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EXPERT REVIEWS

Stroke in patients with sickle cell disease

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Stroke is a significant cause of morbidity and mortality in children and adults with sickle cell disease. Great advances in the past couple of decades have enabled identification and treatment of children at risk of stroke, with a resultant dramatic reduction in stroke incidence in children. However, prevention and treatment of silent cerebral infarcts remain a challenge. This article reviews our current understanding of the epidemiology, risk factors and pathophysiology of small and large vessel disease with a focus on pediatric patients. The presentation and acute management of stroke in patients with sickle cell disease are discussed. Current recommendations for primary and secondary stroke prevention, as well as ongoing research studies and potential new therapies are reviewed.

Keywords: cerebrovascular accident • chronic transfusion therapy • review • sickle cell anemia • stroke

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Stroke is a significant cause of morbidity and mortality in children and adults with sickle cell disease (SCD). Strokes or cerebrovascular accidents (CVAs) are felt to represent the culmination of large and small vessel disease and altered cerebral autoregulation, as well as the sequelae of chronic inflammation, hemolysis and anemia. Although the precise pathophysiology of stroke in SCD is still an area of active research, clinical research studies have made significant advances in understanding and identifying those patients who are at highest risk of stroke and in implementing strategies for reducing that risk.

Epidemiology

CSSCD, the largest US multicenter longitudinal observational study of complications of SCD, reported an overall prevalence of stroke of 3.75% in all patients with SCD [1]. The prevalence of CVA was 11% in patients under 20 years of age with homozygous sickle-cell disease (SCD-SS). In childhood, the highest incidence (1.02 per 100 person-years) was found in children between 2 and 5 years of age with SCD-SS [1]. The rates of CVA vary by sickle cell genotype. The age-adjusted incidence of CVA is highest for those with SCD-SS (0.61 per 100 person-years) compared with SCD-SC (0.15 per 100 person-years) or hemoglobin $S\beta^+$ or $S\beta^0$ thalassemia (0.09 per 100 person-years and 0.08 per 100 person-years, respectively) [1].

In CSSCD, strokes were classified as ischemic, hemorrhagic and transient ischemic attacks (TIAs). Ischemic strokes disproportionately affect the youngest and oldest patients with SCD, while hemorrhagic strokes have the highest prevalence in patients between the ages of 20 and 29 years with SCD [1].

Silent infarcts, defined in CSSCD as an increased T2 signal abnormality on multiple views on MRI without corresponding neurologic deficit, were identified in 21.8% of children between 6 and 19 years of age with SCD-SS [2]. Further studies have shown an estimated cumulative incidence of silent infarct as high as 37% in patients with SCD by 14 years of age [3]. The increased prevalence of silent infarcts may be due to changes in the definition of silent infarct, as well as improvements in MRI techniques. Currently, the most widely accepted definition of silent infarct in pediatric patients requires an abnormality of at least 3 mm in greatest linear dimension visible on at least two planes of T2-weighted MRI sequences [4].

The pathogenesis of silent infarcts appears to begin very early in life. Screening MRIs performed at early ages have demonstrated a prevalence of silent infarcts of 13% in infants and toddlers with SCD-SS at an average age of 13.7 months [5]. Other studies have demonstrated silent infarcts in 27.7% of children with SCD-SS less than 6 years of age [6]. In a longitudinal follow-up of the CSSCD cohort, silent infarcts progressed in number and in size over time [2]. In girls with SCD-SS, most lesions appeared by 6 years of age. In boys with SCD-SS, new lesions continued to appear through to 10 years of age. Of those children in this cohort with normal MRIs at baseline, only 2.5% developed new silent infarcts during the follow-up period, compared with 24.5% of those with silent infarcts already present on their baseline MRI [2]. Although initially felt to be clinically 'silent', research has demonstrated an association between silent infarcts and neurocognitive deficits and academic difficulties in pediatric patients [7–13]. It is unclear whether the age at which a silent infarct occurs impacts neurocognitive outcomes.

In adults with SCD, silent infarcts are defined as 5-mm signal hyperintensity in T2-weighted images with corresponding hypointensity in the T1-weighted images due to the propensity for adults to naturally accumulate T2 hyperintensities as a function of the aging process [14]. In a large study comparing neuroimaging abnormalities and neuropsychiatric outcomes in adults with SCD-SS without a history of overt stroke to healthy controls, individuals with SCD-SS were found to perform worse on tests of global cognitive functioning, working memory, processing speed and executive function [14]. Although the proportion of SCD-SS patients with evidence of silent infarcts was higher than healthy controls, it was not statistically significant, nor was it independently correlated with poorer performance on cognitive

tests [14]. Other studies have demonstrated a prevalence of silent infarct in up to 50% of the adults with SCD-SS, although there is substantial variability in the literature [15,16].

Pathophysiology

Ischemic strokes

Strokes in patients with SCD were traditionally hypothesized to be due to increased viscosity of sickled red blood cells causing stasis and downstream ischemia. However, this hypothesis does not fully explain the etiology of the large vessel CVAs that mark this disease. Although vasculopathy and stenosis of the large arterial branches off of the circle of Willis are frequently seen in patients with SCD-SS or SCD-Sβ^0 [17], multiple other factors, such as impaired vascular autoregulation, contribute to the ultimate event.

