

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014: Guide to Recommendations



U.S. Department of Health and Human Services
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Table of Contents



Chapter 1	
Introduction to the Guide to Recommendations	1
Definition of Recommendation Ratings	1
Chapter 2	
Health Maintenance for People With Sickle Cell Disease	6
Prevention of Invasive Pneumococcal Infection.	6
Screening for Renal Disease	7
Screening for Pulmonary Hypertension	7
Electrocardiogram Screening.	7
Screening for Hypertension	7
Screening for Retinopathy	8
Screening for Risk of Stroke Using Neuroimaging	8
Screening for Pulmonary Disease	9
Reproductive Counseling.	9
Contraception	11
Clinical Preventive Services.	12
Immunizations.	13

To view the full Expert Panel Report, please visit:

<http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/>



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Table of Contents



Chapter 3	
Managing Acute Complications of	
Sickle Cell Disease	14

Vaso-Occlusive Crisis	14
Fever	18
Acute Renal Failure	19
Priapism	19
Hepatobiliary Complications	20
Acute Anemia	21
Splenic Sequestration	21
Acute Chest Syndrome	22
Acute Stroke	23
Multisystem Organ Failure	24
Acute Ocular Conditions	25

Chapter 4	
Managing Chronic Complications of	
Sickle Cell Disease	26

Chronic Pain	26
Avascular Necrosis	28
Leg Ulcers	28
Pulmonary Hypertension	29
Renal Complications	29
Stuttering/Recurrent Priapism	30
Ophthalmologic Complications	30



Table of Contents



Chapter 5
Hydroxyurea Therapy in the
Management of Sickle Cell Disease 31

Chapter 6
Blood Transfusion in the
Management of Sickle Cell Disease 35

Indications for Transfusion 35
Recommendations for Acute
and Chronic Transfusion Therapy 36
Appropriate Management/
Monitoring 38
Recommendations for the
Management and Prevention of
Transfusion Complications 40

Chapter 1: Introduction to the Guide to Recommendations

This report was developed by an expert panel composed of health care professionals with expertise in family medicine, general internal medicine, adult and pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine. Panel members were selected by the National Heart, Lung, and Blood Institute's (NHLBI's) leadership.

The purpose of this Guide to Recommendations is to provide clinicians with a digital resource of the treatment recommendations extracted from the full report. For more information, please refer to the full report, <http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/>.

Definition of Recommendation Ratings

The expert panel evaluated the existing evidence base and made graded recommendations based on the strength of the evidence. Additional recommendations were based on statements from other organizations (consensus - adapted) or the expert panel (consensus - panel expertise) and are further defined below:

Chapter 1: Introduction to the Guide to Recommendations

Exhibit 4. GRADE Recommendations—A Closer Look

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong Recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong Recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on our confidence in the estimate of effect and may change the estimate.
Strong Recommendation Low-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong Recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.

Chapter 1: Introduction to the Guide to Recommendations

Grade of Recommendation	Clarity of Risk/ Benefit	Quality of Supporting Evidence	Implications
Weak Recommendation High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Chapter 1: Introduction to the Guide to Recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Weak recommendation Very low-quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

Source: Reprinted with permission of the American Thoracic Society. Copyright© 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med.* 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.

* Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists

Chapter 1: Introduction to the Guide to Recommendations

Consensus—Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).
- Recommendations were based on the panel’s expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus—Adapted

- These recommendations were based on the panel’s expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD).

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Prevention of Invasive Pneumococcal Infection

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.

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Screening for Renal Disease

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

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.

Electrocardiogram Screening

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

Screening for Hypertension

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)

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Screening for Retinopathy

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

1. In children with Sickle Cell Anemia (SCA), screen annually with transcranial Doppler ultrasound (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., HbS β ⁺-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)

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Screening for Pulmonary Disease

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

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.

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)

Chapter 2: Health Maintenance for People With Sickle Cell Disease

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)
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.

Chapter 2: Health Maintenance for People With Sickle Cell Disease

- 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

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)

Chapter 2: Health Maintenance for People With Sickle Cell Disease

Clinical Preventive Services

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 U.S. Preventive Services Task Force (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>.

