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Practice Patterns for Neuroimaging and Transfusion Therapy for Management of Neurologic Complications in Sickle Cell Anemia: DISPLACE Consortium

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Abstract

Background: Children with sickle cell anemia (SCA) are at risk for neurologic complications (stroke and silent cerebral infarct). The 2014 National Heart, Lung, and Blood Institute (NHLBI) guidelines for sickle cell disease include recommendations for initiation and maintenance of chronic red cell transfusion (CRCT) therapy for children with SCA at risk for or with ischemic stroke. The guidelines do not include well-delineated recommendations for cerebral imaging for stroke screening. The purpose of this study was to evaluate current stroke risk screening, prevention, and intervention practices amongst the Dissemination and Implementation of Stroke Prevention Looking at the Care Environment (DISPLACE) study sites.

Procedure: A survey was administered to DISPLACE site Principal Investigators to identify current stroke prevention practices relative to the STOP study protocols and the 2014 NHLBI guidelines. Data were analyzed using descriptive statistics and line-by-line analysis of comments.

Results: Sites consistently applied NHLBI recommendations to initiate CRCT for ischemic stroke and abnormal transcranial Doppler ultrasound (TCD) results. Similarly, nearly all sites

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reported obtaining an MRI/MRA following an abnormal TCD result. There was wide variation for other indications for MRI/MRA, frequency of MRI/MRA, and other neurological indications for initiating CRCT.

Conclusions: Guideline-based practices for preventing ischemic stroke through TCD and CRCT initiation were evident in nearly all sites. Wide variation in practices pertaining to MRI/MRA exist, potentially influenced by more recent stroke prevention trials. New guidelines from the American Society of Hematology were published in April 2020, which may reduce practice variation.

Keywords

sickle cell anemia; transfusion; neuroimaging; clinical practice

Introduction

Ischemic stroke and silent cerebral infarct (SCI) are two common and potentially life-changing complications of sickle cell anemia (SCA). By age 20, the estimated risk of having an overt ischemic stroke is 11% without intervention.¹ SCI is estimated to occur in around 1/3 of children (or more) with SCA and may be progressive over time.² Current stroke prevention guidelines in pediatric SCA specify use of transcranial Doppler ultrasound (TCD) and chronic red cell transfusion (CRCT) therapy for detection of individuals at high risk of ischemic stroke and prevention of overt stroke. CRCT is also recommended for secondary stroke prevention in individuals with SCA and prior stroke. Guidance on use of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) in the context of stroke prevention, screening, and monitoring is less clear.³ While ischemic stroke can be identified clinically, SCI can be more difficult to identify, and screening guidelines have only recently been released by the American Society of Hematology (ASH).

We recently published findings on TCD screening practice patterns among the Dissemination and Implementation Looking at the Care Environment (DISPLACE) Consortium.⁴ DISPLACE is a multi-center National Heart, Lung, and Blood Institute (NHLBI)-funded study to evaluate and improve implementation of stroke prevention guidelines. This paper is a complement to the prior publication and provides information on clinical practice patterns for MRI/MRA and CRCT for primary and secondary stroke prevention within the DISPLACE consortium for pediatric patients with SCA. As with our prior publication, we sought to illustrate practice patterns implemented after the 2014 NHLBI guidelines. We also describe the 2020 ASH cerebrovascular and transfusion guidelines as part of the discussion; however, it should be noted that providers were surveyed prior to the development and publication of these newer guidelines.

Brief Summary of 2014 NHLBI Guidelines for MRI/MRA and CRCT

Table 1 provides a summary of the 2014 NHLBI guidelines on neuroimaging and CRCT.³ The 2020 ASH guidelines pertaining to these practices are described in Table 2.^{5,6} Regarding neuroimaging, the 2014 NHLBI guidelines did not provide a firm recommendation for or against MRI use for screening asymptomatic children with SCA for

stroke. The guidelines also did not address whether and how frequently neuroimaging techniques (including TCD and MRI/MRA) should be used for cerebrovascular monitoring for those at high risk for stroke, including children with abnormal TCD, those with cerebral vessel narrowing or moyamoya disease, or those who had a previous stroke. For CRCT, the guidelines recommended consulting with an expert in CRCT for children with abnormal TCD and recommended CRCT for those with prior stroke for secondary prevention, with a target hemoglobin S (HbS) level of <30%. A recommendation was also made for initiating hydroxyurea (HU) when CRCT was not possible for stroke prevention.

