Special Communication

Management of Sickle Cell Disease
Summary of the 2014 Evidence-Based Report by Expert Panel Members

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IMPORTANCE Sickle cell disease (SCD) is a life-threatening genetic disorder affecting nearly 100 000 individuals in the United States and is associated with many acute and chronic complications requiring immediate medical attention. Two disease-modifying therapies, hydroxyurea and long-term blood transfusions, are available but underused.

OBJECTIVE To support and expand the number of health professionals able and willing to provide care for persons with SCD.

EVIDENCE REVIEW Databases of MEDLINE (including in-process and other nonindexed citations), EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, TOXLINE, and Scopus were searched using prespecified search terms and keywords to identify randomized clinical trials, nonrandomized intervention studies, and observational studies. Literature searches of English-language publications from 1980 with updates through April 1, 2014, addressed key questions developed by the expert panel members and methodologists.

FINDINGS Strong recommendations for preventive services include daily oral prophylactic penicillin up to the age of 5 years, annual transcranial Doppler examinations from the ages of 2 to 16 years in those with sickle cell anemia, and long-term transfusion therapy to prevent stroke in those children with abnormal transcranial Doppler velocity (≥200 cm/s). Strong recommendations addressing acute complications include rapid initiation of opioids for treatment of severe pain associated with a vasoocclusive crisis, and use of incentive spirometry in patients hospitalized for a vasoocclusive crisis. Strong recommendations for chronic complications include use of analgesics and physical therapy for treatment of avascular necrosis, and use of angiotensin-converting enzyme inhibitor therapy for microalbuminuria in adults with SCD. Strong recommendations for children and adults with proliferative sickle cell retinopathy include referral to expert specialists for consideration of laser photocoagulation and for echocardiography to evaluate signs of pulmonary hypertension. Hydroxyurea therapy is strongly recommended for adults with 3 or more severe vasoocclusive crises during any 12-month period, with SCD pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome. A recommendation of moderate strength suggests offering treatment with hydroxyurea without regard to the presence of symptoms for infants, children, and adolescents. In persons with sickle cell anemia, preoperative transfusion therapy to increase hemoglobin levels to 10 g/dL is strongly recommended with a moderate strength recommendation to maintain sickle hemoglobin levels of less than 30% prior to the next transfusion during long-term transfusion therapy. A strong recommendation to assess iron overload is accompanied by a moderate strength recommendation to begin iron chelation therapy when indicated.

CONCLUSIONS AND RELEVANCE Hydroxyurea and transfusion therapy are strongly recommended for many individuals with SCD. Many other recommendations are based on quality of evidence that is less than high due to the paucity of clinical trials regarding screening, management, and monitoring for individuals with SCD.

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Sickle cell disease (SCD) was first reported in November 1910 by Herrick,[1] an internal medicine specialist in Chicago, Illinois, who referred to "peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia." Substantial knowledge about SCD has been gained since that first description. Yet the 2 most widely available disease-modifying therapies, hydroxyurea and long-term transfusions, are underused,[2,3] and hematopoietic stem cell transplantation, the only curative approach, has been used in only a small proportion of affected individuals.[4]

ACS *acute chest syndrome*

GRADE *Grading of Recommendations Assessment, Development, and Evaluation*

PAH *pulmonary arterial hypertension*

PSR *proliferative sickle retinopathy*

RCT *randomized clinical trial*

SCA *sickle cell anemia*

SCD *sickle cell disease*

Sickle hemoglobin (HbS), the predominant hemoglobin that is present in the red blood cells of persons with SCD, results from substitution of the amino acid valine for glutamic acid at the sixth position of the β-globin chain.[5] When deoxygenated, red blood cells from persons with SCD can develop a sickle or crescent shape, become inflexible, and increase blood viscosity through intrinsic properties of the sickled cells as well as abnormal interactions of these cells with leukocytes, platelets, vascular endothelium, and clotting factors.[6,7]

Several SCD genotypes exist (**Table 1**). The most prevalent genotype, HbSS, and the much less common HbSβ^0-thalassemia, are both commonly referred to as sickle cell anemia (SCA) because they are phenotypically very similar and are associated with the most severe clinical manifestations. Between 70 000 and 100 000 individuals in the United States have SCD. Most of those affected are of African ancestry or self-identify as black, with a minority being of Hispanic, Middle Eastern, or Asian Indian descent. An additional 3.5 million people in the United States are heterozygote carriers of HbS (HbAS genotype; ie, they have sickle cell trait).[8]

Care for persons with SCD often lacks continuity. Primary care and emergency care health professionals need up-to-date clinical guidance regarding care of persons with SCD. This report summarizes the *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report 2014* (available at http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/) developed by an expert panel convened in 2009 by the National Heart, Lung, and Blood Institute (NHLBI).

Methods

The expert panel was composed of health care professionals with expertise in the areas of family medicine, general internal medicine, pediatric and adult hematology, psychiatry and mental health, transfusion medicine, obstetrics and gynecology, maternal/fetal medicine, emergency department nursing, and evidence-based medicine. An independent methodology group assisted the expert panel by performing literature searches, preparing evidence tables, and summarizing the evidence. Rating the quality of evidence and assigning the strength of recommendations was based on a modification of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[9]

This summary report and the full SCD guideline (available at http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/) are designed to support primary care physicians, nurses, and other health care professionals who provide continuity of care or outpatient, inpatient, or emergency care to individuals with SCD and thereby enhance the lives of persons living with the disease. Care for the wide array of complications may be complex and often requires consultation with experts in SCD care and management. The guideline is divided into sections related to health maintenance (including prevention and screening recommendations) as well as diagnosis and management of acute and chronic complications. The final 2 sections address hydroxyurea and blood transfusion therapies.

During development of the guideline, measures were taken to ensure the transparency of the evidence review process, and processes were established to manage all potential or perceived conflicts of interest. For each of the 5 topic areas, the expert panel (assisted by the methodology group) developed an initial list of critical questions formatted according to the PICOS (P = Population; I = Intervention, exposure; C = Comparator; O = Outcome; S = Setting) framework[10] for literature searches, formal evidence appraisal, and vetting.

Literature Search

Search strategies were designed to have high sensitivity and low specificity to ensure the broadest capture of relevant data. To be in-

Table 1. Typical Laboratory Findings in Sickle Cell Disease and Sickle Cell Trait

	Hemoglobin, g/dL[a]	Sickle Cell Genotype, %				
		HbS	HbA	HbA_2	HbF	HbC
Sickle cell disease						
SS	6-9	>90	0	<3.5	<10	0
Sβ^0-thalassemia	7-9	>80	0	>3.5	<20	0
Sβ$^+$-thalassemia	9-12	>60	10-30	>3.5	<20	0
SC	9-14	50	0	<3.5	≤1.0	45
Sickle cell trait[b]						
AS	Normal	≤40	>60	<3.5	≤1.0	0

Abbreviations: HbA, normal adult hemoglobin; HbA_2, minor variant of adult hemoglobin; HbC, hemoglobin variant that causes manifestations of sickle cell disease when paired with HbS; HbF, fetal hemoglobin; HbS, sickle hemoglobin.

[a] Levels apply in the absence of a blood transfusion in the past 4 months, are not absolute, and are applicable to adults and children only (not newborns).

[b] Provided for comparison.

Table 2. Dates for Literature Review for Evidence Tables

Section	Dates of Literature Search	No. of Included Studies	Comments
Health maintenance	January 1970 to April 1, 2014	313[a]	Penicillin prophylaxis through January 2011 Blood pressure screening through July 2011 General screening through April 2014 Immunizations through April 2014
Acute and chronic SCD complications	January 1970 to April 2014	552	No systematic reviews were conducted for fever, acute anemia, and multisystem organ failure
Hydroxyurea therapy	January 2007 to April 2014	415	Studies published prior to 2007 were obtained from the 2008 hydroxyurea report,[11] which included a systematic review No literature search was conducted for patient and family education
Transfusion therapy	January 1970 to April 2014	301	No literature search was conducted for details of transfusion management

Abbreviation: SCD, sickle cell disease.