Immunizations

Evidence reviews on this topic were not performed by the methodology team. Therefore, the expert panel based its recommendations on those developed by the Advisory Committee on Immunization Practices (ACIP).

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)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

Vaso-Occlusive Crisis (VOC)

The recommendations labeled “consensus” in this section were based on recommendations developed by the American Pain Society (APS) or on panel expertise. The remaining recommendations are based on the evidence review conducted by the methodology team. These recommendations are intended to be for all settings where patients present with VOC.

1. In adults and children with SCD and pain,
 - When indicated, initiate diagnostic evaluation of causes of pain other than a VOC while beginning to treat pain.
(Consensus–Adapted)
2. In adults and children with SCD and a VOC,
 - Determine characteristics, associated symptoms, location, and intensity of pain based on patient self-report and observation. If the VOC pain is atypical, investigate other possible etiologies of pain.
(Consensus–Adapted)
 - Rapidly assess the patient’s recent analgesic use (opioid and nonopioid).
(Consensus–Adapted)
 - Rapidly initiate analgesic therapy within 30 minutes of triage or within 60 minutes of registration.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

- Base analgesic selection on pain assessment, associated symptoms, outpatient analgesic use, patient knowledge of effective agents and doses, and past experience with side effects.

(Consensus–Adapted)

3. In adults and children with SCD and a VOC,
 - Use an individualized prescribing and monitoring protocol (written by the patient’s SCD provider) or an SCD-specific protocol whenever possible to promote rapid, effective, and safe analgesic management and resolution of the VOC.

(Consensus–Panel Expertise)

4. In adults and children with SCD and a VOC associated with mild to moderate pain who report relief with NSAIDs in the absence of contraindications to the use of NSAIDs, continue treatment with NSAIDs.

(Moderate Recommendation, Low-Quality Evidence)

5. In adults and children with SCD and a VOC associated with severe pain, rapidly initiate treatment with parenteral opioids.

(Strong Recommendation, High-Quality Evidence)

6. In adults and children with SCD and a VOC associated with severe pain,
 - Calculate the parenteral (IV or subcutaneous) opioid dose based on total daily short-acting opioid dose currently being taken at home to manage the VOC.

(Consensus–Panel Expertise)

- Administer parenteral opioids using the subcutaneous route when intravenous access is difficult.

(Consensus–Panel Expertise)

- Reassess pain and re-administer opioids if necessary for continued severe pain every 15–30 minutes until pain is under control per patient report.

(Consensus–Adapted)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

- Maintain or consider escalation of the dose by 25 percent until pain is controlled.
(Consensus–Panel Expertise)
 - Reassess after each dose for pain relief and side effects.
(Consensus–Panel Expertise)
 - Initiate around-the-clock opioid administration by patient-controlled analgesia (PCA) or frequently scheduled doses versus “as requested” (PRN) administration.
(Moderate Recommendation, Low-Quality Evidence)
7. If ordering around-the-clock, continuous infusion of opioids via the PCA, carefully consider whether there is a need to withhold long-acting oral opioids to prevent over-sedation.
(Consensus–Panel Expertise)
- If demand dosing only is ordered via the PCA, continue use of long-acting oral opioids.
(Consensus–Panel Expertise)
 - At discharge, evaluate inpatient analgesic requirements, wean parenteral opioids prior to conversion to oral opioids, and adjust home dose of long- and short-acting opioid prescriptions to prevent opioid withdrawal after discharge.
(Consensus–Panel Expertise)
8. In adults and children with SCD and a VOC, do not use meperidine unless it is the only effective opioid for an individual patient.
(Consensus–Adapted)
9. In adults and children with a VOC, administer oral NSAIDs as an adjuvant analgesic in the absence of contraindications.
(Consensus–Adapted)
10. In adults and children with a VOC who require antihistamines for itching secondary to opioid administration, prescribe agents orally, and do not re-administer with each dose of opioid in the acute VOC management phase. Re-administer every 4 to 6 hours if needed.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

