, and support from the extended family unit [42-44], although in one study children with three or more prior painful events had increased odds of a poor outcome postdischarge, including a negative impact on their caregivers [45]. The development of active coping mechanisms should be encouraged.

Growth and development — Growth failure and delayed puberty are common in children with SCD. Most have detectable growth retardation that affects weight more than height by the age of two years [46]. Normal height is often achieved by adulthood but weight remains lower than that of controls. Neurodevelopment and skeletal maturation are also delayed [47,48]. Boys and girls have retarded sexual maturation and delayed menarche [46,49,50]. (See "Diagnosis and treatment of delayed puberty".) In a report from the Jamaican Cohort Study, for example, extreme growth retardation, defined as absence of the adolescent growth spurt and prepubertal sexual development (Tanner stage 1 or 2) at age 16, was noted in 8 of 52 boys (15 percent) with SCD [51].

These effects on growth and development are more prominent in patients with SCD and sickle cell-beta (0) thalassemia than in HbSC disease or sickle cell-beta (+) thalassemia [46]. The pathogenesis is uncertain although primary hypogonadism [49,51,52], hypopituitarism [53], and hypothalamic insufficiency [54] have been described.

Reduced or absent splenic function — Reduced (hyposplenism) or absent (functional asplenia) splenic function is commonly seen in subjects with SCD, due to repeated episodes of splenic infarction secondary to sickling of red cells within the spleen. As is discussed below, children with SCD are vulnerable to life-threatening infection early in life due to the inability of the spleen to filter microorganisms from the blood stream. (See 'Infection' below.)

Biomarkers of splenic function were studied using baseline data from the BABY HUG Trial to determine the onset and extent of reduced to absent splenic function in 193 infants with SCD (mean age 12.9 months, range 8.1 to 18 months) not selected for clinical severity. Results included the following [55] (see "Approach to the adult patient with splenomegaly and other splenic disorders", section on 'Hyposplenism and asplenia'):

- Results of a ^{99m}Tc sulfur colloid scan indicated normal, decreased, or absent splenic colloid uptake in 12, 73, and 15 percent of the infants, respectively. Splenic function was decreased or absent in 75, 86, and 91 percent of those ≤9, 9.1 to 12, and ≥12.1 months of age, respectively.
- Quantitative measurement of Howell-Jolly bodies (HJB) and membrane vacuoles (PIT counts) in circulating red cells correlated well with each other as well as with results of the colloid scans. Results suggested that PIT

counts ≤1.2 percent predict for normal splenic function, while PIT counts ≥4.5 percent predict for absent function. For Howell-Jolly bodies, ≤55 HJB/10^6 red cells predicts normal and ≥665 HJB/10^6 red cells predicts absent splenic function.

The high rate of splenic dysfunction documented by one year of age in this study mandates that preventive strategies for minimizing risk of infection be adhered to assiduously. (See 'Infection' below.)

Infection — Infection is a major cause of morbidity and mortality in patients with SCD. Affected children are vulnerable to life-threatening infection as early as four months of age because of splenic dysfunction caused by sickling of the red cells within the spleen and the inability of the spleen to filter microorganisms from the blood stream. Splenic dysfunction is followed eventually by splenic infarction, usually by two to four years of age. (See "Approach to the adult patient with splenomegaly and other splenic disorders", section on 'Hyposplenism and asplenia'.)

In the absence of normal splenic function, the patient is susceptible to overwhelming infection by encapsulated organisms, especially Streptococcus pneumoniae and Haemophilus influenzae. Dysfunctional IgG and IgM antibody responses, defects in alternative pathway fixation of complement, and opsonophagocytic dysfunction may also play a role in the predisposition to invasive infection [56,57]. Viral infections such as H1N1 and parvovirus can appear to be more virulent in sickle cell disease, possibly by serving as a catalyst to sickling and associated inflammatory reactions [58-60]. Worldwide, malaria is a common cause of morbidity and mortality in children with sickle cell disease [61]. (See "Clinical features and management of sepsis in the asplenic patient".)

Bacteremia — Bacteremia in children with SCD is most commonly caused by S. pneumoniae [62-65]. Bacteremia typically presents with leukocytosis, a left shift in the differential count, aplastic or hypoproliferative crisis due to associated bone marrow suppression, sometimes disseminated intravascular coagulation, and is associated with a mortality rate of 20 to 50 percent [66]. The risk of recurrent S. pneumoniae sepsis and death is increased in patients who have had previous sepsis. A discussion of the most common bacterial infections seen in children with SCD can be found elsewhere. (See "Management of fever in sickle cell disease", section on 'Empiric antibiotic therapy'.)

Bacteremia occurs less often in adults, although often with devastating results [67-69]. In one study, the most common community-acquired bacteria were E. coli, S. aureus, S. pneumoniae, and Salmonella, while the most common hospital-acquired bacterium was S. aureus [69]. Bacteremia was associated with severe immunosuppression, the presence of indwelling venous catheters, and a high frequency of associated bone-joint infections.

Bacteremia may be associated with episodes of acute chest syndrome. It is most likely to occur in infants (14 versus 1.8 percent in patients over 10 years of age in one series) [70].

S. pneumoniae — Prior to the use of prophylactic penicillin and pneumococcal vaccination, infants with SCD had 4 to 10 episodes per 100 patient years of bacteremia due to S. pneumoniae [62,66]. As described in the next section, pneumococcal bacteremia is associated with a high risk of meningitis unless antibiotics are rapidly administered. Introduction of the pneumococcal conjugate vaccine has led to a significant reduction of over 90 percent in the incidence of pneumococcal infection in children under the age of five years, although infection with pneumococcal serotypes not included in these vaccines, and infection in those not vaccinated has continued to occur [66,71]. (See "Overview of the management and prognosis of sickle cell disease", section on 'Infection prevention'.)

How SCD specifically predisposes to invasive pneumococcal infection is not well understood. Intact pneumococci use phosphorylcholine to tether to the platelet activating factor (PAF) receptor, thereby inserting the bacteria into the PAF receptor uptake pathway and promoting cell entry [72]. (See "Microbiology and pathogenesis of Streptococcus pneumoniae", section on 'Invasion'.)

A possible predisposing mechanism in SCD is the upregulation of PAF receptors on chronically activated

endothelial cells. The following observations in a SCD mouse model are consistent with this hypothesis: higher rates of infection and mortality after exposure to pneumococci compared with wild-type mice; increased expression of PAF receptors on endothelium and pulmonary epithelium; and protection from mortality by genetic deletion or pharmacologic blockade of PAF receptors [73].