[a] Plus updated reports from the Advisory Committee on Immunization Practices and the US Preventive Services Task Force.

clusive of the limited available literature in the field, searches included randomized clinical trials (RCTs), nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm or when rare complications were described.

Literature searches involved multiple databases (MEDLINE [including in-process and other nonindexed citations], EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, TOXLINE, and Scopus) and used controlled (prespecified) vocabulary terms supplemented with keywords to define concept areas. The exact search terms can be found in the full online guideline document. Only studies published in English were included in the literature reviews.

The work of the expert panel was performed in sequence to allow the methodology group sufficient time to complete the literature reviews and prepare the evidence tables. The dates of the initial comprehensive literature review are summarized in **Table 2**. After the public comment period in August 2012, a final review of the literature was repeated for SCD-related RCTs and systematic reviews through April 1, 2014, to ensure that no more recent studies had been published that might change the recommendations. Studies identified in the final, limited literature review were used to supplement the background materials when appropriate, and all RCTs were included in the evidence tables. Nothing in the 8 trials identified in the update from 2010 through April 1, 2014, required modification of the recommendations.

Evidence Synthesis

Literature searches using the criteria described above yielded 12 532 references. The expert panel also identified an additional 1231 potentially relevant references. All abstracts were reviewed independently by 2 reviewers using an online reference management system (DistillerSR) until the reviewers reached adequate agreement ($\kappa \geq 0.90$). A final subset of 1575 original studies was included in the evidence tables by the methodology group to summarize individual study findings and support the level of the quality of evidence (ie, confidence in the estimates of effect).

The tables include descriptions of study populations, SCD genotypes, interventions, and outcomes. Methodological details are discussed in each evidence table, including the search questions. The search strategies, study selection process, and a list of excluded studies appear at http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/. The final update from 2010 through April 1, 2014, included only RCTs that pertained specifically to individuals with SCD. The 8 additional studies identified were added to the evidence tables. Throughout the process, the evidence tables as well as the full articles of all studies included in the evidence tables were available to the expert panel members.

Evidence Framework

The GRADE framework was used to assess and guide the reporting of the quality of the evidence for specific critical questions. The AMSTAR[12] (assessment of multiple systematic reviews) tool was used to assess the methodological quality of systematic reviews. Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in children, adolescents, and adults.[3,11,13] The expert panel and methodology group appraised these reviews and conducted additional searches to update the existing systematic review through April 1, 2014, to find evidence for the benefits, harms, and barriers of using hydroxyurea and acute complications in children with SCD.[14]

During the standard GRADE process, recommendations are reported as either strong based on quality of evidence that is high or weak based on all other evidence.[9] However, the expert panel decided this was insufficient to represent the limited evidence available for SCD and added a category of moderate strength for a recommendation that is based on evidence from lower-quality RCTs and large well-conducted observational studies.

The panel intends for moderate strength recommendations to be used to populate protocols of care and provide guidance based on the best available evidence. Weak or moderate strength recommendations are not intended to generate quality-of-care indicators or accountability measures or to affect insurance reimbursement. Variations 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 high confidence in the evidence supporting net benefit, and the recommendations are expected to apply to most individuals with SCD.

Consensus Statements

In addition to new systematic searches, recommendations from existing evidence-based clinical practice guidelines were incorporated or adapted for the SCD guideline if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence,

Box 1. Criteria for Inclusion of Consensus-Based Recommendations

Consensus-Adapted Recommendations

Recommendations were based on the expert panel's decision to adapt recommendations derived from existing evidence-based guidelines developed by other professional societies (eg, management of acute and chronic pain in sickle cell disease)

Consensus-Panel Expertise

Systematic reviews conducted by the methodology group revealed minimal or no supporting evidence (eg, management of acute hepatic sequestration)

An adequate systematic review of the literature was not feasible because of anticipated low or no yield (eg, comparative effectiveness of management approaches for individuals with sickle cell disease presenting with fever or worsening anemia)

Therefore, these recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from populations without sickle cell disease (eg, management of long-term opioid therapy for chronic sickle cell disease pain)

and included recommendations that were explicitly linked to the quality of supporting evidence. Recommendations based on outside evidence-based recommendations are marked as consensus-adapted recommendations (**Box 1**). The consensus-adapted recommendations were vetted by the expert panel and adapted from the US Preventive Services Task Force,[15] the Advisory Committee on Immunization Practices,[16] the World Health Organization and the US Centers for Disease Control and Prevention,[17] and the American Pain Society.[18] The full set of these consensus-adapted recommendations can be found in the full guideline document (http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/).

Recognizing the need to provide practical guidance for common problems that may lie outside of the evidence reviews, 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 panel members are labeled as panel expertise consensus (Box 1) and can be found in their entirety in the full guideline document. The areas covered by the consensus recommendations represent gaps in the evidence base appropriate for future research.

Review by Experts

Prior to publication, the full guideline was reviewed by the NHLBI Advisory Council, a separate panel of SCD experts, and the National Blood Disorders Program coordinating committee. The guideline was also posted on the NHLBI website in August 2012 for a public review and comment period, which resulted in the submission of more than 1300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed and developed a response to each comment or recommendation, many of which resulted in revisions to the wording in the guideline. The final version of the guideline was then reviewed by SCD experts from the American Academy of Pediatrics, the American Society of Hematology, and the American Society of Pediatric Hematology/Oncology. All comments were again reviewed by the expert panel and NHLBI staff and specific responses were developed. Those responses included downgrading the strength of 2 recommendations and the addition of clarifying language in several sections of the guideline. Specifically, recommendations against screening of asymptomatic children with neuroimaging using magnetic resonance imaging (MRI) or computed tomography (CT) and asymptomatic adults with neuroimaging using transcranial Doppler, MRI, or CT were downgraded from strong to moderate strength. Reviewers' comments and the panel's responses are posted with the full guideline.

Clinical Practice Guidelines and the Institute of Medicine

In April 2011, 12 months after the start of this systematic review process, the Institute of Medicine (IOM) published a report[19] to help guideline users determine what is a high-quality, trustworthy guideline. Although at that point the expert panel's processes were already identified and in progress, it was determined that those processes were well aligned with the main points that the IOM standards identified as critical to trustworthy guidelines (establishing transparency, managing conflict of interest, guideline development group composition, intersection between the clinical practice guideline and systematic review, establishing evidence foundations for and rating strength of recommendations, articulation of recommendations, and external review).

The panel's work began prior to the release of the IOM standards. Therefore, some steps in our guideline development did differ from the IOM recommendations. A patient representative was not included on the panel, the questions considered were not disseminated for public comment prior to the literature review, and at this time, the NHLBI has no timeline to update the full SCD guideline document, but will consider how best to do so in the future.

