Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Managing chronic complications of sickle cell disease. In: Evidence-based management of sickle cell disease.

Bibliographic Source(s)

Managing chronic complications of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 55-70.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines: A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- March 22, 2016 – Opioid pain medicines: The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Definitions of the grades of recommendation (Strong, Weak), the quality of supporting evidence (High, Moderate, Low, Very Low), and consensus statements are presented at the end of the "Major Recommendations" field.

Note from the National Heart, Lung, and Blood Institute (NHLBI) and the National Guideline Clearinghouse (NGC): The evidence-based management of sickle cell disease (SCD) has been divided into five topic areas with individual summaries covering recommendations to assist health care professionals in various aspects of management. In addition to the current summary, the following are available:

- Health maintenance for people with sickle cell disease
- Managing acute complications of sickle cell disease
- Hydroxyurea therapy in the management of sickle cell disease
- Blood transfusion in the management of sickle cell disease

Chronic Pain

Key Question 18

In people with SCD and chronic pain, what are the safest and most effective chronic pain management strategies and treatment algorithms (e.g., patient assessment and follow-up, use of chronic opioids, adjuvant pharmacological therapies, and behavioral therapies)?

Recommendations

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)
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 (AVN)

Key Question 19

In people with SCD and AVN, what are the most effective management strategies to reduce pain and functional disability (e.g., analgesics, physical therapy, surgery, or transfusion therapy)?

Recommendations

1. Evaluate all children and adults with SCD and intermittent or chronic hip pain for AVN by history, physical exam, radiography, and magnetic resonance imaging (MRI) as needed. (Strong Recommendation, Low-Quality Evidence)
2. Treat AVN with analgesics and consult physical therapy and orthopedics for assessment and follow-up. (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

Key Question 20

In people with SCD and leg ulcers, what are the most effective therapies to accelerate ulcer healing (e.g., topical therapy, surgery, or antibiotics)?

Recommendations

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)
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 (PH)

Key Question 21

In people with SCD and PH, what are the most effective therapies to reduce mortality (e.g., transfusion, hydroxyurea, and other pharmacological agents)?

Recommendations

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 tricuspid regurgitant jet velocity (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

Key Question 22

In people with SCD and chronic kidney disease (CKD), what are the interventions (including pharmacotherapy, dialysis, and renal transplant) that slow the deterioration of renal function, prevent the development of end-stage renal disease, and reduce mortality?

Recommendations

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 angiotensin-converting-enzyme (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)
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

Key Question 23

In people with SCD and stuttering priapism, what is the relative efficacy of the available treatments (chronic hormonal therapy, chronic transfusion therapy, alpha-adrenergic agents, phosphodiesterase type 5 [PDE-5] esterase inhibitors, and hydroxyurea) on recurrence of priapism and sexual functional outcomes?

Recommendation

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

Key Question 24

In people with SCD and chronic ophthalmic complications (proliferative sickle retinopathy [PSR] or vitreous hemorrhage), what are the most effective management strategies (surgery, laser therapy, or conservative management) to improve and preserve vision?

Recommendations

1. Refer persons of all ages with 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)

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

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 randomized controlled trials (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 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 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 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.
Weak recommendation	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally	The best action may differ depending on circumstances or patient or societal values.

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
High-quality evidence		strong evidence from unbiased observational studies	Further research is very unlikely to change 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 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 confidence in the estimate of effect and is likely to change the estimate.
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.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

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). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Chronic complications of sickle cell disease (SCD) including:

- Chronic pain
- Avascular necrosis (AVN)
- Leg ulcers
- Pulmonary hypertension (PH)
- Renal complications
- Stuttering/recurrent priapism
- Ophthalmic complications including proliferative sickle retinopathy (PSR) and vitreous hemorrhage

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Hematology

Internal Medicine

Nephrology

Nursing

Ophthalmology

Orthopedic Surgery

Pediatrics

Pulmonary Medicine

Radiology

Urology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To synthesize the available scientific evidence on sickle cell disease (SCD) and offer guidance to busy primary care clinicians
- To help people living with SCD receive appropriate care by providing the best science-based recommendations to guide practice decisions
- To assist health care professionals in the management of common issues, including routine health maintenance, the recognition and treatment of common acute and chronic complications and comorbidities of SCD, as well as the indications for and monitoring of hydroxyurea and blood transfusion therapy
- To help provide the latest evidence-based recommendations to manage this condition and to help engage health care professionals in supporting their implementation at the practice level
- To present recommendations related to the evaluation and management of the most common chronic complications of SCD as well as information regarding their frequency, most common presentations, usual evaluation, and treatment