H. influenzae type b — Haemophilus influenzae type b has been the second most common organism responsible for bacteremia in children with SCD, accounting for 10 to 25 percent of episodes [74,75]. H. influenzae affects older children and is usually less fulminant than pneumococcal bacteremia [66,76]. The incidence of invasive H. influenzae type b infection has declined markedly after introduction of the H. influenzae type b vaccine, both by direct protection of the patient and by decreased carriage of the organism in the general population.

Meningitis — Meningitis in SCD is primarily a problem of infants and young children. It is most frequently caused by S. pneumoniae and occurs in the setting of bacteremia [77]. In older studies, the incidence of meningitis among bacteremic patients was as high as 50 percent, a value that has been markedly reduced by the rapid administration of antibiotics [63,78]. H. influenzae type b is now a less common cause of meningitis. (See "Bacterial meningitis in children older than one month: Clinical features and diagnosis", section on 'Epidemiology'.)

Bacterial pneumonia — Causes of bacterial pneumonia in patients with SCD include Mycoplasma pneumoniae, Chlamydia pneumoniae (which together account for about 20 percent of cases), and Legionella [79]. Respiratory viruses are also common causes of pulmonary infection, while S. pneumoniae and H. influenza type b are uncommon [79]. Patients may present with any combination of dyspnea, cough, chest pain, fever, tachypnea, and leukocytosis, and may develop the acute chest syndrome [79]. (See "Overview of the pulmonary complications of sickle cell disease" and "The acute chest syndrome in children and adolescents with sickle cell disease".)

Osteomyelitis — There is an increased incidence of osteomyelitis in patients with sickle cell anemia resulting from infection of infarcted bone. This subject is reviewed in detail separately, but will be briefly reviewed here. (See "Bone and joint complications in sickle cell disease", section on 'Osteomyelitis and septic arthritis'.)

The most common offending organisms are Salmonella species. Staphylococcus aureus, the most common etiologic agent in patients without sickle cell anemia, accounts for less than 25 percent of cases. Articular infection is less common and is often due to S. pneumoniae.

Osteomyelitis usually affects long bones, often at multiple sites. It may be difficult to distinguish osteomyelitis from vaso-occlusive events involving bone. Bone imaging studies may be helpful and cultures are essential.

Cerebrovascular events — The issues related to cerebrovascular disease in patients with SCD and its variants are discussed in detail elsewhere and will be only briefly reviewed here. (See "Cerebrovascular complications of sickle cell disease".)

Neurologic complications, including transient ischemic attacks, infarctive stroke, intracerebral hemorrhage, spinal cord infarction or compression, vestibular dysfunction, and sensory hearing loss, occur in 25 percent of patients with sickle cell anemia. Cognitive impairment may occur as a consequence of vascular disease and/or silent cerebral infarcts.

The risk of a cerebrovascular accident (CVA) varies with the genotype:

- The likelihood of having a first CVA by age 20, 30, and 45 years was 11, 15, and 24 percent, respectively, for SCD compared with 2, 4, and 10 percent for HbSC disease (figure 1) [5].
- Imaging studies have identified silent infarcts in 10 to 20 percent of patients with SCD compared with 3 percent in HbSC disease [80].

On multivariate analysis, the following major risk factors were identified for infarctive stroke [5]:

- Prior TIA — relative risk [RR] 56
- Low steady state hemoglobin — RR 1.9 per 1 g/dL decrease

- Rate of acute chest syndrome — RR 2.4 per event per year
- Episode of acute chest syndrome within the previous two weeks — RR 7.0
- Elevated systolic blood pressure — RR 1.3 per 10 mmHg increase

Only two major risk factors were identified for intracerebral hemorrhage:

- Low steady state hemoglobin — RR 1.6 per 1 g/dL decrease
- Increased steady state leukocyte count — RR 1.9 per 5000/μL increase

The major issue in relation to infarctive stroke is prevention. Transcranial Doppler can identify children at risk; among such children, institution of a prophylactic chronic transfusion program with a goal HbS of less than 30 percent of total hemoglobin reduces the risk of stroke by 92 percent (figure 2) [81]. Transfusion therapy also markedly reduces the incidence of recurrent stroke. (See "Cerebrovascular complications of sickle cell disease".)

Bone complications — The skeletal system is frequently involved in sickle cell disease due accelerated hematopoiesis and/or bone infarction. The extended hematopoietic marrow resulting from the chronic hemolysis can lead to chronic tower skull, bossing of the forehead, and fish-mouth deformity of vertebrae. These effects cause widening of the medullary space, thinning of the trabeculae and cortices and osteoporosis. Sickle cell patients have a high rate of vitamin D deficiency and osteoporosis, which may increase the bone pathology [82]. This subject is discussed in detail separately, but will be briefly reviewed here. (See "Bone and joint complications in sickle cell disease".)

Bone complications in sickle cell disease include the following:

- Bone infarction and necrosis — Excruciating pain due to bone infarction, the hand-foot syndrome or dactylitis, is the most common initial symptoms of sickle cell disease, occurring in 40 percent of patients overall and 50 percent of children who became symptomatic before age two. It is important to distinguish this syndrome, which resolves spontaneously, from osteomyelitis using nuclear medicine scintigraphy or magnetic resonance imaging (MRI).

Osteonecrosis (also called avascular, ischemic, or aseptic necrosis) results from infarction of bone trabeculae and marrow cells and occurs in all sickle cell disease genotypes. Osteonecrosis occurs with equal frequency in the femoral and humeral heads and a similar relationship to genotype is seen at both sites. The femoral heads more commonly undergo progressive joint destruction as a result of chronic weight bearing. The changes are best detected by MRI. (See "Bone and joint complications in sickle cell disease", section on 'Osteonecrosis' and "Osteonecrosis (avascular necrosis of bone)".)

Bone marrow infarction — Bone marrow infarction in sickle cell disorders causes reticulocytopenia, exacerbation of anemia, a leukoerythroblastic blood picture, and occasional pancytopenia. (See "Evaluation of bone marrow aspirate smears", section on 'Bone marrow necrosis'.)

- Pulmonary fat embolism is a complication of bone marrow infarction, which may be associated with fat globules in the sputum and refractile bodies visible in the optic fundi. Fat embolism is a life-threatening event that may require exchange transfusion, heparin, and corticosteroids. (See "Acute chest syndrome in adults with sickle cell disease", section on 'Bone marrow and/or fat emboli' and "The acute chest syndrome in children and adolescents with sickle cell disease", section on 'Etiology' and "Fat embolism syndrome".)

- Orbital compression syndrome — Vaso-occlusion of the periorbital marrow space with subperiosteal hemorrhage produce a syndrome consisting of headache, fever, and palpebral edema. This syndrome primarily occurs in patients with SCD. Compression of the optic nerve may occur, requiring consideration of surgical decompression. (See "Bone and joint complications in sickle cell disease", section on 'Orbital bone infarction and orbital compression syndrome' and "Congenital anomalies and acquired abnormalities of the optic nerve", section on 'Compression'.)