Results

Health Maintenance

Young children with HbSS are at increased risk of invasive pneumococcal disease. With universal newborn screening for SCD in the United States, it is now possible to institute strategies to greatly reduce mortality from invasive pneumococcal disease. All newborns identified with HbSS should promptly receive twice-daily prophylactic penicillin as well as pneumococcal vaccination (**Table 3**).[22] Recent changes have been made to the recommendations for pneumococcal vaccination in both children and adults including those with SCD. The changes address the use of both the PCV13 (conjugate 13-valent vaccine) and the use of 23-valent polysaccharide vaccine.[20]

Many individuals with SCD have received and will continue to receive multiple red blood cell transfusions putting them at increased risk of blood-borne pathogens. Despite universal screening of all blood products within the US blood banking systems, hepatitis C infections in the donor may occasionally escape notice. Therefore, the US Preventive Services Task Force recommends hepatitis C screening of all individuals at high risk of contracting hepatitis C such as individuals with SCD who have or will receive multiple red blood cell transfusions. Screening includes anti–hepatitis C virus antibody testing followed by confirmatory polymerase chain reaction testing. The frequency of repeated hepatitis C screening should be based on the frequency of the ongoing transfusions.[15]

In addition, individuals with SCD are at increased risk for several complications related directly or indirectly to the vascular sys-

Table 3. Evidence-Based Recommendations for Health Maintenance in Sickle Cell Disease (SCD)

Evidence-Based Health Maintenance Recommendations for SCD[a]	Strength of Recommendation	Quality of Evidence
Prevention of invasive pneumococcal infection		
Administer oral penicillin prophylaxis (125 mg for those aged <3 y and 250 mg for those aged ≥3 y) twice daily until age 5 y in all children with HbSS	Strong	Moderate
Discontinue prophylactic penicillin in children with HbSS at age 5 y unless they have had a splenectomy or invasive pneumococcal infection; ensure completion of pneumococcal vaccination series before discontinuation	Moderate	Moderate
Ensure that persons of all ages with SCD have been vaccinated against *Streptococcus pneumoniae*	Strong	Moderate
Immunizations		
Children aged 6-18 y with functional or anatomic asplenia should receive 1 dose of PCV13 (conjugate 13-valent vaccine)	Consensus	Adapted[b]
Adults aged ≥19 y who have not received pneumococcal vaccine but have functional or anatomic asplenia and who have not previously received PCV13 or PPSV23 (23-valent polysaccharide vaccine) should receive 1 dose of PCV13 first, followed by a dose of PPSV23 at least 8 wk later, with subsequent doses of PPSV23 to follow current PPSV23 recommendations for adults at high risk		
A second PPSV23 dose is recommended 5 y after the first PPSV23 dose for persons aged 19-64 y with functional or anatomic asplenia		
In addition, those who received PPSV23 before age 65 y for any indication should receive another dose of the vaccine at age 65 y or later if at least 5 y have elapsed since their previous PPSV23 dose		
Adults aged ≥19 y with previous PPSV23 vaccination and functional or anatomic asplenia who received ≥1 doses of PPSV23 should be given a PCV13 dose ≥1 y after the last PPSV23 dose was received		
For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 wk after PCV13 dose and at least 5 y after the most recent dose of PPSV23		
Screening for hepatitis C: screen for hepatitis C virus (HCV) infection in persons at high risk for infection (eg, those with multiple transfusions) and offer 1-time screening for HCV infection to all adults born between 1945 and 1965	Consensus	Adapted[c]
Electrocardiogram screening: do not screen asymptomatic children or adults with SCD with electrocardiograms	Weak	Low
Screening for retinopathy		
Refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10 y	Strong	Low
For persons having a normal dilated retinal examination, rescreen at 1- to 2-y intervals	Consensus	Panel expertise[d]
Screening for risk of stroke using neuroimaging		
In children with sickle cell anemia (SCA), screen annually (beginning at age 2 y and continuing until at least age 16 y) with transcranial Doppler, according to the methods used in the STOP studies	Strong	Moderate
In children with conditional (170-199 cm/s) or elevated (≥200 cm/s) transcranial Doppler results, refer to a specialist with expertise in long-term transfusion therapy aimed at preventing stroke	Strong	High
In children with genotypes other than SCA (eg, HbSβ$^+$-thalassemia or HbSC), do not perform screening with transcranial Doppler	Strong	Low
In asymptomatic children with SCD, do not perform screening with magnetic resonance imaging (MRI) or computed tomography (CT)	Moderate	Low
In asymptomatic adults with SCD, do not perform screening with neuroimaging (transcranial Doppler, MRI, or CT)	Moderate	Very low
Screening for pulmonary disease: do not screen asymptomatic children and adults with pulmonary function tests	Moderate	Low
Contraception, reproductive counseling, and opioid use during pregnancy	Consensus	Adapted[e]

Abbreviation: STOP, Stroke Prevention Trial in Sickle Cell Anemia.

[a] The order of the recommendations was chosen to reflect the frequency with which they will likely need to be implemented. For example, immunization recommendations apply to all individuals with SCD, whereas pulmonary function assessment or contraceptive information may be needed for only a portion of those with SCD.

[b] Consensus adapted from 2014 recommendations of Advisory Committee on Immunization Practices (ACIP).[20] Box 1 contains criteria for consensus-adapted recommendations.

[c] Consensus-adapted recommendations from the US Preventive Services Task Force (USPSTF). Box 1 contains criteria for consensus-adapted recommendations.

[d] Box 1 contains criteria for panel expertise consensus.

[e] Consensus-adapted recommendations from the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC).[21] Box 1 contains criteria for consensus-adapted recommendations.

tem. Based on varying quality levels of evidence, strong recommendations are made related to screening for hypertension, retinopathy, and risk of stroke using transcranial Doppler in children aged 2 to 16 years. The frequency of such screening is often based on expert opinion as it is for these recommendations. For example, dilated eye examination is recommended to be completed every 1 to 2 years when the previous evaluation was negative. Recommendations are made against neuroimaging screening in asymptomatic children, adolescents, and adults to assess for risk of future stroke. Other frequently used screening procedures such as electrocardiography and pulmonary function tests also have recommendations against use based on the lack of evidence regarding their efficacy or effectiveness in providing any improved outcomes or advantage in asymptomatic individuals.

The US Preventive Services Task Force and the Advisory Committee on Immunization Practices have developed evidence-based recommendations for preventive services, screening, and immunizations appropriate for all children and adults. The expert panel decided that it is important to highlight the use of these recommendations in the care of all persons with SCD because those living with chronic disease often fail to receive this type of routine preventive care.[23] Pregnancy in women with SCD may present additional health

risks, such as preterm delivery, stillbirth, maternal mortality, and severe fetal anemia.[24,25] Therefore, the ability of health professionals to provide information on available contraception and reproductive issues is important in the care of persons with SCD. The expert panel chose to summarize and include guidance for reproductive issues as reviewed and summarized by the World Health Organization and the US Centers for Disease Control and Prevention.[17]

Managing Acute Complications

New clinical approaches and treatments[22,26,27] have increased rates of survival in persons with SCD. However, the average lifespan of persons with SCD remains about 3 decades shorter than other individuals living in the United States,[28,29] due in large part to acute and chronic complications related to vascular occlusion. Vasoocclusive crisis, commonly referred to as acute pain crisis, is the most common such event and is usually accompanied by severe pain. Nearly all individuals with SCD will experience a vasoocclusive crisis during their lifetime. The first episode may occur as early as 6 months of age, often presenting as dactylitis, and thereafter may occur with variable frequency, usually in the extremities, chest, and back.[30-33]

The vasoocclusive crises are a particularly complex management concern. Health care professionals must appreciate the severe nature of the pain and the urgent need for effective pain relief therapies (**Table 4**). Patients presenting with a vasoocclusive crisis are at risk for other complications such as acute chest syndrome (ACS), requiring rapid triage, evaluation, and administration of analgesics. Patients with SCD experiencing acute pain crises may be incorrectly identified as those with drug-seeking behavior or addiction. It is important that the preferences and needs of the individual seeking care be heard, respected, and responded to with the same attention as applied to any other individuals with serious physiological pain. Pain management should include parenteral opioids for severe pain administered in a timely manner, guided by an individualized prescribing and monitoring protocol written by the patient with his/her SCD health care clinician or team, or by an institutional SCD-specific protocol when an individualized protocol is not available. In children and adults hospitalized for a vasoocclusive crisis, the use of incentive spirometry can limit the risk for ACS.[34]

People with SCA have an increased risk of severe bacterial infection, resulting primarily from reduced or absent splenic function.[35] By 2 or 3 months of age, as their level of fetal hemoglobin declines, infants with SCA develop splenic impairment. The result is an extremely high risk of septicemia and meningitis, primarily due to *Streptococcus pneumoniae*. It is imperative to promptly identify and treat suspected bacterial infections. One of the signs that the expert panel strongly recommends as a reliable indicator of such diseases is fever (≥38.5°C) to which clinicians should respond more aggressively than they might in people without SCD.

