American Society of Hematology 2019 Guidelines for Sickle Cell Disease: Evidence-based Strategies to Prevent, Screen and Treat CNS Disease

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Running Title: ASH **CNS guidelines for sickle cell disease**

Abstract

Background: Central nervous system (CNS) complications are among the most common, devastating sequelae of sickle cell disease (SCD) occurring throughout the life span.

Objective: These evidence-based guidelines of the American Society of Hematology are intended to support the SCD community in decisions about prevention, diagnosis, and treatment of the most common neurological morbidities in SCD.

Methods: The Mayo Evidence-Based Practice Research Program supported the guideline development process, including updating or performing systematic evidence reviews. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations.

Results: The panel placed a higher value on maintaining cognitive function than on being alive with reduced (significantly less than baseline) cognitive function. The panel developed 18 recommendations with evidence-based strategies to prevent, screen, and treat CNS complications of SCD in high-income and low- and middle-income countries.

Conclusions: Three of eighteen recommendations immediately impact clinical care. These recommendations include using transcranial doppler ultrasound screening and hydroxyurea for primary stroke prevention in children with hemoglobin SS (HbSS) and HbSβ^0 thalassemia living in low-income countries; surveillance for developmental delay, cognitive deficits and neurodevelopmental disorders in children; and screening with magnetic resonance imaging of the brain without sedation to detect silent cerebral infarcts at least once in early-school-age children and once in adults with HbSS or HbSβ^0 thalassemia. Individuals with SCD, their family members and clinicians should become aware of these recommendations aiming to reduce the burden of CNS complications in children and adults with SCD.

Keywords

sickle cell disease, stroke, silent cerebral infarct, intracerebral hemorrhage, cerebrovascular, cognitive impairment

Summary of Recommendations

Background

Stroke, silent cerebral infarcts (silent strokes), and cognitive morbidity are the most common permanent sequelae of sickle cell disease (SCD) in children and adults. Prior to 1990 in the United States, a large prospective cohort study demonstrated that by 40 years of age, approximaely 20% and 10% of adults with phenotypes hemoglobin SS (HbSS) or HbSC had a cerebrovacular accident, respectively (Figure 1)[1]. In most low-income countries, approximately 11% of children with HbSS and less than 1% children with HbSC will have a stroke before their 18th birthday. However, screening with transcranial Doppler ultrasound (TCD) and treatment with regular blood transfusion in children with abnormal TCD velocities has resulted in a 10-fold decrease in the prevalence of strokes in children with HbSS and HbSβ^0 thalassemia living in high-income countries.

The most common cause of permaneant neurological injury in HbSS and HbSβ^0 thalassemia is silent cerebral infarcts, occurring in approximately 35% of children by 18 years of age and more than 50% of adults by 30 years of age (Figure 2)[2]. Silent cerebral infarcts require magnetic resonance imaging (MRI) to detect and a formal neurological examination to exclude the presence of an overt stroke. Both stroke and silent cerebral infarcts are associated with significant cognitive deficits that may alter significantly alter educational attainment, employment status, and quality of life.

A key component of the panel's objectives was to establish guidelines applicable to the more than 90% of the children born with HbSS who live in Africa and India as well as for children in high-income countries. Less than 1% of all children born in the world with HbSS live in the United States and Europe[3]. Children and adults with HbSS living in low-income settings without resources to implement evidence-based

strategies for primary and secondary stroke prevention have high lifetime stroke risks similar to children living with HbSS prior to the 1990s in high-income countries, when TCD screening and treatment with regular blood transfusion therapy being introduced.

The panel recognized that most of the recommendations would be difficult to implement in low- and middle-income countries where the majority of children and adults with SCD live; however, when applicable, the panel provided recommendations based on the best available evidence. The major barrier to transferring knowledge for preventing neurological injury from high-income settings to low-income settings, particularly in Africa, is the low number of TCD machines and MRI scanners to detect central nervous system (CNS) pathology, the lack of sufficiently trained health care providers to perform TCD, and low numbers of physicians with expertise in hematology, neurology and neuroradiology. An important rate limiting step for primary stroke prevention in low-income areas is the lack of TCD machines, coupled with a lack of trained personnel to complete TCD screening, and access to hydroxyurea for primary stroke prevention.

The central theme in all guidelines was that the panel placed a higher value on maintaining cognitive function than on being alive with reduced cognitive function (significantly less than baseline functioning). Given the high prevalence of neurological morbidity (strokes, silent cerebral infarcts and cognitive impairment) in children and adults with SCD, critical components of the recommendations are the rights for families to be informed about the presence of neurological morbidity which requires specific diagnostic studies, specifically silent cerebral infarcts (MRI of the brain) and cognitive deficits (cognitive testing), the increased risk for future neurological morbidity, and plausible disease-modifying therapies that may attenuate or abate risks of further neurological injury without data from phase III randomized controlled trials. The panel developed 10 recommendations with evidence-based strategies to prevent, screen, and treat CNS complications of SCD in high- and low-income settings.

These guidelines are based on original and updated systematic reviews of evidence conducted under the direction of the Mayo Evidence-Based Practice Research Program. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN)[4-7]. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[8-13] to assess the certainty of the evidence and formulate recommendations.

Interpretation of Strong and Conditional Recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends..."), or conditional ("the guideline panel suggests…") and has the following interpretation:

Strong Recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional Recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.
- For policy makers: policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.

- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of Good Practice Statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used [14]. Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Primary stroke prevention for children with sickle cell disease living in high- and low-income settings.

Recommendation 1.1. For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years), the ASH guideline panel recommends annual TCD screening (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 1.2. For children who have compound heterozygous sickle cell disease other than HbSC and have evidence of hemolysis in the same range as those with HbSS, the ASH guideline panel suggests TCD screening (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2.1. For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years) who have abnormal TCD velocities and live in a well-resourced setting (where regular blood transfusion therapy is feasible), the ASH guideline panel recommends regular blood transfusion for at least a year (versus

no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.2. For children who have compound heterozygous SCD other than HbSC, who have evidence of hemolysis in the same range as those with HbSS, have an abnormal TCD velocity, and live in a high-income country (where regular blood transfusion is feasible), the ASH guideline panel suggests regular blood transfusion for at least a year (versus no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2.3. For children with SCD (ages 2 to 16 years) and abnormal TCD results who have been receiving transfusion therapy for at least one year and are interested in stopping transfusion, according to the clinical trial risk stratification with an MRI and magnetic resonance angiography (MRA) of the brain (see technical remarks), ASH guideline panel suggests hydroxyurea treatment at maximum tolerated dose can be considered to substitute for regular blood transfusions.(Conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯)

Recommendation 3. For children (ages 2 to 16 years) with HbSS or HbSβ^0 thalassemia or compound heterozygotes for SCD who have abnormal TCD screening and live in resource-restricted settings (where regular blood transfusion therapy and chelation therapy are not available or affordable), the ASH guideline panel suggests hydroxyurea therapy with at least 20 mg/kg/day at a fixed dose or the maximum tolerated dose (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Acute and timely management of suspected or confirmed ischemic stroke or transient ischemic attack

Recommendation 4.1. For children or adults with SCD and acute neurological deficits, including transient ischemic attack, the ASH guideline panel recommends prompt blood transfusion. The transfusion should be given immediately upon recognition of symptoms without delay beyond several hours of acute neurological symptom presentation. The type of transfusion (simple, modified

exchange or apheresis) is dependent on individual patient factors and local transfusion resources (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕).

Recommendation 4.2. For children or adults with SCD and acute neurological deficits including transient ischemic attack, the ASH guideline panel suggests exchange transfusion versus simple transfusion (see details for exceptions). When exchange transfusion is not available within two hours of presentation for medical care and hemoglobin is ≤8.5 g/dl, simple transfusion can be performed to avoid delays in treatment while a manual exchange transfusion or an automated apheresis is planned (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Secondary prevention of ischemic strokes in children and adults with HbSS or HbSβ^0 thalassemia

Recommendation 5. For children with HbSS or HbSβ^0 thalassemia and a history of prior ischemic stroke, the ASH guideline panel recommends that blood transfusion goals for secondary stroke prevention be to increase the hemoglobin above 9 gm/dl at all times and to maintain the HbS level at <30% of total hemoglobin until the time of the next transfusion (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 6. For adults and children with SCD, moyamoya syndrome and a history of stroke or transient ischemic attack, the ASH guideline panel suggests evaluation for revascularization surgery in addition to regular blood transfusion (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Acute management of ischemic strokes and the use of tissue plasminogen activator (tPA) for adults with SCD presenting with stroke symptoms.

Recommendation 7. For adults with SCD presenting with symptoms of acute ischemic stroke and being considered for intravenous tPA (age ≥ 18 years, no hemorrhage on CT scan, within 4.5 hours of

onset of symptoms/signs and without contraindications for thrombolysis), the ASH guideline panel suggests management using a shared decision-making approach that follows these principles.

a. In all patients, the administration of tPA should not delay prompt simple or exchange blood transfusion therapy.

b. Patients may be considered for intravenous tPA based on its established inclusion and exclusion criteria detailed in stroke management algorithms.

c. The following factors suggest likely benefit from intravenous tPA: older age, atrial fibrillation, diabetes, hypertension, and hyperlipidemia. Management of younger patients without these risk factors should emphasize early transfusion.

d. There are no validated risk stratification or reliable age cut-off criteria to guide the choice of initial therapy. Intravenous tPA is not recommended for children with SCD (<18 years of age).

(Conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯.)

Screening for developmental delay or cognitive impairment in children and adults with SCD.

Recommendation 8.1. Given the high prevalence of developmental delay and cognitive deficits and coupled with the guidelines set by the American Academy of Pediatrics, the ASH guideline panel recommends that clinicians supervising care of pediatric SCD patients conduct surveillance using simplified signaling questions for the following:

- Concerns about developmental delays in preschool-age children;

- Concerns about neurodevelopmental disorders in school-age children, such as academic or behavioral problems or symptoms of inattention, hyperactivity, or impulsivity.

(Strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯.)

Recommendation 8.2. For children with SCD who have abnormal surveillance results suggesting increased risk for developmental delay or cognitive deficits, the ASH guideline panel recommends screening or referral for formal screening by a psychologist or a pediatrician able to perform screening with the available validated tools (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 8.3. Given the high prevalence of cognitive impairment in adults with SCD, coupled with the guidelines set by the American Academy of Neurology, the ASH guideline panel recommends that clinicians supervising care of adults with SCD conduct surveillance for cognitive impairment using simplified signaling questions (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 8.4. For adults who have abnormal surveillance results suggesting cognitive impairment, the ASH guideline panel recommends formal referral to a psychologist or a primary care physician able to perform more in-depth cognitive evaluation (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Cognitive rehabilitative strategy for children and adults with cognitive impairments

Recommendation 9.1. For children with SCD and abnormal screening for developmental or cognitive status, the ASH guideline panel recommends the following:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for developmental delays or cognitive deficits;

- following the cognitive domain-specific evidence-based guidelines for these conditions to provide appropriate interventions (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕).

Recommendation 9.2. For adults with SCD and abnormal screening for cognitive status, the ASH guideline panel recommends the following:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for cognitive deficits;

- following the cognitive domain-specific evidence-based guidelines for these conditions to provide appropriate interventions (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕).

Screening for silent cerebral infarcts in children and adults with HbSS or HbSβ^0 thalassemia

Recommendation 10.1. Given the high prevalence of silent cerebral infarcts in children with HbSS or HbSβ^0 thalassemia (1 in 3) and their association with cognitive impairment, poor school performance, and future cerebral infarcts, the ASH guideline panel recommends at least a one-time MRI screening without sedation to detect silent cerebral infarcts in such early-school-age children, when MRI can be performed without sedation (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 10.2. Given the high prevalence of silent cerebral infarcts in adults with SCD HbSS or HbSβ^0 thalassemia (1 in 2) and their association with cognitive impairment, poor school performance and future cerebral infarcts, the ASH guideline panel suggests at least a one-time MRI screening without sedation to detect silent cerebral infarcts in these adults (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Values and Preferences

Overall, the ASH Guideline Panel on Cerebrovascular Disease placed a higher value on maintaining cognitive function than on being alive with reduced cognitive function (significantly less than baseline functioning). Given the high prevalence of neurological morbidity (strokes, silent cerebral infarcts and cognitive impairment) in children and adults with SCD, a critical component of the panel's recommendations is the rights of families to be informed about the presence of neurological morbidity, increased risk for future neurological morbidity, and plausible disease-modifying therapies that may

attenuate or abate risks of further neurological injury without data from phase III randomized controlled trials. All panel members strongly believed that full disclosures should occur with families regarding the cumulative high risk of neurological morbidity in SCD, the utility of screening for neurological disease (abnormal TCD, silent cerebral infarcts, cognitive impairment) and biologically plausible therapies that may attenuate future neurological injury without a phase III randomized controlled trial.

Explanations and Other Considerations

These recommendations take into consideration acceptability, feasibility, cost-effectiveness and impact on health equity. The ASH guideline panel acknowledged variability in knowledge about risks and benefits of treatments, as well variability in the patient, their family members and the providers perceptions of trade-offs between harms versus benefits when developing these recommendations.

Good Practice Statements

Good Practice Statement 1. To adopt a health care system strategy for tracking TCD assessments and treatment of children with SCD and abnormal TCD measurements because these children are at extremely high risk for ischemic strokes. Tracking TCD surveillance and treatment in both high- and low-income settings will have a significant impact in decreasing strokes in children with SCD.

Good Practice Statement 2. To consult with a neurologist and neuroradiologist (when available) for evaluation in all suspected acute neurological events and neuroimaging studies, respectively. For suspected ischemic strokes, timely and appropriate red blood cell transfusion (within 2 hours of presentation to medical care) should be provided.

Good Practice Statement 3. To adopt a multidisciplinary (i.e., hematology, neurology, neurosurgery, and neuroradiology) team management approach when a neurosurgical revascularization procedure is being evaluated for SCD-related moyamoya syndrome, as adjunctive therapy to regular blood transfusion therapy for secondary stroke prevention.

Good Practice Statement 4. To inform children and adults with HbSS and HbSβ^0 thalassemia and their families about whether the affected individual has a silent cerebral infarct based on at least one MRI

of the brain without sedation, coupled with discussion about potential disease-modifying therapy to prevent the high rate of infarct recurrence in those with silent cerebral infarcts.

Good Practice Statement 5. To have ongoing standardized cognitive or behavior surveillance, and when deficits are identified, refer the patient to a specialist who may better evaluate the magnitude f the cognitive deficits and rehabilitative approaches.

Introduction

Aims of these Guidelines and Specific Objectives

The purpose of these guidelines is to provide evidence-based recommendations to facilitate prevention, diagnosis and treatment of neurological morbidity in children and adults with sickle cell disease (SCD), including strokes, silent cerebral infarcts and cognitive morbidity. To achieve this goal, the panel reviewed and critically appraised the literature and provided evidence-based recommendations. Through improved provider and patient education using the available evidence and via evidence-based recommendations, these guidelines aim to provide support for shared decision-making between providers, patients, and their families, which will result in decreased neurological morbidity and mortality of children and adults with SCD.

The target audience includes patients, hematologists, general practitioners, internists, other clinicians, and decision makers. Policy makers interested in these guidelines include those involved in developing local, national, or international plans with the goal to improve access to evidence-based care. Local or national panels may also use this document as a basis for implementation of strategies to prevent neurological morbidity in children and adults with SCD in their health care system. When health care systems and health care providers adopt these guidelines, there will be a decrease in neurological morbidity in children and adults with SCD.

Description of the Health Problem

Stroke, silent cerebral infarcts and cognitive morbidity are the most common permanent sequelae of SCD in children and adults. Prior to 1990 in the United States, a large prospective cohort study demonstrated that by 40 years of age, approximately 20% and 10% of adults with phenotype hemoglobin SS (HbSS) or HbSC had a cerebrovacular accident, respectively (Figure 1)[1]. For most children with HbSS living in low-income countries today, approximately 11% will have a stroke by 18 years of age.

The most common cause of permanant neurological injury in HbSS or HbSβ^0 thalassemia is silent cerebral infarcts, occurring in approximately 35% of children and more than 50% of adults (Figure 2). Silent cerebral infarcts require magnetic resonance imaging (MRI) to detect and a formal neurological examination to exclude the presence of an overt stroke. Both stroke and silent cerebral infarcts are associated with significant risk of infarct recurrence, clinically relevant cognitive deficits which indirectly may alter employment status and quality of life. The importance of "silent" cerebral infarcts is supported by the 2013 American Heart Association/American Stroke Association (AHA/ASA) endorsed definition of stroke that for the first time includes silent cerebral infarctions and silent cerebral hemorrhages typically identified by MRI of the brain. The rationale behind such a change was to move towards a radiological demonstration (tissue-based definition) of infarction or hemorrhage because permanent injury to the brain may occur despite less than 24 hours of symptoms. The AHA/ASA held that treatment of patients with cerebral ischemia should be directed to the cause and not governed only by whether infarction has developed (in the case of TIA) or the size of the infarct. The traditional definition of stroke endorsed by the World Health Organization (WHO) requires clinical symptoms for more than 24 hours and has been in use since the 1970s. Our panel affirmed that importance silent cerebral infarcts given the known impact on cognition. However, we recognize the MRI-based definition is challenging in low resource settings where MRI is not widely available. Hence, the WHO definition of stroke is still important and likely denotes more severe brain injury.

Less than 1% of all children born in the world with HbSS or HbSβ^0 thalassemia live in the United States and Europe[15]. Children and adults with HbSS or HbSβ^0 thalassemia living in low-income settings without

resources to implement evidence-based strategies for primary and secondary stroke prevention have high lifetime stroke risks, similar to individuals living with HbSS or HbSβ^0 thalassemia prior to the 1990s in the United States. The major barriers to transferring new knowledge for primary and secondary stroke prevention from high-income countries to low-income countries, particularly in Africa, are gaps in access to TCD machines required for stroke screening, a lack of sufficiently trained, certified TCD examiners, a lack of expertise in hematology and neurology to manage patients at risk for initial and subsequent strokes, and the low availability of regular blood transfusion therapy. The panel recognized that most of the recommendations would be difficult to implement in low- and middle-income countries where the majority of children and adults with SCD live; however, when applicable, the panel has provided recommendations based on the best available evidence for individuals living in these countries.

