Overview of the management and prognosis of sickle cell disease

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INTRODUCTION — Vasoocclusive phenomena and hemolysis are the clinical hallmarks of sickle cell disease (SCD). 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 even death. Hemolysis of red blood cells (RBC) causes chronic anemia and pigment gallstones. (See "Overview of the clinical manifestations of sickle cell disease".)

There are multiple components to the management of SCD, including the prevention and treatment of the complications of SCD, as well as the potential cure for this illness:

●**Prevention of complications** – Primary prevention of the acute complications of SCD includes routine health management with a hematologist or a health care provider with expertise in SCD. Initial prevention of complications includes the use of penicillin prophylaxis started in the newborn period, appropriate immunizations, and blood transfusions for those at risk for stroke. (See 'Infection prevention' below.)

The only US Food and Drug Administration approved therapy to prevent pain episodes in SCD is the use of hydroxyurea to reduce sickle hemoglobin polymerization process by increasing the production of fetal hemoglobin [1]. This important component of the management of SCD is discussed separately. (See "Hydroxyurea use in sickle cell disease".)

●**Treatment of complications** – Several treatments are available for the complications of SCD, such as pain medications for vasoocclusive events and antibiotics for infection.

●**Cure** – A life-long cure for SCD is available only through hematopoietic cell transplantation. However, this treatment is primarily limited to individuals under 16 years of age due to the risk of severe toxicities and death among individuals >16 years of age with an HLA-matched sibling transplant. This issue is discussed in detail separately. (See "Hematopoietic cell transplantation in sickle cell disease".)

This topic review will focus on the general principles of management of SCD (eg, infection prevention, nutrition, pain management) and on prognosis [2]. Other important management issues are presented separately, as follows:

- Acute chest syndrome – (See "The acute chest syndrome in children and adolescents with sickle cell disease" and "Acute chest syndrome in adults with sickle cell disease".)
- Bone and joint complications – (See "Bone and joint complications in sickle cell disease".)
- Cerebrovascular disease – (See "Acute stroke in sickle cell disease".)
- Children – (See "Routine comprehensive care for children with sickle cell disease".)
- Fever – (See "Management of fever in sickle cell disease".)
- Hepatic disease – (See "Hepatic manifestations of sickle cell disease".)
- Pain management – (See "Vasoocclusive pain management in sickle cell disease".)
- Pregnancy – (See "Pregnancy in women with sickle cell disease".)
- Prenatal testing – (See "Prenatal screening and testing for hemoglobinopathy".)
- Priapism – (See "Diagnosis and management of priapism in sickle cell disease".)
- Pulmonary complications – (See "Overview of the pulmonary complications of sickle cell disease".)
- Pulmonary hypertension – (See "Pulmonary hypertension associated with sickle cell disease".)
- Renal manifestations – (See "Renal manifestations of sickle cell disease".)
- Transfusion – (See "Red blood cell transfusion in sickle cell disease".)

GENERAL PRINCIPLES AND GUIDELINES — Individuals with SCD should be seen regularly by the clinician and treatment team as part of a comprehensive health care maintenance program [3]. Routine office visits are used to educate the affected individual and family about SCD, infection prevention, pain management strategies, and anticipatory guidance for possible complications (eg, splenic sequestration, avascular necrosis of the femoral head, stroke, leg ulcers). Education regarding the nature of the disease, genetic counseling, and psychosocial assessments of individuals and their families are also best accomplished during these visits, reinforced, when possible, with telephone-based outreach programs [4,5].

In addition, obtaining steady state laboratory values (eg, hemoglobin, reticulocyte count, white blood cell count, pulse oximetry readings) during routine visits will provide standards for comparison during clinical exacerbations, because these values are often abnormal at baseline. A comprehensive health care maintenance program for SCD individuals should include the components discussed below [6,7]. (See 'Routine evaluations and treatments' below and 'Nutrition' below and 'Infection prevention' below.)

Evidence-based recommendations for the management of SCD were published in 2014 by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) and endorsed by a number of societies including the American Academy of Pediatrics and the American Society of Hematology; these are available on the NHLBI website and in summary form [8,9]. Recommendations are largely consistent with those presented here. This NIH guideline updates a number of recommendations made in an earlier NIH guideline from 2004 [10].

A Centers for Disease Control and Prevention website (www.cdc.gov/ncbddd/sicklecell/index.html) also provides information on SCD [11].

INFECTION PREVENTION

Overview — Individuals with SCD are highly susceptible to bacterial and viral infections, largely due to functional asplenia that develops early in childhood. Their clinical course from these

infections is often more severe than individuals without SCD. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Infection'.)

The two major measures for preventing infection in individuals with SCD are immunization for all patients, and prophylactic penicillin for all young children (eg, <5 years of age) [8]. A review of the patient's immunizations should be performed at every medical contact to ensure that they are up to date, and parents of young children should confirm that prophylactic penicillin is being used appropriately. Infection prevention in those with variant sickle cell syndromes (eg, hemoglobin SC, sickle cell-beta thalassemia) depends on the degree of functional asplenia. (See 'Immunizations' below and 'Prophylactic penicillin' below and 'Variant sickle cell syndromes' below.)

Parents of infants and children with SCD should also be instructed regarding early recognition of infection, which may present with isolated fever. A formal plan should be created for seeking medical attention for a predetermined elevated temperature (>38.5°C or >101.5°F), and a strategy discussed regarding plans in case a fever develops during travel or when visiting with family members who may not be familiar with the routine. Adults should also have a clear plan for seeking medical attention for signs of infection. Fever should be considered a **medical emergency** requiring prompt medical attention, blood culture, and treatment with antibiotics. This important issue is discussed separately. (See "Management of fever in sickle cell disease".)

Immunizations — Immunizations are a cornerstone of infection prevention in SCD. Children with SCD should receive all routinely recommended childhood vaccines, including those against *Streptococcus pneumoniae*, seasonal influenza, *Neisseria meningitidis*, *Haemophilus influenzae* type B, and hepatitis B virus (table 1) [12-17]. When feasible, antibiotic prophylaxis of individuals with SCD who are household contacts of persons with these infections may be indicated.

Data from a large randomized trial of hydroxyurea use (the BABY HUG trial) are reassuring that the use of hydroxyurea does not interfere with the response to immunizations [18].

Pneumococcal disease — Vaccination has led to a decrease in the incidence of invasive pneumococcal disease in children with SCD [17,19,20]. In the United States, both a 13-valent pneumococcal conjugate vaccine (PCV13, which has replaced the 7-valent conjugate vaccine [PCV7]) and a 23-valent pneumococcal polysaccharide vaccine (PPSV23) are available. All children with SCD should be immunized with both PCV13 and PPSV23. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children".)

Administration of both the conjugate and polysaccharide vaccine provides protection at the earliest possible age and subsequently broadens protection against most of the invasive pneumococcal serotypes [13]. The pneumococcal conjugate vaccine (PCV13 or, if not available, PCV7) can be administered as early as six weeks of age and elicits an effective immunologic response during the first two years of life. The pneumococcal polysaccharide vaccine (PPSV23) includes a greater number of serotypes but is not immunogenic in children younger than two years of age. Penicillin prophylaxis does not appear to interfere with an IgG response to immunization [15].