Acute chest syndrome is another frequently occurring and serious acute complication of SCD.[36,37] Clinically, ACS can develop at any time and typically presents as sudden onset of some combination of cough, shortness of breath, retractions, and rales accompanied by a new pulmonary infiltrate on chest radiograph. Children usually have a fever and upper- or middle-lobe involvement, whereas adults are often afebrile and present with multilobe disease. There are no distinctive laboratory features of ACS, although hemoglobin concentration often declines sharply.[37] The most common etiology is infection (eg, viral, bacterial, or mycoplasma), especially in children, but the complication also may result from bone marrow embolism, intrapulmonary aggregates of sickled cells, atelectasis, or pulmonary edema. Acute chest syndrome can rapidly proceed to respiratory failure or death and requires immediate hospitalization and thorough evaluation. Treatments include antibiotics, oxygen supplementation, and exchange transfusion in those who experience severe respiratory distress. Risk of ACS can be reduced by the use of incentive spirometry during hospital admissions for vasoocclusive crises[34] or by preoperative transfusion.[37] Acute chest syndrome occurs with increased frequency in persons with asthma or prior ACS events.

Acute stroke is a common and devastating complication of SCD, particularly among persons with SCA.[38] In the absence of primary stroke prevention, approximately 10% of children with HbSS will have overt stroke and an additional 20% to 35% will have silent cerebral infarction, which can cause cognitive decline and predispose them to additional silent infarcts and overt strokes.[39] Stroke in those with SCD often has similar presenting signs and symptoms as in persons without SCD, including being preceded by transient ischemic attacks. Regular transfusion therapy or, when transfusion therapy is not possible or has had to be discontinued, hydroxyurea therapy may prevent recurrent strokes.[40]

Additionally, transfusion therapy may prevent an initial stroke in children with abnormal transcranial Doppler velocity identified by regular transcranial Doppler ultrasound screening (see the health maintenance and blood transfusion management sections of this summary report). Silent central nervous system infarcts can present with nonfocal signs such as developmental delays or poor or declining school performance in children, or changes in social, role, or work functioning in adults. Throughout their lives, persons with SCD should be considered for formal neurocognitive evaluation when assessments reveal any of these concerns.

Other less common complications include priapism, hepatobiliary complications, acute splenic sequestration, acute kidney injury, acute cholecystitis, and acute aplastic crisis due to parvovirus B19 infection. Each of these complications requires immediate attention, often similar to the care provided to individuals with the same problems but without SCD. Several of these acute complications (eg, acute aplastic crisis) had no available evidence for management, limiting the panel to consensus recommendations based on expert opinion, which are not the focus of this report but can be found in the full guideline document.

Managing Chronic Complications

Chronic complications of SCD can involve most organs and organ systems during the lifespan of affected individuals. In addition, certain acute complications, such as stroke and priapism, often do not resolve completely but evolve into subacute or chronic phases that require special approaches to management. A unified definition of each complication of SCD was published in 2010,[41] which should continue to facilitate clinical communications, management, and further research to better describe the etiology, natural history, and care for these conditions.

Most of the chronic complications have not been the subject of high-quality observational studies or RCTs, thus leaving few areas in which strong recommendations were possible (**Table 5**). The expert panel's evidence-based recommendations for managing chronic complications are supplemented with information on chronic pain

Table 4. Evidence-Based Recommendations for Managing Acute Complications of Sickle Cell Disease (SCD)

Evidence-Based Recommendations for Managing Acute Complications of SCD[a]	Strength of Recommendation	Quality of Evidence
Vasoocclusive crisis[b]		
Continue treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in adults and children with a vasoocclusive crisis associated with mild to moderate pain in those who report relief with NSAIDs in the absence of contraindications	Moderate	Low
Rapidly initiate treatment with parenteral opioids in adults and children with a vasoocclusive crisis associated with severe pain	Strong	High
Initiate around-the-clock opioid administration by patient-controlled analgesia or frequently scheduled doses vs as requested administration in adults and children with a vasoocclusive crisis associated with severe pain	Moderate	Low
Use incentive spirometry during hospitalization for vasoocclusive crisis to reduce the risk of acute chest syndrome (ACS)	Strong	Moderate
Do not administer a blood transfusion unless there are other indications for transfusion in children and adults with a vasoocclusive crisis[c]	Moderate	Low
Use an individualized prescribing and monitoring protocol (written by the patient's SCD clinician) or an SCD-specific protocol whenever possible to promote rapid, effective, and safe analgesic management and resolution of the vasoocclusive crisis in children and adults[d]	Consensus	Panel expertise[e]
Acute chest syndrome		
Treat persons with SCD who have ACS with an intravenous cephalosporin, an oral macrolide antibiotic, supplemental oxygen (to maintain oxygen saturation of >95%), and close monitoring for bronchospasm, acute anemia, and hypoxemia	Strong	Low
In persons with sickle cell anemia, give simple blood transfusion (10 mL/kg of red blood cells) to improve oxygen-carrying capacity to persons with symptomatic ACS whose hemoglobin concentration is >1.0 g/dL below baseline; if baseline hemoglobin is ≥9 g/dL, simple blood transfusion may not be required	Weak	Low
In persons with HbSC disease or HbSβ$^+$-thalassemia, consult an SCD expert regarding decisions about transfusion	Strong	Low
Perform urgent exchange transfusion in consultation with hematology, critical care, or apheresis specialists, when there is rapid progression of ACS as manifested by oxygen saturation of <90% despite supplemental oxygen, increasing respiratory distress, progressive pulmonary infiltrates, decline in hemoglobin concentration despite simple transfusion, or all of these	Strong	Low
Encourage use of incentive spirometry while awake	Strong	Moderate
Acute stroke		
Consult an SCD expert and perform exchange transfusion in persons with SCD who develop acute stroke confirmed by neuroimaging	Consensus	Panel expertise[e]
Initiate a program of monthly simple or exchange transfusions in children and adults who have had a stroke	Moderate	Low
Initiate hydroxyurea therapy when it is not possible to initiate a transfusion program in children and adults who have had a stroke	Moderate	Low
Priapism		
Initiate interventions to include vigorous oral or intravenous hydration and oral or intravenous analgesia when an episode of priapism lasts ≥4 h	Strong	Low
Consult with a urologist when an episode of priapism lasts ≥4 h	Consensus	Panel expertise[e]
Do not use transfusion therapy for immediate treatment of priapism associated with SCD	Moderate	Low
Consult with a hematologist for possible preoperative transfusion if surgical intervention is required	Consensus	Panel expertise[e]
Hepatobiliary complications		
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	Moderate
Splenic sequestration		
Provide immediate intravenous fluid resuscitation in persons with hypovolemia due to severe acute splenic sequestration	Strong	Low
Consult an SCD expert and begin transfusion in persons who have acute splenic sequestration and severe anemia to increase hemoglobin to a stable level, while avoiding overtransfusion	Strong	Low
Consult an SCD expert to address the performance and timing of splenectomy in persons with recurrent acute splenic sequestration or symptomatic hypersplenism	Moderate	Low
Acute renal failure		
In a patient with an acute increase in serum creatinine level of ≥0.3 mg/dL, (1) monitor renal function daily, including serum creatinine level, fluid intake, and fluid output; (2) avoid potential nephrotoxic drugs and imaging agents; and (3) evaluate the patient thoroughly for all potential etiologies in consultation with a nephrologist as needed	Consensus	Panel expertise[e]
Do not give blood transfusions to treat acute renal failure unless there are other indications for transfusion	Consensus	Panel expertise[e]
Use renal replacement therapy (eg, hemodialysis) when needed for acute renal failure	Consensus	Panel expertise[e]

[a] The order of the recommendations was chosen to reflect the frequency with which they will likely need to be implemented. For example, vasoocclusive crisis is more common than episodes of ACS or priapism.