11. To reduce the risk of acute chest syndrome in adults and children hospitalized for a VOC,
 - Encourage use of incentive spirometry while awake.
(Strong Recommendation, Moderate-Quality Evidence)
 - Encourage ambulation and activity as soon as possible.
(Consensus–Panel Expertise)
12. In adults and children with VOC, use adjunctive nonpharmacologic approaches to treat pain such as local heat application and distraction.
(Consensus–Adapted)
13. In euvolemic adults and children with SCD and a VOC who are unable to drink fluids, provide intravenous hydration at no more than maintenance rate to avoid over-hydration.
(Consensus–Adapted)
14. In adults and children with SCD and a VOC being treated with opioids, monitor for excessive sedation by measuring sedation with an objective measurement sedation scale and oxygenation levels.
(Consensus–Panel Expertise)
15. Gradually titrate down parenteral opioids as VOC resolves.
(Consensus–Panel Expertise)
16. In adults and children with SCD and a VOC, do not administer a blood transfusion unless there are other indications for transfusion (see the chapter “Blood Transfusion in the Management of Sickle Cell Disease” in this report).
(Moderate Recommendation, Low-Quality Evidence)
17. In adults and children with SCD and a VOC with an oxygen saturation <95 percent on room air, administer oxygen.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

Fever

1. In people with SCD and a temperature $\geq 101.3^{\circ}\text{F}$ (38.5°C), immediately evaluate with history and physical examination, complete blood count (CBC) with differential, reticulocyte count, blood culture, and urine culture when urinary tract infection is suspected.
(Consensus–Panel Expertise)
2. In children with SCD and a temperature $\geq 101.3^{\circ}\text{F}$ (38.5°C), promptly administer ongoing empiric parenteral antibiotics that provide coverage against *Streptococcus pneumoniae* and gram-negative enteric organisms. Subsequent outpatient management using an oral antibiotic is feasible in people who do not appear ill.
(Consensus–Panel Expertise)
3. Hospitalize people with SCD and a temperature $\geq 103.1^{\circ}\text{F}$ (39.5°C) and who appear ill for close observation and intravenous antibiotic therapy.
(Consensus–Panel Expertise)
4. In people with SCD whose febrile illness is accompanied by shortness of breath, tachypnea, cough, and/or rales, manage according to the preceding recommendations and obtain an immediate chest x ray to investigate for ACS.
(Consensus–Panel Expertise)
5. In febrile people with SCD who have localized or multifocal bone tenderness, especially when accompanied by erythema and swelling, include bacterial osteomyelitis in the differential diagnosis and manage accordingly.
(Consensus–Panel Expertise)

Acute Renal Failure (ARF)

1. In the setting of an acute rise in serum creatinine of ≥ 0.3 mg/dL,
 - Monitor renal function daily, including serum creatinine and fluid intake/output.
(Consensus–Panel Expertise)
 - Avoid potential nephrotoxic drugs and imaging agents.
(Consensus–Panel Expertise)
 - Evaluate the patient thoroughly for all potential etiologies in consultation with a nephrologist as needed.
(Consensus–Panel Expertise)
2. Do not give blood transfusions to treat ARF unless there are other indications for transfusion.
(Consensus–Panel Expertise)
3. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure.
(Consensus–Panel Expertise)

Priapism

1. For an episode of priapism lasting 4 hours or longer, initiate interventions to include
 - vigorous oral or intravenous hydration and oral or intravenous analgesia
(Strong Recommendation, Low-Quality Evidence); and
 - consultation with a urologist who can perform further evaluation and intervention for symptoms which do not remit with initial conservative medical management.
(Consensus–Panel Expertise)
2. Do not use transfusion therapy for immediate treatment of priapism associated with SCD.
(Moderate Recommendation, Low-Quality Evidence)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

3. Consult with a hematologist for possible preoperative transfusion if surgical intervention is required.
(Consensus–Panel Expertise)