In the United States, we recommend administering both the conjugate and the polysaccharide vaccines using the American Academy of Pediatrics (AAP) guideline as follows (table 2 and table 3) [21,22]:

●The pneumococcal **conjugate** vaccine (PCV13) is administered as four doses before 23 months of age on the same schedule as is routinely given to all children. The first three doses are administered at two, four, and six months of age. The first dose can be given as early as six weeks of age. A minimum of four weeks between the three doses is acceptable. The fourth dose should be given at 12 to 15 months of age but at least two months after the third dose. Children who had been fully immunized with PCV7 should receive a supplemental dose of PCV13 [23].

●The pneumococcal **polysaccharide** vaccine (PPSV23) is given as two doses: the first dose at 24 months of age (at least eight weeks after the last dose of PCV13). A second dose three to five years after the first dose of the pneumococcal polysaccharide vaccine also is recommended; this was used in clinical trials, and probably provides additional protection [24]. In patients younger than five years of age who did not receive the full complement of pneumococcal immunization based upon the above schedule, catch-up doses of vaccines should be given. The timing and number of doses depend upon the number of total doses of the conjugate and/or polysaccharide vaccines that have been given by five years of age [22]. (See "Pneumococcal (Streptococcus pneumoniae) conjugate vaccines in children", section on 'Vaccine schedule'.)

Recommendations for functionally asplenic adults are presented separately. (See "Prevention of sepsis in the asplenic patient", section on 'Adults'.)

Influenza — Annual seasonal influenza vaccination is recommended for all individuals with SCD. Vaccination should be administered annually at the start of the flu season, beginning at six months of age. Individuals with SCD should receive that inactivated vaccine rather than the live-attenuated vaccine because of the increased risk of severe or complicated infection (table 4). (See "Seasonal influenza in children: Prevention with vaccines" and "Seasonal influenza vaccination in adults".)

Standard influenza vaccination is also protective against the H1N1 strain of influenza. (See "Treatment and prevention of pandemic H1N1 influenza ('swine influenza')".)

Analysis of Healthcare Cost and Utilization Project (HCUP) 2003 to 2005 state inpatient data indicated that although children with SCD were hospitalized for influenza 56 times more often than those without SCD, neither the length nor cost of hospitalization differed [25]. Therefore, effective influenza vaccination may decrease the hospitalization rate by decreasing the number of febrile episodes that require evaluation and treatment. (See "Prevention of sepsis in the asplenic patient", section on 'Influenza vaccine'.)

Meningococcus — In the United States, early meningococcal vaccination is recommended for all asplenic children, including those with SCD. A two-dose series of quadrivalent meningococcal conjugate vaccine (MCV4; Menactra or Menveo) may be given at least two months apart, starting between 2 and 10 years of age (table 5) [26]. A single booster dose of MCV4 is advised every five years thereafter. Children aged ≥10 years should receive the serogroup B meningococcal (MenB) vaccine. The efficacy of the meningococcal vaccines in asplenic children has not been clearly established, but they are used for this group because they are at increased risk for meningococcal infections. Other details regarding meningococcal vaccination are discussed separately. (See "Meningococcal vaccines".)

Other standard vaccinations — Children with SCD should receive all standard childhood vaccinations, including those against hepatitis A and B; measles, mumps, and rubella; varicella; rotavirus; *Haemophilus influenzae*; tetanus, diphtheria, and pertussis; and poliovirus in countries where it is still endemic (table 1). (See "Hepatitis B virus vaccination" and "Standard immunizations for children and adolescents" and "Rotavirus vaccines for infants" and "Prevention of Haemophilus influenzae type b infection" and "Poliovirus vaccination".)

Most of these vaccinations should be updated periodically during adulthood, according to the recommendations of the Centers for Disease Control (table 1) or other national regulatory agency. Inactivated virus vaccines are preferred. (See "Approach to immunizations in healthy adults".)

Prophylactic penicillin — Prophylactic penicillin should be given to all individuals with SCD at least until age five [8,10]. The dose from age three months to three years is 125 mg penicillin V orally twice daily, and at age three years this should be increased to 250 mg twice daily until the age of five [24,27]. (See "Prevention of sepsis in the asplenic patient", section on 'Antibiotic prophylaxis'.)

After the age of five years, some parents, with consultation of their clinicians, elect to stop penicillin prophylaxis, while others will continue [28]. This is an important issue given the lifelong persistence of splenic dysfunction starting in late childhood and continuing through adulthood. Patients and families should be reminded that fever is a medical emergency for a patient with SCD, regardless of whether they are taking penicillin.

Patients with penicillin allergies should receive prophylactic erythromycin BID. Other alternative antibiotic choices for penicillin-allergic individuals are discussed separately. (See "Prevention of sepsis in the asplenic patient", section on 'Antibiotic prophylaxis'.)

The benefit of prophylactic penicillin has been demonstrated in two large randomized trials [29,30]. A 2012 Cochrane review of these trials included data from 457 patients with SCD [31]. As compared with no treatment or placebo, penicillin prophylaxis was associated with a decreased risk of pneumococcal infection (odds ratio 0.37; 95% CI 0.16-0.86) and a decreased risk of death (odds ratio 0.11; 95% CI 0.01-2.11). Adverse effects were minimal. Further discussion of these trials and related issues, such as penicillin resistance and country-specific guidelines, is presented elsewhere. (See "Prevention of sepsis in the asplenic patient", section on 'Antibiotic prophylaxis'.)

A randomized trial directly evaluated the safety of stopping penicillin prophylaxis in 400 children with SCD who had received penicillin prophylaxis for at least two years immediately before their fifth birthdays and had received the 23-valent pneumococcal vaccine between two and three years of age, and again at the time of randomization (ie, had received optimal prophylaxis) [24]. The incidence of systemic pneumococcal infection during 3.2 years of follow-up was very low and not significantly different in those receiving placebo or continued penicillin prophylaxis (2 versus 1 percent).

The decision of whether to continue antibiotic prophylaxis after age five must be made on a case-by-case basis. Based upon the above data, many pediatric clinicians elect to stop prophylaxis if the child has not had a prior severe pneumococcal infection or splenectomy and is receiving comprehensive care, including administration of the pneumococcal polysaccharide vaccine (PPSV23) [8,28]. However, others will continue penicillin prophylaxis through adulthood

because of the lifelong risk of pneumococcal infection, including infection with pneumococcal disease with serotypes not included in the vaccines [32]. (See 'Pneumococcal disease' above.) Regardless of the decision, careful monitoring should be continued because fever is a life-threatening condition among individuals with SCD. Pneumococcal sepsis does occur in children taking penicillin who have received the pneumococcal vaccine, and factors affecting adequacy of pneumococcal prophylaxis should be explored [33,34]. As an example, publicly insured children with SCD often receive inadequate antibiotic prophylaxis. In a review of Washington State and Tennessee Medicaid programs, the average SCD patient was dispensed only 148 days of prophylactic medication per year [35]. Efforts to improve penicillin access should therefore be investigated. (See "Management of fever in sickle cell disease".)