Cardiac complications — Cardiac complications are a common, often unrecognized, cause of morbidity and

mortality in sickle cell disease, and are a major cause of death in adult patients [83-85]. There is no specific cardiomyopathy in sickle cell disease [86]. There are, however, two important cardiac effects: an increased cardiac output and acute myocardial infarction. The chronic anemia of SCD and/or asleep and waking oxygen desaturation results in a compensatory increase in cardiac output that leads to chronic chamber enlargement and cardiomegaly even in young children [87-91]. In older patients, right heart, as well as left heart, failure may develop. The electrocardiogram shows evidence of left ventricular hypertrophy, and less often first-degree block and nonspecific ST-T wave changes [92]. Arrhythmias appear to be an important component of death in older patients [83]. Patients may have a higher rate of prolonged QT intervals secondary to their disease or medications, ie, methadone [93,94]. Left sided diastolic dysfunction is increasingly being identified in patients with pulmonary hypertension and early cor pulmonale [95]. Hemosiderosis-induced cardiomyopathy has been observed in older sickle cell patients [96,97].

Exercise capacity of sickle cell patients is often diminished, but heart failure is uncommon and restriction of activity is seldom necessary [98,99]. However, an age-dependent loss of cardiac reserve may predispose to heart failure in adulthood following fluid overload, transfusion, reduced oxygen carrying capacity, or hypertension [88,100]. Exercise performance can be improved by transfusion therapy to lower the HbS percentage [101].

Myocardial infarction — Acute myocardial infarction in the absence of epicardial coronary artery disease has been described in patients with SCD, and is often misdiagnosed [102-104]. In one autopsy series, 7 of 72 consecutive patients with SCD (9.7 percent) had myocardial infarction; gross obstructive and atherosclerotic lesions were absent in all seven patients [103]. Infarction in this setting may reflect increased oxygen demand exceeding limited oxygen-carrying capacity or abnormal myocardial microvasculature.

Dermatologic complications — Vasoocclusion in the skin produces leg ulcers and myofascial syndromes in patients with sickle cell disorders.

Leg ulcers — Leg ulcers are a frequent complication in SCD, causing significant physical disability and a negative psychologic and social impact, occurring usually after the age of 10 [105,106]. They are most common in SCD, less frequent in sickle cell-beta (0) thalassemia and sickle cell-alpha thalassemia (10, 5.7, and 2.4 per hundred patient-years, respectively), and nonexistent in HbSC disease and sickle cell-beta (+) thalassemia [106]. The risk is highest in tropical regions, and is increased in males and in those with a low hematocrit and increased evidence for hemolysis; HbF appears to be protective [106-109]. (See "Clinical variability in sickle cell anemia", section on 'Leg ulcers'.)

In a study of 225 subjects from the Jamaican Cohort Study, chronic leg ulcers occurred in 53 subjects (24 percent), with a median age of initial ulceration of 17 years (range: 13 to 24) [110]. The mode of onset was traumatic, spontaneous, or unknown in 60, 28, and 12 percent, respectively. On multivariate analysis, risk factors included venous incompetence, low socioeconomic status, and increased levels of LDH.

Most leg ulcers occur near the medial or lateral malleolus and are frequently bilateral [106,107]. They may begin spontaneously or occur after trauma, and may become infected, most commonly by S. aureus, Pseudomonas, streptococci, or Bacteroides [111]. Systemic infection, osteomyelitis, and tetanus are rare complications [107]. The ulcers are resistant to healing, tend to be recurrent in well over one-half of patients [112], and may be associated with venous incompetence [113].

Management — Prevention is the best treatment with well-fitting shoes or sneakers and aggressive treatment of early signs of skin injury. Management of leg ulcers in patients with SCD begins with gentle debridement to remove nonviable, superficial tissue from more vital areas. Wet to dry dressings and Duoderm hydrocolloid dressings facilitate devitalization. Once debridement is complete, zinc oxide-impregnated Unna's boots are used to promote healing. Bed rest speeds healing by improving tissue perfusion [114,115]. Other modalities that may be required include topical antibiotics [116] and elastic wraps or leg elevation to control edema, which can retard healing. Extensive lesions may require skin grafting and the use of soft tissue flaps [117].

Use of oral zinc supplementation (eg, zinc sulfate 200 mg orally three times per day) has been suggested, although definitive evidence for its efficacy is not available [118]. A six-month course of transfusion therapy may accelerate

healing [119]. Several other modalities have been advocated:

- A phase II trial studied the effectiveness of arginine butyrate in 26 subjects with SCD and chronic lower extremity ulcers refractory to standard care for at least six months. Subjects were randomly assigned to receive either standard local care (SLC, 12 subjects) or SLC plus arginine butyrate (SLC+AB, 14 subjects). AB was delivered by intravenous infusion at a total daily dose of 500 mg/kg infused over a period of 6 to 8 hours through a long vascular catheter or port device and given five days per week for 12 weeks [120]. After three months, proportions of ulcers which healed were 24 and 78 percent in the SLC and SLC+AB arms respectively.
- Apligraf, an artificial wound membrane, may accelerate healing. (See "Medical management of lower extremity chronic venous disease", section on 'Ulcer care'.)
- Local or topical low-dose GM-CSF has anecdotally been beneficial [121,122]. However, parenteral dosing has been reported to cause sickle events.
- Bosentan has been utilized in refractory ulcers [123].
- Local topical opioids appear to accelerate healing in sickle cell disease and in the animal model [124,125].

Hepatobiliary complications — There are multiple causes of hepatic dysfunction in patients with SCD ("sickle cell hepatopathy"). These include, but are not limited to, the following:

- Acute hepatic ischemia
- Benign cholestasis
- Hepatic sequestration crisis
- Transfusional iron overload
- Acute and chronic cholelithiasis secondary to pigmented gallstones
- Acute and chronic liver disease secondary to hepatitis C virus infection (HCV) complicating blood transfusion
- Drug toxicity (eg, deferasirox, hydroxyurea)

(See "Hepatic manifestations of sickle cell disease".)

Pregnancy — Pregnancy is associated with both fetal and maternal complications, which are more common with SCD compared with sickle cell trait or HbSC disease.

- Fetal complications are related to compromised placental blood flow and include spontaneous abortion, intrauterine growth restriction, fetal death in utero, and low birthweight.
- Maternal complications occur in as many as one-half of pregnancies, including acute chest syndrome, bacteriuria, urinary tract infection, pyelonephritis, endometritis, preeclampsia, thromboembolic events, and the use of cesarean section.