Hepatobiliary Complications

1. Treat acute cholecystitis in children and adults with SCD with antibiotics and surgical consultation.
(Consensus–Panel Expertise)
2. Treat asymptomatic gallstones with watchful waiting in children and adults with SCD. In those who develop symptoms specific to gallstones, treat with cholecystectomy. The laparoscopic approach is preferred if surgically feasible and available.
(Strong Recommendation, Moderate-Quality Evidence)
3. Consult with a hematologist or sickle cell expert for possible preoperative transfusion if surgical intervention is required.
(Consensus–Panel Expertise)
4. In children and adults with SCD and signs and symptoms of AHS or AIC, provide hydration, rest, close observation, and consult a sickle cell expert for further management.
(Consensus–Panel Expertise)
5. In children and adults with SCD and signs and symptoms of possible AHS or severe AIC, obtain urgent consultation with a sickle cell disease expert for diagnosis confirmation.
(Consensus–Panel Expertise)
6. In children and adults with SCD with confirmed AHS or severe AIC, perform simple or exchange transfusion.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

Acute Anemia

1. During all acute illnesses in people with SCD, obtain a CBC and reticulocyte count, repeat daily in all hospitalized patients, and compare the results with the patient's prior measurements.
(Consensus–Panel Expertise)
2. Assess people with SCD whose hemoglobin concentration is 2 g/dL or more below their baseline (or less than 6 g/dL when the baseline is unknown) for acute splenic sequestration, an aplastic episode, a delayed hemolytic transfusion reaction, ACS, and infection.
(Consensus–Panel Expertise)
3. Use simple transfusion in people with SCD and acute anemia whose symptoms are due to anemia.
(Consensus–Panel Expertise)
4. Perform a CBC and reticulocyte count promptly and again 7 to 10 days later in siblings and others with SCD who are exposed to a person with an aplastic episode.
(Consensus–Panel Expertise)
5. Manage aplastic events with immediate red blood cell transfusion aimed at restoring the hemoglobin to a safe (not necessarily baseline) value. Isolation of hospitalized patients (droplet precautions) is required to prevent spread of the parvovirus B19 to pregnant women and others with SCD or compromised immunity.
(Consensus–Panel Expertise)

Splenic Sequestration

1. In people with hypovolemia due to severe acute splenic sequestration, immediately provide IV fluid resuscitation.
(Strong Recommendation, Low-Quality Evidence)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

2. In consultation with a sickle cell expert, transfuse people who have acute splenic sequestration and severe anemia to raise the hemoglobin to a stable level, while avoiding over-transfusion.
(Strong Recommendation, Low Quality Evidence)
3. In consultation with a sickle cell expert, address the performance and timing of splenectomy in people with recurrent acute splenic sequestration or symptomatic hypersplenism.
(Moderate Recommendation, Low-Quality Evidence)

Acute Chest Syndrome

1. Evaluate people with SCD who develop acute onset of lower respiratory tract disease signs and/or symptoms (cough, shortness of breath, tachypnea, retractions, or wheezing) with or without fever for ACS. This should include a chest x ray and measurement of oxygen saturation by pulse oximetry.
(Consensus–Panel Expertise)
2. Hospitalize people with ACS.
(Consensus–Panel Expertise)
3. Treat people with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of greater than 95 percent), and close monitoring for bronchospasm, acute anemia, and hypoxemia.
(Strong Recommendation, Low-Quality Evidence)
4. In people with SCA, give simple blood transfusion (10 mL/kg red blood cells) to improve oxygen carrying capacity to people with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline. If baseline hemoglobin is 9 g/dL or higher, simple blood transfusion may not be required.
(Weak Recommendation, Low-Quality Evidence)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

5. In people with HbSC disease or HbS β +/-thalassemia with ACS, decisions about transfusion should be made in consultation with an SCD expert.
(Strong Recommendation, Low-Quality Evidence)
6. In all persons with SCD, perform urgent exchange transfusion—with consultation from hematology, critical care, and/or apheresis specialists—when there is rapid progression of ACS as manifested by oxygen saturation below 90 percent despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, and/or decline in hemoglobin concentration despite simple transfusion.
(Strong Recommendation, Low-Quality Evidence)
7. Encourage use of incentive spirometry while awake.
(Strong Recommendation, Moderate-Quality Evidence)

Acute Stroke

1. In people with SCD who present with severe headache, altered level of consciousness, seizures, speech problems, and/or paralysis, evaluate for acute stroke by seeking neurologic consultation and performing an urgent head computerized tomography (CT) scan followed by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) if available.
(Consensus–Panel Expertise)
2. In consultation with a sickle cell expert, perform exchange transfusion in people with SCD who develop acute stroke confirmed by neuroimaging.
(Consensus–Panel Expertise)
3. Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with SCD who have mild, subtle, or recent history of signs or symptoms consistent with transient ischemic attack.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