Target Population

Infants, children, adolescents, and adults with sickle cell disease (SCD)

Interventions and Practices Considered

1. Management of chronic pain: pain assessment, nonpharmacologic interventions, and long-term opioid therapy
2. Evaluation and management of avascular necrosis (AVN): history and physical exam; radiography; magnetic resonance imaging (MRI); analgesic therapy; referral to physical therapy, orthopedic surgeon, and sickle cell disease (SCD) specialist
3. Evaluation and management of leg ulcers: inspection; standard therapy (i.e., debridement, wet to dry dressings, and topical agents); evaluation for osteomyelitis and venous insufficiency; wound culture; antibiotic treatment; referral to wound specialist/wound team
4. Evaluation and management of pulmonary hypertension (PH): echocardiography referral and PH specialist consultation for further assessment and management (right heart catheterization and PH therapy)
5. Evaluation and management of renal complications: 24-hour urine test for protein, serum creatinine, angiotensin-converting enzyme (ACE) inhibitor therapy, renal replacement therapy (e.g., hemodialysis, peritoneal dialysis, renal transplantation)
6. Evaluation and treatment of stuttering/recurrent priapism in consultation with a SCD specialist and urologist
7. Management of chronic ophthalmic complications (proliferative sickle retinopathy [PSR] or vitreous hemorrhage): referral to ophthalmologist for possible laser photocoagulation therapy or vitrectomy

Major Outcomes Considered

- Complication-specific outcomes including resolution of complication
- General sickle cell disease outcomes if relevant (death, stroke, pain crises, need for transfusion, hemoglobin and hemoglobin F levels)
- Outcomes of diagnostic studies: accuracy of diagnosis if reported

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Literature Search

Due to the comprehensive scope of the guidelines, the search strategies for the systematic reviews were designed to have high sensitivity and low specificity; hence, the strategies were often derived from population and condition terms (e.g., people with sickle cell disease [SCD] who have priapism) and not restricted or combined with outcome or intervention terms. To be inclusive of the available literature in the field, searches included randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm (e.g., the adverse effects of hydroxyurea) or when rare complications were expected to be reported.

Literature searches involved multiple databases (e.g., Medline® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature [CINAHL®], TOXLINE®, and Scopus) and used controlled vocabulary (prespecified) terms supplemented with keywords to define concept areas.

An updated search was performed to span the time from June 1, 2010 through July 11, 2014.

Guideline-specific Literature Search

A comprehensive study of several databases was conducted, and all human studies in English published from 1970 to July 2010 that addressed each Patient, Intervention, Comparison, Outcomes, and Study Design (PICOS) question were identified. When the literature search found insufficient evidence on a topic (e.g., chronic pain management), these topics were supplemented with recommendations derived from other published guidelines by professional organizations which were based on systematic reviews of broader population groups; these recommendations are labeled "Consensus–Adapted."

Detailed information on the search questions, search strategy, study selection process, and list of excluded studies used in this guideline can be found in the systematic review (see the "Availability of Companion Documents" field).

Number of Source Documents

General Literature Search

The initial literature searches performed to support these guidelines yielded 12,532 references. The expert panel also identified an additional 1,231 potentially relevant references. An updated search of randomized controlled trials (RCTs) added eight trials. All abstracts were reviewed independently by two reviewers using an online reference management system (DistillerSR—http://systematic-review.net) until reviewers reached adequate agreement (kappa ≥0.90). A total of 1,575 original studies were included in the evidence tables.

Guideline-specific Literature Search

A total of 549 studies of complications were included.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

See the "Rating Scheme for the Strength of the Recommendations" field.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Methodology

Evidence Synthesis

Methodologists developed evidence tables to summarize individual study findings and present the quality of evidence (i.e., confidence in the estimates of effect). The tables included descriptions of study population, sickle cell disease (SCD) genotypes, interventions, and outcomes. Additional methodological details are discussed in each evidence table, including the search question, search strategy, study selection process, and list of excluded studies (see the "Availability of Companion Documents" field).

Evidence Framework

The methodology team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to grade the quality of evidence, and, in concert with the panel, determine the strength of recommendations. The GRADE framework is accepted by more than 75 national and international organizations (see exhibit 3 in the original guideline document). It provides the advantages of: (a) separately judging the quality of supporting evidence and strength of recommendations, and (b) incorporating factors other than evidence in decisionmaking (e.g., the balance of benefits and harms; the perceived values and preferences of those with SCD; resources; and clinical and social context). GRADE emphasizes the use of patient-important outcomes (i.e., outcomes that affect the way patients feel, function, or survive) over laboratory and physiologic outcomes.