As a result of these complications, close maternal-fetal surveillance is warranted. This subject is discussed in detail separately. (See "Pregnancy in women with sickle cell disease".)

Priapism — Priapism is a common, serious, and often underdiagnosed problem that leads to erectile dysfunction. This complication of SCD and its management are discussed in detail separately. (See "Diagnosis and management of priapism in sickle cell disease".)

Pulmonary complications — The pulmonary arterial circulation, which has low oxygen tension and low pressure in a slow-flow system, is ideally suited to facilitate the polymerization of sickle hemoglobin, causing both acute and chronic pulmonary manifestations that collectively are the most common cause of death in SCD [126-128]. The pulmonary manifestations of SCD are reviewed in detail separately, but will be briefly summarized here. (See "Overview of the pulmonary complications of sickle cell disease" and "The acute chest syndrome in children and adolescents with sickle cell disease".)

Evaluation of the pulmonary status in patients with sickle cell disease may reveal a variety of chronic manifestations including restrictive and obstructive lung disease, hypoxemia, and pulmonary hypertension singly or in combination. Undetected, acute worsening of pulmonary arterial hypertension during acute sickle cell events has been associated with acute cor-pulmonale and sudden death [129,130].

CT scanning may reveal chronic interstitial fibrosis. These abnormalities are more common in, but not restricted to, those with a past history of multiple episodes of acute chest syndrome. Pulmonary hypertension usually occurs in adults and carries a poor prognosis.

Other pulmonary manifestations of SCD have been described. Airway hyperreactivity occurs in nearly two-thirds of children with sickle cell disease not diagnosed as having asthma and as many as one-third of children have sleep-related upper airway obstruction. Recurrent episodes of hypoxemia with sleep apnea may be a risk factor for vaso-occlusive events.

Oxygen saturation — Baseline oxygen saturation (SaO2) measurements by pulse oximetry are below normal in patients with SCD. This was illustrated in the following studies:

- In a prospective cohort study of 130 children from the Cooperative Study for Sickle Cell Disease (CSSCD), mean and median daytime SaO2 were 94 and 95 percent, respectively [131].
- Similar results (95 to 96 percent) were seen in three other studies of mean daytime SaO2 [132-134].

In contrast to nocturnal hypoxemia, daytime SaO2 does not appear to independently predict subsequent pain or acute chest episodes [131]. In addition, there are currently no data correlating daytime SaO2 with nighttime SaO2, which generally is lower than daytime values [131]. Nevertheless, SaO2 values below baseline measurements for individual patients with SCD, either at rest or following exercise, are useful in detecting and monitoring for the presence of pulmonary complications.

Acute chest syndrome — The acute pulmonary complications of SCD, which have been referred to as the acute chest syndrome (ACS), include pneumonia, infarction due to in situ thrombosis, and embolic phenomena due to fat embolism and bone marrow infarction. The acute chest syndrome is the most common form of acute pulmonary disease in SCD, occurring in 30 to 50 percent of patients. It is the second most common cause of hospitalization in SCD and the leading cause of death. Acute complications of ACS include acute multiorgan failure with neurologic and/or renal events. Long-term complications include pulmonary hypertension and chronic lung disease.

Acute chest syndrome (ACS) has been defined as the new appearance of an infiltrate with pulmonary symptoms in a patient with sickle cell anemia [58,135]. Patients often have fever, chest pain, and cough, although many present with a fever, mild hypoxia, and an initially negative chest x-ray. A fall in hemoglobin and platelet count and rise in phospholipase A2 may precede radiographic changes.

The etiology of ACS is multi-factorial, including pulmonary infarction, infection (S. pneumoniae, mycoplasma, chlamydia, and common viral pathogens), and pulmonary fat embolism. Infection is a more common cause in children than in adults. ACS often follows a vaso-occlusive event and may be prevented by incentive spirometry, optimal analgesic control, and transfusion.

Therapy may require oxygen, antibiotics, and transfusion therapy. Undetected bronchoreactive lung disease is common and therefore, treatment with bronchodilators is often selectively used. Corticosteroids may result in rapid improvement but have been associated with frequent rebound readmissions [136]. Hydroxyurea significantly reduces the frequency of ACS. (See "Overview of the pulmonary complications of sickle cell disease" and "The acute chest syndrome in children and adolescents with sickle cell disease".)

Renal complications — Renal involvement is common in sickle cell disease, leading to renal failure in up 18 percent of patients. Asymptomatic albuminuria is often a precursor of progressive renal disease [137,138]. New predictors of renal injury have been identified. Urinary kidney injury molecule, N-acetylb-D-glucosaminidase (NAG),

and cystatin C correlate with proteinuria and kidney disease [137]. The primary event appears to be occlusion of the vasa recta capillaries in the renal medulla. The normal medullary environment plays an important role in this process, because it has both a low oxygen tension and high osmolality (osmotically dehydrating the red cells, thereby increasing the concentration of HbS) [139]. The lesions are most marked in patients with SCD, but are less severe with heterozygous sickle cell trait (HbAS) or HbSC disease.

Increased in vitro sickling has been noted following intravenous iodinated contrast material used for imaging studies, but may be less when second-generation low- and iso-osmolar contrast agents are employed. This was shown in a study of 132 imaging studies in 79 patients, most of whom had HbSS disease [140]. Contrast-induced nephropathy occurred in 1.5 percent, at a rate similar to the general population, resolving in all cases. Prehydration was associated with a significantly decreased incidence of adverse events.

The renal manifestations of sickle cell disease are discussed in detail separately. (See "Renal manifestations of sickle cell disease".) They include:

- Enuresis secondary to hyposthenuria
- Painless hematuria due to papillary infarcts
- Proteinuria and hypertension
- Renal infarction, papillary necrosis, and renal colic
- Nephrogenic diabetes insipidus that can lead to polyuria
- Focal segmental glomerulosclerosis that can lead to end-stage renal disease; dialysis is well tolerated and increasing numbers of patients are being treated with renal transplantation
- Renal medullary carcinoma is a malignancy found almost exclusively in black patients with HbSC disease or sickle cell trait.

Retinopathy — Sickle cell disease in the eye primarily affects the retina, with manifestations such as proliferative retinopathy, retinal artery occlusion, and retinal detachment and hemorrhage [141,142]. The vaso-occlusions may begin in childhood. Lesions are first observed in the periphery, resulting in a nonperfused and presumably ischemic peripheral retina. New blood vessels develop at the border of perfused and nonperfused retina. The elaborate preretinal neovascular structures that form during proliferative sickle cell retinopathy are called "sea fans" because of their resemblance to a marine invertebrate. Postmortem studies suggest that autoinfarction occurs at the preretinal capillary and that sea fans tend to develop at the site of arteriovenous crossings [143].