Current research suggests that early events in the pathogenesis of stroke are the attachment of sickled cells to vascular endothelium where endothelial activation and damage occur [18]. Patients with SCD have been shown to have high expression of endothelial and erythrocyte adhesion molecules [19], which have been implicated in the pathogenesis of vaso-occlusion including integrins [20,21], endothelial selectins [22,23], soluble adhesion molecules [24] and immunoglobulin family members [25]. Procoagulants, such as von Willebrand factor [26], fibrinogen [27] and thrombin [28], have also been implicated. Chemoattractants, cytokines and adhesion molecules recruit leukocytes that can cause microvascular obstruction and ischemia [29,30]. This pro-inflammatory state leads to intimal hyperplasia, fibrosis and, ultimately, thrombosis [18].

Additional research into the role of nitric oxide (NO), a locally acting vasodilator, has implicated NO and NO-related pathways as part of the pathophysiology of stroke. Much of the research has focused on pulmonary hypertension (PH), a vascular complication of SCD similar to stoke that is associated with increased risk of mortality in adults [31]. In patients with PH, hemolysis of sickled cells leads to increased plasma-free hemoglobin, which scavenges local NO [32,33]. Furthermore, patients with SCD have a relative depletion of L-arginine compared with healthy controls, due to increased release of erythrocyte arginase from sickled red blood cells. The lack of L-arginine, a substrate for NO production, prevents reconstitution of NO in the acute setting. Among patients with SCD, arginase activity has been demonstrated to be highest in those with concomitant PH and is correlated with severity of PH [31]. A recent review noted that further disruption of the arginine–NO pathway due to the downstream effects of uncoupling of NO synthase, formation of polyamines and L-proline, competition for intracellular transport and overproduction of reactive oxygen species may have roles in the development of sickle cell-related pulmonary vasculopathy [32], although its role in stroke is less clear. Supporting this mechanism is the evidence that chronic transfusion therapy (CTT), which has long been the treatment for primary and secondary stroke prevention, has been shown to decrease levels of free plasma hemoglobin [34] and decrease the rate of hemolysis [35,36]. Additionally, lactate dehydrogenase level, a marker of intravascular hemolysis, has been showed to correlate significantly with transcranial Doppler (TCD) ultrasound velocities, a marker of stroke risk in children with SCD-SS [37].

Hemorrhagic strokes

Imaging studies have demonstrated a high prevalence of cerebral vasculopathy in patients with SCD. Patients with SCD have been shown to develop cerebral aneurysms, although their exact prevalence is unknown. Aneurysms are the most common identified cause of hemorrhagic stroke in adult patients with SCD [38]. Compared with patients without SCD, aneurysms in SCD patients are often multiple, have an increased propensity for the posterior cerebral circulation and may be prone to rupture at smaller sizes [39]. Moyamoya disease, a progressive stenosis of the internal carotid arteries resulting in the formation of fragile arterial collaterals, has been found to be present in 20–35% of the patients with SCD who undergo cerebral angiography [40]. If present, moyamoya syndrome is an indication of severe cerebrovascular disease. Patients with this finding are at high risk of recurrent stroke in spite of the initiation of CTT for secondary stroke prevention [41].

Silent infarcts

Silent infarcts may represent a different pathogenesis from either ischemic or hemorrhagic strokes as they involve small vessels in watershed distributions instead of the larger cerebral vessels [42]. Their watershed distribution suggests defective regulation of cerebral perfusion pressure or diminished reserve as potential physiologic mechanisms [43,44]. However, these theories are under active research. Further supporting a difference in pathogenesis, transcranial Doppler ultrasound velocities are not predictive of risk of silent infarct, unlike with overt ischemic stroke [45]. Additionally, silent infarcts may continue to progress in spite of initiation of CTT [46].

Risk factors

Ischemic strokes

The CSSCD identified several risk factors for ischemic stroke in patients with SCD including prior TIA, frequency of acute chest syndrome (ACS), ACS in the 2 weeks preceding the event, and increased systolic blood pressure [1]. Prior silent infarct has also been found to increase the risk of ischemic stroke 14-fold in pediatric patients with SCD [15,47]. Nocturnal hypoxemia (<90%) has been associated with an increased risk of CVAs and other CNS events in patients with SCD-SS [48]. Studies have further shown that there is a high incidence of sleep disordered breathing in patients with SCD [49], and one large cohort study using Medicaid data on 768 children with SCD showed a decreased rate of outpatient visits, emergency room visits and inpatient hospital days for stroke and TIAs in children who had undergone adenotonsillectomy [50].

Various imaging techniques have been used to prospectively identify that pediatric patients with SCD who are at risk for ischemic stroke. TCD ultrasound, which measures the time-averaged mean of the maximal (TAMM) velocity in large

intracranial arteries, is a powerful, noninvasive tool that can be utilized to classify an individual patient's risk of stroke [51]. Children with SCD-SS with abnormal velocity (TAMM: ≥200 cm/s) in the middle cerebral artery or distal internal carotid artery or its bifurcation have a 40% risk of stroke within 40 months. Children with TAMM velocities of 170–199 cm/s (conditional TCD) have a modestly elevated risk of stroke of approximately 7% in the subsequent 40 months, while those with normal studies (TAMM: <170 cm/s) have the lowest risk of stroke (<1% per year) [52,53]. Children with abnormal TAMM who also have evidence of silent infarcts or brain magnetic resonance angiography (MRA) abnormalities are at the highest risk of stroke [42,54].