Methods

The methodology of this guideline is published in detail elsewhere[16]. The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach[8-13]. The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review and organizational approval, was guided by ASH policies and procedures derived from the Guideline International Network (GIN)–McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN[4-7].

The Mayo Evidence-Based Practice Research Program conducted or updated systematic reviews based on clinical questions developed and defined by the ASH guideline panel. This was a multidisciplinary group and included multiple stakeholders (four hematologists who provide medical care for children and adults with SCD, three neurologists who provide medical care for children, two neuroradiologists who review the neuroimaging of children and adults with SCD, a pediatric psychologist with expertise in SCD, an individual with SCD who has had a stroke, a parent of a child with SCD who had a stroke after she was not offered TCD screening and a physician with expertise in evidence-based medicine methodology). Following the GRADE approach, randomized trials and observational studies provide an initial level of certainty in evidence classified as high or low, respectively. Factors which modify this initial level can lead

to upgrading or downgrading this level[17]. Then evidence-to-decision (EtD) factors are applied to make a recommendation. These factors are a balance of benefits and harms, patient values, resources, feasibility, acceptability and impact on equity[18]. The EtD tables for all the recommendations are attached as an online supplement

Recommendations are either strong or conditional. Strong recommendations imply a high certainty of net benefit, such that the recommended action should be applied to most patients as a standard of care. Conditional recommendations imply that the balance of benefits and harms is less clear. Although the recommended action should be offered to the majority of patients, there will be important variation in context, and in some cases, an alternative action is reasonable[17].

Values and Preferences and Patient Engagement When Addressing All 10 Recommendations

The values invoked in developing these 10 recommendations reflect the combined view of all panelists, including the two patient representatives. In all 10 recommendations, there was near unanimous agreement regarding the importance of the question at hand, which was about the prevention, detection, and treatment of central nervous system (CNS) morbidity. The panelists rated the importance of outcomes on a scale of 1 to 9, where ratings of 7 to 9 reflect outcomes of critical importance to the decision at hand. As a guiding principle, all members of the panel placed a higher value on maintaining cognitive function than on being alive with minimal cognitive function (significantly less than baseline functioning).

Organization, Panel Composition, Planning and Coordination

The work of this panel was coordinated with that of four other guideline panels (addressing other aspects of SCD) by ASH and the Mayo Evidence-Based Practice Research Center (funded by ASH under a paid agreement). Project oversight was provided by a coordination panel, which reported to the ASH Guideline Oversight Subcommittee. ASH vetted individuals and appointed them to the guideline panel. The Mayo Center vetted and retained researchers to conduct systematic reviews of evidence and coordinate the

guideline development process including the use of the GRADE approach (reference to detailed methods article). The membership of the panels and the Mayo Center team is described in supplement 1.

In addition to synthesizing evidence systematically, the Mayo Center supported the guideline development process, including determining methods, preparing meeting materials and facilitating panel discussions. The panel's work was done using web-based tools (www.gradepro.org) and face-to-face and online meetings.

Guideline Funding and Management of Conflicts of Interest

Development of these guidelines was wholly funded by ASH, a non-profit medical specialty society that represents hematologists. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representatives received honorariums of $100 per day for in-person meetings and $25 per conference call. The panelists received no other payments. Through the Mayo Clinic Evidence-Based Practice Research Program, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed through disclosure, panel composition, and recusal, according to recommendations of the Institute of Medicine[19] and the Guidelines International Network[7]. Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the panel, including the co-chairs, had no such conflicts. None of the Mayo-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was also used to manage conflicts of interest[7,20-22]. During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting about individual domains (e.g., magnitude of desirable consequences) and the direction and strength of the recommendation. The EtD framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2019, after the guideline panel had agreed on recommendations, it was discovered that one panelist had a direct financial conflict with an affected company (meals in 2017) that had not been previously reported. The panelist had been recused for a similar disclosure during the guideline meeting held to form recommendations. Members of the Guideline Oversight Subcommittee reviewed this late disclosure and determined no additional action was required.

Supplement 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years prior to appointment; in part B, indirect financial interests; and in part C, not mainly financial interests. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplement 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Formulating Specific Clinical Questions and Determining Outcomes of Interest

The panel met in-person and via conference calls to generate possible questions to address. The panel then used an iterative process to prioritize the questions described in Table 1. Questions were formulated using the standard format of population, intervention, comparison and outcomes (PICO).

Table 1. The 10 questions that the Cerebrovascular Disease Panel included. The 10 questions were based on the importance of the clinical questions in preventing or decreasing neurological morbidity in children and adults with SCD.

1	Should transfusion (versus no transfusion or hydroxyurea therapy) be used for children aged 2 to 16 years with HbSS or HbSβ^0 thalassemia and abnormal non-imaging transcranial Doppler (TCD) measurements?
2	Between 2 and 16 years of age, should children with HbS/Lepore disease, HbSE disease, HbS/O Arab disease, or HbS/D disease phenotypes or other compound SCD heterozygotes other than hemoglobin SC have TCD screening at the same frequency and interval as children with HbSS or HbSβ^0 thalassemia?
3	Should annual screening with TCD be used for children between 2 and 16 years of age with HbSS or HbSβ^0 thalassemia phenotypes from low-income and middle-income countries?
4	Should simple blood transfusion versus exchange transfusion be used for children and adults with SCD and suspected acute symptomatic stroke, including transient ischemic attack?
5	Should red blood cell transfusion targeted to keep HbS levels below 30% (versus no treatment), red blood cell transfusion targeted to keep HbS levels above 30% or hydroxyurea therapy be used for children with sickle cell disease with a history of stroke?
6	Should cerebral revascularization surgery (including encephalo-duro-arterio-synangiosis [EDAS], encephalo-duro-arterio-myo-synangiosis [EDAMS], pial synangiosis, or direct anastamosis) plus transfusion therapy versus regular blood transfusion therapy alone be used for patients with SCD and moyamoya syndrome?
7	Should intravenous thrombolysis with tissue plasminogen activator (tPA) versus no treatment with tPA be used for adults with SCD presenting with acute ischemic stroke and no hemorrhage on CT within 4.5 hours of onset of symptoms?
8	Should clinicians perform or refer for screening for developmental delay and cognitive impairment versus no screening in children and adults with SCD?

9	Should cognitive rehabilitation therapy versus no rehabilitation be used for children and adults with SCD and cognitive deficit?
10	Should screening with MRI for silent cerebral infarcts versus no screening be used for children and adults with HbSS or HbSβ^0 thalassemia?

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere[23]. In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach[23]. While acknowledging considerable variation in the impact on patient outcomes, the panel considered the following outcomes critical for clinical decision-making across questions:

Table 2. Outcomes Prioritized by the ASH Guideline Panel on Cerebrovascular Disease

Question 1.	Stroke
Question 2 and 3.	Silent cerebral infarct
Question 4 and 5.	Transient ischemic attack Acute chest syndrome Painful crisis Total adverse events
Question 6.	Stroke Silent cerebral infarct Mortality Post-operative complications including post-operative subdural hygroma; Seizure; Cerebral edema; Subarachnoid and interventricular hemorrhage
Question 7.	Stroke Silent cerebral infarct Mortality Intracranial and other major haemorrhage
Question 8.	Intelligent quotient/cognitive impairment/developmental delay/school performance
Question 9.	Cognitive impairment and school performance
Question 10.	Silent cerebral infarct

	developmental delay and school performance

Evidence Review and Development of Recommendations

Researchers at the Mayo Clinic evidence-based Practice Center conducted new systematic reviews or updated existing systematic reviews to answer the ten PICO questions. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences and costs and summarized findings within the EtD frameworks[13,18,24]. Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into four levels ranging from very low to high[9-11].

For each guideline question, the Mayo Center prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool (www.gradepro.org)[13,18,24]. The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost effectiveness), values and preferences (relative importance of outcomes), equity, acceptability and feasibility. The guideline panel reviewed draft EtD tables before, during or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, in addition to searches presented in Supplement 4, panel members were asked to suggest any studies that might have been considered missed and fulfilled the inclusion criteria for the individual questions.

During a two-day in-person meeting followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to a consensus on the following: the

certainty of the evidence, the balance of benefits and harms of the compared management options and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly considered the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. The approach is described in detail in the accompanying article describing the methods of development (reference to detailed methods article).

Interpretation of Strong and Conditional Recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table 3provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers and researchers.

Table 3. Interpretation of Strong and Conditional Recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values and preferences.
Clinicians	Most individuals should follow the recommended course of action.	Different choices will be appropriate for individual patients; clinicians must

	Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of Good Practice Statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used[14]. Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Document Review

Draft recommendations were reviewed by all members of the panel, revised and then made available online on September 24, 2018, or for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Eighteen individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. The guidelines were reviewed by the ASH Guideline Oversight Subcommittee on October 10, 2019. On October 21, 2019 the ASH Committee on Quality confirmed that the defined guideline development process was followed, and on October 25, 2019, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to Use these Guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods

of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by the related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Recommendations

Questions 1, 2, and 3 (screening with transcranial Doppler and primary stroke prevention)

1. *Should transfusion (versus no transfusion or hydroxyurea therapy) be used for children aged 2 to 16 years with HbSS or HbSβ^0 thalassemia and abnormal non-imaging transcranial Doppler (TCD) measurements?*
2. *Between 2 and 16 years of age, should children with HbS/Lepore disease, HbSE disease, HbS/O Arab disease, or HbS/D disease phenotypes or other compound SCD heterozygotes other than hemoglobin SC have TCD screening at the same frequency and interval as children with HbSS or HbSβ^0 thalassemia?*
3. *Should annual screening with TCD be used for children between 2 and 16 years of age with HbSS or HbSβ^0 thalassemia phenotypes from low-income and middle-income countries?*

Recommendation 1.1. For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years), the ASH guideline panel recommends annual TCD screening (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 1.2. For children who have compound heterozygous sickle cell disease other than HbSC and have evidence of hemolysis in the same range as those with HbSS, the ASH guideline panel suggests TCD screening (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2.1. For children with HbSS or HbSβ^0 thalassemia (ages 2 to 16 years) who have abnormal TCD velocities and live in a well-resourced setting (where regular blood transfusion therapy,

typically every 3-4 weeks, is feasible to maintain the maximum hemoglobin S level less than 30% and maintain the hemoglobin level greater than 9.0 g/dl), the ASH guideline panel recommends regular blood transfusion for at least a year (versus no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.2. For children who have compound heterozygous SCD other than HbSC, who have evidence of hemolysis in the same range as those with HbSS and an abnormal TCD velocity and who live in a high-income country (where regular blood transfusion is feasible), the ASH guideline panel suggests regular blood transfusion for at least a year (versus no transfusion) with the goal of keeping maximum HbS levels below 30% to reduce the risk of stroke and maintaining the minimum hemoglobin greater than 9.0 g/dl (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2.3. For children with SCD (ages 2 to 16 years) and abnormal TCD results who have been receiving transfusion therapy for at least one year and are interested in stopping transfusion, according to the clinical trial risk stratification with an MRI and magnetic resonance angiography (MRA) of the brain (see technical remarks), ASH guideline panel suggests hydroxyurea treatment at maximum tolerated dose can be considered to substitute for regular blood transfusions.

Remarks: - For children with abnormal TCD results and without MRA-defined vasculopathy or silent cerebral infarcts who have received at least one year of transfusions, based on the entry criteria of the TWiTCH trial suggests that hydroxyurea therapy treatment at the maximum tolerated dose be considered to replace regular blood transfusion therapy.

- For children with abnormal TCD results, MRA-defined vasculopathy or silent cerebral infarcts, based on the exclusion criteria of the TWiTCH Trial continuing regular blood transfusions indefinitely.

(Conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯.)

Remarks for recommendations 1 and 2

Recommendations 1 and 2 are applicable to countries or settings in which regular blood transfusion is feasible and acceptable.

The suggested threshold for treatment is two non-imaging TCD measurements greater than 200 cm/s, a time-averaged mean of the maximum velocity (TAMMV) of ≥200 cm/s or a single measurement more than 220 cm/s in the distal internal carotid artery or proximal middle cerebral artery.

If the imaging TCD technique is used, then two measurements greater than a time-averaged mean maximum (TAMX) of ≥185 cm/s or a single measurement greater than 205 cm/s is required in the distal internal carotid artery or proximal middle cerebral artery.

Predictive values of the TCD measurements in the other intracranial arteries have not been rigorously addressed and should not be used to stratify into high- and low-risk groups for future strokes.

For recommendations 1.2 and 2.2, the threshold for hemolysis requiring regular TCD surveillance should be determined based on the individual patient characteristics. Consideration should be given to hemoglobin level, reticulocyte count, and degree of hemolysis in relationship to HbSS.

For recommendations 1.2 and 2.2, we could not define a laboratory threshold to determine who should undergo TCD. Also, no evidence was available demonstrating that children with hemoglobin SC should undergo TCD screening for primary stroke prevention.

Recommendation 3. For children (ages 2 to 16 years) with HbSS or HbSβ^0 thalassemia or compound heterozygotes for SCD who have abnormal TCD screening and live in resource-restricted settings (where regular blood transfusion therapy and chelation therapy are not available or affordable), the ASH guideline panel suggests hydroxyurea therapy with at least 20 mg/kg/day at a fixed dose or the maximum tolerated dose (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks for recommendation 3

> Recommendation 3 is applicable to low- and middle-income countries and settings in which regular blood transfusion is not feasible. For children with abnormal TCD velocities in this setting, the optimal hydroxyurea dose and the appropriate infrastructure support required to safely administer hydroxyurea and to follow the patients for expected toxicities have not been determined.

Specific background

Applying the results of Optimizing Primary Stroke Prevention in Sickle Cell Anemia Trial (STOP) is one of the greatest advances in management of SCD. TCD screening coupled with regular blood transfusion therapy for those with an abnormal TCD measurement is associated with a 92% reduction in stroke incidence compared to observation alone[25]. The threshold for regular blood transfusion therapy is two non-imaging TCD measurements greater than or equal to 200 cm/s, a TAMMV of ≥200 cm/s, or a single measurement more than 220 cm/s in the proximal portion of the middle cerebral artery or the distal portion of the internal carotid artery (Supplement 5, Figure 1). The two TCD measurements are required for the values greater than or equal to 200 cm/s and less than 220 cm/s because of the ultra-sonographer's large coefficient of variation of TCD measurement in the same child with HbSS measured only three hours apart[26] and the large intra-subject standard deviation of the TCD measurement, 14.9 cm/s, in children with HbSS[27]. The peak systolic velocity has not been applied as predictor of initial stroke in a randomized controlled trial are generated automatically from the TCD machine and can not be used for primary stroke prevention. Unfortunately, the TCD peak systolic velocity is confused with TAMMV and patient can be inadvertently transfused.

STOP II demonstrated that for participants in STOP who received transfusions for 30 months or longer and whose TCD measurements became normal, continued regular blood transfusion was required to prevent strokes or reversion to abnormal TCD measurements[28]. Thus, children with abnormal TCD measurements are presumed to have an indefinite risk of strokes. Summary of the results for STOP and STOP II demonstrated a clear benefit of regular blood transfusion compared to no transfusions (observation) (Figure 3). STOP II excluded children with severe stenotic lesions on cerebral MRA.

The optimal interval for reassessment of children with conditional TCD measurements (170 to 199 cm/s) has not been determined, but reassessment is commonly done within six months. The HbSS and HbSβ^0

thalassemia phenotypes were both eligible for STOP and STOP II, in part because of clinical challenges of distinguishing HbSS from HbSβ^0 thalassemia using clinical laboratory values[29] and the fact that both diagnoses have been included in primary stroke prevention stroke trials[25,28].

If the imaging TCD technique rather than the non-imaging technique is used, then two measurements greater than the TAMX (≥185 cm/s) or a single measurement greater than 205 cm/s is required[30]. To ensure that proper velocity thresholds are utilized for clinical decision-making, clinicians should determine which type of TCD (imaging or non-imaging) is utilized at their center. Regardless of whether the non-imaging or imaging TCD is used, the threshold for treatment should not be based on peak systolic velocity (Supplement 5 Figure 1). Measurements should be done at the terminal portions of the internal carotid artery and proximal portion of the middle cerebral artery[25]. The child should not have had a recent blood transfusion when TCD is performed because of the known association between TCD velocities and transfusions[31]. Typically, the TCD measurement should be done at least three months after the last transfusion and not when the child is ill.

Treatment with regular blood transfusion commonly requires iron chelation therapy to attenuate excessive stores of iron that accumulate with blood transfusion. If a child who had abnormal TCD screening meets the criteria for transitioning to maximum tolerated dose of hydroxyurea after one year of regular blood transfusion therapy, a discussion with the family should include whether hydroxyurea is preferable to regular blood transfusion therapy[32]. Prior to consideration of transitioning from regular blood transfusion therapy to maximum tolerated hydroxyurea per the TCD With Transfusions Changing to Hydroxyurea (TWiTCH) protocol[32], MRI of the brain should be completed to exclude silent cerebral ischemic lesions (see PICO #10) and intracranial MRA should be completed to determine the presence and extent of cerebral vasculopathy.

Given that the incidence rate of strokes was extremely low in the blood transfusion arm of the STOP Trial, less than 1 stroke per 100 patient years, no formal assessment of stroke risk factors in the treatment arm of STOP can be used to determine the subgroup of children likely to have a stroke while receiving regular blood transfusion therapy[25]. In the STOP Trial for those randomly allocated to receive regular blood

transfusion therapy, 21.6% (19 of 88) had persistent abnormal TCD measurements, with a mean follow-up of 2.4 years[33].

A small population of children with SCD (less than 3%) who are compound heterozygotes for SCD and do not have HbSC are at high risk of stroke. The utility of TCD screening in children with SCD who compound heterozygotes are not well defined. This group of children will benefit from TCD screening and treatment if the values are abnormal. Given the statistical relationship between TCD values and hemoglobin levels in children with HbSS[34] and the association between low hemoglobin levels and strokes[1], the evidence suggests that TCD screening and treatment will likely prevent strokes for children that are compound SCD heterozygotes and have evidence of hemolysis in a range similar to that of children with HbSS. The decision as to which children who are compound heterozygotes should receive TCD screening and subsequent treatment should be made on an individual basis. In children who are SCD compound heterozygotes, we cannot identify a single marker of hemolysis or a threshold for markers of hemolysis which should be screened. For children with HbSC or HbSβ$^+$ thalassemia, the risk of abnormal TCD measurements and stroke is less than for those with HbSS.

