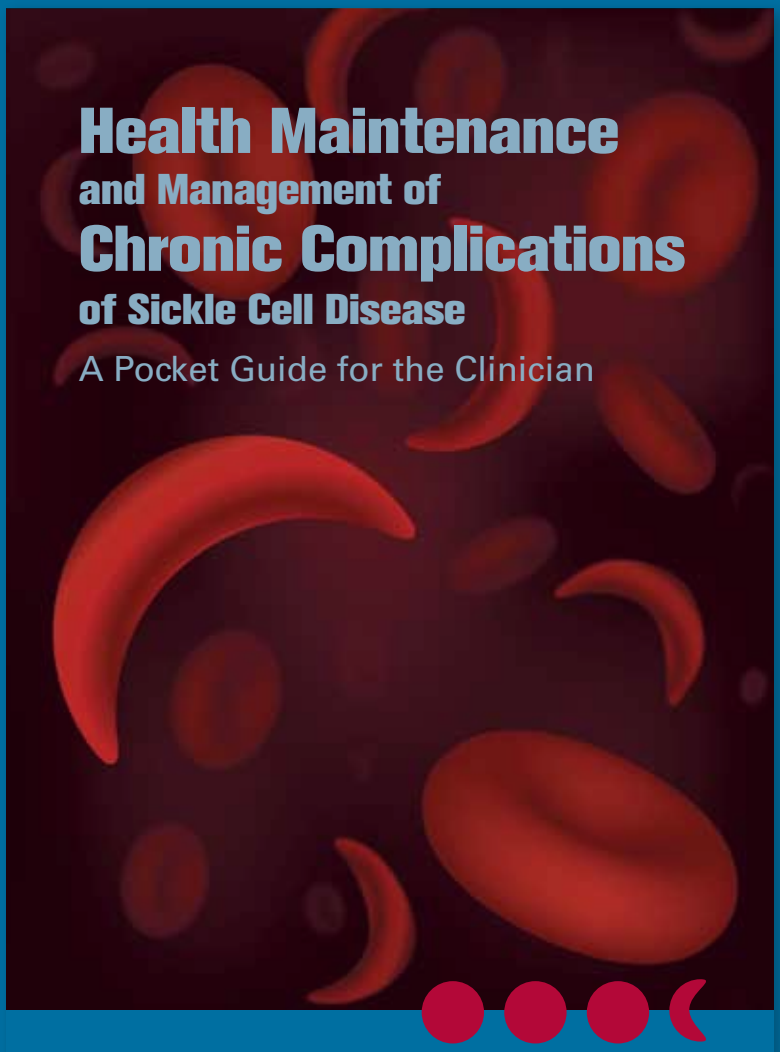

Health Maintenance and Management of Chronic Complications of Sickle Cell Disease

A Pocket Guide for the Clinician

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Screening and Follow-Up for Common Complications of Sickle Cell Disease (SCD)