Variant sickle cell syndromes — Compared with patients with SCD (ie, hemoglobin SS [Hb SS]), those with variant sickle cell syndromes (hemoglobin SC, sickle cell-beta thalassemia) may have reduced susceptibility to serious infections, depending on the disease severity. The risk of infection is proportional to disease severity due to the resulting effect on splenic function.

●**Hb SC** – Those with HbSC disease are less likely to develop invasive bacterial infection than those with HbSS [36-38], because they maintain some splenic function during early childhood [39]. In addition, patients with HbSC who develop bacteremia are less likely to develop sepsis and septic shock [36,38]. Although there are case reports of fatal bacterial infection in children with HbSC disease [40], the risk of death due to overwhelming sepsis is significantly lower than that of patients with HbSS. While routine childhood immunizations and a clear plan for seeking medical therapy for any febrile episode are important, individuals with HbSC are not routinely prescribed prophylactic penicillin [38].

●**Sickle cell-beta thalassemia** – Among patients with sickle cell-beta thalassemia, severity of the disease varies with the production of hemoglobin A (HbA), and management varies accordingly:

•Patients with sickle cell-beta^0 thalassemia (HbS-beta^0 thalassemia) have a clinical course similar to patients with HbSS disease, with development of functional asplenia early in childhood and a similar risk of invasive bacterial infection. As a result, their infection prevention strategy should be the same as those with HbSS, including immunizations, prophylactic penicillin, and empiric antibiotic therapy when they are febrile.

•Patients with sickle cell-beta$^+$ thalassemia (HbS-beta$^+$ thalassemia) produce variable amounts of HbA and in general have less severe SCD complications, although limited data are available regarding their risk of infection [38]. In general, they are treated in a manner similar to those with HbSC.

INFECTION MANAGEMENT — Infection is a frequent complication of SCD, and historically it has been the major cause of death in children. Fever may be the first indication of a serious bacterial infection, and as such should be considered a **medical emergency**. Patients should seek prompt medical attention and be rapidly evaluated for a temperature >38.5°C (101.5°F). The evaluation should include a brief history for localizing symptoms and an abbreviated physical examination focused on hemodynamic stability, signs of localized or generalized infection, splenic size, and evidence of stroke.

Blood cultures and complete blood count with differential and reticulocyte count should be obtained. Empiric parenteral antibiotics should be started as soon as possible, ideally within 60

minutes of triage. Evaluation for pneumonia is important [41]; however, antibiotics should not be delayed while awaiting chest radiography. The important issue of infection management in individuals with SCD is discussed in detail separately. (See "Management of fever in sickle cell disease".)

LEG ULCERS — The clinical characteristics and natural history of skin ulcers in individuals with SCD differ from those seen in individuals with other hemolytic anemias. Severe pain at the wound site is disproportionately greater in SCD than in other populations. Animal models support this observation.

The best approach to leg ulcers is prevention, which includes attention to properly fitting shoes and immediate treatment for early signs of skin injury. (See "Basic principles of wound management".)

If a patient develops a leg ulcer, we routinely use lower extremity Doppler to evaluate for deep vein thrombosis (DVT). Forty-four percent of leg ulcers in patients with SCD are associated with a DVT, likely due to lower extremity edema [42]. In addition, since pulmonary hypertension is associated with the development of lower extremity ulcers, we evaluate for pulmonary hypertension with a transthoracic Doppler echocardiography and obtain a complete blood count (CBC), lactate dehydrogenase (LDH) level, and serum chemistries. We do not routinely evaluate for peripheral vascular disease with ankle brachial pressure index or for osteomyelitis, unless there is clinical suspicion.

Management of large skin ulcers requires a multidisciplinary team. Although many systemic and local therapies have been examined, the mainstays of therapy are wound care, compression, and SCD-based therapy with hydroxyurea or chronic transfusion. Components of management may include the following [43-47]:

●Immediate attention to the pain. Many providers use systemic opioids. Topical opioids also have been examined and found to relieve pain and facilitate healing [48,49]. Topical opioids also decrease local fluid extravasation.

●Local edema must be minimized with rest, lower extremity elevation, and compression bandages. In some cases diuresis is also appropriate. Coban compression may be more beneficial than Unna boots.

●We have found bedrest, though difficult to comply with, is essential for healing of large and/or recalcitrant ulcers [50,51].

●Therapeutic debridement is important in order to remove fibrotic tissue and stimulate healing. In general, we initially refer the patient to a wound care specialist for debridement, dressing changes and, if necessary, topical antibiotics [52]. Wet to dry dressings and Duoderm hydrocolloid dressings may also facilitate healing.

●Infections require treatment, but antibiotics are often not helpful and should be used appropriately.

●In our experience, repeated transfusion therapy accelerates wound healing and is often a core therapy [53]. Alternatively, hydroxyurea may be beneficial, even though hydroxyurea-related skin ulcers have been reported. Patients can be managed initially with hydroxyurea and transitioned to chronic transfusion, or treated with chronic transfusion initially, depending on other comorbidities and patient factors.

●Grafts may be necessary, but they have a very high failure rate and should be used conservatively [54].

These therapies are discussed in more detail separately. (See "Overview of treatment of chronic wounds".)

In addition to the specific therapies listed above, many patients with SCD and skin ulcers have multiple other problems that impair wound healing, including malnutrition, vitamin D and nutritional deficiencies, pulmonary hypertension, and depression. These co-founding factors also need to be addressed.

There are multiple therapies that may be beneficial but remain unproven, including Apligraf (a skin equivalent), topical sodium nitrite 2% cream, RGD peptide dressings, and topical Timolol [55-58]. We do not routinely use these therapies, but rely on pain relief, bedrest, transfusion therapy, local wound care, and when necessary, consultation with chronic ulcer programs.

NUTRITION — There are few prospective data regarding clinical benefit of nutritional interventions that can be used to guide nutritional management in patients with SCD. However, growing evidence suggests that these individuals have vitamin and micronutrient deficiencies that may influence the course of their disease [59-63]. We therefore use the following in our patients:

●Folic acid is given to all individuals in an oral dose of 1 mg daily. However, some clinicians may reasonably omit folic acid supplementation for patients who have sufficient dietary intake, especially in settings where grains and cereals are routinely supplemented. Folate deficiency has been found in several observational studies of patients with SCD [62,64-67]. Increased folate consumption from ongoing hemolytic anemia is often proposed as a rationale for the use of folic acid in these patients. However, there are no data that folic acid supplementation increases the hematocrit in individuals with SCD; a randomized trial of folic acid supplementation in 117 children with SCD showed that compared with controls, those receiving folic acid did not show an improvement in hemoglobin levels or growth characteristics but did have a decrease in mean cell volume and less dactylitis [65]. Despite this, we believe that the potential yet unknown benefit from folic acid supplementation outweighs the potential harms.