These fragile blood vessels can hemorrhage into the vitreous and produce traction retinal detachments, the major cause of blindness in sickle cell subjects. The stimuli for sea fan formation are unknown. Autocrine production of angiogenic factors such as basic fibroblast growth factor and vascular endothelial growth factor may play an important role [144]. Superficial and deep retinal hemorrhages have a characteristic appearance:

- Superficial hemorrhages have a pink "salmon patch" appearance that resolves into an iridescent "schisis cavity".
- Deeper retinal hemorrhages have a black "sunburst" appearance, which is the most common abnormality [145].

Proliferative sickle retinopathy — The incidence of proliferative sickle retinopathy (PSR) varies with the type of disease. In two reports of over 500 patients from England, PSR occurred in 11 percent with SCD and 37 percent with HbSC disease [141,146]. In the latter condition, the disease usually occurred between the ages of 20 and 30 and 68 percent of those over age 45 [146]. Other studies have confirmed that the risk of proliferative retinopathy is higher in HbSC disease than it is in HbSS disease [147,148]. Although rare, retinopathy and serious ocular complications can occur in patients with HbC trait [149].

Risk factors in males with both disorders are higher hematocrits and a low HbF level [141,146]. The greater frequency among patients with HbSC disease suggests that retinal vessels are more susceptible to occlusion by more viscous blood than by more rigid individual cells.

Loss of visual acuity in untreated patients with PSR ranges from 5 to 10 percent [147,150]. One report, for example, followed 120 patients with SCD disease and 220 with HbSC disease for a mean of 6.9 years; loss of visual acuity occurred in 10 percent of untreated eyes [145]. The incidence of visual loss was 31 per 1000 eye-years of observation among eyes with PSR compared with 1.4 per 1000 among eyes with nonproliferative disease. Similar findings were noted in another report of 97 patients over age 18 with HbSC disease [147]. PSR occurred in 50 percent; vitreous hemorrhage in 18 percent; retinal detachment in 8 percent; and blindness in one eye in 6 percent.

Prophylactic photocoagulation may have a role in the treatment of PSR in selected patients. However, no controlled studies have established that the long-term outcome is improved compared with the natural history of the disease [151]. There is a greater predilection for spontaneous regression, involution, or autoinfarction of the neovascular tissue in sickle retinopathy as opposed to the neovascularization in other retinal vascular diseases [148].

LABORATORY FINDINGS

CBC and routine laboratory testing — The chronic hemolysis of sickle cell disease is usually associated with a mild to moderate anemia (hematocrit 20 to 30 percent), reticulocytosis of 3 to 15 percent, unconjugated hyperbilirubinemia, elevated serum lactate dehydrogenase, and low serum haptoglobin. (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Diagnostic approach'.)

The peripheral blood smear may reveal sickled red cells, polychromasia indicative of reticulocytosis, and Howell-Jolly bodies reflecting hyposplenia secondary to repeated splenic infarctions (picture 1). The red cells are generally normocytic and normochromic unless there is coexistent alpha or beta thalassemia or iron deficiency, in which case microcytosis and hypochromia may be present. (See "Approach to the adult patient with anemia", section on 'Microcytic anemia'.)

Fetal hemoglobin (HbF) is usually slightly to moderately elevated and is a function of the number of reticulocytes that contain HbF, the extent of selective survival of HbF-containing reticulocytes to become mature HbF-containing erythrocytes, and the amount of HbF per red cell. Each variable is separately regulated and the expression of each shows interpatient variability [152]. In some patients with SCD alone, values are as high (1 to 4 percent) as the modest elevations seen in heterocellular hereditary persistence of fetal hemoglobin [152]. Patients treated with hydroxyurea may have levels of HbF of 15 percent or more. (See "Hydroxyurea and other disease-modifying therapies in sickle cell disease", section on 'Use of hydroxyurea'.)

In addition, certain beta globin haplotypes appear to be related to factors that regulate production of HbF. As examples, the Arab-Indian and Senegal haplotypes are associated with higher levels of HbF (over 20 percent in some cases), probably due to linkage with important gamma globin regulatory sequences in the locus control region [153-155]. In one study of Senegalese patients, the mean HbF was 8.2 percent, and approximately one-half of patients had a benign form of sickle cell anemia [155]. Genetic linkage and genome-wide association studies have identified single nucleotide polymorphisms that modulate fetal hemoglobin and the clinical phenotype of sickle cell disease. BCL11A, a regulator of gamma globin gene expression, is an important regulator that has been identified through these studies [156]. (See "Clinical variability in sickle cell anemia", section on 'Control of HbF expression' and "Structure and function of normal human hemoglobins", section on 'Fetal hemoglobin'.)

A comprehensive analysis of the clinical laboratory data collected from 2600 subjects with sickle cell disease found the following [157]:

- In patients with SCD, mean white blood cell (WBC) counts were higher than normal, particularly in those under the age of 10, and mean platelet counts were elevated, particularly in those under the age of 18. Mean WBC and platelet counts were not elevated in HbSC disease or sickle cell-beta (+) thalassemia. Elevated WBC is linked to the pathophysiology of sickle cell disease and increases the morbidity [158]. (See "Vasoocclusion in sickle cell disease", section on 'Leukocytes and inflammation'.)
- Mean serum bilirubin concentrations were higher in SCD than in HbSC disease or sickle cell-beta (+) thalassemia due to the greater hemolytic rate. The serum bilirubin rose after the first decade, possibly due to

chronic hepatobiliary dysfunction. Serum aminotransferase concentrations were often elevated, particularly in adults with SCD, but mean levels were normal. Serum alkaline phosphatase was elevated in all genotypes until puberty, which occurred later in males and in those with SCD.

- Serum creatinine concentrations were low in all genotypes until 18 years of age, due in part to an initial elevation in glomerular filtration rate, when males experienced a rise apparently related to increasing muscle mass. Serum creatinine increased with age in all genotypes due to declining renal function. (See "Renal manifestations of sickle cell disease".)

Hemoglobin electrophoresis — Hemoglobin electrophoretic patterns in the various sickle cell disorders are discussed separately. (See "Diagnosis of sickle cell disorders", section on 'Findings in sickle cell anemia' and "Variant sickle cell syndromes".)

Anemia — The anemia of SCA is usually a chronic, reasonably well-compensated hemolytic anemia with an appropriate reticulocytosis. In one series, for example, the mean hemoglobin and hematocrit concentrations were 7.9 g/dL and 22.9 percent, respectively, with an absolute reticulocyte count of 501,000/microL (normal 25,000 to 75,000/microL) [159]. The erythrocytes in SCD are destroyed randomly, with a mean life span of 17 days (normal: 110 to 120 days) [157,160]. Other SCD variants are less anemic with an appropriate compensated reticulocytosis. (See "Red blood cell survival: Normal values and measurement".)

