



Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014



U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

<http://www.nhlbi.nih.gov/guidelines>

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Background

Efforts to coordinate care throughout the lifespan between community settings, primary care practices, specialists' practices, emergency departments, laboratories, and hospitals can significantly improve the health and well-being of individuals with a chronic disease such as SCD. Coordination models such as the medical home can facilitate this coordination.³³ Individuals with SCD are at high risk for developing multisystem acute and chronic conditions associated with significant morbidity and mortality. Undetected signs and symptoms can begin in early childhood. For example, silent CNS infarcts can present with non-focal signs such as developmental delays or poor or declining school performance in children or changes in social role or work functioning in adults. Throughout their lives, people with SCD should be considered for formal neurocognitive evaluation when assessments reveal any of these concerns. In another example, loss of the kidney's ability to concentrate urine occurs in most individuals with SCD and can result in large urine volumes. In children, this may result in enuresis or bedwetting.

Although treatment of SCD may ameliorate some of these complications, such therapies are often unsuccessful in completely preventing them. Therefore, the next best approach may be screening to identify risk factors and early signs of complications in order to implement measures to reduce morbidity and mortality in individuals with SCD. However, not all screening is useful. The expert panel determined that, in order for evidence that supports screening to be considered high-quality, it needed to meet the following requirements, which were based upon the WHO criteria but modified by the panel:¹⁹

1. The condition targeted by screening is sufficiently prevalent and clinically significant in persons with SCD.
2. An accurate screening test that identifies the condition is available.
3. There is evidence that early intervention in populations identified by screening is beneficial (e.g., effective therapy exists for preventing or treating a condition).
4. Screening is associated with minimal harm.
5. Screening is cost-effective.

The methodology team conducted systematic reviews of the evidence to synthesize and evaluate relevant research on the utility of commonly used diagnostic tests in individuals with SCD (e.g., electrocardiograms, echocardiograms, pulmonary function tests, kidney function tests, various screening eye exams, brain imaging, and transcranial Doppler (TCD)) and presented the panel with evidence tables which included determinations of the evidence quality.

Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbS β 0-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSD, and HbS β +thalassemia. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

This chapter reviews the available evidence for health maintenance and screening and makes recommendations for children and adults with SCD. In addition to SCD-specific recommendations, this chapter also includes the USPSTF’s recommendations on clinical preventive services.²⁰ The expert panel also identified recommendations from the Centers for Disease Control and Prevention/World Health Organization (CDC/WHO) report on contraceptive use, which were deemed to be particularly relevant for women with SCD and their partners; these recommendations are included in the latter part of this chapter.²¹ The expert panel reviewed the methods used by the CDC, WHO, and USPSTF, and concluded that the processes used by these organizations were consistent with those used by the panel’s methodology team.

Methodology

Complete information about the methodology for these guidelines can be found in the [“Introduction and Methodology” chapter \(pages 1–9\)](#). The following information, specific to this chapter, supplements the standard methodology that was conducted for all clinical chapters of these guidelines.

A comprehensive study of several databases was conducted, and all human studies in English published from January 1970 to December 2010 that addressed each PICOS question were identified^c. A total of 313 studies were included. In the specific instances of antibiotic therapy and blood pressure screening, the review began from database inception through January and July 2011, respectively. In the case of screening, the review went through July 2010. Meta-analysis was only feasible in two areas: (1) efficacy of antibiotic prophylaxis in children and (2) hypertension (HTN) in SCD. The topics of reproductive counseling, contraception, clinical preventive health care services, and immunizations were not searched; recommendations were derived from guidelines published by professional organizations that were based on systematic reviews of broader population groups; these recommendations are labeled “Consensus–Adapted.” The key questions for this chapter can be found immediately before the Summary of the Evidence sections for the individual topics.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the evidence tables for this chapter (The Use of Prophylactic Antibiotic Therapy in Children With Sickle Cell Disease: A Systematic Review and Meta-Analysis, 2012; Blood Pressure and Sickle Cell Disease: A Systematic Review and Meta-Analysis, 2012; and The Use of Screening Tests in Patients With Sickle Cell Disease: A Systematic Review, 2012) available at <http://www.nhlbi.nih.gov/guidelines/scd/index.htm>.

Prevention of Invasive Pneumococcal Infection

Background

Young children with SCA have a very high risk for septicemia and meningitis in the absence of appropriate prophylaxis.^{34,35} These infections result from defective or absent splenic function that typically has its onset in people with SCA early in the first year of life. Case fatality is high, and the risk is greatest in young people who lack humoral immunity against the specific pneumococcal serotype causing infection. People with HbSC and HbS β^+ -thalassemia have a much lower incidence of life-threatening infection because their spleen function is normal or only minimally impaired during infancy. However, older children and adults with all SCD genotypes are at increased risk for invasive bacterial infection.

^c An updated search was performed to span the time from June 1, 2010 through July 11, 2014. No additional RCTs were identified that were relevant to this chapter.

Universal newborn screening identifies babies with all forms of SCD, including those with SCA, who are most at risk for invasive pneumococcal infection, and allows for the opportunity to initiate the following three-step prevention strategy: (1) twice-daily prophylactic penicillin beginning in early infancy and continuing through at least age 5; (2) vaccination against pneumococcus and other encapsulated pathogens; and (3) education of those with SCD and their parents and caregivers regarding the need to seek immediate medical attention in the event of fever.^{34,36} Employing such measures has resulted in a greatly reduced incidence of septicemia and meningitis in infants and young children with SCD.¹⁵

Key Questions

KQ1. What are the benefits and harms of prophylactic antibiotic use in children with SCD? What are the recommended antibiotic administration regimens and schedules?

Summary of the Evidence

In addition to the systematic review for these key questions, a meta-analysis was conducted. Three RCTs and one observational study were included.^{34,36-38} The studies enrolled a total of 951 children under the age of 5; of these, 94 percent were HbSS, 5 percent were HbSC, and 1 percent were HbS β^0 -thalassemia. The studies showed that prophylactic antibiotic therapy reduces the risk for pneumococcal infections in children with HbSS disease.