Of note, the NHLBI guidelines did not include findings from two important clinical trials, the TCDs with Transfusions Changing to Hydroxyurea (TWITCH) trial and the Silent Cerebral Infarct Multi-Center Trial (SIT). TWITCH was a multi-site trial that determined children with abnormal TCD, but no significant vasculopathy on MRI/MRA could be safely transitioned to HU after one year of transfusions to maintain TCD velocities and prevent stroke.⁷ SIT determined that regular blood transfusion therapy could significantly reduce progression of new cerebral infarcts in children with SCA who had history of SCI.⁸ The influence of these trials can be seen in the newer 2020 ASH guidelines in terms of HU use for stroke prevention and MRI screening.

Methods

Sample and Setting

The sample consisted of site Principal Investigators (PIs) from each of the 28 DISPLACE consortium sites. Sites varied in terms of geographical location, region (rural versus urban), size, and prior participation in clinical studies on stroke prevention. All site PIs were pediatric hematology/oncology specialty providers with expertise in SCA.

Data Collection

The practice patterns survey was developed during the needs assessment phase of DISPLACE for evaluation of current practices in the 28-site consortium. Survey development was guided by the 2014 NHLBI guidelines and was carried out by our interdisciplinary core study team with expertise in nursing, psychology, medicine, and public health, using an iterative process. The final survey included 37 items to assess practice patterns on TCD screening, CRCT initiation and implementation, MRI and MRA, echocardiograms, developmental-behavioral screening, and immunizations. Questions pertaining specifically to MRI/MRA included the following: indications for MRI/MRA, frequency of MRI/MRA for children on CRCT and (separately) on HU for stroke prevention. Questions pertaining specifically to CRCT included: indications for CRCT, type of CRCT and reason for preference, target HbS, and frequency of CRCT.

Data Analysis

Data were collected using REDCap⁹ then exported to SAS statistical software, version 9.4 (Copyright © 2016 by SAS Institute Inc., Cary, NC, USA.) for analysis. Analysis consisted of descriptive statistics, including proportions and frequencies for categorical variables and measures of central tendency (mean, median, range) for continuous variables. In addition,

free-text comments were analyzed using line-by-line examination to establish a comprehensive understanding of complex practice patterns.

Results

Table 1 provides results of practice patterns compared to the 2014 NHLBI guidelines, with complex response patterns and free-text comments described below. All 28 (100%) site PIs completed the survey; however, one site PI did not respond to items on MRI/MRA or CRCT and was excluded from proportion calculations. Of the 28 site PIs, most were White (77.8%), followed by Asian (11.1%), and African American (7.4%); 7.4% were Hispanic or Latino. Approximately half (53%) were female.

Use of MRI/MRA for Stroke Identification and Monitoring

Indications for MRI/MRA—Some indications for MRI or MRA were based on TCD screening results, while some were for “other” neurological indications. Of 24 sites that would obtain MRI for abnormal TCD results, 11 (45.8%) would only do so with abnormal result and 13 (54.2%) would obtain MRI for abnormal or conditional result. Similarly, of 25 sites that would obtain MRA following abnormal TCD result, 11 (44.0%) would only obtain MRA for abnormal result while 14 (56.0%) would obtain MRA for abnormal or conditional TCD result. In comments, site PIs indicated that MRI and/or MRA would be obtained for high conditional TCD result only if sedation was not necessary or when the TCD was unreadable or inadequate. Additional indications for MRA included persistent asymmetric flow and evidence on MRI of previous ischemic stroke or SCI.