Determining Evidence Quality

In the GRADE framework, the quality of evidence (in this case, the body of evidence) is rated as high, moderate, low, or very low. The quality of evidence derived from randomized trials starts as "high," and the quality of evidence derived from observational studies starts as "low." The quality of evidence can then be lowered due to methodological limitations in individual studies (risk of bias), inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals), and the presence of publication and reporting biases. Conversely, the quality of evidence can be upgraded in certain situations such as when the treatment effect is large or a dose-response relationship is evident.

Existing Systematic Reviews and Clinical Practice Guidelines

The expert panel and methodology team identified existing systematic reviews and clinical practice guidelines that were relevant to the topics of this guideline, even though they were not necessarily specific to people with SCD. If the methodological quality of these resources was found to be appropriate by the methodology team, they were used. Using this external evidence was considered helpful because well-conducted systematic reviews made the process of identifying relevant studies more feasible. In addition, using existing guidelines developed by professional organizations enabled the panel to develop more comprehensive recommendations that addressed specific aspects of care in individuals with SCD. Usually, this external evidence was derived from studies in non-sickle cell patient cohorts because it was felt that they offered more precise and useful inferences than evidence derived from sickle cell patient studies. For example, comparative evidence in the area of pain management in people with SCD was sparse. In this situation, pain management guidelines from individuals with other pain-related conditions proved to be helpful.

The methodology team used the AMSTAR tool to assess the methodological quality of systematic reviews. Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in pediatric and adult patients. The expert panel and methodology team appraised these reviews and conducted additional searches to update the existing systematic review through May 2010 to find evidence for the benefits, harms, and barriers of using hydroxyurea. Regarding the management of children with SCD complications, the panel also used recent evidence that had been systematically reviewed.

Existing clinical practice guidelines were considered acceptable if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence, and included recommendations that were explicitly linked to the quality of supporting evidence. The expert panel and methodology team used relevant recommendations from the U.S. Preventive Services Task Force (USPSTF), the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention's (CDC) adaptation of the World Health Organization's (WHO) "Medical Eligibility Criteria for Contraceptive Use," and the American Pain Society's "Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease," and "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain."

Guideline-specific Methodology

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the evidence table in the systematic review (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These guidelines were 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.

Process and Methodology

The expert panel first convened in the spring of 2009 to establish the vision and purpose of the panel, discuss the process and schedule for producing the guidelines, and determine the critical areas to be addressed. Prior to this meeting, the expert panel participated in a conference call to introduce the panel's work and discuss the overarching questions that should be answered by the guidelines. Before beginning the writing of the guidelines report, the expert panel divided its work into sections dealing with preventive care or health maintenance, recognition and management of acute sickle-cell disease (SCD)-related complications, recognition and management of chronic SCD-related complications, and the two most broadly assessed and available disease-modifying therapies for SCD, hydroxyurea and chronic blood transfusions.

With the assistance of the methodology team and the supporting evidence center, the panel then developed key questions and literature search terms to identify evidence. The field of SCD has a limited number of randomized controlled trials (RCTs) or large prospective cohort studies to guide clinical decisionmaking; therefore, few of the recommendations in this document are based on this highest quality evidence. For common health issues, the panel included the evidence-based recommendations of the United States Preventive Services Task Force (USPSTF) as well as vetted recommendations of other groups. These recommendations include the SCD reproductive-related recommendations of the World Health Organization (WHO), the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP), and the acute and chronic pain management recommendations of the American Pain Society (APS). These recommendations are denoted as "Consensus–Adapted."

Recognizing the need to provide practical guidance for common problems that may lie outside of the panel's evidence reviews or available science, in many areas the published evidence was supplemented by the expertise of the panel members, who have many years of experience in managing and studying individuals with SCD. Recommendations based on the opinions of the expert panel members are labeled as "Consensus–Panel Expertise." Each is clearly labeled with the strength of the recommendation and the quality of evidence available to support it.