The three RCTs were of moderate methodological quality and compared penicillin to no prophylaxis. The initiation of penicillin prophylaxis was associated with a significant reduction in the risk for developing serious pneumococcal infections (2/105 vs. 13/110) and a nonsignificant reduction in mortality (0/105 deaths vs. 3/110 deaths; very low-quality evidence due to severe imprecision). A single trial evaluated the consequences of discontinuing penicillin prophylaxis; it suggested that prophylaxis in children who have not had a prior severe pneumococcal infection or a splenectomy may be discontinued at age 5.³⁶ Children who continued penicillin had a nonsignificant reduction in systemic pneumococcal infections; there was no effect on mortality. The observational study compared penicillin to spiramycin and demonstrated that penicillin was superior. However, the penicillin group had a higher rate of pneumococcal vaccination, confounding the effect of antibiotics and making strong conclusions difficult. The quality of evidence is very low due to severe imprecision (i.e., small number of events) and methodological limitations. Evidence is lacking in children with genotypes other than SS, even though many clinicians prescribe prophylactic penicillin for them both before and after age 5.

Recommendations

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

* Refer to the [“Immunization” section](#) of this chapter for comprehensive information on immunizations.

Screening for Renal Disease

Background

Sickle cell nephropathy is a major complication of SCD causing tubular and medullary dysfunction. The most common renal pathologies identified from biopsies are glomerular enlargement, perihilar focal segmental glomerulosclerosis, and global sclerosis. In individuals with SCA, glomerular filtration rate (GFR) and renal plasma flow are increased in childhood, normalize during adolescence, and decline with age. Renal abnormalities can start with defects in urine concentration and acidification³⁹ beginning in childhood and progress with age to microalbuminuria, overt proteinuria, glomerulosclerosis, and, in some people, renal failure. Preclinical markers of glomerular damage in other conditions associated with hyperfiltration and hyperperfusion such as diabetes mellitus can be measured as early predictors of progressive renal nephropathy. Microalbuminuria can be detected long before a positive urine test for proteinuria. Chronic renal failure (CRF) occurs with a variable frequency of 4–20 percent when significant proteinuria or azotemia is present.⁴⁰

Key Question

KQ2. In asymptomatic individuals with SCD, what is the effect of screening for renal disease, by measuring serum creatinine and urine albumin and protein, on mortality and the development of end-stage renal disease (ESRD)?

Summary of the Evidence

There were no RCTs found that examined the utility of screening for renal disease in individuals with SCD. Fifty-seven observational studies assessed screening with kidney function tests. Nine of these studies were longitudinal and enrolled more than 1,500 subjects but provided no outcomes; the other 48 studies were cross-sectional. Potential screening modalities explored in the studies included serum creatinine, creatinine clearance,

presence of albuminuria, and urine albumin excretion. Overall, the screening studies reported inconsistent results, and the quality of evidence was very low. No data were found on screening intervals.

No consistent differences were found in the presumed “normal” or average creatinine levels between people with and without SCD, and none were found among individuals with different genotypes of SCD.⁴¹ No studies evaluated the utility of screening or compared the effect of screening versus no screening. In one study of 368 individuals with HbSS, 78 (20.6 percent) had proteinuria, and 17 people (4.6 percent) had renal insufficiency.⁴² Long-term followup revealed that five people (1.9 percent) progressed to ESRD requiring chronic dialysis, and three people (0.8 percent) died from complications of renal failure.⁴²

The data are limited for early intervention through screening for renal disease in people with SCD. Therefore, the panel chose to consider indirect evidence from non-SCD populations in which pharmacological interventions were beneficial in people with proteinuria. In developing a recommendation for screening for renal disease, the panel placed a low value on the cost and inconvenience of screening (as both are minimal) and a high value on the potential benefits of treating people with signs of early renal impairment.

Recommendations

1. Screen all individuals with SCD, beginning by age 10, for proteinuria. If the result is negative, repeat screening annually. If the result is positive, perform a first morning void urine albumin-creatinine ratio and if abnormal, consult with or refer to a renal specialist.
(Consensus–Panel Expertise)

Screening for Pulmonary Hypertension

Background

Pulmonary hypertension (PH) is defined as an elevation of the resting mean pulmonary arterial pressure (≥ 25 mmHg) as determined by right heart catheterization.⁴³ There are several potential etiologies for elevation in mean pulmonary artery pressure in people with SCD. Chronic hemolytic anemias, including SCD, may result in pulmonary vascular changes leading to pulmonary arterial hypertension (PAH), and are placed in Group 1 of the current classification.⁴⁴ This type of pulmonary hypertension may occur in up to 10 percent of those with SCA and accounts for 40–50 percent of all types of PH in SCD.^{45,46} The second most common type of PH in SCD is pulmonary venous hypertension (PVH), which is assigned to Group 2 in the current classification and is associated with an elevated mean pulmonary artery pressure (≥ 25 mmHg) but also an elevated pulmonary capillary wedge pressure of ≥ 15 mmHg.^{43–47} This is often associated with left ventricular diastolic dysfunction in SCD.⁴⁸ PH also occurs in the setting of chronic lung disease, chronic thromboembolic disease, or can be due to unclear or multiple mechanisms (Groups 3, 4, and 5 of the classification, respectively). The main symptoms of PH include shortness of breath during routine activity, such as climbing two flights of stairs; fatigue; lethargy; chest pain; palpitations; syncope; peripheral edema; and decreased appetite.⁴⁹ Distinguishing the etiology of these common and diverse symptoms can be difficult.

Initial assessment for PH has been done with an echocardiography evaluation to estimate pulmonary artery pressure using tricuspid regurgitant jet velocity (TRV),^{43,45–47} but diagnosis requires right heart catheterization and direct measurement of the pulmonary arterial pressure and vaso-reactivity of the vessels.^{43,45,50} Transient elevation in TRV has been observed during acute vaso-occlusive crises in individuals with SCD,⁵¹ which may not reflect baseline values or represent chronic PH.

Both elevated TRV and PH are risk factors for premature death in people with SCD. Elevated TRV in adults with SCA is associated with an increased risk for all-cause mortality; however, this is not the case in children with SCA.⁵²⁻⁵⁴ Observational studies show an increase in hospitalization and mortality in people with all types of SCD who also have PAH documented by right heart catheterization, compared to those who do not (55 percent vs. 21 percent in 10 years).^{48,52,55,56} A commonly associated finding is renal insufficiency.^{47,57,58} The typical age of onset of PH and prevalence of PH in people with forms of SCD other than SCA remain unclear.^{48,52}

Use of screening (testing asymptomatic individuals) to detect conditions in the presymptomatic stage is generally justified by the ability to impact the course to prevent or reduce morbidity and/or mortality.⁵⁹ Therapies for treating PAH are generally initiated when symptoms are present, with a goal to ameliorate or mitigate these symptoms and improve functional capacity.^{43,60} There are no studies demonstrating a change in mortality or course of PH when therapies are introduced in the presymptomatic stage. Identification of underlying conditions that may be associated with PH (e.g., scleroderma, HIV) permits treatment of these conditions, but clinical trials demonstrating long-term benefit or reduced mortality are lacking.⁶⁰ Similarly, there are no data yet available to demonstrate that treatment of SCD itself impacts PH or the all-cause mortality associated with an elevated TRV in adults with SCD. Despite this lack of evidence, some groups advocate screening individuals with some diseases, including SCD, when PH is relatively prevalent.⁶⁰

Key Question

KQ3. In asymptomatic individuals with SCD, what is the effect of screening for PH on mortality and the development of future cardiac and pulmonary complications?