[b] The consensus-adapted pain recommendation appears in eSection 1 of the Supplement.

[c] More information appears in the chapter entitled "Blood Transfusion in the Management of Sickle Cell Disease" in the full guideline document at http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/.

[d] More information on the pain algorithm appears in the eFigure in the Supplement.

[e] Box 1 contains criteria for panel expertise consensus.

Table 5. Evidence-Based Recommendations for Managing Chronic Complications of Sickle Cell Disease (SCD)

Evidence-Based Recommendations for Managing Chronic Complications[a]	Strength of Recommendation	Quality of Evidence
Chronic pain recommendations[b]	Consensus	Adapted[c]
Avascular necrosis		
Evaluate all children and adults with SCD and intermittent or chronic hip pain for avascular necrosis by history, physical examination, radiography, and magnetic resonance imaging, as needed	Strong	Low
Treat avascular necrosis with analgesics and consult physical therapy and orthopedic departments for assessment and follow-up	Strong	High
Pulmonary hypertension		
Refer persons who have symptoms or signs suggestive of pulmonary hypertension for echocardiography	Strong	Moderate
Renal complications		
Refer persons with proteinuria (>300 mg/24 h) to a nephrologist for further evaluation	Strong	Low
For adults with microalbuminuria without other apparent cause, initiate angiotensin-converting enzyme (ACE) inhibitor therapy	Moderate	Moderate
For adults with proteinuria without other apparent cause, initiate ACE inhibitor therapy	Moderate	Low
Initiate ACE inhibitor therapy for renal complications when indicated even in the presence of normal blood pressure	Moderate	Low
Renal replacement therapy (eg, hemodialysis, peritoneal dialysis, renal transplantation) should be used in persons with SCD if needed	Strong	Low
Ophthalmologic complications		
Refer children and adults with vitreoretinal complications of proliferative sickle retinopathy (PSR) refractory to medical treatment for evaluation and possible vitrectomy	Strong	Low
Refer persons of all ages with PSR to an ophthalmologist for evaluation and possible laser photocoagulation therapy	Strong	Moderate
Leg ulcers		
Treat leg ulcers in persons with SCD with initial standard therapy (eg, debridement, wet to dry dressings, topical agents)	Moderate	Low
Evaluate persons with chronic recalcitrant deep leg ulcers for osteomyelitis	Moderate	Low
Evaluate possible etiologies of leg ulcers to include venous insufficiency and perform wound culture if infection is suspected or if the ulcers deteriorate	Moderate	Low
Treat with systemic or local antibiotics if leg ulcer site is suspicious for infection and wound culture is positive and organisms are susceptible	Moderate	Low
Stuttering or recurrent priapism		
Consult an SCD specialist and urologist for evaluation and therapy of recurrent or stuttering priapism, especially when episodes increase in severity or frequency	Weak	Low

[a] The order of the recommendations was chosen to reflect the frequency with which they will likely need to be implemented. For example, chronic pain will probably be more common than avascular necrosis or leg ulcers.

[b] More information appears in eSection 1 and in the eFigure in the Supplement.

[c] Box 1 contains criteria for consensus-adapted recommendations.

management in eSection 1 in the Supplement. The panel recommends that primary care clinicians and other clinicians involve appropriate consultants and specialists in management decisions for chronic complications.

Sickle cell pain often becomes chronic, resulting in poorer quality of life.[33,42] Early and aggressive treatment of acute sickle cell pain may reduce the development of chronic pain.[43] Adults reported chronic SCD pain on more than 50% of days surveyed,[33] and children reported SCD pain on nearly 10% of days surveyed.[41] Chronic pain is often associated with other morbidities, including depression, anxiety, despair, insomnia, loneliness, helplessness, and dependence on pain medications.[30,44,45] In the systematic review, little evidence was found related specifically to the chronic pain of persons with SCD. Therefore, the expert panel chose to adapt selected recommendations from the American Pain Society developed in collaboration with the American Academy of Pain Medicine[18,30] (eSection 1 and eFigure in the Supplement).

Avascular necrosis, which is also known as aseptic necrosis, osteonecrosis, or ischemic necrosis, is a syndrome of bone death due to compromised blood supply. Avascular necrosis occurs in about 10% of persons with SCD, and the hip joint is the most common site.[46] Avascular necrosis of the femoral head often causes chronic severe pain and disability. Therapy is usually conservative, nonsurgical management until joint replacement is determined to be necessary.

Pulmonary arterial hypertension (PAH) is caused by restriction in the lumen and stiffening of the walls of the pulmonary arteries. It is defined as an elevation of the mean pulmonary arterial pressure (>25 mm Hg at rest) as determined by right heart catheterization. Pulmonary arterial hypertension is an independent risk factor for mortality in individuals with SCD.[47] The expert panel found insufficient evidence to recommend for or against screening for PAH in asymptomatic people with SCD. Conversely, individuals with SCD who have symptoms that may indicate the presence of PAH (eg, exercise intolerance, fatigue, peripheral edema, chest pain) should be evaluated for PAH initially by echocardiography, with confirmation of diagnosis by right heart catheterization.

An estimated 23 million individuals living in the United States have chronic kidney disease, including 4% to 18% of persons with SCD.[48] In 1 study,[49] renal failure was observed in 4.2% of persons with SCA. In those developing renal failure, 68% previously had proteinuria, 40% had nephrotic syndrome, and 33% had hypertension.[49] Evaluation of proteinuria and microalbuminuria may provide opportunities to treat renal complications and delay renal failure.

Table 6. Evidence-Based Recommendations for Use of Hydroxyurea Therapy

Evidence-Based Recommendations for Use of Hydroxyurea Therapy	Strength of Recommendation	Quality of Evidence
In adults with sickle cell anemia (SCA) who have ≥3 moderate to severe pain crises associated with sickle cell disease (SCD) during a 12-mo period, initiate treatment with hydroxyurea	Strong	High
In adults with SCA who have sickle cell–associated pain that interferes with daily activities and quality of life, initiate treatment with hydroxyurea	Strong	Moderate
In adults with SCA who have a history of severe or recurrent acute chest syndrome (ACS), initiate treatment with hydroxyurea[a]	Strong	Moderate
In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, initiate treatment with hydroxyurea	Strong	Moderate
In infants 9 mo of age or older, in children, and in adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce complications (eg, pain, dactylitis, ACS, anemia) related to SCD	Strong[b] and moderate[c]	High[b] and moderate[c]
In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, add hydroxyurea therapy to improve anemia	Weak	Low
Discontinue hydroxyurea therapy in women who are pregnant or breastfeeding	Moderate	Low
Use an established prescribing and monitoring protocol to ensure proper use of hydroxyurea and maximize benefits and safety	Strong	High
In persons with HbSβ$^+$-thalassemia or HbSC who have recurrent SCD-associated pain that interferes with daily activities or quality of life, consult an SCD expert for consideration of hydroxyurea therapy	Moderate	Low
In persons not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult an SCD expert	Moderate	Very low

[a] More information appears in the chapter entitled "Managing Acute Complications of Sickle Cell Disease" in the full guideline.

[b] Strong recommendation and high quality of evidence for persons aged 9 to 42 months.

[c] Moderate recommendation and moderate quality of evidence for children older than 42 months and adolescents.