A number of factors other than chronic hemolysis can contribute to the anemia. These include:

- Inappropriately low serum erythropoietin (EPO) concentrations, which may result in deficient compensation for hemolysis (ie, chronic relative reticulocytopenia, chRR) [161]. This effect is more pronounced in adults, possibly due to progressive renal disease [157,161]. However, in one study, chRR along with inappropriately low levels of EPO was found even in patients with normal serum creatinine, and was associated with a significantly increased risk of death (HR 3.60; 95% CI 2.05-6.33) [162]. Increased plasma viscosity may play a contributory role [163]. (See "Renal manifestations of sickle cell disease".)

- Folate and/or iron deficiency resulting from increased utilization of folate [164,165] and enhanced urinary losses of iron. The net effect is that iron deficiency is present in approximately 20 percent of patients with sickle cell disease [166,167]. The diagnosis of iron deficiency may be obscured by the elevated serum iron concentration associated with chronic hemolysis and the normal to increased mean corpuscular volume. A serum ferritin <25 ng/mL or an elevated serum transferrin should be used to make this diagnosis [167]. (See "Causes and diagnosis of iron deficiency anemia in the adult".)

Acute severe anemia — There are three settings in which an acute fall in hemoglobin concentration may be superimposed upon the chronic anemia: splenic sequestration crisis, aplastic crisis, and hyperhemolytic crisis. Affected patients with these complications usually present with pallor, weakness, and lethargy; fatalities are not uncommon.

Splenic sequestration crisis — With splenic sequestration crisis, vaso-occlusion within the spleen and splenic pooling of red cells produce a marked fall in hemoglobin concentration accompanied by persistent reticulocytosis and a rapidly enlarging spleen [7,168-170]. There is a risk of hypovolemic shock, particularly in children. Although primarily associated with aplastic crisis, parvovirus B19 infection may also be a risk factor for splenic sequestration [171]. (See 'Aplastic crisis' below.)

The subjects who are susceptible to this syndrome are those with SCD whose spleens have not yet undergone fibrosis secondary to multiple episodes of splenic infarction. Sequestration can occur as early as a few weeks of age and may cause death before sickle cell disease is diagnosed [172,173]. Young children with SCD have as much as a 30 percent incidence of this complication [169] and, as noted above, it is the initial symptom in as many as 20 percent of patients overall and one-third before age two [7]. In comparison, patients with HbSC disease and sickle cell-thalassemia are at a much lower risk of early-onset functional asplenia because of the lesser incidence of splenic scarring and atrophy [170].

Infants with SC disease rarely have functional asplenia. However, after age four, functional asplenia increases and reaches 45 percent of patients over 12 years of age [174]. While acute splenic sequestration crises occur in SC disease and S-Beta thalassemia, they are much less common. These patients more often develop chronic hypersplenism.

Splenic sequestration crisis is associated with a 10 to 15 percent mortality rate, occurring before transfusions can be given [168,169]. Sequestration is recurrent in 50 percent of survivors; as a result, splenectomy is usually recommended after the first acute event [169].

In a report of 15 children who underwent elective open splenectomy for recurrent acute splenic sequestration crisis, the median age at splenectomy was 5 years (range: 13 months to 15 years) [175]. No postsurgical complications were noted, and, at a median follow-up of 12 months, no child had developed bacterial infection. As had been noted by others, vasoocclusive events appeared to be more common post-splenectomy than before this procedure [176].

Aplastic crisis — An aplastic crisis is characterized by the transient arrest of erythropoiesis, leading to abrupt reductions in hemoglobin concentration and red cell precursors in the bone marrow, and a markedly reduced number of reticulocytes in the peripheral blood (ie, reticulocytes <1.0 percent and an absolute reticulocyte count <10,000 per microL). (See 'Anemia' above and "Acquired pure red cell aplasia in the adult", section on 'Presentation'.)

Impaired erythropoiesis can be associated with a variety of infections. Most cases in children follow infection with human parvovirus B19, which specifically invades proliferating erythroid progenitors [177-179]. (See "Treatment and prevention of parvovirus B19 infection", section on 'Transient aplastic crisis' and "Clinical manifestations and diagnosis of human parvovirus B19 infection", section on 'Transient aplastic crisis'.)

In one report, aplastic crisis occurred in 118 of 177 B19-infected patients [178]. Over 60 percent of the children at risk showed serologic evidence of B19 infection by age 15; the high incidence of protective antibodies following infection makes parvovirus an uncommon cause of aplasia in SCD after this age.

Other reported causes of transient aplasia are infections by Streptococcus pneumoniae, salmonella, streptococci, and Epstein-Barr virus [180,181]. Affected patients require acute transfusion therapy. Reticulocytes typically reappear within 2 to 14 days [179]. Recurrent aplasia from parvovirus is rare, presumably due to persistent immunity [177,178]. However, recurrence due to other causes is not uncommon.

Parvovirus B19 infection also may be associated with other manifestations of SCD. One study examined the risks attendant to B19 infection in a population of children with SCD in which cumulative B19 infection rates were 26, 47, and 73 percent at 5, 10, and 20 years of age, respectively [171]. When compared with 4262 acute events in children not acutely infected with B19, the 76 events in acutely B19-infected children were associated with significantly higher risks for acute splenic sequestration (relative risk [RR] 11.4), painful episodes (RR 1.9), and fever (RR 3.2).

Hyperhemolytic crisis — Hyperhemolytic crisis refers to the sudden exacerbation of anemia with reticulocytosis. This complication is rare, its cause is unknown, and some experts doubt its existence. Most such cases probably reflect occult splenic sequestration or aplastic crisis detected during a period of resolving reticulocytosis [182].

However, some episodes have been documented in multiply-transfused patients, consistent with a delayed transfusion reaction in which the patient's own cells ("bystander hemolysis"), as well as the transfused cells, were being destroyed [183-185], although the cause of this destruction is unclear [186-190]. A number of anecdotal reports have noted response of this potentially fatal complication to treatment with IV immunoglobulin (eg, 0.4 g/kg per day for five days) plus corticosteroids (eg, intravenous methylprednisolone 500 mg/day for two days) [185,186,191,192]. Rituximab has been used in hemolytic transfusion reactions with some success in sickle cell anemia [193]. (See "Transfusion-associated immune and non immune-mediated hemolysis", section on 'Hyperhemolytic crisis'.)