Extracranial internal carotid artery vasculopathy has also been associated with ischemic strokes and silent infarcts [55,56]. However, many of these children have concomitant intracranial vasculopathy. Further research is necessary to determine its prognostic significance and implications for intervention.

In children with SCD-SC, TAMM velocities are significantly lower than in those with SCD-SS and have not been shown to predict stroke risk [57]. In adult patients with SCD, TCD velocities have been shown to be higher than adult controls without SCD [58,59]; however, they are lower than in children with SCD and have not been found to be predictive of vascular stenosis or CVAs [60].

Hemorrhagic strokes

The CSSCD also identified risk factors for hemorrhagic stroke including older age, low steady state hemoglobin and high steady state leukocyte count [1]. A multicenter, retrospective case–control study of pediatric patients with primary hemorrhagic stroke compared with those with ischemic stroke demonstrated that hemorrhagic stroke was associated with older age, a reported history of hypertension, transfusion within the 2 weeks prior to the events, higher frequency of admission to the hospital for acute pain event in the preceding year, and treatment with corticosteroids or nonsteroidal anti-inflammatory medication within 2 weeks of the event [61].

Silent infarcts

Associations have been found between silent infarcts and leukocytosis, low pain event rate, SEN haplotype and prior history of seizures [62]. Additional studies have shown an association between silent infarcts and lower baseline hemoglobin [3,63], as well as identified higher systolic blood pressure and male gender as additional risk factors [3,63]. In patients under 6 years of age, silent infarcts were associated with lower rates of vaso-occlusive pain and ACS [6]. No association has been found between silent infarcts and abnormal TCD velocity [45] or hemoglobin F percentage [62]. Two studies have found associations between vasculopathy identified using MRA and silent infarcts [6,64], but this requires further study. Glucose-6-phosphate dehydrogenase deficiency has also been associated with silent infarcts [64]; however, its role remains unclear due to conflicting data on its association with other CNS risk factors and ischemic strokes [3,65–67].

Concomitant α-thalassemia in patients with SCD is associated with reduced rates of silent infarct and stroke [1,35,68,69], as well as with decreased frequency of abnormal TAMM velocities [65]. Risk factors for the various types of CVAs are reviewed in Table 1.

The phenotypic variation among patients with SCD with regard to CVAs indicates that there are additional disease modifiers. Sibling studies of patients with SCD have shown significant correlation in TCD values [70], as well as in the frequency of CVA [71]. Genetic studies have found that polymorphisms in the promoter for *TNF-α* were associated with a greater than threefold increased risk of large vessel stroke in children [72,73] and various HLA alleles have been shown to convey differential risk for large and small vessel strokes, further suggesting different underlying pathophysiologic mechanisms [74,75]. Multiple other candidate genes suspected of modifying stroke risk are currently under study, including *VCAM-1* [72,76] and *IL4R* [72]. However, as the effect of individual polymorphisms on overall stroke risk may be moderate, there is a need for simultaneous evaluation of multiple candidate genes in a combinatorial fashion in order to predict presymptomatic vasculopathy [77,78].

Clinical presentation

Acute ischemic stroke often presents as it would in others without SCD. Frequent symptoms include motor deficits including hemiparesis and monoparesis, aphasia or seizure [79,80]; however, symptoms may vary by the size and location of the stroke. Posterior circulation strokes may present with ataxia, headache, vertigo or vomiting. In young children, symptoms may be subtle and mistaken for other illnesses. Hemorrhagic stroke may present with acute, severe headache. TIAs may present similarly to acute ischemic strokes; however, they spontaneously resolve.

Fortunately, of those pediatric patients with SCD with an overt stroke, many are able to become physically independent with few difficulties with self-care activities [79]. However, most demonstrate persistent cognitive deficits that range from language problems and reduced intelligence quotient to moderate mental retardation [81]. Evidence of poor educational attainment and neurocognitive disabilities in this population has been an impetus to implement ongoing evaluation and standardized cognitive rehabilitation programs [82,83].

Acute treatment of stroke

Few studies have investigated the optimal medical management for acute ischemic stroke in pediatric patients with SCD and it is unclear if initial management plays a role in later outcomes. The initial assessment of a pediatric patient with SCD where there is a clinical concern for stroke should focus on stabilization, vital sign support and oxygenation. A history and physical exam, including a complete neurological exam, should be performed. Initial laboratory evaluation should include a complete blood count with differential and reticulocyte count, coagulation studies, hemoglobin quantification to determine the hemoglobin S percent, blood chemistries and evaluation for meningitis if clinically indicated. The patient's blood should be typed and screened for any red blood cell antibodies. A noncontrast CT

scan of the brain should be performed as soon as possible if there is a concern of acute hemorrhage. However, CT scans are limited in their ability to detect acute infarct. If there is enough clinical concern, MRI/MRA/magnetic resonance venography with diffusion-weighted imaging is the preferred modality for evaluating ischemic stroke, vasculopathy and eliminating dural venous sinus thrombosis as the etiology of the event [84]. Intravenous fluids should be carefully monitored to maintain euvolemia. Additional supportive care measures to control glucose, maintain cerebral perfusion pressure and reduce fever should be performed. Currently, there is no role for anticoagulation or antifibrinolytics as they have not been studied in patients with SCD and may increase the risk of hemorrhagic conversion.