4. In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions.
(Moderate Strength, Low-Quality Evidence)
5. In children and adults who have had a stroke, if it is not possible to implement a transfusion program, initiate hydroxyurea therapy.
(Moderate Strength, Low-Quality Evidence)

Multisystem Organ Failure

1. In people with SCD who exhibit severe deterioration during a VOC, immediately evaluate for potential MSOF.
(Consensus–Panel Expertise)
2. In people with SCD and respiratory failure, support respiratory status with supplemental oxygenation and mechanical ventilation when needed.
(Consensus–Panel Expertise)
3. Use renal replacement therapy (e.g., hemodialysis) when needed for acute renal failure.
(Consensus–Panel Expertise)
4. In people with SCD and MSOF, immediately initiate either simple or exchange transfusion in consultation with a sickle cell expert or hematologist.
(Consensus–Panel Expertise)

Chapter 3: Managing Acute Complications of Sickle Cell Disease

Acute Ocular Conditions

1. Immediately examine for hyphema anyone with SCD who presents with eye trauma. If hyphema is present, immediately refer to an ophthalmologist for further management.
(Consensus–Panel Expertise)
2. Promptly refer anyone with SCD exhibiting signs and symptoms such as protrusion of the eye, changes in visual acuity (flashers or floaters), and unilateral or bilateral loss of vision to an eye specialist capable of performing a dilated eye exam to assess visual acuity, intraocular pressure, and the peripheral retina.
(Consensus–Panel Expertise)
3. Manage acute ocular complications in consultation with an ophthalmologist, hematologist, and other specialists with expertise in SCD.
(Consensus–Panel Expertise)

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

Chronic Pain

1. 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)
2. Use a combination of the patient’s response to treatment—including pain relief, side effects, and functional outcomes—to guide the long-term use of opioids.
(Consensus–Adapted)
3. Encourage people to use deep tissue/deep pressure massage therapy, muscle relaxation therapy, and self-hypnosis as indicated.
(Weak Recommendation, Low-Quality Evidence)
4. Use long- and short-acting opioids to manage chronic pain that is not relieved by nonopioids.
(Consensus–Adapted)
5. Assess all people with SCD for chronic pain annually or more often as needed. This assessment should include descriptors of the pain; its severity on a numerical scale; its location; factors that precipitate or relieve it, including biopsychosocial factors; and its effect on the patient’s mood, activity, employment, quality of life, and vital signs.
(Consensus–Adapted)

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

6. Use a partnership agreement leading to a written, individualized treatment plan (to include risks, benefits, and side effects) with the patient if long-term opioids are indicated. The partnership agreement should list the patient's rights and responsibilities, and the treatment plan should list the type, amount, and route of administration of the opioid in question, including random drug urine testing.
(Consensus–Adapted)
7. Appoint one physician or other clinician to write the biweekly to monthly prescriptions for long-term opioids. Refills without seeing the patient should be kept to a minimum, and people on chronic opioid therapy must be evaluated in person every 2–3 months.
(Consensus–Adapted)
8. Document all encounters with a patient, including medical history, physical exam, diagnosis, plan of management, type and amount of opioids prescribed and their side effects, if any, and lab data as needed.
(Consensus–Adapted)
9. Encourage people receiving opioids to increase their fluid intake, maintain dietary fiber intake per the current dietary fiber recommendations, and to use stool softeners and bowel stimulant laxatives such as senna and/or docusate as needed.
(Consensus–Adapted)
10. Believe the patient's report of pain and optimize therapeutic outcomes to achieve adequate pain relief and improve the patient's quality of life.
(Consensus–Adapted)
11. Refer patients for evaluation by a mental health professional such as a psychiatrist, social worker, or addiction specialist as needed.
(Consensus–Adapted)
12. Assess all people 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)