In addition, accelerated hemolysis has been associated with acute sickle events including acute chest syndrome and painful crises. Other causes include drug exposure, infections, and occasionally associated enzyme deficiencies. In one report, seven of eight children with hyperhemolysis had associated glucose-6-phosphate dehydrogenase deficiency [194,195], an inherited disorder found in 10 to 15 percent of African-Americans, which is usually quite mild. (See "Genetics and pathophysiology of glucose-6-phosphate dehydrogenase deficiency", section on 'G6PD A- variant'.)

ADDITIONAL INFORMATION — The Centers for Disease Control and Prevention has a website that provides additional information concerning sickle cell trait and sickle cell disease. It is available at: www.cdc.gov/ncbddd/sicklecell/index.html [196].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Sickle cell anemia (The Basics)" and "Patient information: When your child has sickle cell disease (The Basics)")

SUMMARY

- Vasoocclusive phenomena (acute painful episodes) and increased red blood cell destruction (hemolysis) are the clinical hallmarks of sickle cell disease (SCD). These phenomena result in recurrent painful episodes (previously called sickle cell crisis), a life-long transfusion requirement, and a variety of serious organ system complications that can lead to life-long disabilities and/or early death. (See 'General overview' above and "Overview of the management and prognosis of sickle cell disease", section on 'Survival and prognosis'.)
- The major clinical manifestations of SCD include painful episodes, symptomatic anemia, susceptibility to infection, stroke, cardiopulmonary complications, renal involvement, leg ulcers, and recurrent priapism in males. (See 'Major clinical manifestations' above.)
- SCD is associated with a mild to moderate anemia, reticulocytosis of 3 to 15 percent, unconjugated hyperbilirubinemia, elevated serum lactate dehydrogenase, and low serum haptoglobin. The peripheral blood smear reveals sickled red cells, polychromasia due to increased reticulocytes, and Howell-Jolly bodies reflecting hyposplenia secondary to repeated splenic infarctions (picture 1). (See 'Laboratory findings' above and "Diagnosis of sickle cell disorders".)
- Management of the complications of SCD is discussed separately. (See "Overview of the management and prognosis of sickle cell disease".)

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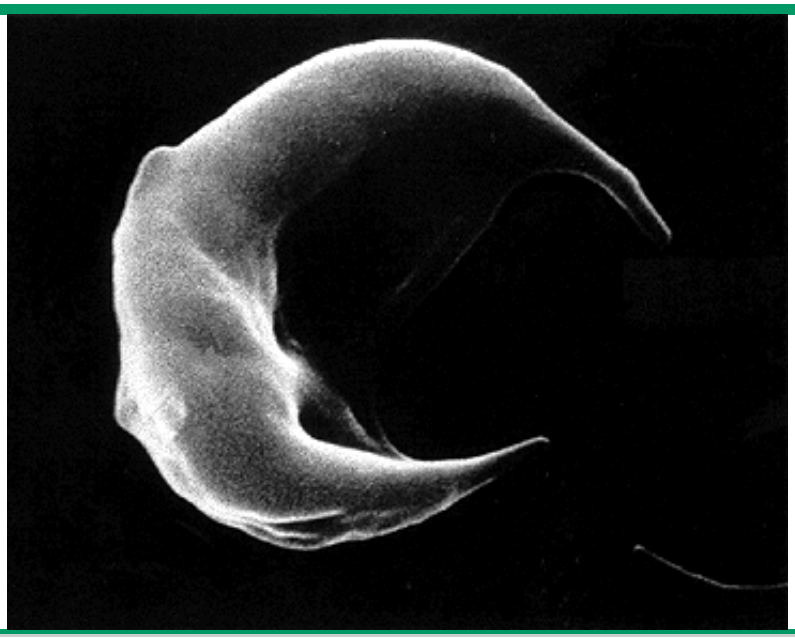
Topic 7119 Version 28.0

GRAPHICS

Sickle cell by scanning electron micrography (scanning EM)

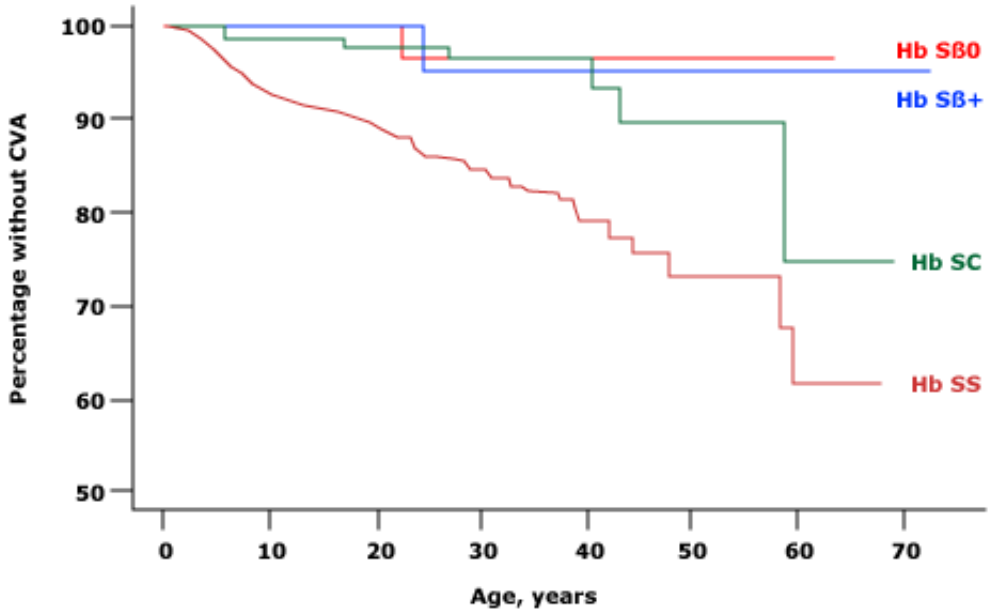


Scanning electron micrograph of a single red blood cell from a patient with sickle cell disease, illustrating the classical "sickle" shape.

Courtesy of RL Nagel, MD.