Table 1. Risk factors for cerebrovascular events.

Ischemic stroke	Hemorrhagic stroke	Silent infarcts
Prior TIA	Low hemoglobin	Low hemoglobin
Frequent/recent ACS	High white blood count	High white blood count
Increased SBP	History of hypertension	Increased SBP
Prior silent infarct	Older age	History of seizures
Nocturnal hypoxemia (<90%)	Recent PRBC transfusion	Male gender
High velocity blood flow on TCD	Frequent admissions for VOE Recent treatment with steroids or NSAIDs	SEN haplotype

ACS: Acute chest syndrome; PRBC: Packed red blood cell; SBP: Systolic blood pressure; TCD: Transcranial Doppler; TIA: Transient ischemic attack; VOE: Vaso-occlusive events.

A manual or automated exchange transfusion should be performed with a goal of decreasing the hemoglobin S to below 30% and increasing the hemoglobin to 10–12 g/dl to improve oxygen carrying capacity. However, if exchange transfusion leads to significant delays in treatment initiation, straight transfusions may be used to increase the hemoglobin to approximately 10 g/dl. Increasing the hemoglobin higher than 12 g/dl in the acute setting may lead to increased viscosity and should be avoided. In a retrospective, multicenter cohort study of pediatric patients with SCD presenting with stroke, those who received a straight transfusion rather than exchange transfusion as part of their initial management had a fivefold greater risk of secondary stroke over the subsequent 5 years in spite of initiation of CTT [80].

Patients with acute hemorrhagic stroke should receive similar supportive care measures as clinically indicated. Additionally, acute neurosurgical evaluation is required as there may be a role for placement of coils or embolization if an aneurysm is identified [85]. Depending upon the size of the hemorrhage, a patient may require surgical decompression and control of vasospasm as well [86].

Secondary stroke prevention

CTT has long been used to prevent secondary ischemic strokes. Transfusions are generally administered every 3–4 weeks with the goal to maintain the hemoglobin S under 30% of the total hemoglobin. The post-transfusion hemoglobin is increased to between 10 and 12 g/dl. Without treatment, the risk of recurrent stroke is approximately 70% [38], but with CTT, that risk is reduced to 10–20% [87–89]. In a retrospective review of 137 pediatric patients treated at 14 centers with CTT due to a history of ischemic stroke, 22% of the patients had a recurrent stroke (2.2 per 100 person-years) [88]. However, vasculopathy and silent infarcts, when present in patients who also have a history of acute stroke, can progress despite optimal transfusion [46,90–93]. Children with more severe vasculopathy at initiation of CTT appear to have a greater risk of progression. This supports the need for routine TCD surveillance and the use of primary stroke prevention strategies (see below).

Attempts to discontinue CTT after periods of up to 10–12 years resulted in a high rate of recurrent stroke, so lifelong treatment is recommended [94]. CTT is complicated by potential risks of alloimmunization [95], infectious disease exposure [96] and iron overload [97], which has prompted a search for alternative therapies. Erythrocytapheresis, automated red blood cell exchange, can limit iron loading and obviate the need for chelation therapy, but is associated with a two- to three-fold greater donor exposure and requires adequate venous access [98–101]. Strategies that relax transfusion goals after several years to maintain a hemoglobin S under 50% have reduced the amount of blood products required and the resulting iron load without an increased risk of infarctive stroke; however, the long-term effect on progression of vasculopathy and silent infarcts remains to be studied [102,103].

Single institutions have explored hydroxyurea as an alternative therapy for secondary stroke prevention in pediatric patients with SCD in countries where blood products are scarce. One institution in Jamaica followed 43 children with SCD with evidence of acute ischemic stroke between 2000 and 2009 [104]. Of these, ten initiated therapy with hydroxyurea alone. In those patients, the incidence of recurrent stroke was two per 100 person-years, compared with 29 per 100 person-years in the untreated group [104].

In a single-center study, 35 children with SCD and a history of stroke were transitioned to hydroxyurea after a mean of 56 ± 33 months of CTT [105]. The rate of stroke recurrence was 5.7 events per 100 person-years. When an overlap period of transfusions and hydroxyurea was employed, the recurrence rate was further reduced to 3.6 events per 100 person-years. In addition, 26 subjects were able to tolerate phlebotomy to reduce iron load [105]. This set the stage for the multicenter stroke with transfusions changing to hydroxyurea (SWiTCH) trial. In that study, subjects who had initiated CTT after an overt stroke and had evidence of iron overload were randomized to either continue CTT or transition to hydroxyurea and scheduled phlebotomy [106]. While increasing to the maximally tolerated dose of hydroxyurea, subjects continued to receive transfusion therapy. The primary end point was a composite end point allowing for a slight increased stroke risk, but with superior removal of iron as measured by liver iron concentration. In total, 10% of subjects

(n = 7) randomized to the hydroxyurea arm developed strokes; however, none of the subjects who continued with CTT had strokes. In addition, no significant difference in liver iron concentration was noted at the planned interim analysis, although the long overlap period of transfusions in the hydroxyurea arm may have contributed to the lack of significant improvement in iron reduction. These findings led to the study's premature closure by the Data and Safety Monitoring Board [106]. Therefore, chronic red cell transfusion therapy remains the mainstay of secondary stroke prevention. See Table 2 for a summary of stroke recurrence rates with hydroxyurea [104–109].