Complication	Screening	Follow-Up
Avascular necrosis (AVN)	See Pain, below. The hip joint is the most common site of AVN. About 40–80% of cases of AVN of the hips are bilateral. AVN can develop in children as young as 5 years of age.	In individuals with intermittent or chronic hip pain, evaluate for AVN by history, physical exam, radiography, and MRI as needed ***(Strong recommendation, low-quality evidence)***. Treat with analgesics and consult physical therapy and orthopedics for assessment and follow-up ***(Strong recommendation, high-quality evidence)***. For advanced AVN, refer to an orthopedic surgeon and SCD specialist for evaluation and possible hip arthroplasty ***(Consensus–Expert Panel)***.
Leg ulcers	Inspect the lower extremities during physical examination for active or healed ulcers, record their number, and measure their depth ***(Weak recommendation, low-quality evidence)***. Trauma, infection, and severe anemia are associated with ulcer formation. Leg ulcers may be seen starting at age 10.	Treat with initial standard therapy (ie, debridement, wet to dry dressings, and topical agents) ***(Moderate recommendation, low-quality evidence)***. In individuals with chronic recalcitrant deep leg ulcers, evaluate for osteomyelitis ***(Moderate recommendation, low-quality evidence)***. Consult or refer to a wound care specialist or multidisciplinary wound team for persistent or recalcitrant leg ulcers ***(Consensus–Expert Panel)***.
Hypertension	Screen for hypertension ***(Consensus–Adapted [1,2])***.	Treat to lower systolic blood pressure to ≤140 and diastolic blood pressure ≤90 ***(Consensus–Adapted [1])***. For children, see NHLBI guidelines.[2]
Ophthalmologic complications	Beginning at age 10, refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy ***(Strong recommendation, low-quality evidence)***.	If examination is normal, re-screen at 1–2 year intervals ***(Consensus–Expert Panel)***. If retinopathy is suspected, refer to a retinal specialist ***(Consensus–Expert Panel)***.
Pain	Pain is considered chronic if it lasts >3 months. Types of SCD-associated chronic pain include the following: • Chronic pain of unclear etiology • Chronic pain in a specific tissue or organ, such as AVN of the hips or leg ulcers • Chronic neuropathic pain • "Breakthrough" pain Determine the cause and type of SCD-related chronic pain. This includes chronic pain with objective signs such as avascular necrosis (AVN) and leg ulcers, and chronic pain without objective signs due to neuroplasticity of the peripheral or central nervous system ***(Consensus–Adapted [3])***. Assess for pain annually or more often as needed ***(Consensus–Adapted [3])***. Assessment should include a numerical rating of severity, factors that precipitate or relieve the pain, including biopsychosocial factors, and the effect of the pain on the patient's mood, activity, employment, quality of life, and vital signs ***(Consensus–Adapted [3])***. Assess for other types of non-SCD related chronic pain including postoperative pain, pain due to trauma, pain due to therapy, iatrogenic pain, and pain due to comorbid conditions ***(Consensus–Adapted [3])***.	Goals For pain from an acute complication, see the ASH companion pocket guide "Management of Acute Complications of Sickle Cell Disease." When managing chronic pain, goals are to restore function and improve quality of life while minimizing risk of abuse, misuse, or diversion of opioids. Treatment Options Treatment options include NSAIDs, opioids, antidepressants, and anticonvulsant medications. Nonpharmacological approaches include psychological intervention, occupational therapy, behavioral and cognitive interventions, acupuncture, mild to moderate exercise if tolerable, and aqua therapy. Low-quality evidence supports massage, muscle relaxation therapy, and self-hypnosis. Chronic pain is often associated with other conditions that enhance chronicity, including depression, anxiety, and dependence on pain medications. As needed, refer for evaluation by a mental health professional. Long-Term Use of Opioids Use long- and short-acting opioids to manage chronic pain not relieved by nonopioids ***(Consensus–Adapted [3])***. Partner with the patient to develop a written, individualized treatment plan that includes risks, benefits, and side effects of treatment; patient rights and responsibilities; and type, amount, and route of administration of the opioid, including random drug urine testing ***(Consensus–Adapted [3])***. Let the patient's response guide treatment. Believe the patient's report of pain ***(Consensus–Adapted [3])***. Appoint one clinician to write the biweekly to monthly prescriptions for long-term opioids. Evaluate the patient in person every 2–3 months ***(Consensus–Adapted [3])***. Encourage the patient to increase fluid intake, maintain dietary fiber intake, and use stool softeners and bowel stimulant laxatives as needed ***(Consensus–Adapted [3])***.

Screening and Follow-Up for Common Complications of Sickle Cell Disease (SCD), cont'd

Complication	Screening	Follow-Up
Pulmonary complications	Assess for signs and symptoms of respiratory problems (such as asthma, chronic obstructive pulmonary disease, restrictive lung disease, or obstructive sleep apnea) by history and physical examination *(Consensus–Expert Panel)*.	If signs or symptoms are present, further assess including with pulmonary function tests *(Consensus–Expert Panel)*. In individuals with symptoms or signs suggestive of pulmonary hypertension (eg, dyspnea on exertion, lower extremity edema), refer for echocardiography *(Strong recommendation, moderate-quality evidence)*. If tricuspid regurgitant velocity is elevated ≥2.5 m/sec by echocardiography, consult a provider with expertise in pulmonary hypertension to guide further assessment and management, including right heart catheterization and consideration of pulmonary hypertension therapy *(Consensus–Expert Panel)*.
Renal complications	Beginning at age 10, screen annually for microalbuminuria and proteinuria with spot urine to estimate protein/creatinine ratio *(Consensus–Expert Panel)*. Hyposthenuria, or inability to concentrate urine, is common, resulting in increased risk of dehydration and enuresis. Between 4 and 18% of people with SCD will develop chronic kidney disease (CKD). Early identification is important. Significant impairment may be masked because of hypersecreted creatinine. Once the serum creatinine rises, it often reflects significant renal dysfunction. Microalbuminuria is most often the first manifestation of CKD in SCD.	If microalbuminuria or macroalbuminuria is identified, order a 24-hour urine test for protein *(Consensus–Expert Panel)*. Refer to or consult a nephrologist: • Adults or children with proteinuria (>300 mg/24 hours) *(Strong recommendation, low-quality evidence)* • Children with microalbuminuria *(Consensus–Expert Panel)* • Adults or children with modest elevations of serum creatinine (0.7 mg/dL children, >1.0 mg/dL adults) *(Consensus–Expert Panel)* Initiate ACE inhibitor therapy for adults with either microalbuminuria *(Moderate recommendation, moderate-quality evidence)* or proteinuria *(Moderate recommendation, low-quality evidence)* without other apparent causes. Use ACE inhibitor therapy even in the presence of normal blood pressure *(Moderate recommendation, low-quality evidence)*. Use renal replacement therapy (eg, hemodialysis, peritoneal dialysis, and renal transplantation) as needed *(Strong recommendation, low-quality evidence)*.
Stroke	In children with sickle cell anemia, screen annually with transcranial doppler (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)*.	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)*. In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions *(Moderate recommendation, low-quality evidence)*. If a transfusion program is not possible to implement, initiate hydroxyurea therapy *(Moderate recommendation, low-quality evidence)*.