Graphic 77366 Version 3.0

Cerebrovascular accidents in sickle cell disease and its variants

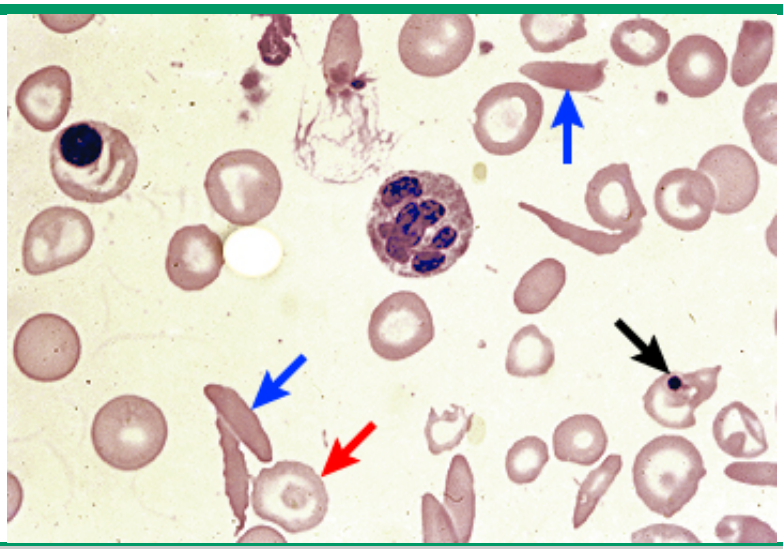


Age at first cerebrovascular accident (CVA) and cumulative incidence of CVA in 2436 patients with sickle cell anemia (Hb SS), 839 with Hb SC disease, 188 with Hb S-beta (0) thalassemia, and 184 with Hb S-beta (+) thalassemia. Cerebrovascular accidents occurred earlier and more frequently with age in patients with Hb SS.

Adapted from Ohene-Frempong, K, Weiner, SJ, Sleeper, LA, et al, Blood 1998; 91:288.

Graphic 61397 Version 2.0

Peripheral blood smear in sickle cell anemia

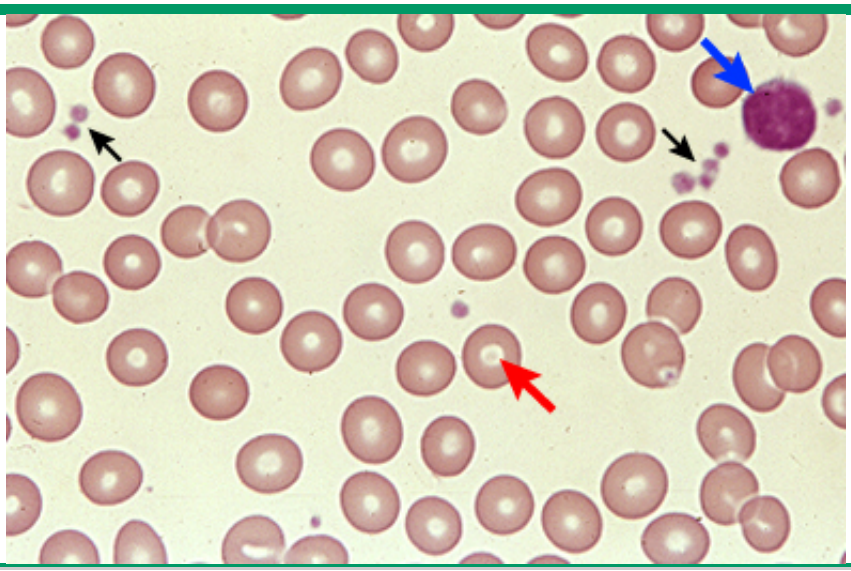


Peripheral blood smear from a patient with sickle cell anemia. This smear shows multiple sickle cells (blue arrows). There are also findings consistent with functional asplenia, including a nucleated red blood cell (upper left), a red blood cell containing a Howell-Jolly body (black arrow), and target cells (red arrow).

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 64449 Version 8.0

Normal peripheral blood smear

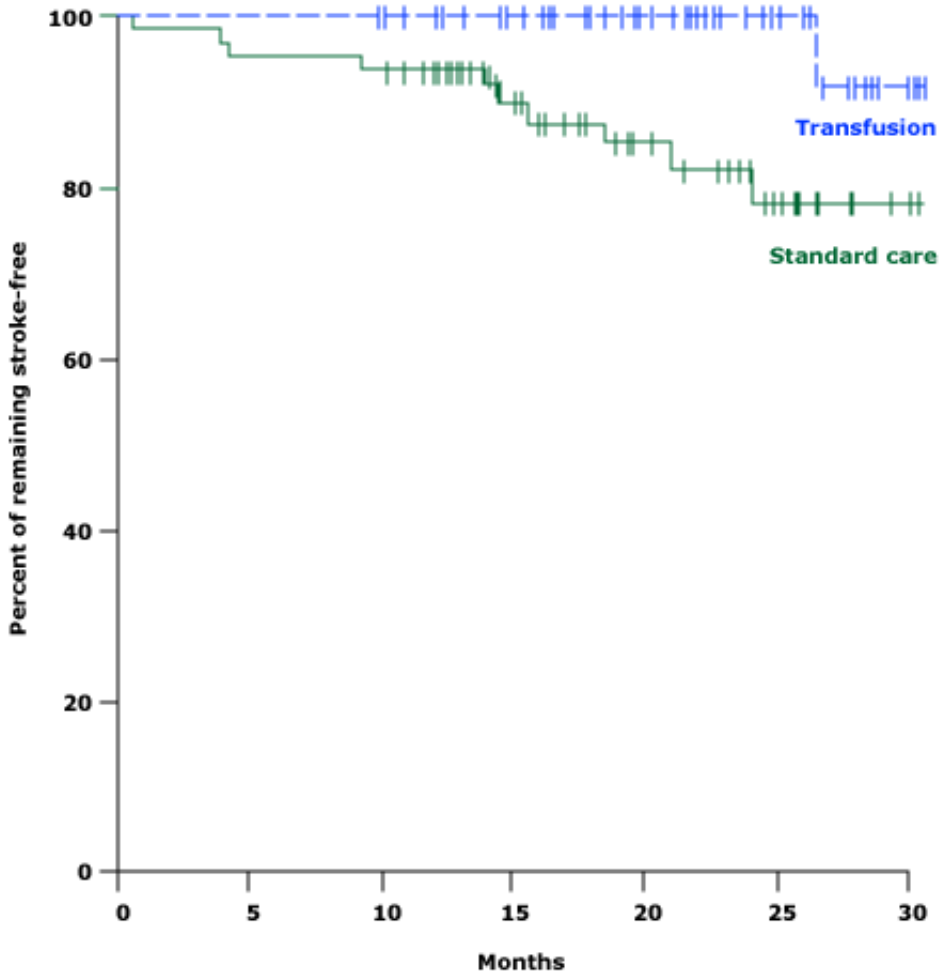


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Blood transfusion prevents first stroke in sickle cell anemia



Kaplan-Meier estimate of the probability of not having a stroke among 130 patients with sickle cell anemia at high risk of stroke as determined by transcranial Doppler; the patients were randomized to chronic long-term transfusion therapy or standard care. There was a significant benefit from transfusion therapy ($p = 0.02$). One patient in the standard-care group who had an intracerebral hematoma was excluded. The tick marks represent the lengths of observation in patients who did not have a stroke.

Data from Adams, RJ, McKie, VC, Hsu, L, et al, N Engl J Med 1998; 339:5.

Graphic 57656 Version 1.0

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Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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