●We use a daily multivitamin **without** iron for all of our patients. This replaces some of the vitamins and micronutrients commonly reported to be deficient in these individuals, including zinc, vitamin D, vitamin E, vitamin C, vitamin A, magnesium, selenium, carotenoids, and flavonoids [59-62]. Excessive iron stores and oxidative injury may contribute to the depletion of antioxidant vitamins.

●We screen all infants with SCD for risk factors for iron deficiency, including those not receiving transfusions, during the first two years of life. We also use laboratory screening at one year of age, as advised by the American Academy of Pediatrics (AAP). All children with SCD who have evidence of iron deficiency anemia should be treated because iron deficiency has a negative effect on neurodevelopment. (See "Iron deficiency in infants and young children: Screening, prevention, clinical manifestations, and diagnosis", section on 'Screening recommendations'.)

●Non-transfused young women with risk factors for iron deficiency or those who practice breast feeding also should undergo screening and treatment. In patients with iron deficiency, it is important to establish the cause. However, in contrast with children, in adults with SCD there is a controversy surrounding management of iron deficiency since preliminary data suggest iron

deficiency may decrease polymerization of sickle hemoglobin [68,69]. (See "Causes and diagnosis of iron deficiency and iron deficiency anemia in adults" and "Sickle hemoglobin polymer: Structure and functional properties" and "Mechanisms of vasoocclusion in sickle cell disease".)

●For individuals found to be vitamin D deficient, additional supplementation with oral vitamin D and calcium is appropriate. Vitamin D deficiency is under-recognized and undertreated in the SCD population; observational studies have demonstrated that a majority of children with SCD are vitamin D deficient and have inadequate calcium intake [70,71]. These deficiencies may contribute to osteopenia and osteoporosis, which affect up to 80 percent of patients with SCD. There is also an incompletely understood relationship between vitamin D deficiency and chronic pain in children with SCD [71,72].

ROUTINE EVALUATIONS AND TREATMENTS — Routine evaluations and associated treatments of individuals with SCD are extensive [3]. While the following list serves as a guideline for screening, it is important to adopt a comprehensive approach that can be followed by the patient. The transition from pediatric to adult providers can be associated with lapses in care, and this is an important time to ensure that routine evaluations have been performed. We screen for the following:

●**Hypertension** – Blood pressure screening should be done at every visit. Early treatment of systemic hypertension is critical because mild elevations in blood pressure are associated with an increased risk of overt stroke and silent cerebral infarct in individuals with SCD [73,74]. (See "Overview of hypertension in adults" and "Choice of drug therapy in primary (essential) hypertension".)

●**Cerebral complications** – In children ≤16 years of age with hemoglobin SS or hemoglobin S-beta thalassemia that produces no hemoglobin A, referred to as S beta thalassemia zero, cerebral blood flow should be evaluated by transcranial Doppler (TCD) annually, because children at risk for strokes can be identified with this technique and the incidence of stroke can be reduced by the use of regular blood transfusion therapy aimed at maintaining the maximum hemoglobin S level at less than 30 percent [75]. (See "Prevention of stroke (initial or recurrent) in sickle cell disease", section on 'Risk assessment for first stroke'.)

We also screen individuals with any sign of cognitive/neurologic dysfunction (eg, poor school performance, headaches, concerns expressed by family members) for silent infarcts using magnetic resonance imaging (MRI), based on observations that silent infarcts correlate with cognitive deficits and these findings may identify individuals who would benefit from early interventions. (See "Prevention of stroke (initial or recurrent) in sickle cell disease", section on 'Cognitive and behavioral dysfunction'.)

In contrast, children with hemoglobin S beta[+] thalassemia and hemoglobin SC disease do not require TCD screening [10].

Optimal intervals for TCD measurements have not been formally evaluated, but TCD measurements should be started at two years of age and performed annually [8]. Serial TCD screening is recommended because normal flow velocity on a single screening does not assure a continued low risk status. Individuals with abnormal velocity on TCD should be seen by a specialist with expertise in chronic transfusion therapy and stroke prevention. These issues are discussed in detail separately. (See "Red blood cell transfusion in sickle cell disease", section

on 'Primary and secondary stroke prevention' and "Prevention of stroke (initial or recurrent) in sickle cell disease", section on 'Prevention of a first ischemic stroke (primary stroke prophylaxis)'.)

TCD measurements are lower in adults with SCD compared with children, and there is no evidence to suggest that TCD velocities are predictive of stroke risk in adults. We do not recommend TCD screening in individuals >16 years of age [76,77]. (See "Prevention of stroke (initial or recurrent) in sickle cell disease", section on 'Risk assessment for first stroke'.)

●**Retinopathy** – Retinal evaluation is begun at 10 years of age and continued routinely to detect early proliferative sickle retinopathy [8,10]. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Retinopathy'.)

●**Asthma/obstructive lung disease** – Asthma is common in children with SCD. We perform a baseline pulmonary evaluation that includes at least assessment of severe recurrent wheezing [78], shortness of breath with exercise, or persistent cough as part of routine review of systems with ongoing health maintenance visits. We also perform spirometry in asymptomatic children in intervals of one to two years, starting when they are able to perform the spirometry and continuing until adulthood. (See "Overview of the pulmonary complications of sickle cell disease", section on 'Children'.)

For individuals with a positive history or abnormal spirometry results, we perform spirometry at least annually, and more frequently if respiratory symptoms change. For individuals with evidence of respiratory symptoms, but no obstruction on pulmonary function testing, we may also measure lung volumes. (See "Overview of the pulmonary complications of sickle cell disease" and "Overview of pulmonary function testing in adults", section on 'Lung volumes'.)

●**Pulmonary hypertension (PH)** – We take a thorough history of respiratory symptoms in all patients. For **symptomatic** patients, we have a low threshold for evaluation of PH risk. It is important to note that symptoms of PH are variable; patients may report chronic dyspnea, chest pain, presyncope, or exercise intolerance; or they may gradually limit activities without recognizing specific symptoms. Details of the evaluation of symptomatic patients are presented separately. (See "Pulmonary hypertension associated with sickle cell disease", section on 'Evaluation for PH'.)

It is also important to note that children presenting with acute or chronic respiratory symptoms should be evaluated for more common conditions, such as asthma and acute chest syndrome, in addition to evaluation for PH. (See "The acute chest syndrome in children and adolescents with sickle cell disease" and "Overview of the pulmonary complications of sickle cell disease".)

For patients who are truly **asymptomatic**, clinical judgment is required to determine the optimal screening approach [8,10]:

•**Children** – We prefer to wait until late adolescence, early adulthood, or the development of symptoms before initiating screening of **asymptomatic** children for PH [8]. The rationale includes a lack of data showing a morbidity or mortality benefit from detecting an elevated tricuspid jet regurgitant velocity by echocardiography in children; the burden and cost of increased screening for some patients; the potential risks of subsequent invasive testing; and

concerns that the measurement of elevated tricuspid jet regurgitant velocity in children may not be reliable [79,80]. Additional concerns include the relative priority of this screening amongst the large number of other testing required, which may be burdensome and expensive for the patient and family. Other UpToDate authors prefer to screen children with a one-time transthoracic Doppler echocardiogram for estimation of pulmonary artery systolic pressure between ages 8 and 18, consistent with an American Thoracic Society practice guideline [79]. This practice is discussed in more detail separately. (See "Pulmonary hypertension associated with sickle cell disease", section on 'Screening and risk stratification'.)