Summary of the Evidence

Eighty-three observational studies are included in the evidence table, and they describe the use of echocardiography as a screening test for PH in people with SCD. Of these studies, 27 were longitudinal, 56 were cross-sectional, and 9 had a comparison group. However, no study evaluated the utility of screening or compared an approach of screening versus no screening on patient outcomes, and there were no data on screening intervals. The overall quality of the data was considered very low.

Bachir and colleagues⁵² showed that rates of presumed PAH based on echocardiography (32–38 percent) were only confirmed in 6 percent of those using right heart catheterization. A similar false-positive rate (68 percent) was noted in a cross-sectional study.⁶⁰ The findings of a study evaluating right heart catheterization-confirmed PAH in persons with SCD showed that 44 percent of the people with PAH died compared to 17 percent of the people without PAH, and the median survival after diagnosis with PAH was 25.6 months (range: 1–46).⁶¹

Numerous studies showed that the prevalence of elevated TRV in people with SCD ranged from 11 percent to 59 percent. This was much higher than in individuals without SCD and was associated with increased mortality.^{53,54} TRV increased over 2 years of followup, with the greatest increases occurring in the presence of elevated systemic blood pressure.⁶² The echocardiography studies assessing TRV did demonstrate several other abnormalities in individuals with SCD, such as increased left ventricle end-diastolic diameter, increased chamber size of the right ventricle and left atrium, early-diastolic mitral flow velocity and late-diastolic mitral flow velocity, and lowered ejection fraction (EF).⁶³ Low EF was also found to be a significant independent risk factor for death.⁵³ No studies were found that demonstrated reduction in mortality in SCD using treatments for PH or to modify the SCD itself.

Based on the insufficient evidence, the expert panel was unable to make a recommendation for or against screening for PH. However, this does not diminish the importance of evaluating individuals who have symptoms or who have had abnormal echo testing.⁵⁶

Electrocardiogram Screening

Background

The electrocardiogram (ECG) may offer diagnostic information to guide clinical decisionmaking. However, there is minimal evidence for the value of obtaining a screening ECG in asymptomatic individuals with or without SCD to detect abnormalities such as prolonged corrected QT interval (QTc), ST-T segment abnormalities, and electrocardiographic cardiac enlargement.

Although observational studies of the prevalence of ECG abnormalities in persons with SCD have been done, they reveal abnormalities that are of unknown clinical significance. Studies found that the prevalence of cardiac enlargement ranged between 22 percent and 76 percent,^{64,65} and ventricular hypertrophy prevalence was found to be between 28 percent and 37 percent.^{66,67} The presence of nonspecific S-T abnormalities was found to be between 18.5 percent and 52 percent.⁶⁸ First-degree atrioventricular block was found in 8 percent of people in one study,⁶⁷ and intraventricular conduction delay was found in 4 percent of people in another study.⁶⁶ Prolonged QTc ranged between 15 percent and 50 percent prevalence. Overall, there was no significant difference in the prevalence of prolonged QTc between people with and without SCD, and the presence of prolonged QTc did not significantly affect mortality.⁶⁹

Key Question

KQ4. In asymptomatic individuals with SCD, what is the effect of screening with ECG on mortality and the development of future cardiac disease?

Summary of the Evidence

Fourteen observational studies (4 longitudinal and 10 cross-sectional) described the use of ECG as a screening test in people with SCD; however, all of the studies focused on estimating the prevalence of ECG abnormalities of unknown clinical significance. No study evaluated the utility of ECG screening or compared an approach of ECG screening versus no screening, and no data exist about the effect of obtaining a screening ECG on clinical outcomes in people with SCD. There were no data on screening intervals or diagnostic accuracy of the test, and the overall quality of the evidence supporting screening using ECG was very low.

The USPSTF recommends against routine screening with resting electrocardiography, exercise treadmill test (ETT), or electron-beam computerized tomography (EBCT) scanning for coronary calcium for either the presence of severe coronary artery stenosis (CAS) or the prediction of coronary heart disease (CHD) events in adults at low risk for CHD events (Grade D—moderate to high certainty that the benefits do not outweigh the harms).

Recommendations

1. Routine ECG screening is not recommended in children and adults with SCD.
(Weak Recommendation, Low-Quality Evidence)

Screening for Hypertension

Background

The “Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (JNC 7)⁷⁰ recommends medication for hypertension (HTN), defined as blood pressure (BP) $\geq 140/90$ mmHg; medication for prehypertension (defined as BP 120–139/80–89 mmHg) if accompanied by a comorbidity such as chronic kidney disease or diabetes mellitus; and lifestyle changes for prehypertension not accompanied by a comorbidity. The USPSTF recommends blood pressure screening in all individuals aged 18 or older (Grade A—high certainty that the benefits substantially outweigh the harms).²⁰ The “Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report”⁷¹ recommends annual blood pressure screening in children aged 3 and older and in younger children with a history of renal, urologic, or cardiac diagnosis or a history of time in the neonatal intensive care unit (ICU). However, the quality and strength of the evidence supporting these recommendations is not provided.

No specific recommendations are made by the USPSTF for individuals with SCD. Individuals with HbSS often have significantly lower diastolic, systolic, and mean BP compared with age/sex-matched healthy controls or individuals with confirmed HbA.^{72,73} Higher baseline systolic pressure was reported to be a risk factor for silent cerebral infarction in a publication subsequent to the original systematic review.⁷⁴

Key Questions

KQ5. In people with SCD, what is the effect of screening for HTN on mortality, stroke, and heart disease? What are the acceptable limits for BP parameters above which cardiovascular and cerebrovascular morbidity occur?