Recurrent headache was the primary indication for MRI and MRA not related to TCD screening results. Among 22 sites that would obtain MRI for recurrent headache, 15 (68.2%) would also obtain MRI for behavior issues, though 4 (18.2%) additional sites specified issues for which MRI would be obtained including poor school performance, neurocognitive delay, or as recommended by a psychologist. Of 16 sites that would obtain MRA for recurrent headaches, 9 (56.3%) would also obtain MRA for behavior issues, and one would obtain MRA specifically for poor school performance.

While no participants selected a response item indicating a routine screening schedule, several described situations in which routine MRI or MRA would be obtained. Only one site would routinely obtain MRI without clinical indication, every 5 years once sedation is less likely needed. Six sites would obtain a baseline MRI around school age (5 or 6 years) when sedation is less likely needed. Of these six, two indicated MRI would be repeated only with clinical concerns and two clarified that MRI would be obtained every 1 – 2 years with abnormalities or evidence of SCI. Four additional sites described stroke or stroke risk indications for routine screening. One would obtain MRI for high conditional TCD results at baseline then every 3 years, once sedation is not likely needed. Two would obtain MRI every 1 – 2 years for overt stroke, one would use sedation if needed. The fourth site would obtain annual MRI without sedation with prior documentation of micro infarcts. Fewer sites described situations when MRA would be routinely obtained; only 1 described obtaining a baseline MRA once sedation is not likely needed. Similar to MRI, one site would obtain

MRA every 5 years. Two sites would obtain MRA every 1 – 2 years for overt stroke, and one would obtain MRA annually without sedation with history of micro infarcts.

Reasons why a screening MRI/MRA not performed—Sites were asked to select reasons explaining why screening MRI or MRA is not performed; 17 responded to the question. Nine sites noted they would not obtain screening because it is not part of the NHLBI guidelines, of which 3 sites (33.3%) also responded that they do not believe screening MRI or MRA is necessary, and 2 sites (22.2%) responded that insurance barriers contribute to the decision. Eight sites, one of which selected “other”, (47.1%) indicated insurance barriers alone as the reason screening MRI or MRA is not obtained, and 6, one of which selected “other”, (35.3%) indicated they do not believe a screening MRI or MRA is necessary as the sole reason. Six of the sites (35.3%) that selected “other” in response to the question described risk of sedation as the reason screening MRI or MRA is not obtained.

Frequency of MRI/MRA for Patients on CRCT for Primary or Secondary Stroke Prevention—Six sites (22.2%) selected “other” frequencies for MRI and 5 sites (18.5%) selected “other” frequencies for MRA. One site responded that MRI would be obtained annually for patients with overt ischemic stroke. The other 5 sites provided the same responses for MRI and MRA frequency indications. One site would obtain MRI/MRA annually with parental agreement, and another would also obtain MRI/MRA annually until stable findings and would change to every two years. Similarly, another site would obtain MRI/MRA every 1 – 2 years, but only if results were previously concerning or with clinical changes. Two sites would obtain MRI/MRA every 1 – 2 years in patients on CRCT for history of stroke but would not obtain routine MRI/MRA for patients on CRCT for abnormal TCD results. One site further specified that MRI/MRA would be obtained prior to changing from CRCT to HU as per TWITCH protocol.

Frequency of MRI/MRA for Patients on Hydroxyurea for Stroke Prevention—Four sites (14.8%) described “other” frequencies for MRI and 3 sites (11.1%) described “other” frequencies for MRA. Of these, one site specified that MRA would be obtained with every MRI, and one indicated that MRI and MRA would be obtained annually until stable findings, then only repeated with clinical change. One site indicated MRI would be obtained if the TCD became abnormal while the patient is on HU. A different site noted it was required per their parameters to transition a patient from CRCT to HU. Similarly, one site specified that MRA would be obtained once and then repeated annually only if results were abnormal or if TCD results remained abnormal. One site explained frequency based on SCI and would obtain MRI every 1 – 2 years for patients with SCI, but otherwise only with new clinical concerns.