•**Adults** – Approaches to screening **asymptomatic** adults differ slightly among authors of this topic. Some (MRD) generally perform initial screening with Doppler echocardiography once during early adulthood, and repeat this testing more frequently if findings are abnormal or if symptoms develop. Others (JJF) perform transthoracic Doppler echocardiography and N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) measurement every one to three years, consistent with practices outlined in an American Thoracic Society practice guideline [79].

Of note, an elevated tricuspid regurgitant jet velocity on echocardiographic screening may be a marker of risk for conditions other than PH, including venous thromboembolic disease and disordered sleep breathing [79]. Details of the management of patients with abnormal findings from non-invasive screening, which may include additional screening, supplemental oxygen, diuretics, escalation of hydroxyurea therapy, anticoagulation, and/or pulmonary vasodilator therapy, are presented separately. (See "Pulmonary hypertension associated with sickle cell disease" and "Overview of the pulmonary complications of sickle cell disease".)

●**Priapism** – It is appropriate to ask male patients about a possible history of priapism, which is usually not volunteered because of the sensitivity of the issue. (See "Diagnosis and management of priapism in sickle cell disease".)

●**Renal disease** – Identifying renal disease is important because individuals with sickle cell disease hyperexcrete creatinine, which may mask renal impairment; however, high quality evidence for the optimal screening is lacking. Renal function can be assessed with a chemistry panel including creatinine and a urine for proteinuria and/or albuminuria. Evaluation is initiated often by age three to five or no later than the age of 10 years; adults are monitored at regular visits, typically four to six times per year [8,10]. Individuals receiving an iron chelator may require more frequent monitoring. Abnormal findings are evaluated further, as discussed separately. (See "Renal manifestations of sickle cell disease" and "Evaluation of proteinuria in children" and "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults".)

●**Hepatitis C virus** – We screen for hepatitis C virus, as discussed in detail separately. (See "Screening for chronic hepatitis C virus infection".)

●**Birth control and family planning** – We assess family planning and birth control needs in all adults and in adolescents in an age-appropriate manner, with ongoing discussion of options. (See "Prenatal screening and testing for hemoglobinopathy" and "Pregnancy in women with sickle cell disease".)

Pre-conception counseling and screening for red blood cell alloantibodies is provided to individuals of childbearing age who are planning a pregnancy [8,10]. Referral of a partner of

unknown SCD status for hemoglobinopathy screening is appropriate prior to conception. (See "Pregnancy in women with sickle cell disease".)

●**Stress and depression** – Patients should have ongoing assessment of psychological well-being; depression is a serious component of chronic disease. At least annual screening for depression and, when appropriate, therapy should be considered, along with an annual screening for neurocognitive deficits that may impair decision making and complex problem solving. In high risk individuals, such as those with major school difficulties or signs of neurocognitive dysfunction, detailed neurocognitive testing is advised. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'General medical illness'.)

●**Leg ulcers** – Evaluation for leg ulcers and education concerning their prevention are important, particularly in areas with warm climates. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Leg ulcers'.)

●**Bone health** – We assess contributors to bone health including calcium intake, vitamin D status, and bone density at 12 years of age, and perform a screening physical exam for avascular necrosis [70,81]. We repeat vitamin D screening annually and bone density testing every one to three years. (See "Bone and joint complications in sickle cell disease".)

●**Growth** – We measure height and weight in children and adolescents, and weight in adults, because children with SCD may show delayed growth trajectories [82]. If children have decreased growth trajectories, we evaluate nutritional and environmental factors as potential contributors. Growth disturbances are common in sickle cell disease and have multiple etiologies that can be corrected. Correction of nutritional deficiencies may be beneficial, particularly zinc, which is associated with improved linear growth and weight gain [83]. An increased metabolic rate resulting in elevated resting energy expenditure and increased caloric requirements is common and may be improved by caloric intake or decreasing energy expenditures [84-86]. Transfusion therapy or hydroxyurea decreases metabolic rate and improves growth. Finally, monitoring growth and weight velocity may uncover growth hormone disturbances, which are responsive to growth hormone replacement [87]. In general, we watch closely before we initiate a more extensive evaluation because of the known rate delayed maturation.

These routine evaluations and treatments should be tailored for individual patients when co-morbidities are present (eg, chronic renal insufficiency, interstitial lung disease). This is especially true for adults with SCD, as end-organ dysfunction is prevalent.

HYDROXYUREA — The use of hydroxyurea is a **mainstay** in the overall management of individuals with SCD, since it reduces the incidence of acute painful episodes and hospitalization rates, and prolongs survival. This important subject is discussed in detail separately. (See "Hydroxyurea use in sickle cell disease".)

HEMATOPOIETIC CELL TRANSPLANTATION — Hematopoietic cell transplantation (HCT) is the only available curative option in individuals with SCD, and a discussion of the risks and benefits of HCT should be offered to all individuals with SCD. This important issue is discussed in detail separately. (See "Hematopoietic cell transplantation in sickle cell disease".)

BLOOD TRANSFUSION — Blood transfusions are used to treat and prevent complications of SCD, including preparation for surgery; treatment of symptomatic anemia, acute stroke, multiorgan failure, and acute chest syndrome; and prevention of stroke, acute chest syndrome,

and recurrent priapism. These indications, along with practical aspects of central venous access, crossmatching, leukoreduction, simple versus exchange transfusion, and management of excess iron stores, are discussed in detail separately. (See "Red blood cell transfusion in sickle cell disease".)

PAIN MANAGEMENT — Acute vasoocclusive pain episodes are one of the most frequent reasons for individuals with SCD to seek medical attention, and chronic pain affects a large number of these individuals. There are a number of issues related to the treatment of SCD pain that differ from other acute and chronic pain syndromes. These include common misperceptions about the severity of pain, the need for opioid analgesia for the majority of patients, the need to evaluate for SCD complications associated with pain, and the avoidance of certain medications such as meperidine and ketorolac. Blood transfusion is not used for uncomplicated pain episodes in the absence of other complications. The management of acute pain episodes, chronic pain, and opioid side effects are discussed in detail separately. (See "Vasoocclusive pain management in sickle cell disease".)

MANAGEMENT DURING HOSPITALIZATION — Individuals with SCD who are hospitalized require vigilance for many of the same conditions as those without SCD, as well as some that are specific to their disease. Management of individual complications of SCD is discussed separately. (See 'Introduction' above and 'Pain management' above.)

Inpatient management issues that should be considered regardless of the admission diagnosis include consideration of hydration status and venous thromboembolism prophylaxis, and reinstitution of prophylactic penicillin upon discharge. Hydroxyurea should be continued during hospitalization as long as there is no excess hematologic toxicity. (See "Hydroxyurea use in sickle cell disease", section on 'Hospitalization'.)