Summary of the Evidence

Thirty-two studies (including 2 RCTs, 14 prospective cohort, 4 retrospective cohort, and 12 cross-sectional studies) involving both adults and children were included and are available in the evidence table.^{75,76} Random effects meta-analysis of these 32 studies was conducted to pool the differences in BP between people with SCD and people without SCD. Individuals with HbSS had significantly lower diastolic, systolic, and mean BP compared with age/sex-matched healthy controls or individuals with confirmed normal hemoglobin. However, no studies were found that prognostically defined “normal” or “elevated” BP for people with SCD at any age. The overall quality of evidence to establish baseline BP in persons with SCD, manage elevated BP, or make prognostic associations was low.

However, in studies involving individuals with SCD both with and without HTN defined according to normal population values, HTN was associated with increased mortality^{72,77} and increased risk for stroke in people with SCA.^{73,77,78} The risk of stroke was also increased for people with SCD even when BP was $\leq 140/90$.⁷³ For people with SCD, HTN (which had varying definitions in the studies) was associated with increased risk for hospitalization^{78,79} and microalbuminuria.^{80,81}

There are no published clinical studies in individuals with SCD demonstrating that treatment of blood pressure to specific target values results in improved outcomes. Thus, in developing consensus recommendations for screening for HTN, the panel adapted recommendations from “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure”⁷⁰ (see <http://www.nhlbi.nih.gov/guidelines/hypertension>) and the NHLBI report “The Fourth Report on the Diagnosis,

Evaluation, and Treatment of High Blood Pressure in Children and Adolescents”⁸² (see http://www.nhlbi.nih.gov/guidelines/hypertension/hbp_ped.htm).

Recommendations

1. In adults with SCD, screen for hypertension and treat to lower systolic blood pressure ≤ 140 and diastolic blood pressure ≤ 90 according to “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” (JNC 7).
(Consensus–Adapted)
2. In children with SCD, measure blood pressure, and evaluate and treat hypertension following recommendations from the NHLBI’s “Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.”
(Consensus–Adapted)

Screening for Retinopathy

Background

All individuals with SCD and especially those with HbSC are at risk for retinal disease due to vaso-occlusion and its resultant ischemia.^{83,84} Proliferative sickle retinopathy (PSR) is of greatest concern because progression is associated with loss of visual acuity. PSR is the development of sea-fan-shaped neovascular fronds in response to local ischemia from peripheral retinal arteriolar occlusion. The fronds can lead to other complications including vitreous hemorrhage and retinal detachment. Prevalence of proliferative retinopathy reported in a contemporary retrospective study of children with SCD was 4.3 percent.⁸⁵ In a study from Jamaica, visual acuity loss attributed to retinopathy was reported in 10 percent of untreated eyes during a 10-year observation period.⁸³ Prospective clinical studies have demonstrated the benefit of laser photocoagulation in reducing rates of visual acuity loss and decreasing incidence of vitreous hemorrhage.⁸⁶⁻⁸⁸ Surgical intervention may be indicated for certain complications such as vitreous hemorrhage. The onset of sickle retinopathy is in childhood; however, screening requires a dilated eye examination and the ability to do so will vary according to the child’s ability to tolerate the exam.

Key Question

KQ6. In asymptomatic individuals with SCD, are dilated eye examinations useful, and, if so, with what frequency should they be done?

Summary of the Evidence

No RCTs of retinal screening in people with SCD were found. Twelve observational studies addressed eye examinations for individuals with SCD, primarily children and adolescents. Of these, five were longitudinal and involved 1,261 individuals, and seven were cross-sectional. Genotypes involved were HbSS, HbSC, and HbS β -thalassemia.^{83,84,89-91} No studies have been published comparing screening for retinopathy with no screening, nor were data found to evaluate diagnostic accuracy or screening intervals. The overall quality of the screening data were considered low.

In these studies, “eye examinations” varied, and not all included dilation of the pupils. The most comprehensive report describes a 20-year prospective study of an inception cohort of 473 individuals from Jamaica.⁸⁴ Annual eye exams including dilation were performed from age 5, and fluorescein angiography was performed from age

6 unless patients had an allergy to fluorescein. Fifty-nine of those studied developed proliferative retinopathy. The incidence of retinopathy increased with age, and by the ages of 24 to 26, PSR was present in 43 percent of those with HbSC and 14 percent of people with HbSS. In a retrospective study of 263 children with SCD, including people with HbSS, HBSC, and HbS β -thalassemia, the age of onset of retinopathy (proliferative and nonproliferative) was, on average, 12.8 years.⁸⁹

Recommendations

1. In people with SCD, refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10.
(Strong Recommendation, Low-Quality Evidence)
2. For people having a normal dilated retinal examination, re-screen at 1–2 year intervals.
(Consensus–Panel Expertise)
3. Refer people with suspected retinopathy to a retinal specialist.
(Consensus–Panel Expertise)

Screening for Risk of Stroke Using Neuroimaging

Background

Stroke is one of the most common and devastating complications of SCD.^{77,92} In the absence of primary stroke prevention, approximately 10 percent of children with SCA will have overt stroke.

This complication presents as sudden onset of weakness, numbness, or other focal neurological signs such as visual disturbances, dysarthria, aphasia, or ataxia. Transient ischemic attacks (TIAs) often precede stroke and may be a harbinger of stroke.⁷⁷ Overt stroke in children is generally secondary to stenosis or occlusion of the internal carotid or middle cerebral artery. Events may be precipitated by acute chest syndrome (ACS), parvovirus infection, or other acute anemic events.^{77,93} Overt stroke recurs in most children with SCA who do not receive chronic transfusions or successful hematopoietic stem cell transplantation.⁹⁴

Transcranial Doppler (TCD) imaging of large intracranial blood vessels to detect increased velocities secondary to stenosis can predict risk of stroke in children with SCA.⁹⁵ Primary stroke prevention using regular blood transfusions in children with such elevated velocities proved successful in the NIH-funded STOP trial.⁹⁶ This approach—which used transfusions for an abnormal TCD velocity (>200 cm/sec)—has resulted in a declining incidence of primary overt stroke in children with SCD.⁹⁷ Unfortunately, discontinuation of such transfusions was shown in the STOP-2 trial to result in a high rate of reversion to increased TCD velocities or to overt stroke.⁹⁸ Therefore, such transfusions may be necessary indefinitely.

Adults with SCA also have a high risk of both ischemic and hemorrhagic stroke.⁹⁹ The latter is usually sudden, with severe headache, seizures, and loss of consciousness. The mortality rate is high. Limited data suggest that TCD is not predictive of either ischemic or hemorrhagic stroke in adults.¹⁰⁰

Performing neuroimaging with MRI often reveals silent cerebral infarcts, atrophy, or other findings in children or adults with SCA who lack signs or symptoms of stroke but who often have a history of transient ischemic episodes and/or cognitive impairment. However, the specific indications for these imaging studies are controversial, and management of abnormal findings is uncertain.