Hemoglobin levels in children with HbSβ$^+$ thalassemia vary. The range is from hemoglobin levels of 7 g/dl to values within the normal range. The low hemoglobin levels are accompanied by magnitudes of hemolysis markers similar to those seen in children with HbSS. Consequently, we cannot state with high certainty which children with HbSβ$^+$ thalassemia should not receive TCD screening.

Approximately 99% of all children with HbSS live in low- and middle-income countries[3]. For ASH's guidelines to have a significant impact on primary stroke prevention in children with HbSS or HbSβ^0 thalassemia, a meaningful strategy must be aligned with a public health policy that can be implemented in a low-income country. Of children with HbSS living in low-income countries, approximately 11% will have a stroke[1], as opposed to children living in high-income settings that have implemented a stroke screening strategy with treatment. Optimally in high-income countries, less than 1% of the children who receive TCD screening coupled with treatment for abnormal TCD measurements will have strokes[1]. For children with an abnormal TCD measurement, the risk of ischemic strokes is exceptionally high, 10.7 strokes per 100 patient years[1]. As a comparison, in untreated adults with atrial fibrillation, the stroke incidence rate is approximately 4.4 events per 100 patient years[35]. The comparison of ischemic stroke risk for children with abnormal TCD measurements to adults with untreated atrial fibrilliation clearly

demonstrated the opportunity to prevent strokes in children with HbSS or HbSβ^0 thalassemia in both low- and high-income settings.

Clinical experience of the panel, coupled with evidence from the literature, indicates that regular blood transfusion therapy is not a feasible option for the majority of children living in Africa or other low- or middle-income settings. When presented with the benefits of blood transfusion for primary and secondary stroke prevention in Nigeria, caregivers uniformly elected for patients not to receive regular blood transfusion[36]. The reasons for not accepting regular blood transfusions include the annual cost of transfusions, the cost of iron chelation therapy, and the risk of a blood-borne infection or of life-threatening transfusion reactions.

Summary of the evidence

The systematic review identified three randomized controlled trials at low risk of bias addressing the first question (transfusion of children with HbSS or HbSβ^0 thalassemia and abnormal TCDs), no comparative studies addressing the second question (transfusion of other genotypes) and one nonrandomized study for question 3 (hydroxyurea in children with abnormal TCDs in low-income countriess). The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 1-3 to be added here).

Rationale and expected benefits

The primary premise for our recommendations is that there is clear evidence from three National Heart Lung and Blood Institute (NHLBI)-funded controlled trials describing[25,28,32] the benefit of identifying children between 2 and 16 years of age with HbSS or HbSβ^0 thalassemia, and abnormal TCD measurements (TAMMV, >200 cm/s). The initial treatments for abnormal TCD measurements were regular blood transfusion, with therapy transitioned to maximally tolerated hydroxyurea therapy after one year of transfusion, in patients with MRA-defined vasculopathy. Secondary benefits of regular blood transfusion therapy include a decrease in the severity of the disease. No dissent was observed in the panel regarding the importance of identifying the risk of an initial stroke and the option for the caregiver to select the best treatment for primary stroke prevention option for the child.

The controlled clinical trials primarily addressed the question of whether children with abnormal TCD measurements (TAMMV, >200 cm/s) should receive regular blood transfusion, hydroxyurea therapy, or no therapy to reduce the high risk of stroke. One randomized controlled trial, STOP[25], included children with HbSS and HbSβ^0 thalassemia screened for abnormal TCD measurements (TAMMV, >200 cm/s) and then randomly allocated to be treated with regular blood transfusion therapy or observation for primary stroke prevention. One follow-up trial, STOP II[28], included those randomly allocated in STOP who received regular blood transfusions for 30 months or longer and whose TCD measurements became <200 cm/s during that time. The former eligible STOP participants were randomly assigned to continue regular blood transfusion therapy or observation. The results demonstrated a clear benefit of ongoing regular blood transfusion therapy despite TCD measurements decreasing to <200 cm/s[28]. Our recommendations are based on the strength of the evidence of these trials, which demonstrate the benefit of transfusion for primary stroke prevention.

TWiTCH is the only randomized controlled trial providing evidence for the safety of transitioning children with abnormal TCD velocities to the maximum tolerated dose of hydroxyurea. Children in this trial had no evidence of MRA-defined vasculopathy, had been receiving regular blood transfusion therapy for at least one year, and were escalated to the maximum tolerated dose of hydroxyurea[32]. We do not have sufficient evidence to determine whether the group of children with abnormal TCD measurements and MRA-defined vasculopathy would remain stroke-free if transitioned from regular blood transfusion therapy to hydroxyurea, because they were excluded from the trial.

In STOP, the group of children with the highest rate of stroke were those in the observation arm who had both abnormal TCD measurements and silent cerebral infarct at baseline. In this group, 51% (15 of 29 had a stroke, compared with 22% (9 of 40 in the observation group with abnormal TCD measurements and no silent cerebral infarct[37]. Early evidence from small observational studies suggests that hydroxyurea alone may not attenuate cerebral infarct recurrence in adults with SCI[38,39].

A consortium of French investigators demonstrated that children with HbSS or HbSβ^0 thalassemia treated with regular blood transfusion for abnormal TCD velocities had lower TCD velocities one year after matched sibling donor hematopoietic stem cell transplantation (HSCT) compared to children treated with hydroxyurea therapy[40]. These data suggest that HSCT is a reasonable option for children with SCD and

abnormal TCD when performed in a clinical trial setting[40]. However, this work should be considered preliminary because the long-term benefit versus the risk of using HSCT for primary stroke prevention has not been systematically studied, including the late effects of myeloablative and non-myeloablative therapy in children and adults with SCD. Formal clinical trials are required to determine the optimal HSCT strategy for primary stroke prevention in HbSS or HbSβ^0 thalassemia.

The primary premise for our PICO #3 recommendation is based on the observation that approximately 99% of children with HbSS live in low- or middle-income countries[15], coupled with the urgency to prevent strokes in children in the absence of a randomized controlled trial conducted in the low-income settings. Among children with HbSS and abnormal or conditional TCD measurement living in low-middle-income and high-income countries, data from observational studies consistently demonstrate that hydroxyurea lowers TCD measurements[41-50].

The largest observational study that focused exclusively on primary stroke prevention in a low-income country was conducted in Ibadan, Nigeria, and demonstrated the benefit of hydroxyurea for primary stroke prevention[47]. Lagunju et al.[47] showed that children with conditional (*n* = 60) and abnormal (*n* = 44) TCD velocities taking hydroxyurea which started at 10 mg/kg, escalated to the maximum tolerated dose (20 to 35 mg/kg), and was followed for a mean of 3.6 years had a mean drop in TAMMV from 198 cm/s to 169.3 cm/s. One stroke occurred in a child whose TAMMV remained abnormal despite adherence to hydroxyurea, and the calculated incidence rate for overt stroke was 0.27 per 100 person-years[47]. There was also a child with transient ischemic attack whose TAMMV remained abnormal after 15 months; this child had hydroxyurea discontinued because of mucositis but had achieved a dose of 20 mg/kg/day. Leukopenia and neutropenia were not seen at this hydroxyurea dose[47]. Another study, conducted in Kano, Nigeria, was a feasibility trial for primary stroke prevention for children with abnormal TCD measurements. In this study, 27 children with abnormal TCD measurements were given a fixed dose of hydroxyurea 20 mg/kg/day[26]. Among the children with abnormal TCD measurements, hydroxyurea resulted in a mean velocity decrease of 18 cm/s.

To obtain additional evidence that hydroxyurea decreases TCD measurements, the panel reviewed 10 studies in children with HbSS or HbSβ^0 thalassemia that had TCD measurements at baseline and several months after starting hydroxyurea therapy (Figure 4). The decrease in TCD measurements can occur as

early as three months after starting hydroxyurea therapy with a sustained impact of hydroxyurea therapy on decreasing TCD measurements for at least 36 months. The average drop was clinically relevant, 21 cm/s (Figure 4).

Further data on the safety of hydroyxurea therapy in low-income countries was clearly demonstrated in a large prospective controlled trial recently reported from four sub-Saharan African centers (Luanda, Angola; Kinshasa, Democratic Republic of the Congo; Kilifi, Kenya; and Mbale, Uganda). The rate of clinical adverse events during the pre-treatment phase (2 months) was compared to the treatment phase (mean of 29 months). During the treatment phase, there was a significant decrease in the incidence rates for death, malaria, and acute vaso-occlusive events; data on stroke were not presented separately[51].

Taken together, these studies demonstrate that hydroxyurea therapy[26,47,51] is safe for children in Africa, is effective in decreasing TCD velocities and reduces the incidence rate of mortality and morbidity. These studies provide a compelling rationale for the use of hydroxyurea for primary stroke prevention in children with abnormal TCD measurements in low- and middle-income settings[51] as additional trials with CNS complications as end points are conducted[26].

The hydroxyurea dose utilized in Nigeria for primary stroke prevention ranges from a fixed moderate-dose of 20 mg/kg[26] which typically does not require monthly full blood count monitoring, as performed in clinical trials, to maximum tolerated dose (typically approximately 25 to 35 mg/kg/day.) that requires monitoring every two to three months with complete blood counts[47,51] While there is currently no evidence that fixed low-dose hydroxyurea (10 mg/kg/day) is efficacious in primary stroke prevention for children with abnormal TCD measurements, a randomized clinical trial for primary stroke prevention in Nigeria for children with HbSS and abnormal TCD is comparing moderate-dose hydroxyurea (20 mg/kg/day) to low-dose hydroxyurea (10 mg/kg/day) with results anticipated to be available in 2021 (NCT02560935).

The optimal health care visit schedule for monitoring hydroxyurea therapy for primary stroke prevention in low-income countries is not known. The primary purpose for this visit is for the health care provider to reinforce adherence to the therapy, adjust the dose of hydroxyurea due to the increasing weight of the growing child, monitor benefit versus harm, and evaluate for toxicity, particularly myelosuppression.

After stabilization on the maximum tolerated dose of hydroxyurea, monitoring blood counts every eight weeks appears to be safe[51].

Insufficient data was available to make a recommendation on the clinical utility of TCD screening in adolescents greater than 16 years of age and adults with HbSS and HbSβ^0 thalassemia.

Summary of harms and burden

The potential harms associated with regular blood transfusion therapy have been quantified in controlled clinical trials for primary and secondary prevention strokes in children with HbSS or HbSβ^0 thalassemia. These adverse events include, but are not limited to, the following, in decreasing order of prevalence: excessive iron stores[52,53] that may eventually require chelation therapy[54,55], red blood cell alloimmunization[30,56] and adverse blood transfusion reactions[54,55].

The family makes a significant time commitment when they agree to regular blood transfusion therapy. Typically, blood transfusion occurs monthly, and it often requires two visits (the first for crossmatching of the red blood cell units and the second for the actual blood transfusion). We did not find a study describing the full range of challenges of regular blood transfusion therapy for families, but the panel, including the two patient representatives, believed strongly that family preferences and the inconvenience and financial resources associated with regular blood transfusion therapy should be considered.

In low- and middle-income countries without public health care insurance systems to pay for hydroxyurea, the costs of hydroxyurea and complete blood cell counts for myelosuppression may be prohibitive for most families. We did not identify a study reviewing the challenges of regular hydroxyurea therapy for families living in low- or middle-income countries. The consensus among the panel was that some form of local or federal government subsidy for primary stroke prevention is required to longitudinally treat the maximum number of children with abnormal TCD measurements living in low- or middle-income countries. For instance, in Nigeria alone, 150,000 children are born with HbSS each year[57]. Conceivably, 10% of each cohort of children born in the same year (15,000 children before 16 years of age) will have an abnormal TCD and will require primary stroke prevention. All panel members believed strongly that regardless of location in a high-income country or a low- or middle-income country, the health care

systems' first obligation for following the panel guidelines was to prevent strokes in children with HbSS and HbSβ^0 thalassemia.

EtD criteria and implementation consideration

We combined HbSS and HbSβ^0 thalassemia phenotypes because of the clinical challenges of distinguishing HbSS from HbSβ^0 thalassemia based on clinical laboratory values[29] and the fact that both diagnoses were eligible for primary stroke prevention trials[25,28].

Patient representatives on the panel disclosed that regular blood transfusion therapy is less acceptable to some individuals with SCD and their caregivers. However, based on the extensive experience of the panel, blood transfusion therapy is acceptable to many caregivers and children with HbSS or HbSβ^0 thalassemia phenotypes and abnormal TCD measurements. Transfusion is more feasible in high-income countries than low-income countries. Despite the lack of adequate cost effectiveness studies, preventing strokes in children will always be less expensive than the long-term direct and indirect consequences of stroke and stroke-related disability, regardless of whether stroke prevention treatment is with transfusion and chelation therapy or hydroxyurea. The decision criteria are likely the same for children with other SCD phenotypes at increased risk for stroke.

Hydroxyurea therapy requires at least the same health care system resources in a low- and middle-income setting as those in high-income settings, including laboratory surveillance at the same interval as in a high-income setting (initially every 2 weeks and eventually every 2 or 3 months). Most likely hydroxyurea therapy is more acceptable than transfusion for primary stroke prevention for patients and families. Health equity for stroke prevention in children living with SCD in high-, low- and middle-income countries can potentially reduce the existing health disparities in childhood stroke prevalence between children with and without SCD.

The objective of regular blood transfusion is to maintain hemoglobin levels above 9 g/dl but below 13 g/dl and pre-transfusion HbS below 30%. Some patients will be difficult to transfuse effectively to keep the HbS less than 30% on a consistent basis. If the HbS cannot be kept consistently less than 30% with either simple transfusion, manual exchange transfusion or automated exchange transfusion, higher values are acceptable provided that the patient is consistently transfused at 3- to 4-week intervals.

After one year of regular blood transfusion therapy, a gradual transition from transfusion to hydroxyurea can be considered. This involves a period of both hydroxyurea therapy and transfusion therapy, with eventual discontinuation of transfusion therapy. The transition may occur provided that the patient does not have intracranial MRA-defined vasculopathy as per TWiTCH. Prior to consideration of transitioning from regular blood transfusion therapy to maximum-tolerated-dose hydroxyurea, MRI of the brain should be undertaken to exclude silent cerebral ischemic lesions (see PICO #10) and intracranial MRA to determine the presence and extent of cerebral vasculopathy. Children with cerebral vasculopathy were excluded from TWiTCH; therefore, transition from blood transfusion therapy to hydroxyurea is not recommended for these children. A discussion with the family should include whether hydroxyurea at the maximum tolerated dose is preferable to regular blood transfusion with chelation therapy to attenuate excessive stores of iron[32].

Research needs

The panel identified the following additional areas in need of research.

1. Best practices and implementation strategies for primary stroke prevention after using TCD as a screening tool should be determined. Over a 6-year study period among 4775 children with HbSS or HbSβ^0 thalassemia from six U.S. states, 22% to 44% of children received TCD screening[58].
2. Alternative options for primary stroke prevention other than initial regular blood transfusion therapy for a year for some, then followed by maximum tolerated dose of hydroxyurea therapy should be identified for children living in high-income countries.
3. Imaging strategies to identify the subgroup of children with an abnormal TCD measurement who are most likely to have a stroke should be improved. The current number needed to treat is 7 (i.e., 7 children with abnormal TCD measurements must receive at least monthly blood transfusion therapy for at least a year to prevent one stroke). Strategies to personalize the risk of stroke for children with abnormal TCD measurements would be preferred to the current standard of red blood cell transfusion therapy for at least a year for children living in high-income settings for at least a year.

4. The optimal hydroxyurea dose (20 mg/kg/day versus 10 mg/kg/day versus the maximum tolerated dose) for primary stroke prevention in children with abnormal TCD measurement living in low- and middle-income countries should be determined.
5. Use of a liquid formulation of hydroxyurea which is stable at room temperature when stored at home and can be provided to children less than 5 years of age unable to swallow a capsule.
6. The best strategies to partner with local, state and federal health care authorities in low- and middle-income countries to provide hydroxyurea therapy for primary stroke prevention programs should be determined.
7. Training and quality assurance of TCD practitioners to increase the pool of qualified TCD practitioners, particularly in low- and middle-income settings, is needed.

Question 4

Should simple blood transfusion versus exchange transfusion be used for children and adults with SCD and suspected acute symptomatic stroke, including transient ischemic attack?

Recommendation 4.1. For children or adults with SCD and acute neurological deficits, including transient ischemic attack, the ASH guideline panel recommends prompt blood transfusion. The transfusion should be given immediately upon recognition of symptoms without delay beyond several hours of acute neurological symptom presentation. The type of transfusion (simple, modified exchange or apheresis) is dependent on individual patient factors and local transfusion resources (strong recommendation based on high certainty of the evidence about effects ⊕⊕⊕⊕).

Recommendation 4.2. For children or adults with SCD and acute neurological deficits including transient ischemic attack, the ASH guideline panel suggests exchange transfusion versus simple transfusion (see details for exceptions). When exchange transfusion is not available within two hours of presentation for medical care and hemoglobin is ≤8.5 g/dl, simple transfusion can be performed to avoid delays in treatment while a manual exchange transfusion or an automated apheresis is planned (conditional recommendation based on low certainty of the evidence about effects ⊕⊕◯◯).

Remarks

Optimal timing of therapy is to have prompt (within 2 hours of presentation to medical care) transfusion in children and adults with SCD presenting within 72 hours of symptom onset of a suspected acute stroke, new neurologic deficit or transient ischemic attack.

In children and adults with a new neurologic deficit or transient ischemic attack presenting to medical care more than 72 hours after onset and without recent worsening, an assessment for anemia and percentage of sickle hemoglobin with consideration of transfusion on a case-by-case basis is suggested.

For individuals with hemoglobin levels greater than 8.5 g/dl presenting with focal neurological deficits or transient ischemic attack, exchange transfusion therapy to decrease the possibility of hyperviscosity syndrome is suggested.

Specific background

Ischemic strokes in children and adults with SCD are one of the most important and common medical emergencies, particularly in regions where primary stroke prevention is not standard care. When a patient with SCD presents with an ischemic stroke or a transient ischemic attack, timely response is required to minimize further ischemic injury. Optimal timing of intervention with blood transfusion therapy and brain imaging modality has not been rigorously studied. However, in SCD the principles of management of acute ischemic strokes and transient ischemic attacks, coupled with observational studies, provide evidence for best practices.