Hydration — Adequate hydration is important to reduce complications of SCD during hospitalization. The choice of replacement fluid depends on the patient's volume status and whether transfusion is required.

●For those who require transfusion (eg, acute splenic sequestration crisis, transient aplasia from infection), transfusion should not be delayed while giving other fluids. (See "Red blood cell transfusion in sickle cell disease", section on 'Symptomatic or severe anemia'.)

●If the patient is hypovolemic, normal saline (ie, 0.9 percent saline) is appropriate to maintain hemodynamic stability. (See "Treatment of severe hypovolemia or hypovolemic shock in adults" and "Treatment of hypovolemia (dehydration) in children".)

●If the patient is euvolemic and receiving maintenance intravenous fluids, we use one-quarter or one-half normal saline with or without glucose. Of note, this differs from maintenance fluid replacement in patients without SCD, who often receive normal saline. Patients with SCD may have a decreased ability to excrete sodium and may become hypernatremic from receiving normal saline. Hypernatremia in turn may lead to red blood cell dehydration, which increases sickling. (See "Maintenance fluid therapy in children" and "Maintenance and replacement fluid therapy in adults".)

●If the patient is euvolemic and able to take oral fluids adequately, this should be encouraged.

Thromboembolism prophylaxis — Patients with SCD appear to have a hypercoagulable state at baseline, and they often have other factors that further increase the risk of venous thromboembolism (VTE) (eg, indwelling catheter, immobility, infection) [88]. For all **adults** (ie,

those >18 years) with SCD who are admitted to the hospital for an acute medical condition, we recommend thromboprophylaxis with one of the following:

●One of the low molecular weight heparins (eg, enoxaparin, dalteparin, tinzaparin) at prophylactic doses

●Low dose unfractionated heparin (eg, 5000 units SQ three times a day)

●Fondaparinux (eg, 2.5 mg SQ daily)

Details regarding the choice of agent, dosing, and contraindications are discussed separately. (See "Fondaparinux: Dosing and adverse effects" and "Heparin and LMW heparin: Dosing and adverse effects" and "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults", section on 'Pharmacologic thromboprophylaxis'.)

Examples of acute medical illnesses for which VTE prophylaxis would be appropriate include pregnancy and delivery, acute pain crisis, pneumonia or other febrile illness, and priapism.

This practice is consistent with the 2008 American College of Chest Physicians (ACCP) guidelines, which recommend VTE prophylaxis for all patients admitted to the hospital with an acute medical illness [89], as well as the 2012 ACCP guidelines, which recommend thromboprophylaxis for all acutely ill hospitalized medical patients at increased risk of thrombosis [90].

In contrast, we do not use routine thromboprophylaxis for VTE in hospitalized children with SCD (ie, those less than 18 to 21 years). General recommendations regarding thromboprophylaxis in children are discussed separately. (See "Diagnosis and treatment of venous thrombosis and thromboembolism in infants and children".)

Splenic and hepatic sequestration

Overview — Splenic sequestration is a potentially life-threatening complication of SCD that requires admission to the hospital for maintenance of hemodynamic stability [91,92]. Splenic sequestration in SCD is characterized by the following four features:

●Splenic enlargement, often tender

●A drop in hemoglobin concentration of at least 2 g/dL

●Thrombocytopenia

●Reticulocytosis

Splenic sequestration is commonly observed in infants and children, including those as young as two months of age [93]. Less commonly, acute splenic sequestration episodes may occur in adolescents and adults, particularly those with SCD-SC [94,95]. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Splenic sequestration crisis'.)

The primary concern in the event of a splenic sequestration episode is hypovolemic shock resulting from a disproportionate amount of the intravascular blood volume being sequestered in the spleen because of ensnared red and white blood cells. Hence, management should be directed at maintaining the individual in a euvolemic state.

Hepatic sequestration can also occur; this complication and its management are discussed separately. (See "Hepatic manifestations of sickle cell disease", section on 'Hepatic sequestration crisis'.)

Initial management — The optimal management of an acute splenic sequestration episode in adults is based on the following principles:

●A high index of suspicion when an individual presents with a sudden drop in hemoglobin, thrombocytopenia, reticulocytosis, and an enlarged spleen.

●Assessment of volume status and immediate intravenous fluid resuscitation if needed, with the goal of maintaining the individual in a euvolemic state [8,10]. This may require administration of isotonic solution. (See 'Hydration' above.)

When the individual is hypovolemic and is symptomatic from anemia, a simple blood transfusion therapy should be considered. However, caution should be used when transfusing the individual, as the blood trapped in the spleen is still available to **re-enter** the circulation. Accordingly, following such transfusion the individual's hemoglobin may rise acutely to levels that result in hyperviscosity syndrome. (See "Red blood cell transfusion in sickle cell disease", section on 'Symptomatic or severe anemia'.)

To decrease the likelihood of hyperviscosity syndrome occurring after a simple blood transfusion, we typically transfuse the individual with approximately 50 percent of what we would commonly transfuse. Thus, instead of transfusing the adult individual with two units of blood, we transfuse a single unit of blood or calculate (and deliver) the amount of blood needed to get the individual back to his/her baseline level and re-evaluate the clinical status after transfusion. (See "Red blood cell transfusion in sickle cell disease", section on 'Risk of hyperviscosity syndrome from simple transfusion'.)

Follow-up care — The natural history of splenic sequestration in infants and toddlers with SCD is well documented, with a reasonable proportion having a second event within 12 months of the first event. In adults with SCD there are limited data to describe the risk of subsequent splenic sequestration episodes, but in general we would manage them in similar way [96].

●Future management should include education about self-palpation of the spleen and instructions on what to do in the event of an enlarging spleen.

●After consideration of risks and benefits, there should be a discussion of the potential removal of the spleen in a non-acute setting.

●Institution of regular blood transfusion therapy to prevent subsequent episodes of acute splenic episodes is not indicated and has not proven to be of benefit.

AVOIDANCE OF G-CSF — Case reports have indicated that the use of granulocyte colony-stimulating factor (G-CSF) in individuals with SCD and variant sickle cell syndromes (eg, HbSC, HbS-beta⁺thalassemia) has been associated with sickle cell crisis and multiorgan failure; at least one individual (a hematopoietic stem cell donor for a sibling) has died as a result of this complication [97-99]. G-CSF may also play a role in the acute chest syndrome and the complications associated with it [100].

We and others therefore **do not** use G-CSF administration in individuals with SCD or variant sickle cell syndromes [101,102]. However, there may be a rare case in which the potential benefits of G-CSF therapy outweigh the risks (eg, treatment of chemotherapy-induced fever with sepsis), and the judicious use of G-CSF may be justified [101,103].

In contrast to those with sickle cell syndromes, individuals with sickle cell trait may receive G-CSF [101,104]. (See "Sickle cell trait", section on 'Blood and stem cell donation'.)

SURVIVAL AND PROGNOSIS — The survival for individuals with SCD who have access to comprehensive care has improved dramatically, with the major causes of death shifting from infections to progressive end-organ damage.