CRCT Practices

Stroke Indications for CRCT—Sites provided various patterns of neurological, stroke-based indications (overt stroke, SCI, blood vessel stenosis, and abnormal TCD) for beginning CRCT. Seven sites (25.9%) would begin CRCT for any of the four indicators, 15 (55.6%) would begin CRCT for three of the four indicators, and 5 (18.5%) would begin CRCT for two of the four indicators.

Type of CRCT—Most sites use a combination of simple transfusion, manual exchange transfusion, and automated exchange transfusion (15; 55.6%). Seven sites (25.9%) use simple transfusion and automated exchange transfusion, two sites (7.4%) use only simple transfusion, one site (3.7%) uses only manual exchange transfusion, and two sites (7.4%) use simple and manual exchange transfusion. When asked whether one method was preferred over another and why, 16 sites responded. The majority (12; 75.0%) prefer automated exchange to prevent iron overload and/or improve control over %HbS. However, despite this preference, several sites described challenges to automated exchange, primarily increased cost and challenges to establishing and maintaining venous access.

Discussion

This paper describes practice patterns relating to MRI/MRA for neurologic evaluation and CRCT for stroke prevention in children with SCA in the DISPLACE consortium, as a complement to a prior publication on TCD screening. Readers should note that the purpose of this paper is to provide data on reported practices in the DISPLACE consortium institutions and to compare these practices with current guidelines for evidence-based care for children with SCA. The 2014 NHLBI guidelines and the 2020 ASH guidelines should be referenced to guide best care practices. In addition, although a primary focus of this paper is neuroimaging, the importance of a complete neurological evaluation when evaluating patients for stroke and SCI cannot be understated. Results of this paper differ somewhat from the prior publication due to the lack of guidance on the use and frequency of radiologic screening in the NHLBI guidelines. Although there was consensus in some areas of clinical practice by the DISPLACE consortium, particularly those relating to children at high risk of or with previous ischemic stroke, there was a fair amount of variation and nuance in other areas.

Regarding neuroimaging, most sites reported obtaining MRI and MRA in children with abnormal TCD, which would be indicated in children being considered for the TWITCH protocol (described below). MRI use was also prevalent for children with recurrent headaches despite the absence of a specific guideline for this practice. DeBaun and Kirkham (2016) describe the current research literature on headaches in relation to cerebrovascular events. They highlight the importance of consulting with neurology to evaluate characteristics of the headaches (e.g., new onset versus chronic) and to identify whether other risk factors are present that would warrant neuroimaging.² Approximately half of the sites also endorsed the use of MRI for children with behavioral issues and/or conditional TCD, though similarly to use for headaches, there are no guidelines for these practices. Of note, about a quarter of sites described obtaining routine or screening MRIs to detect SCI in the absence of other indications, a finding that is consistent with a prior publication of practice patterns among 62 institutions in 2014.¹⁰ For sites not using screening MRIs, responses suggested variation in provider perspectives on screening, concerns with insurance barriers, and risks associated with sedation. These responses are notable given the new 2020 ASH cerebrovascular guidelines, which strongly recommend at least a one-time MRI screening in early school-age if a child can complete the procedure without sedation.⁵

Providers were also asked about the monitoring frequency of MRI/MRA for patients on either CRCT or HU for stroke prevention. Close to half of sites reported annual MRI and MRA for patients on HU or CRCT for stroke prevention. The remaining sites described longer intervals (i.e., 2 years, 5 years). The primary difference in practice between those on HU versus CRCT was the number of sites that would conduct MRI/MRA *only* with changes or concerns (i.e., not at regular intervals). For patients on HU, this category comprised about 1/3 (or 9) of sites whereas only 4–5 sites described this practice for patients on CRCT. The 2020 ASH guidelines describe a suggested plan of action for using MRI to monitor potential progression of SCI in children who have a history of SCI, with a frequency of every 12–24 months.⁵ There are otherwise no existing guidelines for monitoring frequency for MRI/MRA in children with a history of abnormal TCD or overt stroke.