Moyamoya disease, if identified, predicts a high risk of recurrent stroke in patients with SCD in spite of optimal transfusion therapy [41]. Several case series have shown benefit of neurosurgical revascularization procedures in this setting; however, those series have had small numbers of patients with limited follow-up [110,111].

For patients who have suffered a hemorrhagic stroke, there is no clear role for CTT in the prevention of a secondary hemorrhagic stroke [61]. Placement of clips or coils may prevent ongoing bleeding if an aneurysm is identified [86].

Currently, limited data on the treatment or prevention of silent infarcts is available. Among children with both abnormal TCD and silent infarcts, those who received transfusion therapy were significantly less likely to develop new silent infarcts [42]. A subset of those patients later had transfusions discontinued and demonstrated an increased frequency of progression of silent infarcts compared with those who continued transfusion therapy [112]. However, a recent study looking at transfusion in patients with overt stroke found progression of silent infarcts in 25% of subjects despite being optimally transfused [46]. The role of transfusion therapy for children with silent infarcts without abnormal TCD is currently being explored in the SIT trial (ClinicalTrials.gov identifier: NCT00072761) [201]. Subjects are randomized to observation or monthly transfusion therapy. The primary outcome is progression of silent infarcts or overt stroke. This study has completed recruitment, but is not expected to complete data analysis until December 2013 [4]. Studies investigating the effect of hydroxyurea on silent infarcts are lacking.

Hematopoietic stem cell transplant (HSCT) is currently the only curative therapy for SCD. In 2001, a multicenter investigation of HLA-identical sibling bone marrow transplantation (BMT) for pediatric patients with symptomatic SCD demonstrated the safety and efficacy of myeloablative BMT in this population [113]. Of the 59 subjects who underwent BMT, 50 had stable allografts and were free of SCD complications at a median follow-up of 42.2 months (range: 11.8–115 months) following transplantation [113]. Further follow-up of this cohort of subjects demonstrated a 5-year event-free survival of 85% and overall survival of 97% [114]. However, because of an increase in neurologic events during transplant, especially in those subjects with prior history of ischemic stroke, this study established the need for specific supportive care guidelines for this population including seizure

Table 2. Rates of stroke recurrence with hydroxyurea.

Study (year)	Type of study	Use of HU	Individuals (n)	Mean age (years)	Duration of CTT prior to HU (months)	Maximum tolerated dose of HU (mg/kg/day)	Rate of stroke recurrence	Ref.
Sumoza *et al.* (2002)	Prospective study	HU alone or after CTT	5	Range: 3–16	2 subjects received CTT prior to HU for 31 and 33 months	38	No recurrent events after 42–112 months of observation	[108]
Lefèvre *et al.* (2008)	Retrospective case series	HU alone	4	NR	NA	NR	2.9 per 100 person-years	[109]
Ali *et al.* (2011)	Prospective study	HU alone	10	7.7 ± 2.7	NA	25.4 ± 3.4	2 per 100 person-years	[104]
Ware *et al.* (1999)	Prospective study	HU after CTT	16	12.1 ± 4.9	56 ± 36	24.9 ± 4.2	6.8 per 100 person-years	[107]
Ware *et al.* (2004)	Prospective study	HU after CTT	15	13.1 ± 4.9	50 ± 33†	26.0 ± 4.3	7.4 per 100 person-years	[105]
Ware *et al.* (2004)	Prospective study	HU after CTT with transfusion overlap	20	11.1 ± 2.9	50 ± 33†	27.2 ± 5.1	3.6 per 100 person-years	[105]
Ware *et al.* (2012)	Randomized clinical trial	HU after CTT with transfusion overlap	67	13.0 ± 4.0	88.8 ± 45.6	26.2 ± 4.9	5.6 per 100 person-years	[106]

†All subjects in the study included. Duration of chronic transfusion therapy for each of the two cohorts of subjects not reported.
CTT: Chronic transfusion therapy; HU: Hydroxyurea; NA: Not applicable; NR: Not reported.

prophylaxis, strict hematologic goals (maintenance of hemoglobin between 9 and 11 g/dl and platelets at ≥50,000/µl), rapid correction of hypomagnesemia and strict control of blood pressure [115]. Of the 29 subjects with stroke or CNS disease as their indication for BMT, 25 experienced stable engraftment with no further overt CNS events or progression of disease on MRI at a median of 3.2 years after transplant. Among the ten subjects with silent infarcts on baseline MRI prior to transplant, seven out of eight with follow-up MRIs performed a median of 1.7 years after transplant had smaller or stable lesions. In addition, no CNS disease developed following HSCT in ten subjects with prior normal MRI [116]. A study in France of 87 pediatric and young adult subjects with SCD who received HLA-matched sibling BMTs using a variety of conditioning regimens between 1988 and 2004 showed variable effects on cerebrovascular stenosis (five resolved, 16 were unchanged and two progressed), persistence of vascular occlusions and worsening cortical atrophy in two subjects, but a significant reduction in arterial velocities in all 49 patients who were assessed [117]. Of those with a history of stroke (n = 36), one subject experienced a TIA 10 days after transplantation and one died from intracranial hemorrhage 32 days after transplant [117]. Overall, the effect on pre-existing CNS disease was favorable.