Key Question

KQ7. In asymptomatic individuals with SCD, what is the effect of screening with neuroimaging tests (computed tomography (CT) scan, MRI, or TCD) on the risk of stroke?

Summary of the Evidence

Fifty observational studies that evaluated screening with CT scan and MRI were identified. These studies examined the prevalence of certain abnormalities such as silent infarcts; however, no studies compared a screening strategy versus no screening, and no study reported a benefit of screening or early detection on important outcomes. Overall, the quality of evidence supporting the use of screening with MRI or CT scan in adults and children was very low.

Two RCTs and 50 observational studies on the use of TCD were included. The two RCTs evaluated the efficacy of early intervention and demonstrated that screening coupled with prophylactic transfusion can markedly reduce the risk of stroke in children with SCA whose cerebral blood flow velocity measurements are considered at high risk.^{96,101} The fifty observational studies enrolled more than 11,000 patients and assessed the use of TCD as a screening test in children with SCD. The quality of evidence supporting screening with TCD was considered moderate to high.

In an observational study of 274 patients, the cumulative incidence of conversion from a normal TCD velocity (<170 cm/sec) to a conditional TCD velocity (170–199 m/sec) was 18 percent (10–26 percent) within 18 months from the first examination.¹⁰² Risk of stroke was higher in children with abnormal TCD than in children with normal TCD, conditional TCD, or inadequate TCD examination results.¹⁰¹ Children with normal cerebral blood flow had no strokes after 4 years of followup.¹⁰³ No trials were found that addressed the optimal time interval for screening patients with documented normal TCD velocity. Information from a modeling and decision analysis (not a clinical study) suggests that the optimal stroke prevention strategy is annual TCD ultrasonography screening up to age 10, with transfusion for those at high risk until age 18.¹⁰⁴ No clinical trials have been published evaluating this strategy. Outcome data in the studies that evaluated TCD screening are mainly derived from patients with genotypes HbSS and HbSβ⁰-thalassemia; therefore, it was not possible to infer about the utility of TCD screening in other genotypes.

Recommendations

1. In children with SCA, screen annually with TCD according to methods employed in the STOP studies, beginning at age 2 and continuing until at least age 16.
(Strong Recommendation, Moderate-Quality Evidence)
2. In children with conditional (170–199 cm/sec) or elevated (>200 cm/sec) TCD results, refer to a specialist with expertise in chronic transfusion therapy aimed at preventing stroke.
(Strong Recommendation, High-Quality Evidence)
3. In children with genotypes other than SCA (e.g., HbSβ⁺-thalassemia or HbSC), do not perform screening with TCD.
(Strong Recommendation, Low-Quality Evidence)
4. In asymptomatic children with SCD, do not perform screening with MRI or CT.
(Moderate Recommendation, Low-Quality Evidence)
5. In asymptomatic adults with SCD, do not perform screening with neuroimaging (TCD, MRI, or CT).
(Moderate Recommendation, Very Low-Quality Evidence)

Screening for Pulmonary Disease

Background

Respiratory conditions are found in children with SCD at a prevalence of 20 percent to 48 percent¹⁰⁵⁻¹⁰⁷ and are associated with an increased risk of mortality. In a prospective study of 1,963 individuals with SCA followed from birth through adulthood, individuals with SCA and asthma had a more than twofold higher risk of mortality after adjusting for established risk factors.¹⁰⁸ In assessing asthma characteristics in an observational study of 79 adults with SCD who completed respiratory symptom questionnaires, those who reported recurrent, severe episodes of wheezing ($n=34$), regardless of asthma, had twice the rates of pain, ACS, decreased lung function, and increased risk of death compared with adults without recurrent, severe wheezing.¹⁰⁹

Pulmonary function tests (PFTs) provide a method for objectively assessing the function of the respiratory system. Although multiple studies have demonstrated abnormal pulmonary function in children and adults with SCD, little has been reported regarding the meaning of these changes for the functional status or quality of life in people with SCD. No therapies have been suggested to address these changes unless the person is also shown to have another lung disease, such as asthma, chronic obstructive pulmonary disease (COPD), or pulmonary fibrosis. The utility of screening for respiratory disorders in children and adults using PFTs has not been established. A study to characterize the polysomnographic (PSG) findings of children with SCD who displayed behaviors suspicious of sleep disorder ($n=100$) identified using the Children's Sleep Habit Questionnaire found sleep-disordered breathing (SDB) in 79 percent of the SCD group. Compared to children with obstructive sleep apnea syndrome (OSAS) without medical comorbidities, children with SCD and OSAS experienced nocturnal desaturation with a fourfold increased risk for oxygen desaturation below 85 percent and hypercapnia.¹¹⁰ Therefore, routinely taking a thorough respiratory history is valuable to evaluate symptoms that may require further assessment.

Key Question

KQ8. In asymptomatic individuals with SCD, what is the effect of screening with PFTs on cardiac and pulmonary complications?

Summary of the Evidence

Thirty-four studies (11 longitudinal and 23 cross-sectional) described the results of screening using PFTs in people with SCD who had no recognized respiratory symptoms. No study evaluated the utility of screening or compared an approach of screening versus no screening, and there were no data on diagnostic accuracy. Overall, it was unclear whether early intervention was beneficial or whether screening was cost-effective. Screening intervals were not assessed. The supporting quality of evidence was considered low.

The longitudinal and cross-sectional studies enrolled more than 1,500 and 1,700 subjects, respectively. Children with SCA had lower forced expiratory volume at 1 minute (FEV_1), forced vital capacity (FVC), and forced expiratory flow (FEF) 25–75 and slower lung growth curves (FEV_1 and FEV_1/FVC) compared to controls.^{111,112} Lung volume, as a percentage of that predicted, was demonstrated to decline with age in children with SCD, similar to the decline noted in children with cystic fibrosis.^{111,112} A cross-sectional study of African American adults with SCA enrolled in the Cooperative Study of Sickle Cell Disease revealed abnormalities in 90 percent of the subjects (279 of 310). The most common abnormality was a restrictive pattern (74 percent) with isolated decreased diffusing capacity observed in 13 percent of the patients.¹¹³ Other studies demonstrated obstructive changes in 15–21 percent of children and adults with SCD, restrictive changes in 22–27 percent of adults with

SCD, and mixed restrictive/obstructive changes in 6–12 percent of adults with SCD.^{54,62} Compared with controls, people with SCD had lower FVC, FEV₁, and peak expiratory flow rate (PEFR).⁶³ When corrected for hemoglobin levels, children with SCA compared to controls of similar age had elevated gas transfer per unit lung volume.¹¹⁴ People with HbSC also appear to have lung function abnormalities, which are milder than those seen in people with HbSS.¹¹⁵ No studies discussed any type of intervention for children or adults with SCD and abnormal lung function.