Summary of the evidence

The systematic review identified one nonrandomized study that compared simple transfusion to exchange transfusion. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 4 to be added here).

Rationale and expected benefits

In the absence of randomized clinical trials, no set of guidelines is likely to address the full spectrum of brain imaging and interventions for decreasing ischemic injury to the brain that represent evidence-based best practices; however, the principles of cerebral hemodynamics specific to SCD, coupled with multi-disciplinary experiences of the panel, provide practical approaches.

Children and adults with SCD presenting with focal neurological deficits suggestive of stroke or transient ischemic attack require rapid evaluation and close consultative interaction between hematologists, neurologists and acute-care providers because the diagnosis of an acute ischemic stroke can be challenging (Supplement 5 Figure 2). If a hematologist or a health care practitioner not skilled in managing exchange transfusion and acute stroke management in SCA, is not immediately available, appropriate care should be initiated with low-flow oxygen, intravenous fluids, complete blood count, and crossmatching, and the patient should be sent to a facility with the required expertise to manage acute ischemic strokes and SCD. The differential diagnosis is broad (Supplement 5 Figure 2), and management of acute ischemic brain injury in children and adults with SCD continues to evolve. Although MRI of the brain may facilitate a diagnosis of acute cerebral ischemia, the final diagnosis of ischemic stroke or transient ischemic attack is based on a complete neurological history and examination. The absence of abnormality seen on the diffusion-weighted image on MRI of the brain does not definitively exclude the diagnosis of an ischemic stroke[59]. If a patient with SCD presents with an acute-onset focal neurological deficit and the health care provider believes that the patient has had an ischemic stroke or transient ischemic attack, intervention should be the same, irrespective of imaging results, in order to minimize the potential risk of ongoing ischemic brain injury.

Only one observational study in children with SCD provides the empiric data for the recommendation of an exchange transfusion (apheresis or manual) versus only simple transfusion for acute management of ischemic strokes. In this retrospective cohort study, children with HbSS or HbSβ^0 thalassemia and acute ischemic stroke patients receiving simple transfusion for an acute ischemic stroke had a higher rate of recurrent strokes than children who received exchange transfusion (relative risk [RR], 5.0; 95% confidence interval [CI], 1.3 to 18.6)[60].

The preponderance of evidence supporting the recommendation for transfusion is from detailed cerebral hemodynamic studies in children and adults with SCD[61,62]. In SCD, cerebral blood flow is increased compared to that in the general population[63,64], and flow is inversely related to arterial oxygen content (flow increases as oxygen content decreases)[63]. Oxygen delivery to the brain is the product of cardiac output and arterial oxygen content, which is primarily determined by the product of hemoglobin concentration and hemoglobin oxygen saturation. Both children and adults with SCD have altered cerebral hemodynamics resulting from the unique properties of sickle-shaped red blood cells, acute and chronic anemia[1,64,65] and cerebral vasculopathy[66]. Concomitant complications of SCD such as acute chest syndrome can also reduce oxygen delivery[65], and cerebral metabolic demand is increased in conditions such as fever and seizures[65]. Both overt ischemic strokes and silent cerebral infarcts in SCD typically occur in areas between cerebral large vessel vascular territories, also called the cerebral border zone, with the lowest cerebral blood flow[67].

In children and adults presenting with a focal neurological deficit suggestive of an ischemic event, including a transient ischemic attack, increasing the hemoglobin level with a red blood cell transfusion is the best option to achieve the goal of improving oxygen delivery to the brain. If the hemoglobin level is less than approximately 8.5 g/dl, the panel recommends increasing the hemoglobin to approximately 10.0 g/dl with a simple transfusion within two hours after presentation to medical care. After the hemoglobin has reached approximately 10.0 g/dl with simple transfusion or if the baseline hemoglobin level is greater than approximately 8.5 g/dl, the panel recommends an automated-exchange red blood cell transfusion (apheresis)[68]. This procedure will require a timely dialog, initiated soon after presentation to the medical facility, between the transfusion service, the hematologist, and intensivist to ensure an integrative approach to management. If red blood cell exchange with apheresis is not a viable option, the patient should be stabilized and either transferred promptly to a facility that can perform apheresis, or manual red blood cell exchange should be undertaken on site[69,70]. The optimal strategy for manual red blood cell exchange for acute ischemic events has not been determined, but several options exist for reasonable starting points for providers that cannot offer apheresis in high- and low-income countries[69,70].

Unique attributes of SCD that are important for acute ischemic injury (suspected stroke or transient ischemic attack) include the observation that as hemoglobin increases, there is a corresponding increase in oxygen delivery to a point[71,72], above which any increase in hemoglobin concentration decreases the

arterial oxygen delivery. In patients with HbSS or HbSβ^0 thalassemia receiving simple transfusions, the point of diminishing benefit of arterial oxygen delivery is estimated to be between 10 and 11 g/dl[71,72] (Figure 5)[69].

Evidence suggests that oxygen delivery to the brain in SCD is dependent not only on the total hemoglobin concentration but also on the percentage of HbS[73]. Thus, the goal of the red blood cell exchange with apheresis is to lower the percentage HbS level while preventing a rise in hemoglobin level above a threshold that may cause viscosity-related complications. Thresholds for post-apheresis HbS percentage and hemoglobin level are typically set at 15% to 20% and 10 g/dl, respectively. The HbS level of 15% to 20% allows a threshold of less than 30% hemoglobin S to persist for approximately four weeks. When the HbS level is less than 20%, the total hemoglobin level can generally be greater than 10 g/dl, up to approximately 12 to 13 g/dl, without concerns for viscosity-related complications, and the optimal recommended range of hemoglobin level post-apheresis is 10 to 12 g/dl. When the hemoglobin level is less than 5.0 g/dl, a simple transfusion to increase the total hemoglobin to approximately 10.0 g/dl may be required. Generally, red blood cell exchange with apheresis is not recommended for patients with SCD and hemoglobin levels less than 5.0 g/dl, in part because of concerns of lowering the hemoglobin level during priming of the apheresis machine. We identified an algorithm for acute management of suspected ischemic stroke or transient ischemic attack in children and adults (Figures 6 and 7, respectively).

Based on the concept that "Time is brain" and the urgency of rapid stroke care in the general adult population, we suggest similar urgency for treatment in SCD as soon as possible after presentation to medical care[74]. Although we suggest a threshold time interval for consideration of exchange transfusion of 72 hours, this is based only on expert opinion. Few data are available to inform the question of the time interval for potential clinical benefit from red blood cell transfusion therapy after stroke onset in children and adults with SCD. Figure 6 and 7, provides and algorithm for management of suspected ischemic acute strokes in children and adults with SCD, respectively.

Supportive care in the acute post-stroke period should reflect American Heart Association guidelines, which suggest avoiding hyperglycemia, hypoglycemia, hyperpyrexia (treating temperatures of >38°C with antipyretics), and hypotension[75]. As in adult stroke, early evidence in childhood stroke suggests that hypertension in the acute period after stroke is associated with worse outcomes[76]. There is not enough

evidence in children with SCD to make formal recommendations regarding treatment of blood pressure, but many centers allow blood pressure above pre-stroke baseline and treat blood pressures that are consistently above the 95th percentile for age and height[77], given the observation that blood pressures in in individuals with SCD are generally lower than in the general population[78].

Summary of harm and burden

The main complications of prompt treatment with simple blood or an exchange transfusion are those associated with blood transfusion and with the requirement for central line placement for red blood cell exchange with apheresis. Complications of regular blood transfusion include blood transfusion reactions,[54,55] blood-borne infection, alloimmunization,[30,56] and excessive iron stores,[52,53] which typically requires iron chelation therapy.[54,55] Complications of central line placement include inadvertent vascular injury, local infection at the site of the central line placement, and systemic infection and catheter-related venous thrombosis. Overall, timely treatment with blood transfusion therapy for acute ischemic injury of the brain was deemed to outweigh the risk of treatment.

EtD criteria and implementation considerations

Prevention of recurrent stroke or extension of stroke will decrease the magnitude of stroke disability in children and adults with SCD and therefore improve health equity. In terms of feasibility and acceptability, exchange transfusion often requires admission to an intensive care unit (ICU) and central line placement; however, the procedure can also be done in a non-ICU setting and with peripheral venous access if peripheral veins are adequate. Management of central line thrombosis or infection is challenging. Exchange transfusion by automated apheresis is not always immediately available. If apheresis is not available within two hours, strong consideration should be given to manual exchange or transfer to a center where automated apheresis can be performed.

Research needs

The panel identified the following additional areas in need of research.

1. Evidence to define the optimal interval between onset of ischemic stroke or transient ischemic attack and transfusion is needed. The time point at which there is no longer a benefit or at which risk outweighs benefit is unknown.
2. Development of additional therapeutic strategies or alternatives to blood transfusion is needed for better prevention of progressive brain injury after an initial acute ischemic stroke.
3. A more precise understanding of the mechanisms of cerebral hemodynamics in children and adults with SCD is needed to develop targeted therapies and to improve risk stratification for initial and subsequent cerebral infarct and cerebral hemorrhage.

Question 5

Should red blood cell transfusion targeted to keep HbS levels below 30% (versus no treatment), red blood cell transfusion targeted to keep HbS levels above 30% or hydroxyurea therapy be used for children with sickle cell disease with a history of stroke?

Recommendation 5. For children with HbSS or HbSβ^0 thalassemia and a history of prior ischemic stroke, the ASH guideline panel recommends that blood transfusion goals for secondary stroke prevention be to increase the hemoglobin above 9 gm/dl at all times and to maintain the HbS level at <30% of total hemoglobin until the time of the next transfusion (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks

The ASH guideline panel acknowledges that for children who cannot be transfused or refuse transfusion, hydroxyurea therapy is an inferior alternative to regular blood transfusion for secondary stroke prevention but superior to no therapy at all for secondary stroke prevention.

Adolescents who had a stroke as a child should continue transfusion into adulthood for secondary stroke prevention.

> Adults who suffer their first stroke as an adult should receive the recommended evaluation for stroke modifiable risk factors according to American Heart Association (AHA) guidelines. Secondary stroke prevention should include regular blood transfusion and other AHA-recommended measures.

Specific background

Strokes in children and adults with HbSS or HbSβ^0 thalassemia are one of the most common and devastating complications of the disease that produce lifelong sequelae, including but not limited to cognitive morbidity, increased risk of future cerebral infarcts and earlier death.

Summary of the evidence

The systematic review identified 12 studies, one of which was randomized and four of which were nonrandomized comparative studies. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 5 to be added here).

Rationale and expected benefits

Children and adults with HbSS or HbSβ^0 thalassemia and strokes (overt) have ongoing risk for infarct recurrence even when receiving regular blood transfusion therapy. In two large multi-center retrospective cohort studies, children with HbSS or HbSβ^0 thalassemia receiving regular blood transfusion therapy had ongoing risk of future symptomatic strokes. In the first large multicenter retrospective cohort study, 60 children with strokes receiving regular blood transfusion therapy were followed for a total of 191 patient-years. The incidence of stroke recurrence was 4.2 per 100 patient-years. There was a statistically significant reduction in stroke incidence compared to historical controls who had strokes and did not receive regular blood transfusion therapy[79]. In a second large retrospective multi-center study, 137 children were followed for a total of 1382 patient-years (mean, 10.1 years; minimum, 5; maximum, 24) with an incidence rate of 2.2 events per 100 patient-years[65]. HbS levels at the time of stroke recurrence were available for only 19% of patients, and most of the values were <30%.

In a prospective multi-center single-arm trial of 40 children with overt strokes followed for a median of 5.4 years (total of 222 patient-years) the incidence of strokes was 3.1 events per 100 patient-years[80]. All

participants received regular blood transfusion with a mean pretransfusion HbS level of 29%, indicating that the goal of keeping maximum HbS concentration less than 30% was met. Further, in this cohort, there was progressive vasculopathy on MRA imaging, with recurrent overt or silent cerebral infarct (RR, 12.7; 95% CI, 2.65 to 60.5; *P* = 0.01). Taken together, these three studies provide evidence that regular blood transfusion therapy is partially effective for secondary prevention of strokes in children and adults with HbSS or HbSβ^0 thalassemia. Recurrent stroke risk while patients are receiving regular blood transfusion therapy remains significant.

Hydroxyurea is inferior to regular blood transfusion for secondary stroke prevention. In a single-center prospective feasibility study, 35 children on regular transfusion with a previous history of stroke were transitioned to hydroxyurea at the maximal tolerated dose and had serial phlebotomy to reduce transfusion iron overload. The stroke recurrence rate was 5.7 events per 100 patient-years. Phlebotomy significantly lowered iron burden and normalized hepatic iron[81]. However, the analysis was not adjusted for the period of time with the highest rate of recurrent stroke, i.e., the first two years[65,82,83]. Based on these results, a phase III non-inferiority randomized controlled trial, Stroke With Transfusions Changing to Hydroxyurea (SWiTCH), was conducted[84]. In this trial, hydroxyurea at the maximal tolerated dose combined with phlebotomy was found to be inferior to continuing transfusion together with iron, the ongoing requirement of chelation therapy. The rate of secondary stroke was 5.6 events per 100 patient-years in the hydroxyurea arm compared to 0 events per 100 patient-years for children who continued with transfusion (the standard care arm)[84]. The NHLBI leadership closed SWiTCH after interim analysis revealed equivalent liver iron content, indicating futility for the composite primary end point of allowing an increase in stroke but requiring superiority for removing iron.

Where transfusion is not available, medical management with hydroxyurea is better for secondary stroke prevention than no treatment at all. In a prospective non-randomized study in Nigeria[85], 13 children received hydroxyurea therapy, while 18 caregivers declined hydroxyurea therapy for their children. Maximum dose of hydroxyurea ranged from 20 to 25 mg/kg/day. The secondary stroke incidence of 7 events per 100 person-years in the hydroxyurea group was significantly lower than the 28 per 100 person-years in the non-treatment group (*P* = 0.001; odds ratio [OR], 3.808; 95% CI, 1.556 to 9.317)[85].

Overall, studies indicate that regular blood transfusion and hydroxyurea therapy are palliative for secondary prevention of strokes in children and adults with HbSS or HbSβ^0 thalassemia, with blood transfusion being superior to hydroxyurea therapy and both therapies being superior to no therapy.

For children and adults with strokes and severe cerebral vasculopathy (moyamoya syndrome), alternative treatments such as revascularization surgery should be considered as adjunct therapy to regular blood transfusion therapy for secondary stroke prevention. Hematopoietic stem cell transplant (HSCT) is considered curative [40,86,87] and definitive option for secondary stroke prevention for children with matched related donors[86] or haplo-identical BMT with post-transplantation cyclophosphamide and with pre-transplant Thiotepa.[88] Recent studies have revealed new cerebral infarcts are detected after central adjudication of neuroimaging and neurology examination are performed as part of the HSCT protocol[89,90] Individuals and their families should be informed of the potential long-term benefits and long-term risks of secondary stroke prevention therapies.

Future therapeutic options for secondary stroke prevention should be considered in the context of a multi-center clinical trial setting with peer review, a Data Safety Monitoring Board to assess safety and futility, study design that includes long-term follow-up of at least five years, and central adjudication of all neurological events. Without such approaches, there will continue to be less-than-optimal data to inform families about best strategies for secondary stroke prevention.

Summary of harms and burden

The potential harms associated with regular blood transfusion therapy have been quantified in controlled clinical trials for primary and secondary prevention of strokes in children with HbSS or HbSβ^0 thalassemia.

These adverse events include, but are not limited to, the following, in decreasing order of prevalence: excessive iron stores[52,53] that may eventually require chelation therapy[54,55], red blood cell alloimmunization[30,56] and adverse blood transfusion reactions[54,55].

The family makes a significant time commitment when they agree to regular blood transfusion therapy. Typically, blood transfusion occurs monthly and often requires two visits (the first for crossmatching of the red blood cell units and the second for the actual blood transfusion). We did not find a study describing the full range of challenges of regular blood transfusion therapy for families, but the panel, including the

two patient representatives, believed strongly that family preferences and the inconvenience and financial resources associated with regular blood transfusion therapy should be considered.

EtD criteria and implementation considerations

Despite the absence of a randomized controlled clinical trial comparing regular blood transfusion to maintain HbS level < 30% and minimum hemoglobin > 9.0 g/dl, strong recommendation was made despite low-quality evidence based on the large difference in outcomes (stroke rate per 100 patient-years) that favored transfusion to maintain the HbS level at <30% when compared to no treatment for secondary stroke prevention. Additionally, the committee relied heavily on the studies describing the cerebral hemodynamics specific to SCD, the unique rheological studies of SCD, coupled with multi-disciplinary experiences of the panel. The panel placed a high value on the uncertain, but potentially quality of life preserving benefit of the intervention. Moreover, the burden and harms of transfusion were not felt to be prohibitive given the and panelists' and patients' values that focused on reducing the risk of stroke over possible burdens and harms. Regular blood transfusion programs are resource-intensive. Patients' and parents' acceptance are variable. Caring for children in situations where caregivers have strong beliefs against blood transfusion therapy may require a court order to act in the best interest of the minor to provide the maximum benefit of decreasing future stroke recurrences.

Research needs

The panel identified the following additional areas in need of research.

1. Optimal therapeutic strategies for secondary stroke prevention in children and adults (blood transfusion therapy versus blood transfusion therapy plus revascularization surgery versus bone marrow transplant) with long-term follow-up in children and adults with SCD are needed.
2. Optimal therapeutic strategies or secondary stroke prevention in low-income countries where blood transfusion therapy is not available are needed.
3. Optimal transfusion targets and methods for secondary stroke prevention are needed.

4. Risk stratification to identify the group of children and adults with strokes likely to have infarct recurrence should be carried out.
5. Optimal treatment and stroke recurrence rate for children and adults other than those with HbSS or HbSβ^0 thalassemia should be determined.

Question 6

Should cerebral revascularization surgery (including encephalo-duro-arterio-synangiosis [EDAS], encephalo-duro-arterio-myo-synangiosis [EDAMS], pial synangiosis, or direct anastamosis) plus regular blood transfusion therapy versus regular blood transfusion therapy alone be used for patients with SCD and moyamoya syndrome?