Avascular Necrosis

1. Evaluate all children and adults with SCD and intermittent or chronic hip pain for AVN by history, physical exam, radiography, and MRI as needed.
(Strong Recommendation, Low-Quality Evidence)
2. Treat AVN with analgesics and consult physical therapy and orthopedics for assessment and followup.
(Strong Recommendation, High-Quality Evidence)
3. Refer symptomatic patients with advanced stages of AVN to an orthopedic surgeon and SCD specialist for evaluation and possible hip arthroplasty.
(Consensus–Panel Expertise)

Leg Ulcers

1. Inspect the lower extremities during physical examination for active or healed ulcers, record their number, and measure their depth.
(Weak Recommendation, Low-Quality Evidence)
2. Treat leg ulcers in patients with SCD with initial standard therapy (i.e., debridement, wet to dry dressings, and topical agents).
(Moderate Recommendation, Low-Quality Evidence)
3. Evaluate people with chronic recalcitrant deep leg ulcers for osteomyelitis.
(Moderate Recommendation, Low-Quality Evidence)
4. Evaluate possible etiologies of leg ulcers to include venous insufficiency and perform wound culture if infection is suspected or if the ulcers deteriorate.
(Moderate Recommendation, Low-Quality Evidence)

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

5. Treat with systemic or local antibiotics if leg ulcer site is suspicious for infection and wound culture is positive and organism susceptible.
(Moderate Recommendation, Low-Quality Evidence)
6. Consult or refer to a wound care specialist or multidisciplinary wound team for persistent or recalcitrant leg ulcers.
(Consensus–Panel Expertise)

Pulmonary Hypertension

1. If people with SCD have symptoms or signs suggestive of PH, refer them for echocardiography.
(Strong Recommendation; Moderate-Quality Evidence)
2. For people with an elevated TRV ≥ 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 PH therapy.
(Consensus–Panel Expertise)

Renal Complications

1. If microalbuminuria or macroalbuminuria is identified, order a 24-hour urine test for protein.
(Consensus–Panel Expertise)
2. Refer people with proteinuria (>300 mg/24 hours) to a nephrologist for further evaluation.
(Strong Recommendation, Low-Quality Evidence)
3. For adults with microalbuminuria without other apparent cause, initiate ACE inhibitor therapy.
(Moderate Recommendation, Moderate-Quality Evidence)
4. For adults with proteinuria without other apparent cause, initiate ACE inhibitor therapy.
(Moderate Recommendation, Low-Quality Evidence)

Chapter 4: Managing Chronic Complications of Sickle Cell Disease

5. For children with microalbuminuria or proteinuria, consult a nephrologist.
(Consensus–Panel Expertise)
6. Consider patients with SCD with modest elevations of serum creatinine (>0.7 mg/dL in children, >1.0 mg/dL in adults) to have renal impairment and refer to a nephrologist for further evaluation.
(Consensus–Panel Expertise)
7. Give ACE inhibitor therapy for renal complications when indicated even in the presence of normal blood pressure.
(Moderate Recommendation, Low-Quality Evidence)
8. Renal replacement therapy (e.g. hemodialysis, peritoneal dialysis, and renal transplantation) should be used in people with SCD if needed.
(Strong Recommendation, Low-Quality Evidence)

Stuttering/Recurrent Priapism

1. In men and boys with SCD and recurrent or stuttering priapism, offer evaluation and treatment in consultation with a sickle cell disease specialist and a urologist, especially when episodes increase in severity or frequency.
(Weak Recommendation, Low-Quality Evidence)

Ophthalmologic Complications

1. Refer persons of all ages with Proliferative Sickle Retinopathy (PSR) to an ophthalmologist for evaluation and possible laser photocoagulation therapy.
(Strong Recommendation, Moderate-Quality Evidence)
2. Refer children and adults with vitreoretinal complications of PSR refractory to medical treatment for evaluation and possible vitrectomy.
(Strong Recommendation, Low-Quality Evidence)

Chapter 5: Hydroxyurea Therapy in the Management of Sickle Cell Disease

1. Educate all patients with SCA and their family members about hydroxyurea therapy.
(Consensus–Panel Expertise)
2. In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea.
(Strong Recommendation, High-Quality Evidence)
3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea.
(Strong Recommendation, Moderate-Quality Evidence)
4. In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea.*
(Strong Recommendation, Moderate-Quality Evidence)
5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea.
(Strong Recommendation, Moderate-Quality Evidence)
6. In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia).
(Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children >42 months and adolescents).