Recommendations

1. In children and adults with SCD, assess for signs and symptoms of respiratory problems (such as asthma, COPD, restrictive lung disease, or obstructive sleep apnea) by history and physical examination.
(Consensus–Panel Expertise)
2. In children and adults with SCD found to have signs or symptoms of respiratory problems by history and/or physical examination, further assessment, which includes pulmonary function tests, is recommended to determine the cause and develop a plan to address the problem.
(Consensus–Panel Expertise)
3. Do not screen asymptomatic children and adults with pulmonary function tests.
(Moderate Recommendation, Low-Quality Evidence)

Reproductive Counseling

Background

The CDC and its partners released a set of recommendations and goals for preconception health.¹¹⁶ They recommend that women and couples think about their goals for having or not having children and how to achieve these goals, known as a “reproductive life plan.” These recommendations apply to all women and couples, but, given the increased risk of adverse pregnancy outcomes in SCD¹¹⁷ and the risk of maternal morbidity and mortality,^{117,118} the expert panel determined that several recommendations were particularly relevant for women with SCD and their partners. The “Recommendations” section delineates these.

Heritability In Men and Women With SCD

People with SCD are at risk for having a child affected with SCD if their partners have SCD, β -thalassemia trait, or are carriers of other abnormal hemoglobins such as HbC. Women whose partners carry one of these traits can avoid an affected pregnancy by undergoing preimplantation genetic diagnosis (PGD). PGD is testing performed on an embryo during an in-vitro fertilization cycle (see <http://www.acog.org/~media/For%20Patients/faq179.pdf?dmc=1&ts=20130718T1252201251>).¹¹⁹ Alternatively, after spontaneous conception, prenatal diagnosis of SCD is possible by chorionic villus sampling in the first trimester or by amniocentesis in the second trimester of gestation.¹¹⁵

Fetal Anemia Due to Alloimmunization

Women with SCD are frequently exposed to blood products. The fetuses of women who are alloimmunized are at risk of significant hemolytic anemia or mortality.

Summary of the Evidence

Adverse Fetal Outcomes

Multiple case series and two population studies^{117,118} have documented increased risk of growth restriction, preterm delivery, and stillbirth among women with SCD. Fetal surveillance, which includes growth ultrasounds and antepartum testing (nonstress tests, biophysical profiles, and contraction stress tests), may lead to planned early delivery and can reduce but not eliminate risks.

Risks to the Mother

Compared to women without SCD, women with SCD are more likely to experience preeclampsia,^{117,118,120} venous thromboembolism, infections, and maternal mortality during pregnancy.¹¹⁸ During pregnancy, 40–50 percent of women with SCD require at least one hospital admission.¹²⁰⁻¹²²

Although there are no data specifically for women with SCD, the presence of pulmonary hypertension increases the cardiopulmonary demands of gestation. Non-SCD maternal mortality has been reported to be as high as 30–50 percent in women with pulmonary hypertension.¹²³⁻¹²⁵ Even with current multidisciplinary care, maternal mortality in women with pulmonary hypertension is still reported to be 10 percent.¹²⁶

Recommendations

Evidence reviews on this topic were not performed by the methodology team. The expert panel based its recommendations on a review of the literature and consensus opinion.¹¹⁶

Specific Recommendations for Women or Men With SCD

1. Encourage each woman, man, and couple affected by SCD to have a reproductive life plan.
(Consensus–Panel Expertise)
2. As a part of primary care visits, provide risk assessment and educational and health promotion counseling (or refer to individuals with expertise in these disciplines) to all women and men of childbearing age to reduce reproductive risk and improve pregnancy outcomes. Provide contraceptive counseling, if desired, to prevent unintended pregnancy, and if pregnancy is desired, provide preconception counseling.
(Consensus–Panel Expertise)
3. If the partner of a man or woman with SCD has unknown SCD or thalassemia status, refer the partner for hemoglobinopathy screening.
(Consensus–Panel Expertise)
4. After testing, refer couples who are at risk for having a potentially affected fetus and neonate for genetic counseling.
(Consensus–Panel Expertise)

Specific Recommendations for Women With SCD

1. Test women with SCD who have been transfused and are anticipating pregnancy for red cell alloantibodies.
(Consensus–Panel Expertise)
2. If a woman has red cell alloantibodies, test her partner for the corresponding red cell antigen(s).
(Consensus–Panel Expertise)
3. If the partner tests positive for the corresponding red cell antigen(s), counsel the woman and her partner about the risks of hemolytic disease in the fetus and neonate, how it is monitored, and how it is treated, or refer them to a maternal-fetal specialist who can provide this education.
(Consensus–Panel Expertise)

Recommendations

4. Counsel women with SCD and their partners or refer for counseling about the following:
(Consensus–Panel Expertise)
 - a. Pregnancy in women with SCD is considered high risk, and there is an increased risk of adverse pregnancy outcomes including fetal (intrauterine) growth restriction, preterm delivery, and stillbirth.
 - b. Additional fetal surveillance is required during a pregnancy.
 - c. There are increased risks to a woman's health during pregnancy. These risks include an increased frequency of pain crises and an increased risk of thrombosis, infections, preeclampsia, and death relative to women who do not have SCD.

For women who require chronic opioid therapy during pregnancy, there is an increased risk of neonatal withdrawal in their newborns.

Contraception

Background

In women with SCD, regular use of contraception can decrease the health risks associated with an unintended pregnancy. Hormonal contraceptives may also decrease menstrual blood flow, leading to higher hemoglobin levels. Use of progestin-only hormonal contraceptives lowers the risk of thromboembolism compared to use of estrogen-containing contraceptives and has been shown to be safe for women with SCD.^{127,128}

Intrauterine devices (IUDs) and intrauterine implants carry modest risks associated with the insertion procedure, while sterilization carries risks associated with the surgical procedure. There is no evidence that IUDs pose an increased risk for women with SCD.