Recommendation 6. For adults and children with SCD, moyamoya syndrome and a history of stroke or transient ischemic attack, the ASH guideline panel suggests evaluation for candidacy for revascularization surgery in addition to continuing regular blood transfusions (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯).

Remarks

Without evidence, but with compelling extensive experience, the panel endorse a multidisciplinary team evaluation including a hematologist, neurologist, neuroradiologist and neurovascular surgeon for evaluation of the pros and cons of surgical evaluation and optimization of patients' health before, during and after surgery. The evaluation neither supports nor negates performing one of the five different revascularization procedures, but rather provides the background information for shared decision making to consider surgery based on the available evidence for benefits and risks. However, is neurosurgery is considered, then a multi-disciplinary evaluation is strongly preferred.

For individuals that undergo revascularization surgery, standardized care protocols and long-term outcome tracking (for a minimum of five years) through a local, national or international prospective registry are encouraged.

> Which one of the five the revascularization approaches plus ongoing blood transfusion therapy is more effective in secondary stroke prevention than regular blood transfusions alone is unclear? A review of the studies does not for a pooled analysis nor a specific procedure with clear benefit; hence the reason for a prospective standardized protocols and long-term outcome tracking.

Specific background

Progression of cerebral infarcts and cerebral vasculopathy is common despite regular blood transfusion therapy for secondary stroke prevention. Some patients progress to a moyamoya vasculopathy with high risk of transient ischemic attack, ischemic and hemorrhagic stroke[91] and cognitive decline[92]. Outcome studies of children and adults with SCD who have had a stroke have been generally limited to small or single-center series, with little follow-up beyond five years[93-100]. No rigorous prospective controlled trial has been done to compare the benefits and risks of revascularization surgery plus regular blood transfusion therapy to regular blood transfusion therapy alone for secondary stroke prevention in children and adults with SCD and moyamoya syndrome. Several studies have compared the incidence of strokes before and after revascularization surgery; however, such studies are intrinsically limited. The highest incidence rate for cerebral infarct recurrence occurs within two years of initial stroke, with or without preventive treatment[82,65,83] . Supplement 5, Table 1 has the most recent summary of the revascularization procedures performed in children and adults with SCD and the list of adverse outcomes that occur primarily in the first month after revascularization procedures. No pooled analysis of the studies could be completed because of the heterogeneity of the five different neurosurgery procedures (pial synangiosis, encephalo-duro-arterio-myo-synangiosis, encephalo-duro-arterio-synangiosis, encephalo-myo-arterio-synangiosis, multiple burr holes), and the lack of uniform neurological assessment (surveillance of MRI of the brain and neurology assessment for infarct recurrence) during the follow-up period.

Future studies designed to assess the added utility of surgical revascularization in SCD-related moyamoya syndrome for secondary stroke prevention should include surveillance MRIs of the brain to identify silent cerebral infarcts, formal neurological assessment by a neurologist to identify subtle neurologic deficits

associated with overt strokes because these subtle changes may alter the recommendation for future therapy and adjustment for the high-risk period of stroke recurrence. To date, none of the published studies of revascularization in SCD have included these strategies to improve the scientific rigor of these studies, thus limiting the inferences of the potential benefit.

Summary of the evidence

The systematic review identified 13 nonrandomized studies (Table 1). Five of the included studies were comparative (surgical intervention plus transfusion versus regular blood transfusion without surgery). The other eight studies were non-comparative. Most studies did not report the SCD phenotypes of the participants, a major consideration for stroke recurrence. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 6 to be added here).

Rationale and expected benefits

Most studies addressing the benefit and risk with cerebral revascularization surgery (pial synangiosis, encephalo-duro-arterio-myo-synangiosis, encephalo-duro-arterio-synangiosis, encephalo-myo-arterio-synangiosis, multiple burr holes) have been single-center observational studies (Supplement 5, Table 1). Due to the small sample sizes, the variation in revascularization procedures and the incomplete reporting of the outcomes, studies could not be grouped to provide a composite assessment of the benefit of cerebral revascularization surgery. The type of revascularization approach that is most effective is unclear and depends on the individual patient, clinical context and availability of surgical expertise. Further secondary stroke prevention studies in children and adults with SCD are needed to explore the risk/benefit ratio for surgery in addition to other therapies such as HSCT.

Summary of harms and burden

The potential harms associated with cerebral revascularization procedures are considerable and include intra-operative and post-operative complications associated with SCD and peri-procedural ischemic and hemorrhagic stroke. Surgical risk may be higher in children and adults with SCD than in the general population, so studies of cerebral revascularization for moyamoya syndrome in other populations may not be generalizable to patients with SCD. Given the small, single-center studies, coupled with the limited

follow-up time (most less than five years), particularly compared to the life span of adults with SCD, the long-term benefits and risks of these revascularization procedures in children and adults with strokes and moyamoya syndrome have not been adequately assessed. We included studies only of individuals with strokes and moyamoya syndrome. We did not have sufficient evidence to evaluate surgery in children and adults with SCD and moyamoya syndrome alone or moyamoya syndrome and silent cerebral infarcts.

Hydroxyurea is a myelosuppressive agent and may impair wound healing. Hydroxyurea, when given before or after revascularization surgery, may prevent sprouting and growth of new cerebral blood vessels, as well as impairing wound healing after revascularization surgery[101,102].

EtD criteria and implementation considerations

Data on values and preferences, cost effectiveness, acceptability and feasibility of revascularization procedures are lacking. It is expected that variability in surgical expertise can limit the broad implementation of this recommendation. We also expect important variability in how much an individual may value the immediate risk of peri-operative and post-operative complications versus possible reduction of risk of a long-term outcome such as stroke, cognitive decline or both.

Research needs

The panel identified the following additional areas in need of research.

1. Rigorous studies that include longitudinal outcomes after revascularization surgery for moyamoya syndrome in SCD are needed.
2. Multi-center prospective studies or registries for individuals with SCD and moyamoya syndrome should be conducted and implemented as a first step to collect outcome data.

Question 7

Should intravenous thrombolysis with tissue plasminogen activator (tPA) versus no treatment with tPA be used for adults with SCD presenting with acute ischemic stroke and no hemorrhage on CT within 4.5 hours of onset of symptoms?

Recommendation 7. For adults with SCD presenting with symptoms of acute ischemic stroke and being considered for intravenous tPA (age ≥ 18 years, no hemorrhage on CT scan, within 4.5 hours of onset of symptoms/signs, and without contraindications for thrombolysis), the ASH guideline panel suggests management using a shared decision-making approach that follows these principles.

a. In all patients, the administration of tPA should not delay prompt simple or exchange blood transfusion therapy.

b. Patients may be evaluated for intravenous tPA based on its established inclusion and exclusion criteria detailed in stroke management algorithms.

c. The following factors suggest likely benefit from intravenous tPA: older age, atrial fibrillation, diabetes, hypertension, and hyperlipidemia. Management of younger patients without these risk factors should emphasize early transfusion.

d. There are no validated risk stratification or reliable age cut-off criteria to guide the choice of initial therapy.

e. Intravenous tPA is not recommended for children with SCD (<18 years of age).

(Conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯.)

Remarks

For Recommendation 7, the ASH guideline panel recognizes that prompt identification of an adult with SCD presenting to the emergency department with focal neurological deficit and balancing the timely treatment with intravenous tPA and timely treatment with blood transfusion therapy is challenging (Recommendations 4.1 and 4.2).

Evidence does not exist as to which treatment option should be provided first (tPA or blood transfusion). Conceptually, prioritization of treatment should be informed by underlying stroke etiology (SCD versus non-SCD), but this may not be clear in the hyperacute setting.

Given the increased overall survival of adults with SCD into middle and old age with the cumulative effect of traditional cardiovascular risk factors leading to stroke, offering emergent treatment with tPA to older adults with SCD presenting with acute ischemic strokes within 4.5 hours of symptom onset is advised. However, no absolute age cut-off could be defined.

In some cases, the treatment with tPA may occur before the patient has been recognized as having SCD. In such instances, blood transfusion should be considered as soon as possible after SCD is identified.

A systematic review on endovascular thrombectomy was not performed because we are unaware of any interventional studies specific to SCD, although multiple large clinical trials support thrombectomy for stroke in selected patients with acute large vessel occlusion outside SCD.

Evidence supports endovascular thrombectomy for stroke with acute large vessel occlusion in the general population; however, we do not have evidence of the risks and benefits in adults with SCD.

The utility of endovascular thrombectomy in adults with SCD should be carefully evaluated due to the prevalence of cerebral vasculopathy and moyamoya syndrome and the absence of data describing the benefits and risks.

Specific background

To date, only one study has examined the use of tPA in adults with SCD[103]. Overall, the SCD population is younger at the time of a first stroke and includes a higher proportion of people with hemorrhagic stroke compared to all adults with strokes.

Summary of the evidence

The systematic review identified three nonrandomized studies, one of which was comparative. The other two were case reports. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 7 to be added here).

Rationale and expected benefits

For adults presenting within 4.5 hours of the time when they were last seen to be normal after ischemic stroke onset who meet established eligibility criteria, intravenous tPA improves functional outcomes at 3 to 6 months post-stroke[104]. One study of tPA for hyperacute stroke compared outcomes of adults with and without an SCD diagnosis using administrative data from a large U.S. health provider[103]. There was no difference in efficacy or safety outcomes between the two groups, but the study was limited by lack of confirmation of SCD phenotype and probable inclusion of individuals with sickle cell trait. While recognizing that the expected benefit of intravenous tPA for adults with SCD may differ from that in general medical practice because stroke etiologies differ, the ASH guideline panel suggests that adults with SCD and acute ischemic stroke be considered for intravenous tPA following established guidelines because of the strong evidence for improved outcomes in the general population. However, evidence for the benefit of tPA in adults with SCD is scant, and the potential harm associated with tPA is significant.

Summary of harms and burden

Major risks of tPA include symptomatic intracerebral hemorrhage in 3 to 6% and life-threatening systemic hemorrhage[105]. Use of thrombolytics for acute stroke may also delay prompt blood transfusion. tPA administration in a young adult with SCD presenting with an ischemic stroke may delay the administration of regular blood transfusion therapy, a therapy with a clear benefit in this population. The timing of tPA and acute blood transfusion therapy should be individually based.

EtD criteria and implementation considerations

The acceptability and feasibility of the panel's recommendation not to delay transfusion are limited by pre-hospital emergency medical systems that direct patients with suspected stroke to certified stroke

centers, where stroke teams are trained to reduce door-to-needle times for treatment with intravenous tPA. Rapid implementation of stroke protocols for intravenous tPA treatment may result in the missed opportunity for prompt transfusion, particularly if adults are not identified with SCD. Conversely, stroke protocols typically suggest placement of two large-bore intravenous lines on arrival to medical care, which could facilitate more rapid simple transfusion and possibly exchange transfusion. Joint protocols including both intravenous tPA and transfusion should be developed by stroke teams and hematologists for rapid identification and management of patients with SCD presenting with acute ischemic stroke. A proxy with power of attorney is often beneficial for shared decision-making in the emergency setting when an acute stroke occurs.

Research needs

The panel identified the following additional areas in need of research.

1. Rigorous studies of the safety of tPA use in individuals confirmed to have SCD and acute ischemic stroke are needed.
2. Systematic data collection in adults with SCD receiving intravenous tPA that includes stroke risk factors, presumed stroke etiology after workup and outcomes should be carried out.
3. Implementation science studies designed to identify the optimal clinical practice for administering both tPA and acute blood transfusion therapy to adults presenting to the emergency department with acute ischemic strokes are needed.

Question 8

Should clinicians perform or refer for screening for developmental delay and cognitive impairment versus no screening in children and adults with SCD?

> **Recommendation 8.1.** Given the high prevalence of developmental delay and cognitive deficits and coupled with the guidelines set by the American Academy of Pediatrics, the ASH guideline panel recommends that clinicians supervising care of pediatric SCD patients conduct surveillance using simplified signaling questions for the following:

- Concerns about developmental delays in preschool-age children;

- Concerns about neurodevelopmental disorders in school-age children, such as academic or behavioral problems or symptoms of inattention, hyperactivity, or impulsivity.

(Strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯.)

Recommendation 8.2. For children with SCD who have abnormal surveillance results suggesting increased risk for developmental delay or cognitive deficits, the ASH guideline panel recommends screening or referral for formal screening by a psychologist or a pediatrician able to perform screening with the available validated tools (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 8.3. Given the high prevalence of cognitive impairment in adults with SCD, coupled with the guidelines set by the American Academy of Neurology, the ASH guideline panel recommends that clinicians supervising care of adults with SCD conduct surveillance for cognitive impairment using simplified signaling questions (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 8.4. For adults who have abnormal surveillance results suggesting cognitive impairment, the ASH guideline panel recommends formal referral to a psychologist or a primary care physician able to perform more in-depth cognitive evaluation (strong recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks

For Recommendation 8, the ASH guideline panel provides specific examples of signalling questions that can be used for screening in Supplement 5, Table 2.

Specific background

Cognitive impairment is perhaps the most insidious CNS morbidity of SCD. In children, there is a clear gradient in full-scale intelligence quotient (FSIQ) depending on the degree of neurological injury (normal

MRI, silent cerbral infarct, or stroke). In the most comprehensive meta-analysis to date, children with HbSS with normal MRIs of the brain, silent cerebral infarct, and strokes had mean FSIQ s of 91, 84, and 73, respectively[106]. Few comprehensive cognitive studies in adults have been done that include assessment of FSIQ, employment status, and assessment of cerebral infarct status. Despite the high prevalence of cognitive impairment, the diagnosis is difficult to discern and challenging to ascertain because of the requirement of formal cognitive testing.

In several health care settings, the potential for reimbursement is increasing; for example, the American Medical Association Current Procedural Panel has developed a new billing code (96127) for behavioral health screening that can be used to screen for cognitive impairment[107]. There has also been a dramatic increase in cognitive screenings conducted by medical doctors and non-psychologist staff and practitioners, indicating that surveillance and screening are possible in settings without ready access to specialists in psychological assessment[108]. Both the American Psychological Association and the National Academy of Neuropsychology have acknowledged that in many health care settings there is a need for medical doctors or non-psychologist staff or practitioners to provide wider access to cognitive or behavioral health screenings, and these organizations have provided clarification on the distinction between screening and a more comprehensive psychological assessment requiring a specialist[109,110].

The specific tests for cognitive screening in children and adults with SCD, and the optimal strategies to screen for and implement rehabilitation for cognitive deficits, have not been established. Consequently, recommendations are extrapolated from non-SCD populations. Evidence-based practices for screening for cognitive impairments and rehabilitative interventions for cognitive function, specifically executive dysfunction, are well established and endorsed practices in professional societies, such as the American Academy of Pediatrics, American Academy of Neurology, and American Congress of Rehabilitation Medicine. The guideline panel relied heavily on well-established evidence-based practices from these three prominent professional societies to identify strategies for screening and treatment of cognitive morbidities[111-113].

Summary of the evidence

The systematic review did not identify any studies that compared screening to no screening. The review identified 48 studies that evaluated screening without a comparison group and reported outcomes of IQ score, the prevalence of cognitive impairment, developmental delay or school performance. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 8 to be added here).

Rationale and expected benefits

The use of formal screening tools improves the ability to detect developmental delays or cognitive impairment compared with informal observational methods[114,115]. Furthermore, the combination of surveillance and screening appears to work better for identifying children in need of developmental services than either method in isolation[116]. Many screening tools can be used in primary care or community settings, require less administration time than full assessments and can be administered by staff with less training, so that access is increased and burden to patients is decreased. See Supplement 5, Tables 2 and 3, for established initial screening tools and ongoing surveillance questions, respectively.

In the general population and in children and adults with SCD, identification of children and adults with developmental or cognitive delays increases likelihood of access to remediation services. In the United States and most European countries, laws mandate interventions for children with significant developmental delay and conditions that impact learning in a public setting. If the child is less than three years of age, a significant developmental delay results in referral to early intervention therapy and the child and family undergo assessment for an individualized family service plan[117]. Services are typically provided in the home or "natural environment" and include occupational therapy, physical therapy, developmental therapy, and speech therapy. These services are provided to enhance the development of the child. If the child is 3 to 21 years old and a significant deficit is identified, the local public-school district is tasked with working with the family to develop an individualized education program. The program provides services in the public school educational setting, supplemental aides if indicated, learning accommodations and modifications[117]. Both of these plans include measurable goals, assessments, and

meetings to review the children's progress. If a child is not making progress, the plans are typically modified to provide better support.

A recent systematic review of cognition across the life span of people with SCD confirmed that the magnitude of deficits increases as the injury to the brain increases. On average, performance declined from groups without infarct to those with silent cerebral infarct to those with overt stroke[106]. In addition, medium to large differences in cognition between children with SCD and their siblings or controls existed. Fewer adult studies were included, but small to large differences between the adults with SCD and controls were documented, with the greatest difference in processing speed[106].

Vascular cognitive impairment is of particular concern in adults with SCD and requires ongoing efforts to identify cognitive symptoms and medical risk factors[118]. Detection of cognitive impairments is important for identifying treatable causes, helping patients and families to understand the cause of functional deficits, and discussing the prognosis to plan for future needs[113]. Outpatient services such as speech therapy, occupational therapy, or rehabilitation psychology may be indicated and available depending on the results of a full evaluation[119].

In general, children and adults with SCD are a vulnerable population. The overwhelming majority of patients in the Unites States with this condition are African-American[120] and living at or near poverty level[121-123]; associated social factors such as parental education attainment and measures of socioeconomic status impact cognitive performance[124-127]. In addition, disease-associated morbidity such as low oxygen saturation levels, silent cerebral infarcts and overt strokes are all associated with lower IQ[124,128].

Summary of harms and burden

There are few downsides to surveillance and screening for cognitive/developmental deficits as part of routine health care. Available cognitive screening methods improve detection yet lack sufficient sensitivity to be used as a substitute for clinical judgment[110]. For cases in which the patient's history, risk factors, and functional complaints indicate a high risk for cognitive impairment, screening may be skipped in favor of directly referring for a comprehensive assessment. False-positive results from screening can also result in

distress and inconvenience for patients and their families[129,130]. Such distress likely already exists for patients and families who already have concerns about developmental delays or cognitive impairment.