Health Maintenance

Care Coordination

Coordination of care throughout the lifespan, particularly between primary care physicians and specialists, can improve patients' health and well-being. To improve care coordination, specialists should assess if a patient with SCD has a relationship with a primary care physician and is receiving general health-care maintenance.

Preventive Services

Newborns, children, adolescents, and adults with SCD should receive general clinical preventive services, as recommended by the U.S. Preventive Services Task Force. The most up-to-date recommendations are available at *www.USPreventiveServicesTaskForce.org*.

Prevention of Infection

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 sickle cell anemia ***(Strong recommendation, moderate-quality evidence)***.

Assure that people of all ages with SCD have been vaccinated against *Streptococcus pneumoniae* ***(Strong recommendation, moderate-quality evidence)***.

All individuals with SCD should receive immunizations as recommended by the Advisory Committee on Immunization Practices ***(Consensus–Adapted)***.
See *www.cdc.gov/vaccines/schedules*.

Remind people with SCD, their families, and caregivers to seek immediate medical attention whenever fever (temperature >101.3°F or 38.5°C) occurs, due to the risk for severe bacterial infections ***(Consensus–Expert Panel)***.

Reproductive Health

Counseling

SCD increases risks of adverse pregnancy outcomes. Encourage each woman, man, and couple affected by SCD to have a reproductive life plan ***(Consensus–Expert Panel)***. Refer for reproductive counseling as needed.

If the partner of a man or woman with SCD has unknown SCD or thalassemia status, refer the partner for hemoglobinopathy screening ***(Consensus–Expert Panel)***. After testing, refer couples who are at risk for having a potentially affected fetus for genetic counseling ***(Consensus–Expert Panel)***.

Test women with SCD who have been transfused and are anticipating pregnancy for red cell alloantibodies ***(Consensus–Expert Panel)***. If a woman has red cell alloantibodies, test her partner for the corresponding red cell antigen(s) ***(Consensus–Expert Panel)***.

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–Expert Panel)***.

Contraception

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 [4])***. Insufficient data are available on the risk of thrombosis with combined hormonal contraceptives.

If the benefits are considered to outweigh the risks (eg, thrombosis), combined hormonal contraceptives (pills, patches, and rings) may be used in women with SCD ***(Consensus–Adapted [4])***.

Disease Definition

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

Rating System and Implications of Recommendations

As indicated in parentheses in this guide, evidence-based recommendations from the NHLBI report are separately rated according to the strength of the recommendation ***(strong, moderate, or weak)*** and the quality of the supporting evidence ***(high, moderate, low, or very low)***. These ratings are intended to have the following implications (adapted from GRADE[5]):

	High-quality evidence ←–→	Low-quality evidence
Strong recommendation ↕	Recommendation can apply to most patients in most circumstances.	Recommendation may change when higher quality evidence becomes available.
Weak recommendation	The best action may differ depending on circumstances or patient or societal values.	Other alternatives may be equally reasonable.

Consensus statements represent opinion of the expert panel that authored the NHLBI report. Wherever indicated, these statements are based on minimal or no supporting evidence or very indirect evidence ***(Consensus–Expert Panel)*** or were adapted from existing guidelines ***(Consensus–Adapted)***.

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This pocket guide is adapted from the National Heart, Lung, and Blood Institute's *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014*, available at *www.nhlbi.nih.gov/guidelines*. Two companion pocket guides adapted from the same report are available: "Management of Acute Complications of Sickle Cell Disease" and "Hydroxyurea and Transfusion Therapy for the Treatment of Sickle Cell Disease."

This guide is not intended to be construed as a standard of care or to preempt clinical judgment. Recommendations based on expert opinion or less than high-quality evidence should inform shared decisionmaking with the patient about diagnostic and treatment alternatives. Even recommendations based on high-quality evidence may be inappropriate for some patients depending on clinical circumstances including individual patient preferences.

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