Frequency of MRI/MRA is important because providers may use these tools to track the extent of cerebrovascular changes in patients either at risk for or with history of stroke. In the case of children with abnormal TCD who are either currently on or being considered for the TWiTCH protocol, cerebrovascular abnormalities are very important to detect, as these children would no longer be good candidates for transition to HU if changes are found on MRI/MRA (or, if they are on HU, they may need to return to CRCT). Further, while the TWiTCH trial provided evidence for transitioning from CRCT to HU, no recommendations were made on monitoring with MRI/MRA after the transition.⁷ The recent 2020 ASH guidelines note the importance of obtaining an *initial* MRI/MRA for patients under consideration for a change from CRCT to HU for abnormal TCD; however, there is no clear information on how frequently children should be monitored thereafter. For patients on CRCT, worsening cerebral vascular changes, such as development of moyamoya disease, may prompt further evaluation for revascularization surgery.⁵ For patients who are either at risk for stroke or who have history of stroke, cerebrovascular changes may also prompt further evaluation of neurocognitive functioning.^{3,11}

For CRCT, almost all sites would initiate CRCT for children with abnormal TCD or history of overt stroke as recommended by the 2014 NHLBI guidelines. About half of sites would also initiate CRCT for SCI and a smaller subset of sites would initiate CRCT for abnormal MRA. Treatment for SCI with CRCT was the focus of the multi-site clinical trial, SIT, which found a 56% reduction in the progression of SCI or overt stroke in children receiving regular transfusion over observation.⁸ The 2020 ASH guidelines describe an action plan following an abnormal MRI screening, including neurological evaluation to determine appropriate classification of the abnormality as an SCI and cognitive screening assessment. The plan also describes a shared decision making approach to treatment for SCI (i.e., discussion of CRCT or transplant options) as well as surveillance of progression of SCI, followed by further discussion of treatment options if progression is found.⁵

Providers were asked about the transfusion modality used at their site (automated, simple, or manual), with various patterns of modality endorsed. All three modalities received high responses as options, with simple exchange endorsed by nearly all sites, followed by automated exchange endorsed by most sites, and manual exchange endorsed by 2/3 of sites. When asked about provider preference for a particular modality, the comments closely mirrored those of the published 2020 ASH transfusion guidelines, which *suggest* automated

exchange, but which also note decision making should consider other factors (e.g., clinical indication, baseline and target HbS, patient age and preferences, iron overload status and adherence with chelation, feasibility, availability of compatible red cells).⁶ Responses suggest that while providers preferred automated exchange as recommended by guidelines, cost and venous access challenges limited their ability to fully implement automated exchange and adhere to the guidelines. Finally, providers were asked about target %HbS for stroke prevention and CRCT frequency. Most sites endorsed a target of <30% (consistent with guidelines) and a frequency of every 4 weeks, while other sites described specific protocols, including those designed to more rapidly achieve reduction in %HbS.

There are limitations to this study to consider. As with our previous publication on practice patterns on TCD screening in children with SCA, the generalizability of practice patterns on MRI/MRA and CRCT initiation may be limited as only DISPLACE consortium sites were included. However, consortium sites were selected to reflect variation in size, location, region of the U.S., and prior participation in stroke prevention trials. An additional possible limitation pertained to study design, which allowed multiple response options and free-text comments and presented challenges with fully describing complexity of practice patterns. Despite this challenge, analyses were conducted to evaluate not only item responses, but also patterns in responses with line-by-line analysis of free text comments.

In summary, practice patterns endorsed by the DISPLACE consortium suggest convergence for several practices, specifically those related to initial use of MRI/MRA and implementing CRCT in children with high risk of or prior stroke. Significant variation exists for monitoring frequency of MRI/MRA and other reasons for ordering MRI/MRA as well as SCI monitoring and treatment. The new ASH guidelines for SCI screening using MRI will likely prompt additional discussion and investigation about optimal detection and treatment for SCI. Future research on optimal timing for tracking cerebrovascular changes and the use of alternative protocols (e.g., other forms of neurological monitoring) that might prompt MRI/MRA would be beneficial for improving clinical practice.