Determining the Strength of Recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework rates the strength of recommendations as "strong" or "weak." However, the panel modified the GRADE system and used a third category—moderate—when they determined that patients would be better off if they followed a recommendation, despite there being some level of uncertainty about the magnitude of benefit of the intervention or the relative net benefit of alternative courses of action. The panel intends for these moderate-strength recommendations to be used to populate protocols of care and provide a guideline based on the best available evidence. The panel does not intend for weak- or moderate-strength recommendations to generate quality-of-care indicators or accountability measures or affect insurance reimbursement. Variation in care in the areas of weak- or moderate-strength recommendations may be acceptable, particularly in ways that reflect patient values and preferences. Conversely, strong recommendations represent areas in which there is confidence in the evidence supporting net benefit, and the recommendations likely apply to most individuals with sickle cell anemia. For more information, see the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

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 randomized controlled trials (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 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 confidence in the estimate of effect and may change the estimate.

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
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 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.
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 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 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 confidence in the estimate of effect and is likely to change the estimate.
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.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

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 sickle cell disease [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). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Prior to publication, these guidelines were reviewed by the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council, a separate panel of sickle cell disease (SCD) experts, and the National Blood Disorders Program Coordinating Committee. The guidelines were also posted to the NHLBI Web site for an extensive public review and comment period, which resulted in the submission of more than 1,300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed each comment or recommendation, many of which resulted in a revision to the guidelines. The guidelines were then reviewed by SCD experts representing three professional societies.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of chronic complications of sickle cell disease (SCD)

Potential Harms

- Side effects of opioid therapy for pain
- Side effects of interventions for priapism including decreased libido and sexual function
- Serious adverse events associated with sildenafil use for pulmonary hypertension (PH)
- Potentially unknown long-term adverse effects of hydroxyurea therapy

Qualifying Statements

Qualifying Statements

The purpose of the "Evidence-Based Management of Sickle Cell Disease: Expert Panel Report (EPR), 2014" is to synthesize the available

scientific evidence on sickle cell disease and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended to provide guidance for management, not to be rigidly prescriptive. The panel recognizes that the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, the Expert Panel Report is a tool to be adopted and implemented in local and individual settings, and to provide an opportunity for shared decisionmaking in which providers and patients are both fully engaged.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Managing chronic complications of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 55-70.

Adaptation

The panel adapted selected recommendations applicable to people with sickle cell disease (SCD) from the guidelines for the management of chronic pain published by the American Pain Society in collaboration with the American Academy of Pain Medicine:

- Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113-30.

Date Released

2014

Guideline Developer(s)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

Panel Members: George R. Buchanan, M.D. (*Co-chair*), University of Texas Southwestern Medical Center, Dallas, TX; Barbara P. Yawn, M.D., M.Sc., M.S.P.H. (*Co-chair*), University of Minnesota, Rochester, MN; Araba N. Afenyi-Annan, M.D., M.P.H., University of North Carolina at Chapel Hill, Chapel Hill, NC; Samir K. Ballas, M.D., Thomas Jefferson University, Cardeza Foundation, Philadelphia, PA; Kathryn L. Hassell, M.D., University of Colorado Denver, Aurora, CO; Andra H. James, M.D., M.P.H., University of Virginia, Charlottesville, VA; Lanetta Jordan, M.D., M.P.H., M.S.P.H., Foundation for Sickle Cell Disease Research, University of Miami, Miller School of Medicine, Miami, FL; Sophie M. Lanzkron, M.D., M.H.S., Johns Hopkins School of Medicine, Baltimore, MD; Richard Lottenberg, M.D., University of Florida, Gainesville, FL; William J. Savage, M.D., Ph.D., Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Paula J. Tanabe, Ph.D., R.N., F.A.E.N., F.A.A.N., Duke University, Schools of Nursing and Medicine, Durham, NC; Russell E. Ware, M.D., Ph.D., Cincinnati Children's Hospital Medical Center, Cincinnati, OH; M. Hassan Murad, M.D., M.P.H. (*Methodologist*), Mayo Clinic, Rochester, MN

Refer to the original guideline document for members of the National Heart, Lung, and Blood Institute staff and the contractor support.

Financial Disclosures/Conflicts of Interest

The National Heart, Lung, and Blood Institute (NHLBI) established the expert panel and invited the panel members. All members served as volunteers and received no compensation from NHLBI or any other entity for their participation.

During the development of these guidelines, measures were taken to ensure the transparency of the evidence review process and to manage all potential or perceived conflicts of interest. At the initial expert panel meeting, expert panel members were asked by the panel co-chairs to disclose interests and relationships that could potentially influence their participation or pose a potential conflict of interest. The responses are provided below.