Chronic ophthalmological complications of SCD include proliferative sickle retinopathy (PSR) and vitreous hemorrhage. The presence of PSR is associated with significant visual loss,[50] and its peak prevalence occurs earlier in HbSC disease (eg, age ranges of 15-24 years in men and 20-39 years in women) than in HbSS.[51] Evaluation of PSR should include referral to an ophthalmologist for consideration of laser therapy.

Leg ulcers are another form of vascular complication seen in persons with SCD and are treated with standard therapy as well as evaluation for venous etiologies. Antibiotic therapy is reserved for ulcers with culture-proven bacterial infection. When ulcers are persistent, coexistence of osteomyelitis should be assessed.

Stuttering priapism, the occurrence of multiple self-limited episodes of unwanted, often painful erections lasting less than 4 hours, combined with prolonged priapism, affects as many as 35% of males with SCD. Even though stuttering priapism is self-limited, recurrent episodes may lead to chronic or persistent priapism, adversely affecting quality of life or resulting in impotence. Chronic hormonal therapy may reduce or eliminate the episodes but without evidence of improvement in functional outcomes. Therefore, treatment decisions must be based on the balance of potential benefits and the risk of adverse effects including reduced sexual function.[52]

Hydroxyurea Therapy

Long-term daily oral hydroxyurea treatment has been shown to reduce or prevent many acute and chronic complications of SCD. A ribonucleotide reductase inhibitor, hydroxyurea has been in use since the 1970s to treat persons with myeloproliferative neoplasms. In the 1980s, hydroxyurea was identified as a promising drug candidate for SCD by increasing fetal hemoglobin levels. Hydroxyurea has since been shown to have rapid absorption and near-complete bioavailability and to be therapeutic with once-daily oral dosing.[53]

Increasing the concentration of fetal hemoglobin is the primary effect of hydroxyurea and provides the greatest benefit to persons with SCD, but other mechanisms of action and benefits exist. For example, hydroxyurea lowers the number of circulating leukocytes and reticulocytes and decreases their expression of adhesion molecules, thus reducing vascular occlusion.[54] Hydroxyurea also increases red blood cell size (higher mean corpuscular volume) and improves cellular deformability, which increases blood flow and reduces vasoocclusion. In addition, nitric oxide released directly from hydroxyurea metabolism may contribute to local vasodilation.[55]

Hydroxyurea therapy substantially reduces the frequency of painful episodes and ACS events and the need for erythrocyte transfusions and hospitalizations.[56] Long-term hydroxyurea administration results in a reduction in mortality.[57,58]

The primary basis for recommending hydroxyurea therapy in adults come from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia.[56] This RCT enrolled only adults with SCA who had experienced more than 3 vasoocclusive crises during the previous year. The inclusion criteria were based on earlier clinical data showing an association of more than 3 vasoocclusive crises and markedly lower survival rates. Two-year trial results and follow-up at 9 and 17 years[57,58] demonstrated improved outcomes in those who continued hydroxyurea therapy (**Table 6**).

Only a limited population of adults with SCD was studied, failing to account for many individuals with significant SCD burden but who experience less than 3 vasoocclusive crises during a 12-month period. Based on observation studies and extrapolation from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia[56] and other RCTs, the panel recommends hydroxyurea therapy for adults with fewer pain crises but whose SCA results in significant interference with daily activities or quality of life as well as individuals who have severe or recurrent ACS or severe symptomatic anemia.

For infants, children, and adolescents who have SCA, hydroxyurea treatment results have closely and consistently mirrored those of adults. Hydroxyurea treatment of children beginning as early as 9 months of age yields improvements in laboratory parameters such

Box 2. Consensus Treatment Protocol for Implementation of Hydroxyurea Therapy

Recommended Laboratory Tests Before Starting Therapy

Complete blood cell (CBC) count with white blood cell (WBC) differential, reticulocyte count, platelet count, and red blood cell (RBC) mean corpuscular volume (MCV)

Quantitative measurement of fetal hemoglobin if available (eg, hemoglobin electrophoresis, high-performance liquid chromatography)

Renal and liver function tests

Pregnancy test for women

Initiating and Monitoring of Hydroxyurea Therapy

Baseline elevation of fetal hemoglobin 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/d (round up to the nearest 500 mg); 5-10 mg/kg/d if patient has chronic kidney disease

Starting dosage for infants and children: 20 mg/kg/d

Monitor CBC count with WBC differential and reticulocyte count at least every 4 wk when adjusting dosage

Aim for a target absolute neutrophil count ≥2000/μL; however, younger persons with lower baseline counts may safely tolerate absolute neutrophil counts down to 1250/μL

Maintain platelet count ≥80 000/μL

If neutropenia or thrombocytopenia occurs:

- Temporarily stop hydroxyurea dosing
- Monitor CBC count with WBC differential weekly
- When blood counts have recovered, reinstitute hydroxyurea at a dose of 5 mg/kg/d lower than the dose given before onset of cytopenia

If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:

- Increase by 5-mg/kg/d increments every 8 wk
- Give until mild myelosuppression (absolute neutrophil count of 2000-4000/μL) is achieved, up to a maximum of 35 mg/kg/d

Once a stable dose is established, laboratory safety monitoring should include CBC count with WBC differential, reticulocyte count, and platelet count every 2-3 mo

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 mo; 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 fetal hemoglobin levels for evidence of consistent or progressive laboratory response

A lack of increase in MCV, fetal hemoglobin, or both, 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

as total hemoglobin and fetal hemoglobin levels and decreased numbers of sickle cell–related acute clinical events such as pain and ACS.[59] The panel recommends that hydroxyurea therapy be offered in children beginning at 9 months of age, including those who are asymptomatic.

The panel chose to recommend offering treatment as a mechanism to open discussion with families about the risks and benefits of therapy in asymptomatic infants. Long-term observational studies suggest sustained beneficial effects of hydroxyurea therapy for young persons without the adverse effects of excessive myelotoxicity, deleterious effects on growth and development, altered female fertility, accumulation of mutations, or increased carcinogenicity.[59-62] A consensus treatment protocol that includes dosing and monitoring schedules for implementation of hydroxyurea therapy is presented in **Box 2**.

Specific clinical situations can require more specialized approaches. Pregnant or lactating women with SCA are not considered candidates for hydroxyurea. Consideration of reduced dosing strategies should be used in persons with SCA and renal disease. In addition, there are many persons with HbSC disease or other variant SCD genotypes for whom no current evidence is available regarding the risks and benefits of hydroxyurea therapy. In such instances, an SCD specialist should be consulted if one is not already involved in the collaborative care of the patient.

Blood Transfusion in the Management of SCD

Normal donor erythrocytes contain normal hemoglobin (HbA), and their transfusion into patients with SCD reduces the percentage of circulating erythrocytes that contain HbS. Sickled erythrocytes possess many unfavorable physiological properties and induce vascular changes that promote vasoocclusion. Sickled erythrocytes increase blood viscosity through intrinsic properties of the sickled cells as well as through abnormal interactions of these cells with leukocytes, platelets, vascular endothelium, and clotting factors.[6,7] Transfusion of normal donor erythrocytes is used to mitigate these effects.