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Abbreviations list:

ASH	American Society of Hematology
CRCT	chronic red cell transfusions
DISPLACE	Dissemination and Implementation of Stroke Prevention Looking at the Care Environment
HbS	hemoglobin S
HU	hydroxyurea
MRI	magnetic resonance imaging

MRA	magnetic resonance angiography
NHLBI	National Heart, Lung, and Blood Institute
PI	principal investigator
TCD	transcranial Doppler
SCA	sickle cell anemia
SCD	sickle cell disease
SCI	silent cerebral infarct
SIT	Silent Cerebral Infarct Multi-Center Trial
STOP	Stroke Prevention Trial in Sickle Cell Anemia
STOP II	Optimizing Primary Stroke Prevention in Sickle Cell Anemia
TWiTCH	TCDs with Transfusions Changing to Hydroxyurea

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Recommendations for stroke risk screening, prevention, and intervention using MRI/MRA and CRCT and DISPLACE practice patterns

Table 1:

Practice Recommendations per 2014 NHLBI Guidelines		Practice Patterns in DISPLACE Consortium N = 27 (proportion; n)
<i>Practices using MRI/MRA</i>		
Use of MRI for Stroke Screening		
• In asymptomatic children with SCD, do not perform screening with MRI or CT (Moderate Recommendation, Low Quality Evidence)	Indications for MRI	<ul style="list-style-type: none"> • Abnormal TCD; 88.9% (24) • Recurrent headaches; 81.5% (22) • Behavior issues; 55.6% (15) • Other; 51.9% (14)
Use of MRA is not discussed in the guidelines	Indications for MRA	<ul style="list-style-type: none"> • Abnormal TCD; 92.6% (25) • Recurrent headaches; 59.3% (16) • Conditional TCD; 51.9% (14) • Other; 37.0% (10) • Behavior issues; 33.3% (9)
	Reason MRI/MRA not ordered for stroke screening	<ul style="list-style-type: none"> • Non-response; 37.0% (10) • Not part of the NHLBI guidelines; 33.3% (9) • Other; 33.3% (9) • Insurance barriers; 25.9% (7) • Not considered necessary; 18.5% (5)
Frequency of MRI/MRA for patients on CRCT or HU for stroke prevention (not discussed in the guidelines)	Frequency of MRI for patients on CRCT for stroke prevention	<ul style="list-style-type: none"> • Annually; 44.4% (12) • Other; 22.2% (6) • Every 2 years; 14.8% (4) • Only with changes or concerns; 14.8% (4) • Every 5 years; 3.7% (1)
	Frequency of MRA for patients on CRCT for stroke prevention	<ul style="list-style-type: none"> • Annually; 48.1% (13)

Practice Recommendations per 2014 NHLBI Guidelines	Practice Patterns in DISPLACE Consortium N = 27 (proportion; n)
	<ul style="list-style-type: none"> • Only with changes or concerns; 18.5% (5) • Other; 18.5% (5) • Every 2 years; 11.1% (3) • Every 5 years; 3.7% (1) <p>Frequency of MRI for patients on HU for stroke prevention</p> <ul style="list-style-type: none"> • Annually; 44.4% (12) • Only with changes or concerns; 33.3% (9) • Other; 14.8% (4) • Every 2 years; 3.7% (1) • Non-response; 3.7% (1) <p>Frequency of MRA for patients on HU for stroke prevention</p> <ul style="list-style-type: none"> • Annually; 48.1% (13) • Only with changes or concerns; 33.3% (9) • Other; 11.1% (3) • Every 2 years; 3.7% (1) • Non-response; 3.7% (1)
<i>Practices for CRCT</i>	
Neurological Indications for CRCT	Neurological Indications for CRCT
<ul style="list-style-type: none"> • Abnormal TCD (High Quality Evidence, Strong Recommendation) • Previous Overt Stroke (Low Quality Evidence, Moderate Recommendation) 	<ul style="list-style-type: none"> • Abnormal TCD; 100% (27) • Overt stroke; 96.3% (26) • Silent stroke; 55.6% (15) • Blood vessel stenosis on MRA; 51.9% (14) • Other; 29.6% (8)
Transfusion Modality	Transfusion Modality
• Simple, manual, or automated transfusion (not described in guidelines)	<ul style="list-style-type: none"> • Simple; 96.3% (26) • Auto exchange; 81.5% (22) • Manual; 66.7% (18)
Target HbS	Target HbS