Historically, the frequency of HSCT in this population is limited by the number of HLA-matched sibling donors, availability of matched unrelated donors, high frequency of prior alloimmunization, resistance from families, lack of psychosocial support, high risk of acute toxicity during transplant and graft-versus-host disease [118,119]. Advances in conditioning regimens [117] and improved understanding of the therapeutic value of mixed chimerism in nonmalignant conditions [120–122] may reduce the transplant-related toxicity and increase the frequency with which HSCTs are performed in this population. Currently, there is limited experience with cord blood transplants (CBT) in patients with SCD; however, this would increase the potential donor pool and allow for a greater degree of HLA mismatching. Several case reports and case series have shown that outcomes with regard to engraftment and graft-versus-host disease are better in those receiving related CBT compared with those receiving unrelated CBT [123–129]. However, the CBT arm of SCURT was suspended after five out of eight subjects who received unrelated CBT in the setting of reduced-intensity conditioning experienced graft rejection by day 42 post-transplant [130]. Experience with haploidentical or mismatched stem cell transplantation is even more limited than CBT; however, this also would increase the potential donor pool available [131–133].

As the mechanism of stroke has been studied more closely, potential novel therapeutic targets have been identified. NO and sildenafil are being studied as therapeutic options for patients with PH [134]. Although initial studies of sildenafil as potential treatment for PH in patients with SCD were promising, a randomized, double-blind, placebo-controlled study of sildenafil in adult SCD patients with PH was closed early due to increased frequency of admission due to vaso-occlusive events with no evidence of treatment effect [134,135]. In mouse models, supplementation with arginine has been shown to decrease hemolytic rate and NO scavenging [136]. Unfortunately, results of human studies remain inconclusive [137,138]. Statins, which increase NO and decrease leukocyte adhesion, are also being studied [139]. Senicapoc, a Gardos channel blocker that prevents dehydration of red blood cells, has been shown to increase hemoglobin and hematocrit in adult patients with SCD due to decreased hemolysis. However, a recent Phase III trial was closed early due to failure to achieve their primary end point of decreased vaso-occlusive events [140]. Currently, the mainstay for acute treatment of stroke and prevention of secondary stroke in pediatric patients with SCD remains CTT.

Primary stroke prevention

As the utility of TCD as a reproducible, noninvasive and highly predictive method of prospectively identifying risk of stroke in patients with SCD became known, studies focused on the ability to prevent first stroke in pediatric patients with SCD. In 1998, Adams *et al.* published the results of STOP, which identified children with SCD-SS or SCD-Sβ^0 as being at high risk for stroke based on blood flow velocity in the internal carotid artery or middle cerebral artery [141]. Subjects with a TAMM velocity of greater than or equal to 200 cm/s (abnormal) were randomly assigned to CTT to maintain the hemoglobin S percentage at under 30% versus observation. Overall, 9.7% of the screened subjects had abnormal TCD results. Among subjects randomized to standard treatment, ten cerebral infarctions and one intracerebral hematoma occurred compared with only one infarction in the group receiving CTT representing a 90% reduction in the risk of stroke with prophylactic transfusion therapy [141]. This led to premature closure by the Data and Safety Monitoring Board with the recommendation that all children with abnormal TCD be treated with CTT.

Current guidelines for the care of patients with sickle cell disease recommend annual screening with TCD in patients with SCD-SS or SCD-Sβ^0 between the ages of 2 and 16 years. Velocity measurements ≥200 cm/s are considered abnormal and the TCD should be repeated within 1–2 weeks to confirm the finding. If the velocity remains abnormal, CTT is recommended. Velocities of ≥220 cm/s do not need to be confirmed. It is imperative to initiate CTT as early as possible in children with abnormal TCD readings to protect against stroke. In STOP, one subject developed a stroke while awaiting randomization and was withdrawn from the study [141].

The recommendations for the timing of rescreening with TCD are based on the need to identify children who convert from a lower risk TCD to a higher risk TCD in a timely fashion so as to implement a proven prevention strategy as soon as possible in those who convert to abnormal velocities. In a follow-up study of children who were screened to participate in STOP whose initial TCD velocities were not abnormal at the time of screening, 9% converted to abnormal velocities during the 22-month follow-up period. Conversion to an abnormal TCD was highest in younger children and in those with a 'high conditional' TAMM velocity (185–199 cm/s) at first exam [142]. Figure 1 shows the authors' current screening protocol for children with SCD.

For high conditional TCD, the study is repeated within 6 weeks for children under 10 years old and within 3 months for children 10 years and older. Children with low conditional TCD (170–184 cm/s) have their TCD repeated within 3–6 months, while those with a normal TCD (<170 cm/s) without other risk factors have their TCD repeated annually [143].

TCD has been shown to be feasible in infants with SCD as young as 7 months; however, infants have a lower mean velocity than children ≥2 years of age. In 192 infants enrolled in the BABY HUG study, none had a TAMM velocity ≥200 cm/s [144]. It is unclear if a new cutoff can be established to identify those infants at highest risk to develop stroke or abnormal TCD in the future, potentially allowing for even earlier intervention. Interestingly, in the BABY HUG study, which randomized young infants from 9 to 18 months of age with SCD-SS or SCD-Sβ^0 to hydroxyurea or placebo for a 2-year period, the average increase in TAMM velocity was significantly lower in those subjects who had received hydroxyurea. Data regarding the impact this had on future strokes and silent infarcts is still pending [145,146].