When considering transfusion in a patient with SCD, distinctions must be made between episodic (ad hoc, acute, or prophylactic) and long-term (recurrent) transfusion, as well as the transfusion technique (eg, simple, manual exchange, or erythrocytapheresis). Exchange transfusions more efficiently decrease the percentage of HbS-containing erythrocytes, allow transfusion of increased volumes of donor cells, and limit the risk of iron overload. Conversely, exchange transfusions may increase the direct costs of transfusion, require specialized equipment, and often require permanent venous access.[63]

Surgical procedures in persons with SCD are associated with significant risk for SCD and non–SCD-associated morbidity as well as an increased risk of death. Transfusions are commonly used during the perioperative period to prevent postoperative vasoocclusive crises, stroke, or ACS.[64] The Transfusion Alternatives Preoperatively in Sickle Cell Disease study[65] demonstrated a lowered risk of postoperative complications in persons with SCD undergoing medium risk surgery when their preoperative hemoglobin level was increased to 10 g/dL. The expert panel translated this result into the recommendation that red blood cell transfusion be used in all adults and children with SCA to bring their preoperative hemoglobin level to 10 g/dL prior to any surgical procedures involving general anesthesia.[65]

Table 7. Evidence-Based Recommendations for Use of Transfusion Therapy

Evidence-Based Recommendations for Use of Transfusion Therapy	Strength of Recommendation	Quality of Evidence
Indications for prophylactic perioperative transfusion[a]		
In adults and children with sickle cell anemia (SCA), transfuse red blood cells to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia	Strong	Moderate
In persons with HbSS disease who require surgery and who already have a hemoglobin level higher than 8.5 g/dL without transfusion, are receiving long-term hydroxyurea therapy, or who require high-risk surgery (eg, neurosurgery, prolonged anesthesia, cardiac bypass), consult a sickle cell disease (SCD) expert for guidance as to the appropriate transfusion method	Strong	Low
In adults and children with HbSC or HbSβ^+-thalassemia, consult an SCD expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia	Moderate	Low
Appropriate management and monitoring		
Red blood cell units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens	Moderate	Low
In persons with SCA who do not receive transfusions long-term and who are therefore at risk for hyperviscosity due to high percentages of circulating HbS-containing erythrocytes, avoid transfusing to a target hemoglobin level >10 g/dL	Moderate	Low
In children with SCA who receive transfusions long-term, the goal of transfusion should be to maintain a HbS level of <30% immediately prior to the next transfusion	Moderate	Moderate
The expert panel recommends that clinicians prescribing long-term transfusion therapy follow an established monitoring protocol	Moderate	Low
Management and prevention of transfusion complications		
Consult the blood bank for a workup of a possible delayed hemolytic transfusion reaction in a patient with any of the following signs or symptoms: acute anemia, pain, or jaundice within 3 weeks after a blood transfusion	Strong	Moderate
In persons who receive long-term transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, magnetic resonance imaging R2, T2, and R2; the optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics	Strong	Moderate
Administer iron chelation therapy (with consultation with a hematologist) to persons with SCD and documented transfusion-acquired iron overload	Moderate	Moderate

[a] More information appears in eSection 2 in the Supplement.

The benefits of long-term transfusion are varied; the highest-quality evidence is from RCTs related to primary prevention of stroke in children (**Table 7**).[26,66] The use of transfusions for an abnormal transcranial Doppler velocity (≥200 cm/s) has resulted in a declining incidence of primary overt stroke in children with SCA.[67]

Additional recommendations to provide transfusions for acute SCD complications are based on moderate- and low-quality evidence and expert panel consensus in instances in which there is an expectation of high potential risk of mortality when transfusions are withheld (eg, ACS, acute stroke, severe anemia from transient aplastic crisis due to parvovirus B19, and splenic and hepatic sequestration). Persons with previous stroke and children with elevated transcranial Doppler velocities (≥200 cm/s) are candidates for long-term transfusion therapy (**Table 8**).

Transfusions are associated with several possible complications or risks, including hyperviscosity, alloimmunization, hemolysis, and iron overload (eSection 2 in the Supplement). Transfusion of donor erythrocytes will raise the hematocrit of circulating blood, resulting in increased viscosity that could be problematic for persons with SCD by triggering vasoocclusion.

Following a transfusion, if the donor erythrocytes have a different antigenic profile from those of the recipient's own erythrocytes, an immunological response by the recipient against the foreign antigens can result in alloimmunization. Alloantibodies persist for many years, although their titer may wane to low or undetectable levels. Alloimmunization usually limits the ability to identify compatible blood units for future transfusions, so efforts to avoid alloantibody development are warranted.

Delayed hemolytic transfusion reactions develop 7 to 28 days after red blood cell transfusions with minor blood group incompatibilities. These reactions should be considered in the differential diagnosis of a patient with worsening anemia, jaundice, or pain after transfusion. Transfused erythrocytes, whether administered sporadically or on a regularly scheduled basis, present a substantial iron load to the recipient, given the lack of a physiological means to remove excess iron. Repeated transfusion of erythrocytes causes iron accumulation outside the normal pathways of iron regulation and thus can lead to iron overload and organ dysfunction. Chelation therapy can be used to remove excess iron.

Although red blood cell transfusion can help ameliorate many SCD complications, transfusion therapy is associated with a wide variety of adverse reactions from mild to severe or even fatal.[68] Many of the recognized hazards of transfusions are amplified in persons with SCD.[69,70] Decisions to administer blood transfusions in persons with SCD must be based on risk-benefit assessments and are often made in consultation with a hematologist, transfusion medicine specialist, or SCD expert. The expert panel chose to comment on a few such situations in which evidence has shown no benefit or no evidence of benefit has been published but transfusion has been reported to be used. The panel makes explicit recommendations in **Table 9** against the routine use of transfusions in uncomplicated vasoocclusive crises, priapism, asymptomatic anemia, acute kidney injury in the absence of multisystem organ failure.

Discussion

Providing care to individuals with SCD can be challenging. This SCD guideline is being made available to provide the latest evidence-based recommendations to manage this condition and to help en-

Table 8. Sickle Cell Disease Complications and Evidence-Based Recommendations for Use of Transfusion

Complication	Transfusion Method	Strength of Recommendation	Quality of Evidence
Symptomatic severe acute chest syndrome (defined by an oxygen saturation <90% despite supplemental oxygen)	Exchange	Strong	Low
Acute splenic sequestration plus severe anemia	Simple	Strong	Low
In children and adults who have had an acute stroke, initiate a program of monthly transfusions	Simple or exchange	Moderate	Low
Hepatic sequestration	Exchange or simple	Consensus	Panel expertise[a]
Intrahepatic cholestasis	Exchange or simple	Consensus	Panel expertise[a]
Multisystem organ failure	Exchange or simple	Consensus	Panel expertise[a]
Aplastic crisis	Simple	Consensus	Panel expertise[a]
Symptomatic anemia	Simple	Consensus	Panel expertise[a]
Child with transcranial Doppler reading >200 cm/s[b]	Exchange or simple	Strong	High
Adults and children with previous clinically overt stroke	Exchange or simple	Moderate	Low

[a] Box 1 contains criteria for panel expertise consensus.

[b] Indicates the time-averaged mean maximal cerebral blood flow velocity.

Table 9. Sickle Cell Disease Complications and Evidence-Based Recommendations Against Use of Transfusion

Complication	Strength of Recommendation	Quality of Evidence
Uncomplicated painful crisis	Moderate	Low
Priapism	Moderate	Low
Asymptomatic anemia	Consensus	Panel expertise[a]
Acute kidney injury in the absence of multisystem organ failure	Consensus	Panel expertise[a]
Recurrent splenic sequestration	Weak	Low

[a] Box 1 contains criteria for panel expertise consensus.

gage health care professionals in supporting their implementation at the practice level.

Some of the strong recommendations appearing in this guideline are supported by low- or very low–quality evidence. Such disparities in strength of recommendations and quality levels of evidence appear to contradict the evidence basis of the guideline and use of the GRADE system. For example, our recommendation to refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10 years is a strong recommendation with low-quality evidence. Such referrals have become the standard of care and there is observational study evidence of a significant risk of proliferative retinopathy that requires dilated eye examination to accurately identify and stage the extent of retinopathy.

The expert panel decided that the benefit of referral to an ophthalmologist was potentially substantial, and the risk associated with such referrals was low. Furthermore, it is unlikely that any RCTs will ever be performed to assess referral for dilated eye examination (vs not doing dilated eye examinations). The panel acknowledges that studies might be completed that provide higher-quality evidence to modify the frequency but decided this did not justify lowering the strength of the recommendation.