Practice Recommendations per 2014 NHLBI Guidelines	Practice Patterns in DISPLACE Consortium N = 27 (proportion; n)
<ul style="list-style-type: none">• In children who receive CRCT, the goal of transfusion should be to maintain a HbS level of <30% immediately prior to the next transfusion (Moderate Recommendation, Moderate Quality Evidence)	<ul style="list-style-type: none">• HbS< 30%; 88.9% (24)• HbS< 40%; 3.7% (1)• HbS< 50%; 3.7% (1)• Other; 3.7% (1)
Transfusion Frequency (not discussed in guidelines other than goal of reaching target HbS)	Transfusion Frequency <ul style="list-style-type: none">• Every 4 weeks; 63.0% (17)• Other; 37.0% (10)

Abbreviations: CRCT, chronic red cell transfusions; CT, computed tomography; DISPLACE, Dissemination and Implementation of Stroke Prevention Looking at the Care Environment; HbS, hemoglobin S; HU, hydroxyurea; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NHLBI, National Heart, Lung, and Blood Institute; SCD, sickle cell disease; TCD, transcranial Doppler

Table 2: ASH 2020 Guidelines pertaining to stroke risk screening, prevention, and intervention using MRI/MRA and CRCT

<i>ASH Cerebrovascular Disease Guidelines</i>	
Neurological Indications for CRCT	<ul style="list-style-type: none">• Recommended for children with abnormal TCD (target HbS< 30%; Strong Recommendation, Moderate certainty based on the evidence)• Recommended for children with prior stroke (target HbS< 30%; Strong Recommendation, Low certainty based on the evidence)
Guideline for Use of TWiTCH Protocol (Conditional Recommendation, Low certainty based on the evidence)	<ul style="list-style-type: none">• For children with abnormal TCD who have received CRCT for at least one year and who are interested in stopping:• Risk stratification based on MRI/MRA• If no evidence of silent infarct or MRA-defined cerebral vasculopathy, the panel <i>suggests</i> that HU be considered as a replacement for CRCT• If evidence of silent infarct or MRA-defined vasculopathy, continue with CRCT indefinitely
Use of MRI for Silent Cerebral Infarct	<ul style="list-style-type: none">• At least a one-time MRI screening in early school age if child can undergo un-sedated MRI to detect silent stroke (Strong Recommendation, Moderate certainty based on the evidence)• Suggested Action Plan:• Neurological evaluation to determine appropriate classification as a silent infarct• Discussion regarding secondary prevention options, including CRCT and transplant• Cognitive screening assessment• MRI surveillance every 12 to 24 months to assess for progression, followed by a discussion of pros and cons for step-up therapy if progression is found
<i>ASH Transfusion Guidelines</i>	
Transfusion modality	<ul style="list-style-type: none">• Suggests using automated RCE over simple transfusion or manual red cell exchange in patients with SCD receiving CRCT (Conditional Recommendation based on very low certainty in the evidence about effects)

Abbreviations: ASH, American Society of Hematology; CRCT, chronic red cell transfusions; HbS, hemoglobin S; HU, hydroxyurea; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; RCE, red cell exchange; TCD, transcranial Doppler; TWiTCH, TCDs with Transfusions Changing to Hydroxyurea