EtD criteria and implementation considerations

The quality of evidence demonstrating benefits of cognitive and developmental screening specifically in individuals with SCD is low. However, such screening is non-invasive and can lead to timely referral to address those with developmental delays and cognitive impairment. The harms of not addressing such deficits in children or adults are severe on a personal and societal level. Therefore, a low certainty in benefit but high certainty of harm (particularly from other populations) justified a strong recommendation[131]. When considering patient values and preferences, the panel members, including the two patient representatives, reported values with little variation in favor of screening.

Important resources are needed to screen children and adults for developmental delay and cognitive impairment. Such resources are likely more available in medical centers with comprehensive care for SCD patients than in primary care settings. Resources and tools for screenings have been designed for primary care settings and are widely available; however, practitioners need to prioritize screening followed by periodic surveillance as part of routine health care. Patients may have to travel to obtain appropriate neurocognitive and developmental screening, particularly in managed-care settings.

Research needs

The panel identified the following additional areas in need of research.

1. Better documentation of the prevalence and progression of cognitive deficits in adults with SCD is needed.
2. Evaluation of screening and surveillance approaches for cognitive and developmental concerns assessed within the SCD population should be developed, rather than relying on data from broader populations.
3. Research evaluating implementation practices that produce the best access to surveillance, screening and assessment for developmental delays and cognitive deficits, or both, is needed.

4. Future research is required to determine which development and cognitive screening tools have the highest clinical utility in low-middle- and high-income settings

Question 9

Should cognitive rehabilitation therapy versus no rehabilitation be used for children and adults with SCD and cognitive deficit?

Recommendation 9.1. For children with SCD and abnormal screening for developmental or cognitive status, the ASH guideline panel recommends the following:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for developmental delays or cognitive deficits;

- following the cognitive domain-specific evidence-based guidelines for these conditions to provide appropriate interventions (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕).

Recommendation 9.2. For adults with SCD and abnormal screening for cognitive status, the ASH guideline panel recommends the following:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for cognitive deficits;

- following the cognitive domain-specific evidence-based guidelines for these conditions to provide appropriate interventions (strong recommendation based on high certainty in the evidence about effects ⊕⊕⊕⊕).

Specific background

As previously mentioned, cognitive impairment is perhaps the most insidious CNS morbidity of SCD. Evidence-based rehabilitative interventions for cognitive function, specifically executive dysfunction, are well established and endorsed practices in professional societies, such as the American Academy of Pediatrics, American Academy of Neurology, and American Congress of Rehabilitation Medicine[111,113,132].

The guideline panel relied heavily on these well-established evidence-based practices treatments of cognitive morbidities.

Summary of the evidence

The systematic review did not identify any comparative studies in SCD that compared cognitive rehabilitation to no rehabilitation. The review identified one randomized controlled trial that compared academic tutoring with memory rehabilitation versus academic tutoring, one observational study that compared academic tutoring and specific learning and memory strategies with academic tutoring, and one observational study that compared computer-based cognitive training completers with non-completers. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 9 to be added here).

Rationale and expected benefits

Cognitive deficits in SCD characteristically affect specific mental processes such as memory, attention, executive function, processing speed, and visual-spatial function. These deficits can impair one's learning, educational performance, work performance, medical adherence, and activities of daily living. However, these deficits will not be adequately identified without screening. Deficits in executive function are commonly found in children and adults with SCD[133]. These deficits correlate with the frequent injury to the frontal lobe, the most common area of the brain affected by silent cerebral infarcts[30,133].

A systematic review of rehabilitation for impairments of executive functions found a solid evidence base for interventions that incorporate metacognitive strategy instruction that offers strategies to solve problems, increase awareness, and cue for signals that may improve problem solving and internal training. Most of the available studies were conducted among adults with traumatic brain injury or stroke[134]. However, pilot studies that applied similar techniques to children with SCD generated positive results[135].

Cognitive lapses, which occur most often in individuals with cognitive deficits, and aspect of executive dysfunction (e.g., defects in mental flexibility and working memory) are the most common cause of poor adherence to medical therapies[136,137,138].

Functional assessments of executive function can both identify deficits and inform interventions by determining what types of cues patients need while completing multi-step activities (Supplement 5, Figure 3)[139,140]. Once these deficits are diagnosed, interventions can be implemented (Supplement 5 , Figure 4)[132]. Recently, evidence revealed that the intervention that makes the largest difference is the Cognitive Orientation to Daily Occupational Performance (CO-OP)[141]. CO-OP is a top-down approach that reduces impairments and improves health. Defined as "a client-centered, performance-based, problem solving approach that enables skill acquisition through a process of strategy use and guided discovery[142]," CO-OP focuses treatments directly on improving performance in everyday life activity rather than treating the underlying impairments and hoping for secondary improvement in meaningful activities. Three randomized controlled trials have demonstrated that CO-OP is more effective than impairment-focused therapy delivered by occupational therapists[143-145].

Failure to identify and address cognitive deficits contributes to difficulties with medical adherence. Formal assessments of cognition providing an objective evaluation of the patient's cognitive capacities are often requested after cerebral injury is diagnosed by cerebral MRI imaging. The assessment enables health care staff and the family to better understand the patient's need for information, support, and rehabilitation. The identification of neurocognitive deficits is an important first step in obtaining rehabilitation therapy[112] and is recommended by national organizations representing several relevant disciplines[119]. In addition, hematologists and other medical providers can make use of behavioral and family supports (e.g., CO-OP approaches) to better support adherence[119,138,146].

Summary of harms and burden

There is no harm anticipated from providing cognitive rehabilitation. No burdens were identified by the panel. Rather, a commitment to time with occupational therapists is required for patients to receive appropriate services. This requires a shift in the mind-set of both providers and individuals with the disease to increase awareness of cognitive deficits and to offer cognitive rehabilitation therapies. In other words, patients with SCD should be treated in a manner similar to that used for the thousands of non-SCD patients with brain injury due to stroke or trauma.

EtD criteria and implementation considerations

The quality of evidence on the benefits of cognitive rehabilitation specifically in individuals with SCD was low. Hence, the panel formulated recommendations advising clinicians to follow disease-specific evidence-based guidelines for conditions identified through screening. The certainty of the net benefit of this recommendation was considered high. In addition, despite the lack of published literature, input from SCD patient representatives on the panel supported the acceptability of cognitive rehabilitation therapy. Resources are likely more available in academic centers with expertise in SCD.

The American Congress of Rehabilitation Medicine endorses behavioral strategies to support individuals with executive function impairments. Executive functions are a set of processes that focus on managing oneself and one's resources in order to achieve a goal, involving mental control and self-regulation[112]. After recognizing executive dysfunction, the person can be trained to use task-specific approaches, problem-solving strategies, external cues, and internalized strategies[147].

Systematic reviews of randomized controlled trials support the use of goal management training, problem-solving techniques, and time pressure management[147,148]. Challenges with following through on plans of daily life that include medical appointments, medications, education, and work are frequently underappreciated as cognitive deficits and are often labelled as problem behaviors or motivational problems by those around the affected individual. The patient is often unaware as well. Despite endorsement from multiple different professional societies, implementing cognitive screening strategies in high-risk children and adults with SCD will be challenging to implement without basic research strategies to identify barriers and facilitators within SCD care centers.

Research needs

The panel identified the following additional areas in need of research.

1. Testing of specific cognitive rehabilitation strategies for people with SCD is needed.
2. The optimal setting for cognitive rehabilitation therapy should be identified.
3. The individuals most likely to benefit from cognitive rehabilitation therapy should be identified.

Question 10

Should screening with MRI for silent cerebral infarcts versus no screening be used for children and adults with HbSS or HbSβ^0 thalassemia?

Recommendation 10.1. Given the high prevalence of silent cerebral infarcts in children with HbSS or HbSβ^0 thalassemia (1 in 3) and their association with cognitive impairment, poor school performance, and future cerebral infarcts, the ASH guideline panel recommends at least a one-time MRI screening without sedation to detect silent cerebral infarcts in such early-school-age children (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 10.2. Given the high prevalence of silent cerebral infarcts in adults with SCD HbSS or HbSβ^0 thalassemia (1 in 2) and their association with cognitive impairment, poor school performance and future cerebral infarcts, the ASH guideline panel suggests at least a one-time MRI screening without sedation to detect silent cerebral infarcts in these adults (conditional recommendation based on low certainty in the evidence about effects ⊕⊕◯◯).

Remarks

The definition of a silent cerebral infarct-like lesion is "an MRI signal abnormality at least 3 mm in one dimension and visible in two planes on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (or similar image with 3D imaging)."

After an infarct-like lesion is identified, the panel recommends the following plan of action:

1. Neurological evaluation to assure that infarcts are classified as a silent cerebral infarct rather than overt stroke.

2. After a silent cerebral infarct is detected, there should be a discussion regarding:

a. Secondary prevention options including regular blood transfusions, hydroxyurea, and hematopoietic stem cell transplant

b. Cognitive screening assessment, as per recommendation 8

3. MRI surveillance every 12 to 24 months to assess for cerebral infarct progression. If new infarcts are present, then a discussion with the patient and family regarding the pros and cons of a step-up in therapy intensity to prevent cerebral infarct recurrence.

Specific background

Silent cerebral infarcts are common in children and adults with HbSS or $HbSB^0$ thalassemia, with a prevalence of approximately 35% and 50%, respectively (Figure 2)[2]. An individual with SCD is diagnosed as having a silent cerebral infarct if the following three features are present: (1) no history of focal neurologic deficits; (2) on an MRI of the brain, a T_2-weighted image with fluid-attenuated inversion (FLAIR) signal abnormality that is at least 3 mm in one dimension and that is visible in two planes (or similar image with 3D imaging); and (3) a normal neurological examination, preferably conducted by a neurologist, or an abnormality found on examination that could not be explained by the location of the brain lesion or lesions[30].

1. This definition of silent cerebral infarct in children has been validated. A definition of silent cerebral infarcts that requires a 5-mm size will lead to a large misclassification bias, with fewer children being identified with silent cerebral infarcts[149]. A minimum size silent cerebral infarct of 3-mm has been utilized in adult SCD studies and is predictive of infarct recurrence (Figure 8)[39].

2. The diagnosis of a silent cerebral infarct can be challenging, if the radiologist is unfamiliar with the definition of silent cerebral infarct in SCD. The definition of silent cerebral infarct cannot be extrapolated to include the common definition of lacunar strokes in the general population, which includes a T_1 hypointensity in addition to a 5-mm FLAIR hyperintensity[150].

3. When available, the imaging should be done on a 3.0 T magnet instead of a 1.5 T to improve the detection of silent cerebral infarcts (Figure 9). As new FLAIR sequences are acquired via whole-brain 3D imaging with no gaps between slices, the requirement for imaging in two planes to confirm a silent infarct may not be necessary.

4. Imaging examples of silent cerebral infarcts and mimics, specifically, Virchow-Robin spaces and periventricular leukomalacia, that may be useful for a clinician are displayed in Figure 9.

5. The Silent Cerebral Infarct Transfusion (SIT) Trial demonstrated that blood transfusion therapy is superior to observation for secondary stroke prevention (overt or silent cerebral infarct with a 56% relative risk reduction in cerebral infarct recurrence)[30]. However, the number needed to treat to prevent infarct recurrence with regular blood transfusions is 13. There are no controlled trial data demonstrating the non-inferiority of hydroxyurea therapy to regular blood transfusion therapy for children or adults with silent cerebral infarcts.

Given the association with progressive cerebral infarcts (overt or silent), the guideline panel recommends that children with HbSS or HbSB^0 thalassemia be screened at least once for silent cerebral infarcts with an MRI of the brain without sedation. The panel recommended that adults with HbSS or HbSB^0 thalassemia be screened at least once for silent cerebral infarcts even though there is no evidence for secondary prevention of silent cerebral infarcts in the adult age group. The panel, particularly the two non-health care provider representatives, placed a significant value on knowing that a silent cerebral infarct had occurred so that the affected child and adult will have a potential explanation for cognitive impairment and can be informed about a higher risk for infarct recurrence. Further, once a silent cerebral infarct is detected, the affected individual can be monitored for infarct recurrence so that either regular blood transfusion therapy[30] or experimental treatment options can be considered. These experimental therapies include, but are not limited to, HSCT and gene therapy in children and adults.

Summary of the evidence

The systematic review did not identify eligible studies that compared screening by means of MRI to no screening. The review identified 15 studies that reported the yield of screening, a study that showed the cumulative prevalence of silent cerebral infarct in children, and one randomized controlled trial that showed the benefit of regular blood transfusion therapy versus observation in decreasing cerebral infarct recurrence in children with HbSS or HbSB^0 thalassemia that underwent a MRI of the brain without sedation and were noted to have silent cerebral infarcts. The evidence summary and evidence to decision framework are in the appendix (editors: weblink for EtD 10 to be added here).

Rationale and expected benefits

There are five independent reasons justify screening for silent cerebral infarct in children and adults with HbSS or HbSB^0 thalassemia. (1) Silent cerebral infarcts are prevalent; approximately 39% of children and 50% of young adults with HbSS or HbSB^0 thalassemia will have a silent cerebral infarct. (2) Silent cerebral infarcts are progressive in both children and adults. The presence of silent cerebral infarcts predicts future neurological injury to the brain with an incidence rate that exceeds the accepted threshold for prevention of neurological injury in adults with atrial fibrillation not receiving anticoagulation. (3) Silent cerebral infarcts are associated with at least a 5-point full-scale IQ drop in children with SCD, and it is reasonable to believe that there a similar degree of neurological morbidity in adults with SCD. (4) Once silent cerebral infarcts are identified, children and adults are eligible for evaluation for individual education plans and Americans with Disability Act services, respectively. (5) Most silent cerebral infarcts occur in the border zone regions of the brain, which disproportionately affect executive function. The American Congress of Rehabilitation Medicine has formally endorsed evidenced-based strategies to support individuals with executive dysfunction.

After the completion of the Silent Cerebral Infarct Trial[30] for children with HbSS or HbSB^0 thalassemia, a sixth reason exists to screen for silent cerebral infarcts; namely, children with silent cerebral infarcts can be treated with regular blood transfusion to substantially reduce the incidence of a new stroke, silent infarct recurrence or both.

Summary of harms and burden

(Same as PICO question #1 and #2). The potential harms associated with regular blood transfusion therapy have been quantified in controlled clinical trials for primary and secondary prevention strokes in children with HbSS or HbSβ^0 thalassemia.

These adverse events include, but are not limited to, the following, in decreasing order of prevalence: excessive iron stores[52,53] that may eventually require chelation therapy[54,55], red blood cell alloimmunization[30,56] and adverse blood transfusion reactions[54,55].The burden of indefinite regular blood transfusion therapy is significant for the family. Typically, the regular blood transfusion occurs monthly and often requires two visits (the first for crossmatching of the red blood cell units and the second for the

actual blood transfusion). We did not find a study rating the intangible challenges of regular blood transfusion therapy for families, but the panel, including the two patient representatives, believed strongly that family preferences and the inconvenience and financial resources associated with regular blood transfusion therapy should be considered. Despite the burden, the panel believed that both children and adults should be aware of whether they have a silent cerebral infarct, an injury to the brain that places the individual at risk for future cerebral infarcts and may impact education attainment in children and adults, as well as employment in adults.

EtD criteria and implementation considerations

Access to MRI may be limited in some geographic areas or low-resource settings. Younger children will require sedation. Cost effectiveness data are unavailable but can be extrapolated from other environmental exposures associated with neurologic sequelae, low IQ and social outcomes.

A hematologist's diagnosis of silent cerebral infarct in a child with HbSS or HbSB^0 thalassemia will misclassify approximately 7% of the children as having a silent cerebral infarct, when in fact they had a stroke[30]. This misclassification of a stroke as a silent cerebral infarct may result in a different clinical course in treated and untreated individuals. In the presence of a silent cerebral infarct, annual surveillance with MRI may allow for increased therapeutic interventions; thus, a second screening MRI can be considered if new or cognitive impairment occurs or a change in academic performance is noted. An older child who cannot undergo an MRI without sedation may be supported by child life services to attempt MRI without sedation. Given that children and adults with HbSS or HbSβ^0 thalassemia have an increased prevalence of intracranial[151] and extracranial[152] vasculopathy and surgically correctable aneurysms[153], MRA of the intracranial and extracranial vessels should be added to the MRI of the brain.

Research needs

The panel identified the following additional areas in need of research.

1. A therapeutic strategy for primary prevention of silent cerebral infarcts is needed.
2. Imaging strategies to identify subgroups of children and adults that are likely to have infarct recurrence are needed.

3. Alternative treatment strategies, other than regular blood transfusion, for secondary prevention of infarct recurrence in children and adults with silent cerebral infarcts should be developed.
4. The clinical benefit of bone marrow transplant or gene therapy versus regular blood transfusion therapy for secondary prevention of cerebral infarcts in children and adults with pre-existing silent cerebral infarct should be determined.
5. The optimal treatment and infarct recurrence rate for children and adults with other than HbSS or HbSβ^0 thalassemia and with silent cerebral infarcts should be determined.
6. The clinical utility of screening for silent cerebral infarcts in low-and middle- income countries, where MRI scans are limited, and radiology expertise is far less prominent.

What Are Others Saying and What Is New in these ASH Guidelines?

SCD is a rare disease, with few guidelines developed for prevention, screening and treatment of CNS manifestations in children and adult with SCD. For only 2 of 10 PICO questions did we have the benefit of phase III randomized controlled trials on which to base our recommendations, PICO question 1(screening and treatment for primary stroke prevention) with TCD and PICO question 10 (screening and treatment for silent cerebral infarct to prevent cerebral infarct recurrence). The responses to the remaining PICO questions were based on review of all available observational studies, including cerebral hemodynamic studies in SCD.

With the exception of primary and secondary stroke prevention, guidelines for management for the common CNS problems in SCD were not discussed in the 2014 NHLBI Expert Panel Report on the Evidence-Based Management of Sickle Cell Disease. The SIT Trial was published after the 2014 panel review and was not referenced in the 2014 NHLBI Expert Panel Report. The recent AHA/ASA Statement on Pediatric Stroke management[75] provides guidance for initial management of suspected or confirmed acute ischemic strokes in children with SCD, as well as primary and secondary stroke prevention with regular blood transfusion. Their recommendations are similar to the ASH CNS panel recommendation.