Summary of the Evidence

Published data about contraception and SCD were reviewed by the WHO prior to their latest publication of “Medical Eligibility Criteria for Contraceptive Use.”¹²⁹ Eight studies were reviewed.¹³⁰⁻¹³⁷ With the exception of one survey,¹³⁴ the studies were small and compared differences in hematologic parameters or numbers of crises in women before and after starting a particular contraceptive, or between women who were or were not using a particular contraceptive. Progestin-only contraceptives were not associated with an increased risk of thrombosis and may have noncontraceptive benefits in terms of fewer crises and improved hematologic parameters. Data were insufficient on combined hormonal contraceptives.

Women with SCD may have additional considerations that need to be taken into account when assessing the safety of contraceptive methods. For example, a history of stroke is a contraindication to combined hormonal contraception, and by age 20, approximately 11 percent of untreated women with SCD have had a clinically apparent stroke; this statistic increases to 24 percent by age 45.⁷⁷

The CDC adapted the WHO's “Medical Eligibility Criteria for Contraceptive Use” for women with SCD, and those criteria are the basis for the panel's recommendations.²¹

Recommendations

Evidence reviews on this topic were not performed by the methodology team. Therefore, the expert panel based its recommendations on those developed by the WHO and the CDC.

1. Progestin-only contraceptives (pills, injections, and implants), levonorgestrel IUDs, and barrier methods have no restrictions or concerns for use in women with SCD.
(Consensus–Adapted)
2. If the benefits are considered to outweigh the risks, combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD.
(Consensus–Adapted)

Clinical Preventive Services

Background

People with existing chronic diseases such as SCD may fail to receive some of the recommended clinical preventive services because they and their health care physicians are focused on controlling and preventing problems from SCD and its related complications or other comorbid chronic diseases. Unfortunately, this primary focus on SCD may result in people developing other health problems that could have been prevented or treated at an earlier stage, when complications are less frequent. With this situation in mind, the expert panel has identified important recommendations from the USPSTF that should be followed in the care of newborns, children, adolescents, and adults with SCD.

The USPSTF is an independent panel of non-Federal experts in prevention and evidence-based medicine and is composed of primary care clinicians (such as internists, pediatricians, family physicians, gynecologists/obstetricians, nurses, and health behavior specialists). The USPSTF conducts scientific evidence reviews of a broad range of clinical preventive health care services and develops recommendations for the general population in the United States. These recommendations are published in the form of “Recommendation Statements.” The recommendations are aimed at the prevention and early recognition of chronic disease.

We have included only the strong recommendations with high-level evidence from the USPSTF and therefore will not address the strength of recommendation or evidence for each of the recommendations listed in exhibit 5. (Please note that these include grade A and B recommendations from the USPSTF. For more information, see <http://USPreventiveServicesTaskForce.org>.) These general clinical preventive services should be provided to the person with SCD within the patient’s principal health care site. This could be a primary care provider, a sickle cell specialist, or, in many instances, both working together and communicating with one another.

Recommendations of the USPSTF are updated on an ongoing basis. Health care professionals are encouraged to view the most up-to-date recommendations at any time by visiting either <http://USPreventiveServicesTaskForce.org> or by utilizing the searchable and downloadable electronic Preventive Services Selector (ePSS) available at <http://www.ePSS.ahrq.gov>.

Exhibit 5. Summary of U.S. Preventive Services Task Force’s General Recommendations That Are Also Applicable to Persons With Sickle Cell Disease

Newborns

The following should be available to all newborns:

- SCD screening with clinical consideration of confirmatory test within 2 months
- Hypothyroidism screening (primary TSH with T4 backup or primary T4 with TSH backup)
- Hearing loss screening
- Phenylketonuria (PKU) screening
- Prophylactic ocular topical medication for the prevention of gonococcal ophthalmia neonatorum
- Counseling for pregnant women regarding the advantages of breastfeeding (The expert panel notes that current maternal use of hydroxyurea is a contraindication to breastfeeding.)

Source: U.S. Preventive Services Task Force (USPTF). Recommendations [Internet]. Rockville, MD: USPTF; 2010 [updated December 2010; cited 2014 May 30]. Available from: <http://www.uspreventiveservicestaskforce.org/recommendations.htm>.²⁰

Children Aged 3 Months to 12 Years

All children (aged 3 months to 12 years or as stated) should have:

- Fluoride supplement in those over 6 months of age whose water supply is deficient in fluoride
- Routine iron supplementation for asymptomatic infants aged 6 months to 12 months who are at increased risk for iron deficiency anemia
- Children aged 3 to 5 should receive routine evaluation for amblyopia, strabismus, and defects in visual acuity using visual acuity test, stereoacuity test, cover-uncover test, Hirschberg light reflex test, autorefractometry and/or photoscreening.
- Children aged 6 years and older should be screened for obesity. Offer or refer for intensive counseling and behavioral interventions.
- The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection.

Source: U.S. Preventive Services Task Force (USPTF). Recommendations [Internet]. Rockville, MD: USPTF; 2010 [updated December 2010; cited 2014 May 30]. Available from: <http://www.uspreventiveservicestaskforce.org/recommendations.htm>.²⁰

Adolescents Aged 12 to 18 Years

All adolescents (aged 12 to 18 years) should be assessed and offered:

- HIV screening for all sexually active adolescents 15 years of age and older and for younger teens who are at high risk
- Screen for chlamydial infection for all sexually active nonpregnant women aged 24 and younger
- Screen for gonorrhea infection in all sexually active girls at high risk for infection
- The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection.
- Offer high intensity behavior counseling to prevent sexually transmitted infections (STIs) for all sexually active adolescents at increased risk for STIs.
- Provide interventions, including education or brief counseling, to prevent initiation of tobacco use in school-aged children and adolescents (Grade B recommendation)
- Depression screening when systems for diagnosis, treatment, and followup are in place
- Counsel children, adolescents, and young adults aged 10 to 24 years who have fair skin about minimizing their exposure to ultraviolet radiation to reduce risk for skin cancer.
- Screen all teens for obesity and refer obese teens for comprehensive, intensive behavioral interventions

Source: U.S. Preventive Services Task Force (USPTF). Recommendations [Internet]. Rockville, MD: USPTF; 2010 [updated December 2010; cited 2014 May 30]. Available from: <http://www.uspreventiveservicestaskforce.org/recommendations.htm>.²⁰

Adults

Offer all adults:

- Hepatitis C virus screening if
 - At high risk for infection (e.g., those with multiple transfusions)
 - Born between 1945 and 1965 (offer one-time screening)
- Tobacco use screening and counseling (all adults, repeat at each visit for those who are smoking)
- Screening and behavioral counseling interventions to reduce alcohol misuse
- Screen all adults for obesity, and offer or refer patients with a body mass index of 30 kg/m² or higher to intensive, multicomponent behavioral interventions.
- Screen for cervical cancer in women ages 21 to 65 years with cytology (Pap smear) every 3 years; an option for women 30 to 65 is a combination of cytology and human papillomavirus (HPV) testing every 5 years
- HIV screening (offer to all and repeatedly offer to high-risk people)
- Hepatitis B screening (for those on transfusion therapy)
- Assess risk for breast cancer and offer to prescribe risk-reducing medications, if appropriate, for women at increased risk
- Breast screening mammography for women aged 50 to 74 years
- Women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes should be referred for genetic counseling and, if indicated after counseling, BRCA testing.
- Chlamydial infection screening for all sexually active women ≤24, and for older women at high risk
- Folic acid supplementation should be used whenever considering or at risk of pregnancy to prevent neural tube defects.
- Cardiovascular disease risk screening
 - Diabetes screening for people with hypertension
 - Lipids: Screen men ages 25 to 35 at high risk and all men ≥35 years. Screen women 20 years or older who are at high risk
 - Screen for high blood pressure in adults aged 18 and older ([For blood pressure screening recommendations, see page 18](#))
- Screen adults for colon cancer beginning at age 50 and continuing until age 75
- Depression screening when staff assisted support in place for diagnosis, treatment, and followup
- Osteoporosis screening for women ≥65 years. For women younger than 65 years, screen those whose fracture risk is equivalent or higher to a 65-year-old White woman.
- Sexually transmitted infection counseling for all sexually active adults at high risk
- Gonorrhea screening for sexually active women <25 and others at high risk
- One-time ultrasound abdominal aortic aneurysm screening for men who have smoked and are 65 to 75 years old

Source: U.S. Preventive Services Task Force (USPTF). Recommendations [Internet]. Rockville, MD: USPTF; 2010 [updated December 2010; cited 2014 May 30]. Available from: <http://www.uspreventiveservicestaskforce.org/recommendations.htm>.²⁰

Pregnant Women

Offer all pregnant women:

- Bacteriuria screening (asymptomatic)
- Gonorrhea screening for women <25 years old and for older women at high risk
- Hepatitis B screening
- HIV screening
- Syphilis screening
- Chlamydial screening for all pregnant women aged 24 and younger and for older pregnant women who are at increased risk
- Rh compatibility screening

Source: U.S. Preventive Services Task Force (USPTF). Recommendations [Internet]. Rockville, MD: USPTF; 2010 [updated December 2010; cited 2014 May 30]. Available from: <http://www.uspreventiveservicestaskforce.org/recommendations.htm>.²⁰

Immunizations

Background

Immunizations are one of the most useful preventive measures available to infants, children, and adults. This benefit should be extended to all individuals regardless of other chronic conditions, unless there is a specific disease-related or personal (e.g., allergy) contraindication. For people with SCD, there are no disease-related contraindications.

Key Question

KQ9. Which immunizations should be given to people with SCD?

Summary of the Evidence

The Advisory Committee on Immunization Practices (ACIP) reviews the evidence for each immunization it recommends. The expert panel determined that the methodology used for those reviews was compatible with its own methodology. Therefore, evidence reviews for this topic were not performed by the methodology team. The expert panel based its recommendations on those made by the ACIP (see exhibit 6).²²

Recommendations

Evidence reviews on this topic were not performed by the methodology team. Therefore, the expert panel based its recommendations on those developed by the ACIP (see exhibit 6).

1. All individuals with SCD should receive immunizations according to the ACIP harmonized immunization schedule unless they have a personal contraindication as noted in the ACIP schedule.
(Consensus–Adapted)
2. Because of their increased susceptibility to invasive pneumococcal disease, all infants with SCD should receive the complete series of the 13-valent conjugate pneumococcal vaccine series beginning shortly after birth and the 23-valent pneumococcal polysaccharide vaccine at age 2 years, with a second dose at age 5 years.
(Consensus–Adapted)

Exhibit 6. Immunization Recommendations as Adapted from the Advisory Committee on Immunization Practices (ACIP)

All individuals should be immunized as recommended by the ACIP. The most up-to-date schedule should be followed, as changes can be made up to four times per year. Consult the immunization schedule at: <http://www.cdc.gov/vaccines/schedules>. The following immunizations are of special importance or unique to people with SCD as recommended by the ACIP. These recommendations may also change periodically, and the above ACIP recommendations should be consulted for confirmation.

- **Pneumococcal (PCV13) vaccine—Children**
 - Children aged 6 to 18 years with functional or anatomic asplenia should receive one dose of PCV13.
- **Pneumococcal vaccine-naïve Adults**
 - Adults aged ≥19 years with functional or anatomic asplenia who have not previously received PCV13 or PPSV23 should receive
 - One dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later.
 - Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk.
 - A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia.
 - Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.
- **Previous vaccination with PPSV23—Adults**
 - Adults aged ≥19 years with functional or anatomic asplenia who previously have received ≥1 dose of PPSV23 should
 - Be given a PCV13 dose ≥1 year after the last PPSV23 dose was received.
 - For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.
- **Hib**
 - One dose of Hib vaccine for people aged >5 years who have SCD if they have not previously received Hib vaccine
- **Meningococcal vaccine**
 - Vaccinate infants at high risk (including those with SCD) at 2, 4, and 6 months of age, and again at 12 through 15 months with this vaccine, which is generically known as HibMenCY.
 - Persons aged 9 months through 55 years at increased risk for meningococcal disease (e.g., adults with anatomic or functional asplenia or persistent complement component deficiencies) should receive MenACWY.
 - Children aged 2 months to 6 years should receive an additional dose of MenACWY 3 years after primary immunization; boosters should be repeated every 5 years thereafter.
 - Children ≥7 years of age should receive an additional dose of MenACWY 5 years after primary immunization; boosters should be repeated every 5 years thereafter.

Sources: Hib: <http://www.mass.gov/eohhs/docs/dph/cdc/immunization/acip-summary-recommended-groups.pdf>,¹³⁸
Meningococcal vaccine: <http://www.historyofvaccines.org/content/blog/acip-makes-new-tdap-and-meningococcal-vaccine-recommendations>;¹³⁹ PCV 13 and PPSV 23: Use of 13-valent pneumococcal conjugate vaccine and 23 valent pneumococcal polysaccharide vaccine for adults for immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2012 Oct 12;61(40):816-9.¹⁴⁰