Overall survival — Survival of individuals with SCD is reduced compared with those without SCD, but the prognosis for SCD has been steadily improving following the institution of comprehensive care that includes newborn screening, immunizations, antibiotics, hydroxyurea, and more rapid prevention and treatment of disease complications (eg, stroke). In regions where comprehensive care is available, the disease has shifted from a fatal pediatric illness to a chronic disease often associated with progressive deterioration in quality-of-life and organ function [105-108].

Adults — Survival well into adulthood for those with access to comprehensive care was illustrated in 2014 study involving a cohort of adult patients followed at a tertiary care medical center in the United States, in which median survival for HbSS and HbSβ^0 was 58 years, and median survival for HbSC and HbSβ$^+$ was 66 years [109]. In a 2016 study involving 712 patients followed at a tertiary center in the United Kingdom, the median survival for HbSS and HbSβ^0 was 67 years [110]. This improved survival was attributed to care at a specialist hematology clinic, inpatient management by a dedicated team, involvement of specialists in other organ systems, availability of on-site red blood cell (RBC) exchange, and a focused "transition program" to facilitate safe transition from pediatric to adult care.

Data regarding the impact of hydroxyurea on survival include the following:

●In an adult cohort study that evaluated risk factors for death in 383 adults with HbSS, hydroxyurea use was associated with improved survival (hazard ratio [HR] 0.58, 95% CI 0.34-0.97) [111]. The greatest benefit of hydroxyurea therapy was seen in the subgroup taking the recommended dose of 15 to 35 mg/kg/day (HR 0.36, 95% CI 0.17-0.73). Participants with higher fetal hemoglobin (an indication of better response to therapy or greater medication adherence) had the greatest benefit.

●In a cohort study that compared outcomes in 131 patients with SCD of various genotypes who were treated with hydroxyurea versus 199 patients who did not receive hydroxyurea, 10-year survival was 86 versus 65 percent [112].

●In the Belgian cohort discussed above, the use of hydroxyurea therapy was not associated with prolonged survival; however, the analysis only included hydroxyurea prescription, and did not take into account the hydroxyurea dose.

These data are especially impressive because in many cases the individuals treated with hydroxyurea are likely to have had more severe disease and thus would have been expected to have a **higher** overall mortality rate than those with less severe disease. Collectively, these data support the premise that at a minimum all adults with SCD who have genotypes of HbSS and HbS-beta^0 thalassemia should be treated with hydroxyurea. (See "Hydroxyurea use in sickle cell disease".)

Individuals who survive into later adulthood may have long-term disease complications not seen in younger patients. This was illustrated in a cohort of individuals who survived beyond age 60 with SCD [113]. Renal insufficiency was seen in 34 of 40 (85 percent).

Children — The mortality rate of infants and young children with SCD who have access to comprehensive care has decreased more dramatically than that of adults, in large part because of the decrease in sepsis from early use of prophylactic antibiotics and immunizations. Less dramatic decreases in the mortality rate of older children may reflect increased survival beyond infancy, lapses in care during the transition from pediatric to adult care providers, and lack of

adequate preventive measures for non-infectious complications of SCD (eg, acute chest syndrome, organ failure).

The improvements in survival for infants and young children are illustrated by the following studies:

●The Center for Disease Control and Prevention's National Center for Health Statistics analyzed trends in pediatric SCD-related mortality from 1983 through 2002 [114]. Mortality declined over the course of the study in all age cohorts, with decreases of 68, 39, and 24 percent for children aged zero to three years, four to nine years, and 10 to 14 years, respectively. By 1999 to 2002, all-cause death rates per 100,000 were as follows:

•Zero to three years – 0.78

•Four to nine years – 0.43

•Ten to 14 years – 0.44

These declines were temporally correlated with the introduction of the 7-valent pneumococcal conjugate vaccine.

●The Dallas (Texas, United States) Newborn Cohort began prospectively accruing newborns diagnosed with SCD in 1983. A 2010 report on 940 individuals with a median follow-up of 9.2 years found the following [115]:

•The incidence of death has been decreasing steadily, with death rates (deaths per 100 patient-years) of 0.67, 0.37, and 0.15 for the periods 1983 to 1990, 1991 to 1999, and 2000 to 2007, respectively.

•The estimated overall survival at 18 years was 94 percent for those with HbSS and 98 percent for those with HbSC or HbS-beta thalassemia.

•The median age of death gradually increased, from three years of age during the period 1983 to 1990, to 17 years of age during the period 2001 to 2007. All of the seven deaths since 2002 were in individuals ≥18 years of age.

Data on survival benefits related to hydroxyurea use in children include:

●In a cohort of children in Belgium with SCD who were treated with either hydroxyurea, hematopoietic stem cell transplantation, or observation, the estimated 15-year survival rates were 99, 94, and 95 percent, respectively [116].

●In a cohort of 1760 children in the Paediatric Hydroxycarbamide Program, survival was greater in the 267 who received hydroxyurea even after a median of only two years of treatment (99.5 versus 94.5 percent) [117]. The survival benefit was primarily due to fewer deaths from acute chest syndrome and infection.

Details of the use of hydroxyurea in children are discussed separately. (See "Hydroxyurea use in sickle cell disease".)

Causes of death — In regions where comprehensive care is available, the causes of death in patients with SCD have shifted following the introduction of infection prevention measures. As examples:

●In the Dallas Newborn cohort of 940 patients, acute chest syndrome and multi-organ failure have replaced bacterial sepsis as the leading causes of death [115].

●In a study that analyzed clinical and/or autopsy findings among 141 adults with SCD from 1976 to 2001, leading causes of death included pulmonary hypertension (26 percent), sudden death (23 percent), renal failure (23 percent) and infection (18 percent) [118].

●Another study that analyzed the cause of death in 209 adults with SCD found that 18 percent of deaths occurred in individuals with overt organ failure, predominantly renal [105].

In contrast, in regions of Africa where newborn screening for SCD and prophylactic antibacterials are not routinely used, infections are a leading cause of death, including bacterial sepsis and malaria [119]. Despite the protective effect of the sickle mutation against malaria, a study of 1393 children in Kenya with severe malaria reported higher mortality in children with SCD than those without SCD (death rate 80 versus 10 percent, respectively) [119].

Predictors of morbidity and mortality — Overall, markers of more severe disease tend to predict greater morbidity and mortality in individuals with SCD, although some modifiable risk factors (eg, stroke) may be declining in importance [120-122]. As examples:

●Two large comprehensive studies have demonstrated the high survival rate of children with SCD in resource-rich countries in the modern era. In a 2015 study from Belgium, 469 children with SCD were prospectively followed, many since diagnosis, for a total of over 5110 patient-years [116]. Children with more severe SCD treated with hydroxyurea had a Kaplan Meir survival estimate of 99 percent at 15 years. Similar results were seen in a 2016 study from France, in which 1033 children with SCD born between 1995 and 2009 were followed for 6776 patient-years [123]. The five-year survival was over 98 percent for the entire cohort, and over 99 percent for those born after 2006. These studies illustrate that SCD is no longer a life-threatening disease of childhood, but rather is a chronic childhood disease with life-threatening episodes.