- Araba N. Afenyi-Annan, M.D., M.P.H.—Consultant, Transfusion Safety Summit: Risks Associated with Iron Toxicity in Transfusional Medicine—Novartis Pharmaceuticals Corporation (November 2008); Duke University Comprehensive Sickle Cell Center, Mentored Research Training Supplement (April 2005–April 2006); Expert Witness for Hall, Booth, Smith & Slover, P.C. (2010–present)
- Samir K. Ballas, M.D.—Speaker's Bureau, Novartis; Sickle Cell Advisory Board, HemaQuest; U.S. Sickle Cell Advisory Board, Sangart
- Kathryn L. Hassell, M.D.—Advisory Board, ApoPharma; Consultant, AGA Medical Corp.; Consultant and Principal Investigator of Local Site Multicenter Sickle Cell Study, Terumo, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, GlycoMimetics, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, Emmaus, Inc.; Board of Directors, Mount Evans Home Health & Hospice; Medical Advisory Board, Foundation for Women and Girls with Blood Disorders; Medical Advisory Board, PFO Research Foundation
- Andra H. James, M.D., M.P.H.—Consultancy for the von Willebrand Disease Medical Advisory Board for CSL Behring; Research study of antithrombin levels in pregnancy for Grifols/Talecris; Study of von Willebrand factor levels and fibrinogen levels post partum for CSL Behring; Expert witness for Johnson & Johnson and Sanofi-Aventis
- Lanetta Jordan, M.D., M.P.H., M.S.P.H.—National Heart, Lung, and Blood Advisory Council; Faculty Chair, Sickle Cell Disease Association of America, Inc. (SCDAA) and National Initiative for Children's Healthcare Quality (NICHQ) for Health Resources and

Services Administration-funded Sickle Cell Disease Treatment Demonstration Program; AESRx Medical Advisory Council; Prolong Pharmaceutical Medical Advisory Board; Consultant for NKT Therapeutics, TriStem, Pfizer, and Novartis; Board Member, Foundation for Women and Girls with Blood Disorders and Miami YWCA

- Sophie M. Lanzkron, M.D., M.H.S.—Scientific Advisory Board for HemaQuest; Principal investigator on studies sponsored by Emmaus, GlycoMimetics, Inc., and Novartis
- Paula J. Tanabe, Ph.D., R.N., M.S.N., M.P.H.—Partner, ESI Triage Research Team, LLC; Principal investigator on Agency for Healthcare Research and Quality research grant; Subcontractor to the Michigan Public Health Institute and the Health Resources and Services Administration (HRSA) to conduct a project in SCD, pediatrics, emergency department (ED) research; recipient of Duke School of Nursing grant to complete a project to measure the effect of a high dose opioid protocol to treat adults with a vaso-occlusive crisis (VOC) in the ED; Expert witness consultant on one SCD legal case
- Russell E. Ware, M.D., Ph.D.—Consultant for Bayer, Novartis Pharmaceuticals, and Sobi

No relationships to disclose: George R. Buchanan, M.D.; Richard Lottenberg, M.D.; William J. Savage, M.D., Ph.D.; Barbara P. Yawn, M.D., M.Sc., M.S.P.H.

Guideline Endorser(s)

American Academy of Emergency Medicine - Medical Specialty Society

American Academy of Pediatrics - Medical Specialty Society

American Academy of Physician Assistants - Professional Association

American Osteopathic Association - Professional Association

American Society of Hematology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

International Association of Sickle Cell Nurses and Physician Assistants - Professional Association

National Black Nurses Association, Inc - Professional Association

National Institute for Children's Health Quality - Professional Association

National Medical Association - Professional Association

Sickle Cell Disease Association of America - Disease Specific Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Heart, Lung, and Blood Institute (NHLBI) Web site .

Print copies: Available from the NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com.

Availability of Companion Documents

The following are available:

- Evidence-based management of sickle cell disease. Expert panel report quick guide. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. 45 p. Electronic copies: Available from the National Heart, Lung, and Blood Institute (NHLBI) Web site

.
- Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel members. JAMA. 2014 Sep 10;312(10):1033-1048. Electronic copies: Available from the Journal of the American Medical Association (JAMA) Network Web site .
- Hazem A, Mullan R, Lane M, Elraiyah T, Shahrour A, Gupta S, Prokop L, Montori VM, Murad MH. The management of sickle cell disease complications: a systematic review, 2012. 353 p. Electronic copies: Available from the NHLBI Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 24, 2014. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

Copyright Statement

No copyright restrictions apply.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.