In children and adults with SCD presenting with a focal neurological deficit, the panel recommends increasing the hemoglobin level with a red blood cell transfusion to achieve the goal of improving oxygen delivery to the brain. Given the challenge of distinguishing between MRI diffusion-weighted negative ischemic strokes and transient ischemic attacks[154], the clinical decision to manage a patient with a suspected ischemic infarct should not be based solely on the results of the MRI, but rather should be a bedside decision where the risks and benefits of transfusion must be considered. In most cases, the benefit of transfusing a child or adult with SCD and with acute focal neurologic deficits will outweigh the risks.

The panel did not include the role of HSCT for primary and secondary stroke prevention, an emerging treatment strategy in high-income settings. The panel's absence of any recommendation for HSCT for primary stroke prevention or secondary prevention of infarct recurrence does not reflect an absence of data or priority for the panel, but rather a decision to defer this subject matter to the ASH HSCT panel.

The panel members determined there was sufficient evidence to support guidelines for initial screening and subsequently surveillance for developmental delays and cognitive impairment for the general population, where the prevalence of impairments is significantly lower than in children and adults with SCD, should be applied to individuals with SCD. The panel's strong recommendation for screening for developmental delay and cognitive impairment in children with SCD was based on three factors. First, the American Academy of Pediatrics recommends that all children be screened for both developmental delay and cognitive impairment[111]; second, children with SCD have a high prevalence of these impairments; and third, the high impact of securing education resources for children with significant impairments via individualized education plans. Similarly, the ASH guideline panel's conditional recommendation for screening for cognitive impairment in adults with SCD was based on at least two dominant factors. The first was the American Neurology Academy recommendation for screening for mild cognitive impairment in adults[113], and the second was the high prevalence of these impairments in adults with SCD[113]. Research in implementation science is required to define the optimal reach (proportion of individuals that receive screening, and ongoing surveillance) for detecting developmental delay and cognitive impairment in SCD. The ASH guideline panel endorsed the American Congress of Rehabilitation Medicine evidence-based recommendations for cognitive rehabilitation[112].

Figure 1. High incidence of cerebrovascular accidents in children and adults with sickle cell disease prior to the onset of primary stroke prevention with transcranial Doppler (TCD) and regular blood transfusion or hydroxyurea. Data from the 3,647 children and adults with sickle cell disease followed prospectively from 1978 to 1988 in the Cooperative Study for Sickle Cell Disease cohort. The incidence rates of cerebrovascular accidents (CVA) were used to determine CVA-free survival curves. The estimated age at first CVA was significantly different for individuals with hemoglobin SS (HbSS) and HbSC patients ($P < 0.001$). Chances of having a first CVA by 20 years of age, 30 years of age, and 45 years of age were estimated at 11%, 15%, and 24%, respectively, for HbSS patients and 2%, 4%, and 10%, respectively, for those with HbSC[1]. Reproduced from Ohene-Frempong et al[1] with permission.

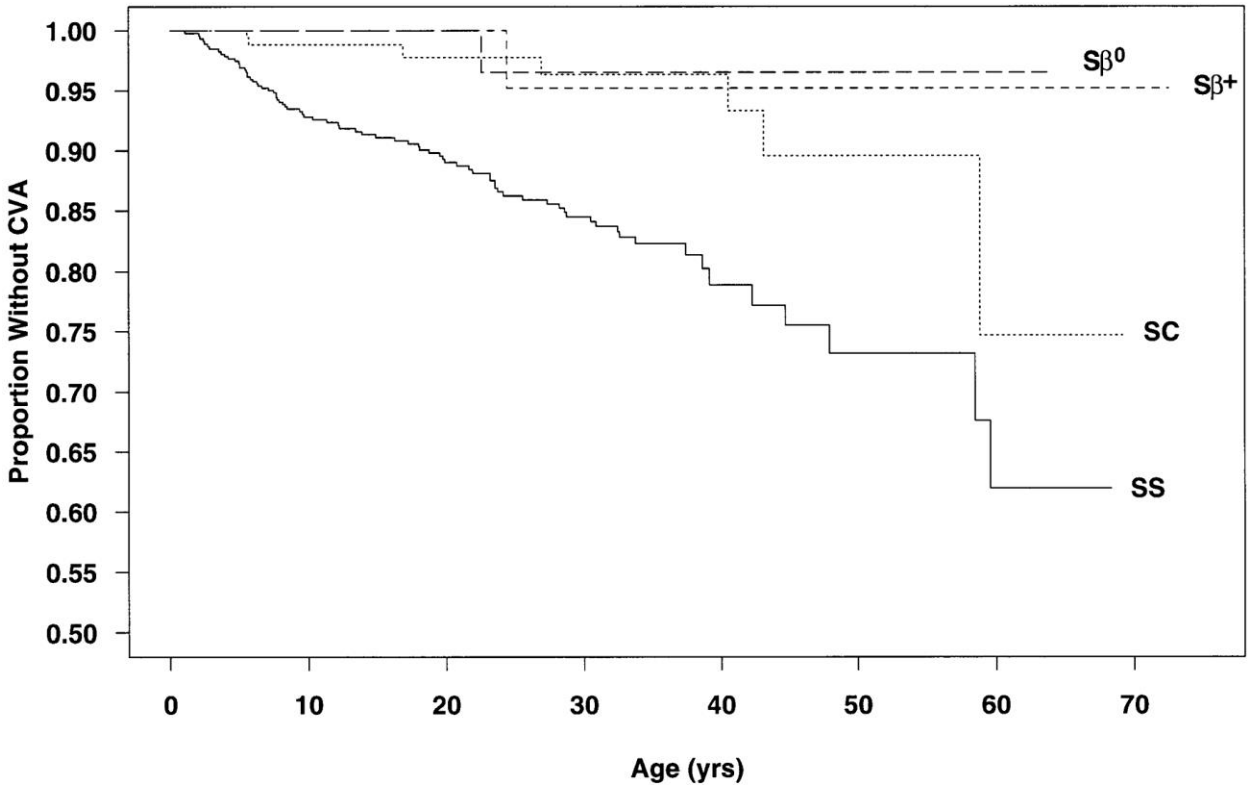


Figure 2. Prevalence of silent cerebral infarcts in unselected children and adults with sickle cell HbSS or HbSβ^0 thalassemia. Silent cerebral infarcts were detected with magnetic resonance imaging of the brain in children and adults with HbSS or HbSβ^0 thalassemia and no history of focal neurological deficits or strokes. Each point represents distinct cross-sectional studies in children and adults with HbSS or HbSβ^0 thalassemia[2] Reproduced from Kassim et al[2] with permission.

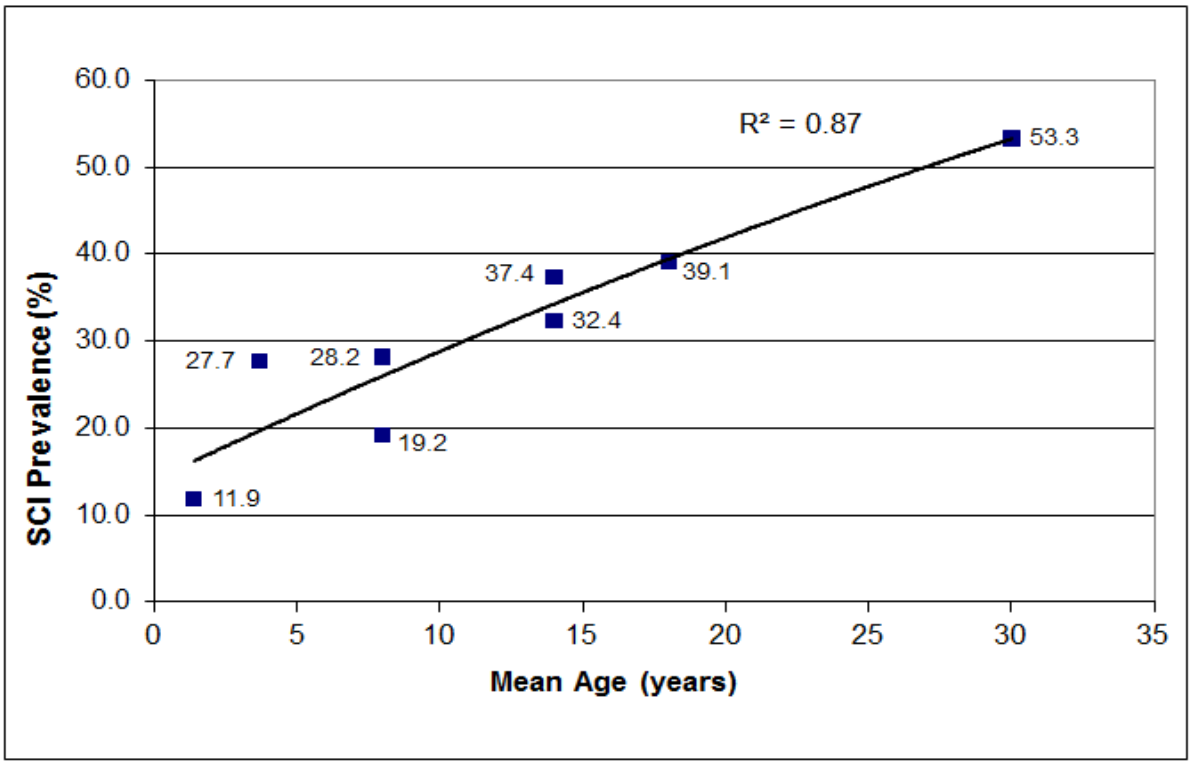


Figure 3. Results of the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP) trial and STOP II[25,28] Transcranial Doppler ultrasound (TCD) screening coupled with regular blood transfusion therapy for those with an abnormal TCD measurement (TAMMV > 200 cm/s) was associated with a 92% reduction in stroke incidence compared to observation alone[28]. The threshold for treatment is two non-imaging TCD measurements greater than 200 cm/s time-averaged mean of the maximum velocity (TAMMV) of ≥200 cm/s or a single measurement more than 220 cm/s[28]. Reproduced from Adams et al.[28] with permission.

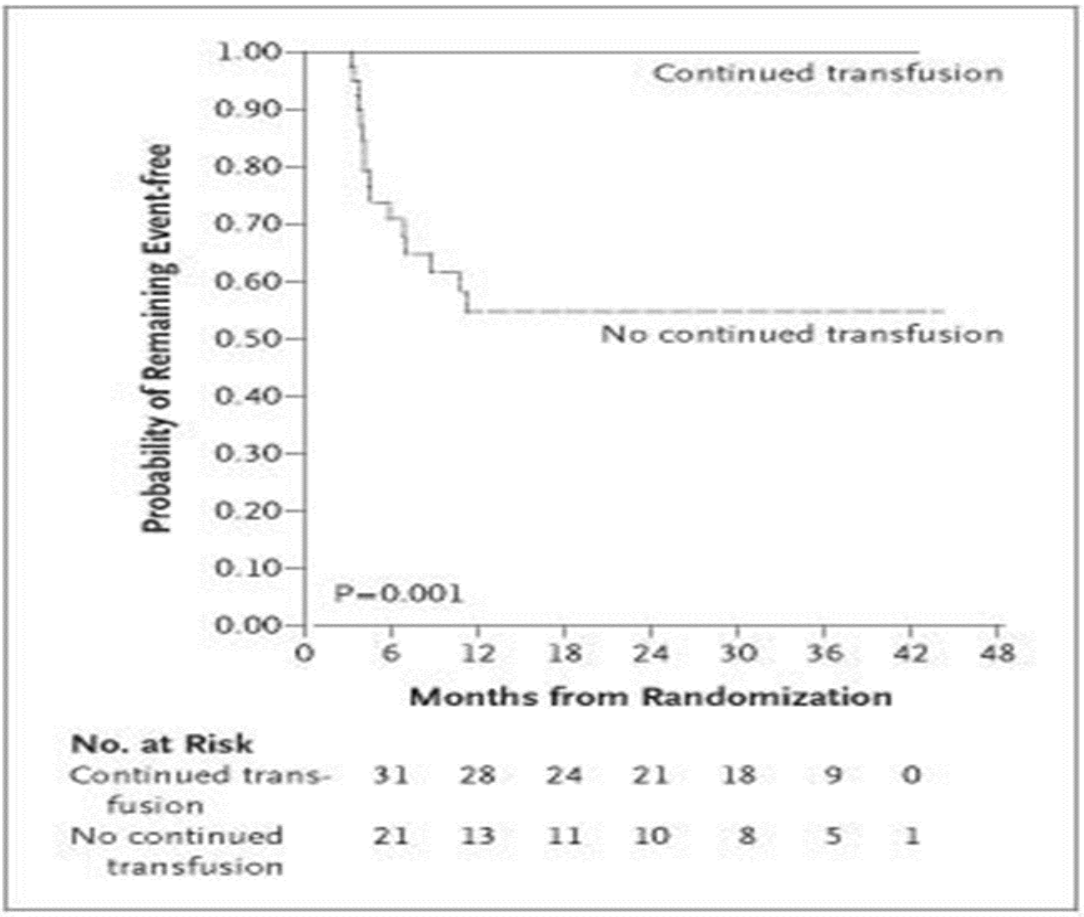


Figure 4. Pooled analysis of the 10 studies documenting TCD measurement before and after hydroxyurea therapy in children with HbSS or HbSβ^0 thalassemia. This meta-analysis demonstrates the average drop in TCD measurement after starting hydroxyurea therapy of 21 cm/s (95% confidence interval of 14.8 to 29.0). The plot also suggests that the decrease in TCD measurements can be seen as early as 3 months after the start of hydroxyurea therapy with a sustained impact of hydroxyurea therapy on decreasing TCD measurements for at least 36 months. The black diamond represents the pooled estimate from a random-effect model. The edges of the diamonds represent the 95% CI. The analysis is updated from a previous one by DeBaun and Kirkham[48], plus additional references [41-47,49,50,156]

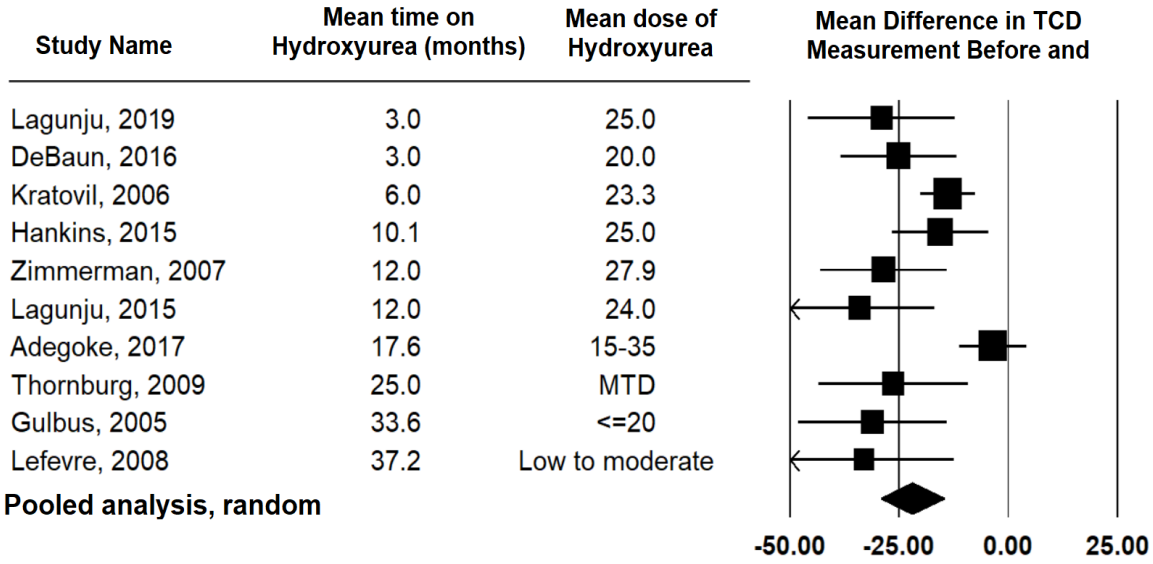


Figure 5. Relationship between hemoglobin level and oxygen delivery in individuals with sickle cell disease. The maximal hemoglobin to deliver oxygen transport in sickle cell patients is 10 to 11 gm/dl because sickle cell disease alters red cell viscosity and decreases oxygen transport. However, when the hemoglobin S level is low (~20 %), this impairment of oxygen transport is improved, and higher hemoglobin level (such as 13 gm/dl) may be beneficial. Red cell apheresis can rapidly lower the hemoglobin S to levels that maximize oxygen delivery, in contrast to the risks of simple transfusion resulting in increased viscosity and decreased oxygen delivery[71,72]. Adapted from Swerdlow[69] with permission.