●An attempt to identify risk factors for mortality in adults was made using computer modeling in cohort of 964 individuals with SCD, 209 of whom died [105]. Predictors of an increased risk of early death in this model included acute chest syndrome, renal failure, a baseline white blood count >15,000/microL, and a fetal hemoglobin (HbF) ≤8.6 percent. Other studies have corroborated an increased mortality rate in individuals with SCD who develop renal failure, even if they are treated with dialysis [124].

●A more sophisticated statistical model for estimating risk of death within five years was developed using clinical and laboratory data from 2280 patients with SCD [125]. The major risk factors for mortality included renal insufficiency, leukocytosis, and the severity of hemolytic anemia. The model was validated using two other data sets; however, it has not been validated by other groups.

●Risk factors for death in two cohorts of adults from tertiary medical centers included greater frequency of hospitalization, iron overload, elevated tricuspid regurgitant jet velocity (TRJV) on Doppler echocardiography (>2.5 m/sec), a history of any cerebrovascular event, a lower estimated GFR, at least one pain episode in the last year [109,110]. Laboratory findings associated with increased risk of death in these cohorts included low hemoglobin, high WBC count, low baseline HbF, high lactate dehydrogenase (LDH), and high C-reactive protein, and elevated NT-proBNP.

●Analysis of data from children enrolled in the Silent Cerebral Infarct Multi-Center Clinical (SIT) trial suggest that higher baseline hemoglobin levels and higher education level of the head of the household correlated with improved growth, whereas household income did not [82].

●An older prospective cohort study (1978 to 1988) in 392 infants with homozygous HbSS looked for predictors of severe SCD before age two years and severe outcomes after 10 years [120].

Adverse outcomes occurred in 70 individuals (18 percent), including stroke, frequent pain episodes, recurrent acute chest syndrome, and death. Significant predictors of an adverse outcome included dactylitis before age one year (relative risk [RR] 2.6; 95% CI 1.39-4.67); hemoglobin concentration <7 g/dL (RR 2.5; 95% CI 1.14-5.33); and leukocytosis without infection (RR 1.8; 95% CI 1.05-3.09). However, these data have become outdated as events in early infancy do not predict adverse events in childhood in the modern era of comprehensive care. The cohort was assembled before the routine use of prophylactic penicillin, conjugate pneumococcal and influenza vaccination, hydroxyurea, and transcranial Doppler screening for stroke risk, coupled with regular blood transfusion therapy for stroke prevention.

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hemoglobinopathies".)

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 education: Sickle cell disease (The Basics)" and "Patient education: When your child has sickle cell disease (The Basics)")

SUMMARY AND RECOMMENDATIONS

●Individuals with sickle cell disease (SCD) should be seen regularly by the clinician and treatment team as part of a comprehensive health care maintenance program. (See 'General principles and guidelines' above.)

●All individuals with SCD should receive age appropriate vaccinations, including those against *Streptococcus pneumoniae*, seasonal influenza, *Neisseria meningitidis*, *Haemophilus influenzae* type B, and hepatitis B (table 1). (See 'Immunizations' above.)

●All individuals with SCD should begin antibiotic prophylaxis within the first three months of life. We suggest that all individuals with SCD continue prophylactic penicillin (or erythromycin if penicillin-allergic) until age five, rather than a shorter duration (**Grade 2C**). The decision of whether to continue antibiotic prophylaxis after age five must be made on a case-by-case basis. (See 'Prophylactic penicillin' above.)

●We suggest that all individuals with SCD receive folic acid supplementation (**Grade 2C**). We also use a multivitamin **without** iron in all patients, and we replace vitamin D and calcium, which are often deficient, as needed. (See 'Nutrition' above.)

●Most individuals with symptomatic SCD should receive treatment with hydroxyurea. This important issue is discussed separately. (See "Hydroxyurea use in sickle cell disease".)

●Individuals with SCD are at risk for stroke. For children with HbSS or HbS-beta^0 thalassemia or other SCD syndromes with low baseline hemoglobins, we recommend that transcranial Doppler ultrasound evaluation of cerebral blood flow be initiated at two years of age and performed annually until 16 years of age to screen for this complication. We also screen children with any sign of cognitive dysfunction for silent infarcts using magnetic resonance imaging (MRI). (See "Prevention of stroke (initial or recurrent) in sickle cell disease", section on 'Risk assessment for first stroke'.)

●Individuals with SCD are at risk for proliferative retinopathy. Retinal evaluation is begun at 10 years of age and continued routinely to detect early proliferative sickle retinopathy. (See "Overview of the clinical manifestations of sickle cell disease", section on 'Retinopathy'.)

●Additional routine evaluations are directed towards detecting and preventing end-organ damage. (See 'Routine evaluations and treatments' above.)

●All individuals with SCD who present with acute pain due to a probable vasoocclusive pain episode should receive adequate oral hydration, or intravenous hydration if they are hypovolemic, as well as pain control. We suggest a fast-acting oral or intravenous opiate as initial therapy, rather than a non-opiate analgesic (**Grade 2C**). Management of acute pain episodes, chronic pain, and opioid side effects is discussed in detail separately. (See "Vasoocclusive pain management in sickle cell disease".)

●We use normal saline (0.9 percent saline) for hydration of patients who are hypovolemic, and one-quarter (0.25 percent saline) or one-half normal saline (0.45 percent saline) with or without glucose for those who are euvolemic and receiving replacement fluids. (See 'Hydration' above.)

●Adults with SCD who are admitted to the hospital with an acute medical illness should receive thromboprophylaxis unless they have a contraindication. (See 'Thromboembolism prophylaxis' above and "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults", section on 'Our approach'.)

●Indications for blood transfusion, including preparation for surgery; treatment of symptomatic anemia, acute stroke, multiorgan failure, and acute chest syndrome; and prevention of stroke and acute chest syndrome, and recurrent priapism, are discussed separately, along with practical aspects of central venous access, crossmatching, leukoreduction, simple versus exchange transfusion, and management of excess iron stores. (See "Red blood cell transfusion in sickle cell disease".)

●We do **not** use granulocyte colony-stimulating factor (G-CSF) in individuals with SCD, due to the risk of multiorgan failure and death. However, there may be a rare case in which the potential benefits of G-CSF therapy outweigh these risks, and the judicious use of G-CSF may be justified. (See 'Avoidance of G-CSF' above.)

●Hematopoietic cell transplantation (HCT) is the only available curative option in individuals with SCD. This important issue is discussed separately. (See "Hematopoietic cell transplantation in sickle cell disease".)

●While survival for individuals with SCD is reduced compared with the general population, the prognosis for SCD has been steadily improving following the institution of comprehensive care. In regions where comprehensive care is available, the disease has shifted from a fatal pediatric illness to a chronic disease often associated with progressive deterioration in quality-of-life and organ function. (See 'Survival and prognosis' above.)

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