The impact of TCD screening and treatment programs on the prevalence of stroke in children with SCD-SS appears to be profound. Studies using hospital-based prevalence data from California (USA), as well as several large single institutions, have demonstrated the effectiveness of the implementation of routine TCD screening on reduction of incidence of stroke in pediatric patients with SCD on a population level [3,147–149]. A recent retrospective analysis of national inpatient admissions data demonstrated a 45% decrease in incidence rates for stroke

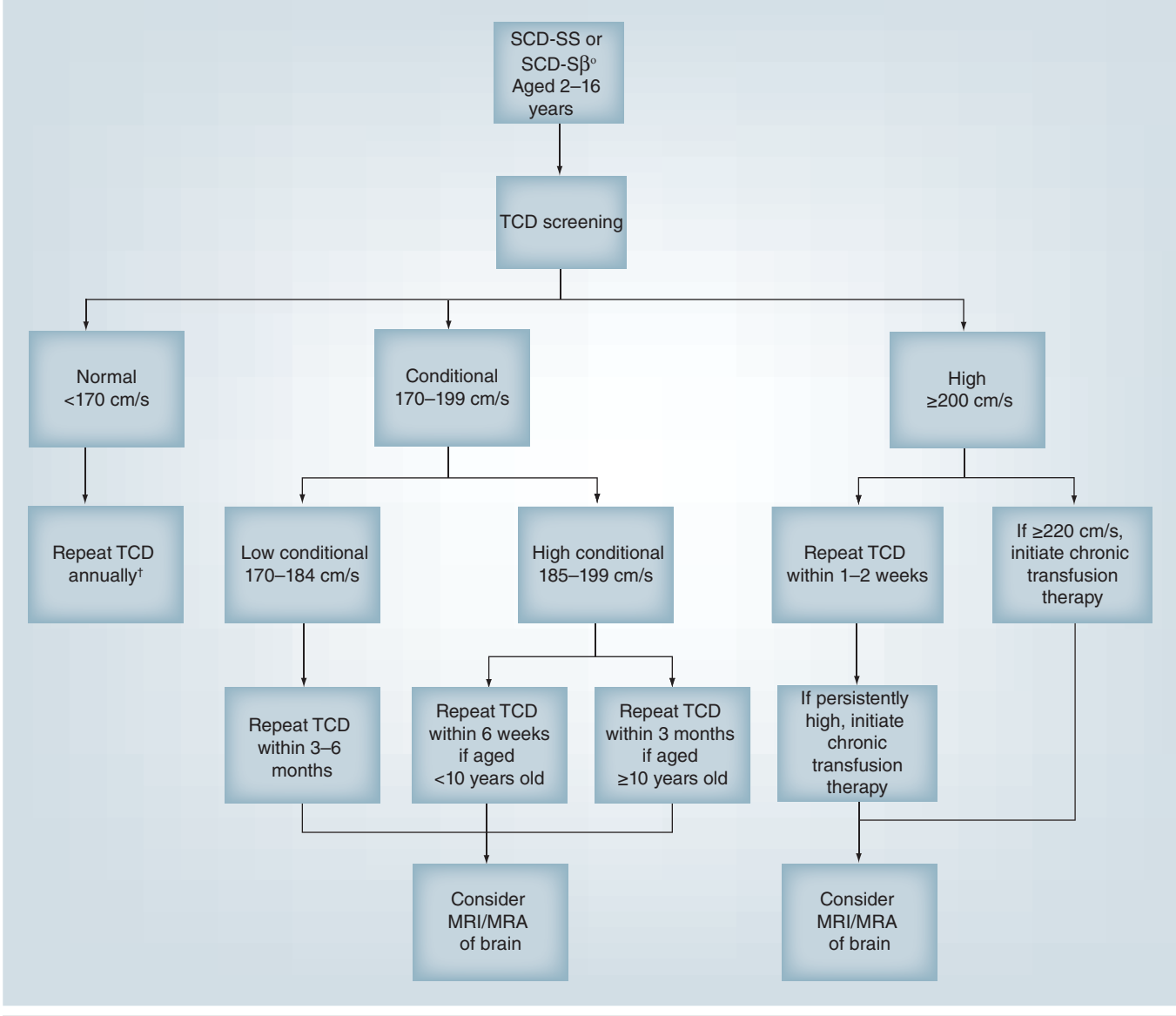

Figure 1. Transcranial Doppler screening recommendations.
†Consider repeating TCD more frequently in those with additional risk factors such as silent infarcts, family history of stroke or abnormal TCD or abnormal MRA.
MRA: Magnetic resonance angiography; SCD-SS: Homozygous sickle-cell disease; TCD: Transcranial Doppler ultrasound.

in pediatric patients with SCD from 1999 to 2009 (the period following STOP results), as compared with 1993 to 1998 (the period prior to STOP results) [150].