Note: The panel intentionally used the term “offer” realizing that patients’ values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients.

Chapter 5: Hydroxyurea Therapy in the Management of Sickle Cell Disease

7. In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia.
(Weak Recommendation, Low-Quality Evidence)
8. In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy.
(Moderate Recommendation, Very Low-Quality Evidence)
9. To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol.
(Strong Recommendation, High-Quality Evidence)
10. In people with HbS β + -thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy.
(Moderate Recommendation, Low-Quality Evidence)
11. In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert.
(Moderate Recommendation, Very Low-Quality Evidence)

** For more information, see the ACS section of the “[Managing Acute Complications of Sickle Cell Disease](#)” chapter.*

Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))

Chapter 5: Hydroxyurea Therapy in the Management of Sickle Cell Disease

- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count $\geq 2,000/\mu\text{L}$; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/ μL .
- Maintain platelet count $\geq 80,000/\mu\text{L}$
- If neutropenia or thrombocytopenia occurs:
 - Hold hydroxyurea dosing
 - Monitor CBC with WBC differential weekly
 - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias

Chapter 5: Hydroxyurea Therapy in the Management of Sickle Cell Disease

- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
 - Increase by 5 mg/kg/day increments every 8 weeks
 - Give until mild myelosuppression (absolute neutrophil count 2,000/uL to 4,000/uL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
 - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
 - Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Indications for Transfusion

Prophylactic Perioperative Transfusion

1. In adults and children with SCA, transfuse RBCs to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia.
(Strong Recommendation, Moderate-Quality Evidence)
2. In patients with HbSS disease who require surgery and who already have a hemoglobin level higher than 8.5 g/dL without transfusion, are on chronic hydroxyurea therapy, or who require high-risk surgery (e.g., neurosurgery, prolonged anesthesia, cardiac bypass), consult a sickle cell expert for guidance as to the appropriate transfusion method.
(Strong Recommendation, Low-Quality Evidence)
3. In adults and children with HbSC or HbS β ⁺-thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia.
(Moderate Recommendation, Low-Quality Evidence)

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Recommendations for Acute and Chronic Transfusion Therapy

Exhibit 14. Acute Complications—Graded Recommendations To Transfuse

Indication	How To Transfuse	Quality of Evidence	Strength of Recommendation
Symptomatic acute chest syndrome (ACS) combined with a decreased Hb of 1 g/dL below baseline	Simple transfusion	Low	Weak
Symptomatic severe ACS (as defined by an oxygen saturation less than 90% despite supplemental oxygen)	Exchange transfusion	Low	Strong
Acute splenic sequestration plus severe anemia	Simple transfusion	Low	Strong
Stroke	Simple or exchange transfusion	Low	Moderate

Exhibit 15. Acute Complications—Consensus Recommendations To Transfuse

Indication	How To Transfuse
Hepatic sequestration	Exchange or simple transfusion
Intrahepatic cholestasis	Exchange or simple transfusion
Multisystem organ failure (MSOF)	Exchange or simple transfusion
Aplastic crisis	Simple transfusion
Symptomatic anemia	Simple transfusion

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Exhibit 16. Acute Complications—Graded Recommendations When Transfusion Is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Uncomplicated painful crisis	Low	Moderate
Priapism	Low	Moderate

Exhibit 17. Acute Complications—Consensus Recommendations When Transfusion Is Not Indicated

Indication
Asymptomatic anemia
Acute kidney injury, unless multisystem organ failure (MSOF)

Exhibit 18. Chronic Complications—Graded Recommendations for When To Initiate a Chronic Transfusion Program

Indication	How To Transfuse	Quality of Evidence	Strength of Recommendation
Child with transcranial Doppler (TCD) reading* >200 cm/sec	Exchange or simple transfusion	High	Strong
Adults and children with previous clinically overt stroke	Exchange or simple transfusion	Low	Moderate

*TCD reading is the time averaged mean maximal cerebral blood flow velocity. See section about Screening for Risk of Stroke Using Neuroimaging in the “Health Maintenance for People With Sickle Cell Disease” chapter.