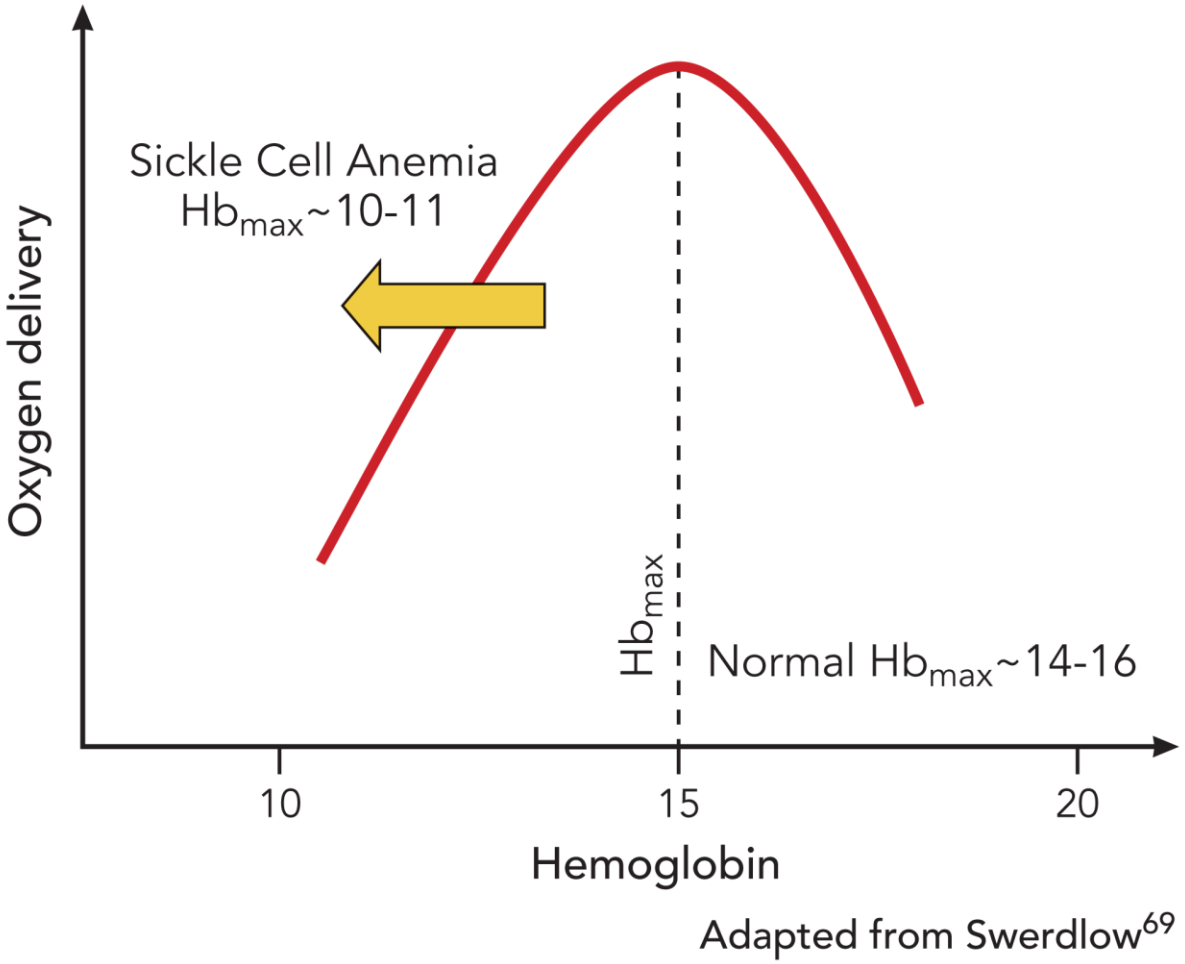


Figure 6. Algorithm of management of acute suspected ischemic strokes in children with sickle cell disease. The goal is prompt transfusion beginning within 2 hours of presentation to medical care to achieve hemoglobin of 10 g/dl and hemoglobin S level of 15% to 20%.

Figure 7. Algorithm of management of acute suspected ischemic stroke in adults with sickle cell disease. The goal is prompt transfusion beginning within 2 hours of presentation to medical care to achieve hemoglobin of 10 g/dl and hemoglobin S level of 15% to 20%. *See list of established inclusion and exclusion criteria.

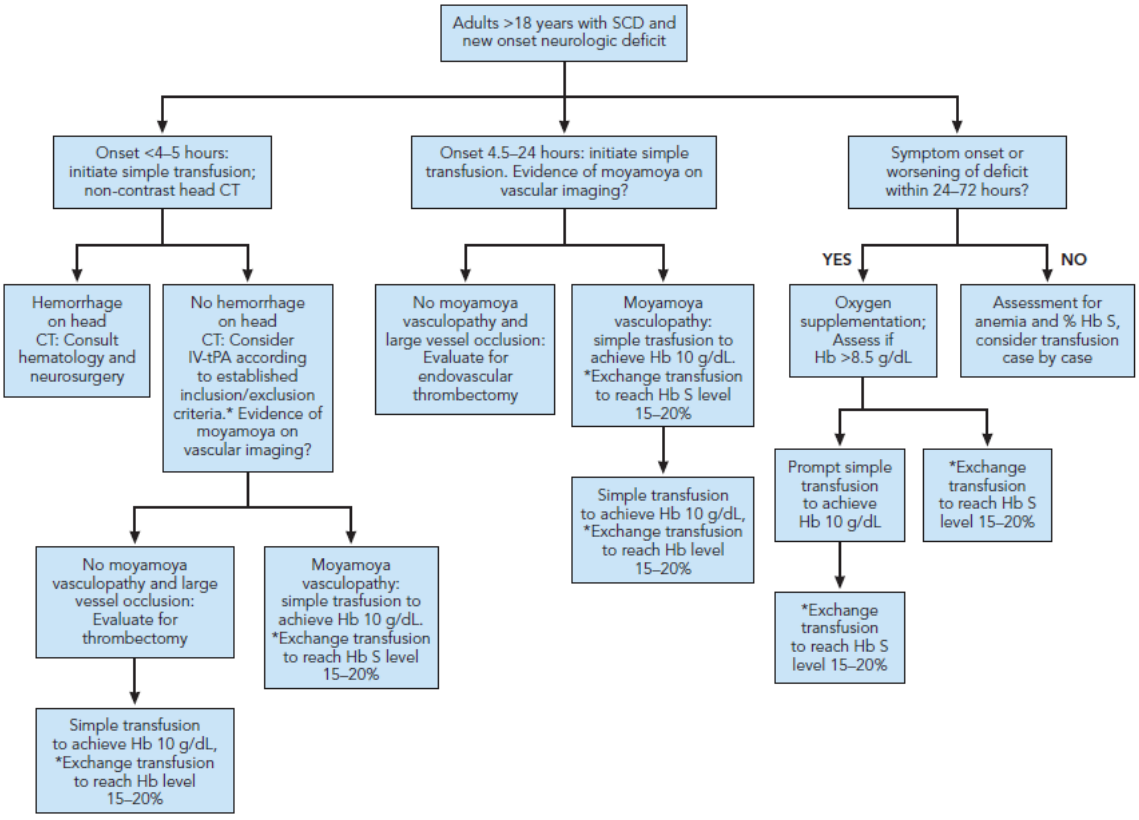
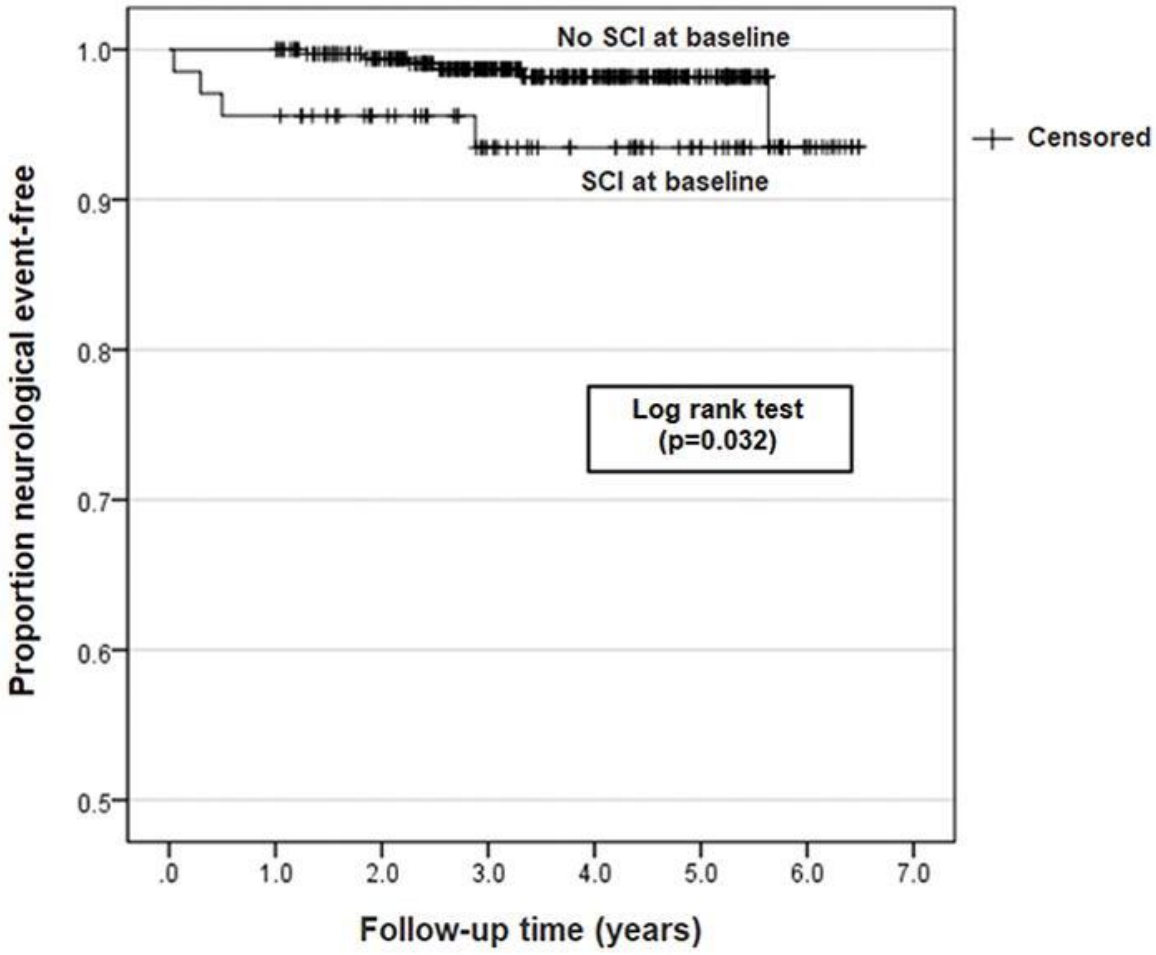


Figure 8. Pre-existing silent cerebral infarcts are associated with subsequent neurological events and recurrent silent cerebral infarcts in children and adults with sickle cell anemia. **Figure 8A.** Time to first neurological event-stroke, seizure, transient ischemic attack (TIA)-for children with normal or conditional transcranial Doppler ultrasound measurements (time averaged mean maximum velocity of < 200 cm/second, non-imaging or < 185 cm/second imaging technique) and with (n=68) and without silent cerebral infarcts (SCIs) on MRI (n=353). Reproduced from Hulbert et al[80] with permission.

Figure 8B. Pre-existing silent cerebral infarcts are associated with recurrent silent cerebral infarcts in adults with sickle cell anemia.

A total of 54 adults with sickle cell anemia had a minimum time of 6 months between MRIs; in this group of adults, 43% (n=23) had silent cerebral infarct (SCI) at baseline, and 57% (n=31) had no SCI at baseline; individuals with overt stroke were excluded based on history and examination by a neurologist. Reproduced from Jordan et al[39] with permission.


No SCI at baseline
SCI at baseline
Censored
Log rank test
(p=0.032)
Proportion neurological event-free
1.0
0.9
0.8
0.7
0.6
0.5
.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
Follow-up time (years)

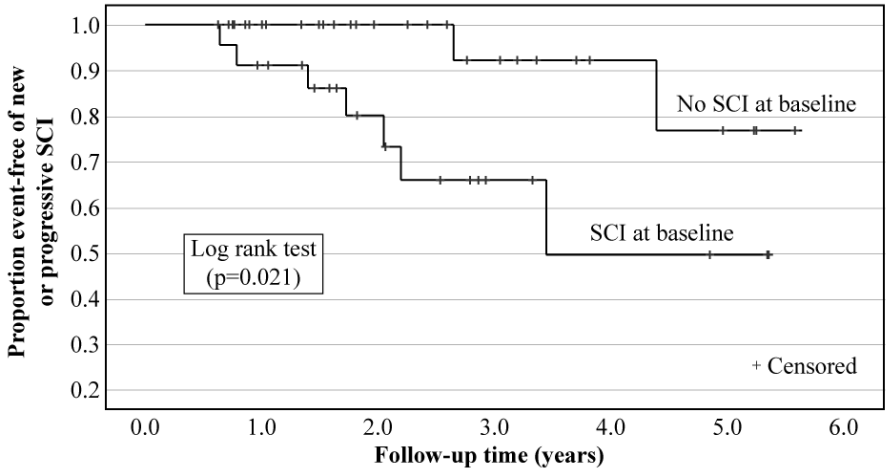

Proportion event-free of new or progressive SCI
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
No SCI at baseline
SCI at baseline
Log rank test
(p=0.021)
Censored
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Follow-up time (years)

Figure 9. Silent cerebral infarct and mimics in sickle cell disease

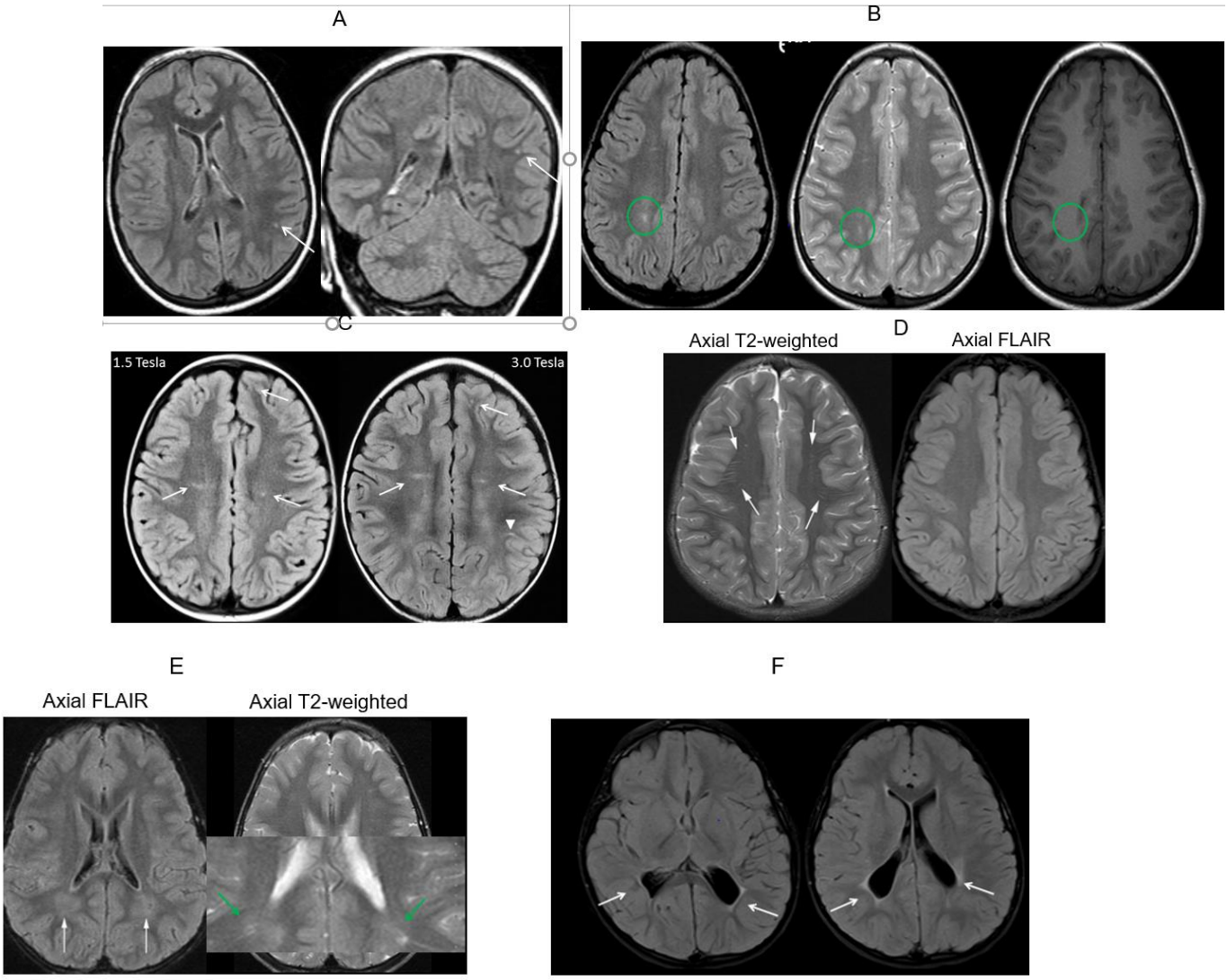
A (i) Axial and (ii) coronal fluid-attenuated inversion recovery (FLAIR) images illustrate a qualifying silent infarct lesion in the left parietal lobe (white arrows). An infarct-like lesion was defined as an MRI signal abnormality that was at least 3 mm in one dimension and that was visible in two planes on fluid-attenuated inversion recovery (FLAIR) T_2-weighted images or similar image with 3D imaging (not shown); and documented neurological examination performed by a neurologist demonstrating the participant has a normal neurologic examination or an abnormality on examination that could not be explained by the location of the brain lesion(s).

B. (i) T1- weighted, (ii) T2-weighted and (iii) axial FLAIR and images at the same level demonstrate that the FLAIR sequence (fluid attenuated inversion recovery) is better for the identification of silent cerebral infarcts (green circles).

C. Axial FLAIR images (see A for comparison) demonstrate a case of white matter injury in a premature infant (periventricular leukomalacia) that can mimic a silent cerebral infarct because of the increased signal in T2-weighted images (white arrows).

D. Terminal zones of myelination on T2-weighted images (see B(ii) for comparison). Axial FLAIR and T2-weighted images show ill-defined symmetrical T2-weighted hyperintensity in the deep parietal white matter. The T2-weighted image on the right illustrates that there are well defined linear perivascular spaces extending throughout the area of subtle hyperintensity (green arrows).

E. Linear and punctate T2 hyperintensities (see B(ii) for comparison) that suppress on FLAIR (see B(iii) for comparison) are consistent with prominent perivascular spaces (Virchow-Robin spaces)


A
B
C
1.5 Tesla
3.0 Tesla
D
Axial T2-weighted
Axial FLAIR
E
Axial FLAIR
Axial T2-weighted
F

Revision or Adaptation of the Guidelines

Plans for Updating these Guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts and regular revisions.

Updating or Adapting Recommendations Locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks[155].

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Authorship

Contribution: M. DeBaun wrote the first draft of the manuscript. As an iterative process, L. Jordan and H. Murad revised the manuscript based on co-authors' suggestions. Guideline panel members (King AA; Schatz J; Vichinsky E; Fox CK, Mckinstry RC, Telfer P, Kraut MA, Daraz L, Kirkham F) critically reviewed the final version of the manuscript and provided suggestions for improvement. L. Daraz led the team of investigators from the Mayo Clinic Evidence-based Practice Center who conducted the evidence synthesis. All authors approved the content. M. DeBaun was chair of the panel, with CNS content knowledge expertise, and H. Murad was co-chair, with content knowledge of guidelines and systematic review expertise; both led multiple panel meetings.

Conflicts-of-Interest Disclosure

All authors were members of the guideline panel or members of the systematic review team or both. As such, they completed a disclosure-of-interest form, which was reviewed by ASH and is available as supplements 2 and 3.

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