A second example highlights an instance in which low-quality evidence is used to support a strong recommendation against use of screening. The panel made a strong recommendation stating, in children with genotypes other than SCA (eg, HbSβ$^+$-thalassemia or HbSC), do not perform screening with transcranial Doppler. The quality of evidence for this recommendation is low, including observational studies, which do not demonstrate benefit from transcranial Doppler screening. Additional observational studies reported a significantly lower incidence of stroke in children with SCD genotypes other than SCA compared with those with SCA. Therefore, the benefit of screening is assessed as low with a moderate to high potential risk from repeated screenings based on unwarranted use of health care resources and the small to modest potential risk of testing and treatment in children who have false-positive test results. In addition, no therapy has been proposed for this group of children if they did have a positive screening test.

Disparity in quality levels of evidence and strength of recommendations is not unique to this guideline. Even though the original descriptions of GRADE reserve strong recommendations for only those areas with high-quality evidence,[8] this appears to ignore the realities of practice and research. In a recent publication in response to publication of the Endocrine Society guidelines,[71] some members of the GRADE working group have identified instances in which strong recommendations are appropriate with low- or even very low–quality evidence. Although this panel made their decisions prior to publication of GRADE's taxonomy, it is a valuable affirmation our work. For example, the strong recommendation for referral for dilated eye examinations based on low-quality evidence fits under the taxonomy category of best practice.[71]

The panel chose a second variation of the GRADE system by adding a third strength of recommendation (moderate) to the usual GRADE system of only strong and weak recommendations.[8] GRADE is a useful tool for guiding the grading of the quality of evidence and the strength of recommendations. Yet, it must be responsive to the needs of the user and to the topic being assessed by allowing flexibility. The expert panel decided that limiting recommendations to only 2 categories of strong and weak unnecessarily constrained the advice it could give to primary care clinicians. Other groups such as the American College of Cardiology have also found it advantageous to modify the number of levels of evidence or levels of recommendations suggested by GRADE.

The American Thoracic Society guidelines[72] also address care of individuals with SCD focusing on the diagnosis of pulmonary

Table 10. Evidence-Based Strong Recommendations With High-Quality Evidence

Recommendation	Strength of Recommendation	Quality of Evidence
In children with conditional (170-199 cm/s) or elevated (≥200 cm/s) transcranial Doppler results, refer to a specialist with expertise in long-term transfusion therapy aimed at stroke prevention	Strong	High
Treat avascular necrosis with analgesics and consult physical therapy and orthopedic departments for assessment and follow-up	Strong	High
Rapidly initiate treatment with parenteral opioids in adults and children with a vasoocclusive crisis associated with severe pain	Strong	High
Use simple or exchange transfusion for children with transcranial Doppler reading >200 cm/s[a]	Strong	High
In adults with sickle cell anemia who have ≥3 moderate to severe pain crises associated with sickle cell disease during a 12-mo period, initiate treatment with hydroxyurea	Strong	High
Use an established prescribing and monitoring protocol to ensure proper use of hydroxyurea and to maximize benefits and safety	Strong	High
In infants 9-42 mo of age or older, children, and adolescents with sickle cell anemia, offer treatment with hydroxyurea regardless of clinical severity to reduce complications (eg, pain, dactylitis, acute chest syndrome, anemia) related to sickle cell disease	Strong	High

[a] Indicates the time-averaged, mean-maximal cerebral blood flow velocity.

hypertension. The American Thoracic Society guidelines recommend "risk stratification guides clinical decision making in SCD," which is mortality risk stratification for adults and morbidity risk stratification in children aged 8 years or older. Even though the guidelines indicate that mortality risk stratification can be accurately assessed by Doppler echocardiography or *N*-terminal pro-brain natriuretic peptide as a reasonable noninvasive alternative, these tests are not clearly recommended, leaving the clinician to determine whether this is a specific recommendation or only a statement of opinion. The guidelines do state "The committee members routinely perform risk stratification on their patients with SCD..." suggesting that this is an expert opinion–based recommendation. For translation into practice, the American Thoracic Society guidelines state for risk stratification, "perform a baseline study ... and intervals of every 1 to 3 years seem reasonable."[72] No age of initiating screening is given.

Justification for risk stratification is based on decision making regarding (1) the frequency of follow-up screening, (2) identifying persons who may benefit from treatment shown to improve outcomes (eg, hydroxyurea), and (3) anticipating future health care needs of that individual. No evidence is presented to show how current test results would predict timing of the next screening or that mortality risk stratification can improve the ability to anticipate future health care needs or exactly what is entailed in anticipating future needs.

Conversely, our guideline reports that there is insufficient evidence to make a recommendation supporting regular screening with Doppler echocardiography and the value of the use of *N*-terminal pro-brain natriuretic peptide for risk stratification was not assessed. No evidence was identified from the published literature of any morbidity or mortality benefit of identifying or treating PAH in asymptomatic individuals. This expert panel agrees that increasing the use of proven SCD therapies (eg, hydroxyurea) should be considered for most persons with SCD but could find no evidence that echocardiographic screening for PAH would increase the use of hydroxyurea or that hydroxyurea therapy provides benefit in management of PAH. Without evidence to demonstrate the value of the initial echocardiographic screening in asymptomatic individuals, the expert panel did not consider such issues as anticipating future health care needs or time to next screening.

This review has a number of limitations. The literature search was conducted in English only, although we are unaware of any major clinical trials published in other languages that would have affected the results. During the extensive review process, none of the external reviewers commented about missing evidence. GRADE was used to guide the evidence review, but was modified. Whenever an existing system of evaluating evidence is modified, issues of validity arise. However, there is limited information about the validity of any commonly used system of evaluating evidence, including GRADE.

The processes used by the panel were able to fulfill most of the criteria that the IOM have recommended for creating high-quality guidelines, but not all.[19] Most significantly, the expert panel did not include a patient or a patient representative.

The literature review concluded in April 2014. We are aware of 2 recent publications that may affect SCD management. The first suggests that nonmyeloablative allogeneic hematopoietic stem cell transplantation may be of value in adults with sickle cell phenotype with or without thalassemia.[73] The second, the Silent Infarct Transfusion Trial,[74] shows that children with SCA and silent stroke have fewer strokes and new silent infarcts when treated with long-term transfusion therapy.

Our systematic review revealed that evidence is lacking in many areas important to care for individuals with SCD. There are only 7 recommendations in which the quality of evidence is high and the strength of the recommendation is strong (**Table 10**). Most of the recommendations for pain management (both acute and long-term) were consensus adapted from general pain guidelines, which may not adequately address the severe, episodic, and difficult to quantify pain associated with SCD. Little evidence exists to guide contraception and maternity care in persons with SCD. Several potential acute and chronic complications also have very limited evidence on which to base recommendations (eg, monitoring and addressing renal function and blood pressure in children and adults with SCD, ocular complications and management of fever in young children with SCD). Research is needed to address many of the identified gaps in the care of persons with SCD in screening for and prevention of complications, as well as treatment and reduction of high morbidity and mortality. Table 10 presents the strongest recommendations supported by high-

quality evidence that the panel could make, highlighting the paucity of evidence available.

Conclusions

The process of developing guidelines for the management of children, adolescents, and adults with SCD has been challenging because high-quality evidence is limited in virtually every area related to SCD management. The systematic review of the literature identified a very small number of RCTs in individuals with SCD, demonstrating the extensive knowledge gaps in SCD and care of affected individuals. The expert panel realizes that this summary report and the guidelines leave many uncertainties for health professionals caring for individuals with SCD and highlight the importance of collaboration between primary care health professionals and SCD experts. However, we hope that this summary report and the SCD guideline begins to facilitate improved and more accessible care for all affected individuals, and that the discrepancies in the existing data will trigger new research programs and processes to facilitate future guidelines.

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