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Exhibit 19. Chronic Complications—Graded Recommendations for When Transfusion is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Recurrent splenic sequestration	Low	Weak

Appropriate Management/Monitoring

1. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens.
(Moderate Recommendation, Low-Quality Evidence)
2. In patients with SCA, who are not chronically transfused and who are therefore at risk for hyperviscosity due to high percentages of circulating HbS-containing erythrocytes, avoid transfusing to a target hemoglobin above 10 g/dL.
(Moderate Recommendation, Low-Quality Evidence)
3. In chronically transfused children with SCA, the goal of transfusion should be to maintain a HbS level of below 30 percent immediately prior to the next transfusion.
(Moderate Recommendation, Moderate-Quality Evidence)
4. The expert panel recommends that clinicians prescribing chronic transfusion therapy follow an established monitoring protocol.
(Moderate Recommendation, Low-Quality Evidence)

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Consensus Protocol for Monitoring Individuals on Chronic Transfusion Therapy

The following is a consensus protocol for the initiation and monitoring of patients on chronic transfusion therapy. It is understood that the recommended testing schedule may not be available to patients everywhere; therefore, this protocol should serve only as a helpful guide for transfusion management.

At Initiation

- Obtain patient treatment history to include locations where prior transfusions were received and any adverse effects.
- Notify the blood bank that the patient being initiated on chronic transfusion therapy has SCD. Ask the blood bank to contact hospitals where the patient reported receiving previous transfusion therapy to obtain transfusion information.
- Obtain a RBC phenotype, type and screen, quantitative measurement of percent HbA and percent HbS, complete blood count (CBC), and reticulocyte count.
- Inform the patient if he or she is alloimmunized, so that this information can be communicated as part of the patient's self-reported medical history.

Suggested Evaluation Before Each Transfusion

- CBC and reticulocyte count—This procedure is done to help guide the frequency and volume of transfusions. It is expected that, with effective chronic transfusion therapy, the patient's bone marrow will be suppressed and the reticulocyte count should decrease, but the value may rise by the time of the next transfusion.
- Quantitative measurement of percent HbA and percent HbS—This procedure is done to confirm the success of chronic transfusion therapy with achieving the target percent of HbS.
- Type and screen—This is done to assess whether the patient has developed any new RBC antibodies from the prior transfusion.

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

Suggested Periodic Evaluations

- Liver function tests annually or semiannually—These tests are done to follow liver function in individuals with iron overload.
- Serum ferritin (SF) quarterly—This test is done to follow iron stores in individuals with iron overload; it can be helpful in evaluating compliance with chelation.
- Screening for hepatitis C, hepatitis B, and HIV annually.
- Evaluation for iron overload every 1–2 years by validated liver iron quantification methods such as liver biopsy, MRI R2 or MRI T2* or R2 techniques.

Recommendations for the Management and Prevention of Transfusion Complications

Recommendations for Both Children and Adults

1. Obtain patient transfusion history to include locations of prior transfusions and adverse effects.
(Consensus–Panel Expertise)
2. Ask the blood bank to contact hospitals where patient reported receiving previous transfusion therapy to obtain transfusion information.
(Consensus–Panel Expertise)
3. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens.
(Moderate Recommendation, Low-Quality Evidence)
4. Consult the blood bank for a workup of a possible DHTR in a patient with any of the following signs or symptoms: acute anemia, pain, or jaundice within 3 weeks after a blood transfusion.
(Strong Recommendation, Moderate-Quality Evidence)

Chapter 6: Blood Transfusion in the Management of Sickle Cell Disease

5. In patients with SCA who are not chronically transfused and who are therefore at risk for hyperviscosity, avoid transfusing to a target hemoglobin above 10 g/dL (unless the patients are already on chronic transfusions or have low percent HbS levels).
(Moderate Recommendation, Low-Quality Evidence)
6. In patients who receive chronic transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, or MRI R2 or MRI T2* and R2* techniques. The optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics.
(Strong Recommendation, Moderate-Quality Evidence)
7. Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload.
(Moderate Recommendation, Moderate-Quality Evidence)