Conventional TCD does not rely on direct visualization of the vessels and is considered a nonimaging technique. In contrast, imaging TCD sonography (TCDi), relies on direct visualization of the vessels, which can improve confidence in anatomic location. TCDi can be performed with and without angle correction. With angle correction, the operator can correct for the difference in angle between the course of the artery and the ultrasound beam to provide angle-corrected measurements of velocity [151,152]. To adhere as closely as possible to the original STOP criteria, which used nonimaging TCD, angle correction may not be recommended as there are no large studies establishing appropriate thresholds for intervention [153]. Additionally, studies have shown that with rigorous protocols, TCDi without angle correction may be equivalent to standard TCD [154,155] However, some studies suggest that TCDi velocities without angle correction can be 10–15% lower than standard nonimaging TCD [51,156]; therefore, a lower cutoff of 185 cm/s is often used to define an abnormal study [157]. However, as no trials have compared TCD with TCDi screening techniques for primary stroke prevention, conventional TCD remains the standard of care.

MRI techniques that include T1, T2, FLAIR, diffusion imaging and susceptibility imaging and MRA protocols that include 3D time-of-flight techniques and reconstruction provide accurate, noninvasive, high-quality images of the cerebral vasculature and evidence of silent infarcts [158,159]. As increasing evidence demonstrates the importance of identifying silent infarcts due to their impact upon neurocognitive abilities, some programs have recommended obtaining a screening brain MRI and MRA at least once for school-aged children with SCD-SS [16]. Brain MRI/MRA is also indicated for children with abnormal or conditional TCD velocities, evidence of neurocognitive difficulties or other high-risk features. Follow-up studies are recommended for children with evidence of prior silent infarct or vasculopathy on prior MRI/MRA due to the risk of progressive disease. Functional imaging techniques, such as PET or single-photon emission computed tomography, are being studied in pediatric patients with SCD as they may able to detect perfusion deficits prior to the development of silent infarcts [160]. Additionally, blood oxygen level-dependent MRI sequences, which can differentiate between deoxyhemoglobin and oxyhemoglobin, are being studied for their ability to detect even minor imbalances in oxygen consumption and delivery [161]. These new techniques may allow providers to identify prospectively those patients at the highest risk of developing silent infarcts prior to any impact on neurocognitive outcomes.

Discontinuation of primary stroke prevention strategies

In the STOP 2 trial, children with abnormal TCD velocities without significant vasculopathy on MRA who had received at least 30 months of transfusion therapy with reversion to normal TCD were randomized to either continue with monthly transfusions or discontinue transfusion therapy. Of the 41 subjects removed from transfusion therapy, 14 reverted to abnormal TAMM velocities and two developed overt strokes. Neither of these end points was observed in the group who continued transfusion therapy [162]. As such, the current recommendation is to continue lifelong transfusion therapy. However, given the downsides to transfusion, alternatives are being actively sought.

Several case series and retrospective reviews have found a benefit of hydroxyurea in lowering TCD velocities in patients with abnormal TCD velocities, but no history of stroke [163,164]. As mentioned previously, in the BABY HUG study, TCD velocities increased at a slower rate in infants who received hydroxyurea compared with those who received standard care [145]. A prospective Phase II study of hydroxyurea in 37 children with SCD with at least one TCD velocity ≥140 cm/s demonstrated a significant reduction in TCD velocity after a mean of 10 ± 5 months [165]. Children with the highest velocities at baseline saw the greatest improvement in their TCD velocities. Five out of six subjects with TCD velocities in the abnormal range whose families declined transfusion therapy experienced a reduction in their TCD velocity into the conditional range on hydroxyurea, and 14 out of 15 subjects with conditional baseline TCD velocities showed improvement to the normal range by the end of follow-up (median: 24 months) [165]. This preliminary data set the stage for the TWiTCH study. TWiTCH is an ongoing, Phase III noninferiority trial of daily hydroxyurea versus continued monthly transfusion therapy to prevent progression of TCD abnormalities in patients with SCD who have had at least 1 year of transfusion therapy for primary stroke prevention. Secondary outcomes include evaluation of stroke events in both arms of the study. This study is currently ongoing and it is not expected to complete until December 2016 (ClinicalTrials.gov identifier: NCT01425307) [201].

Sickle cell trait

Although most patients with sickle cell trait are asymptomatic, individuals with sickle cell trait are at increased risk of renal papillary necrosis, hematuria, renal medullary carcinoma, hyposthenuria, splenic infarction, exertional rhabdomyolysis and exercise-related sudden death [166]. Interestingly, in a study of 21 pediatric patients with sickle cell trait, two were classified as having mild abnormalities on MRI and four were identified as having vascular tortuosity. When compared with a population of patients without sickle cell trait, the subjects with sickle cell trait were significantly more likely to have arterial tortuosity and it was correlated with hemoglobin S percent at the time of the evaluation [167]. This was considered mild vasculopathy and has not been replicated. Thus far, no definitive evidence links sickle cell trait with stroke risk, but larger studies are warranted to examine the association.

Expert commentary

Strokes cause significant morbidity and mortality in pediatric patients with SCD. Overt stroke occurs in approximately 10% of unscreened pediatric patients. Fortunately, TCD can identify children at high risk of developing ischemic stroke and CTT is very effective at preventing stroke in the high-risk group. This primary prevention strategy represents a significant advance in

the care of patients with SCD. The rate of overt stroke in children with SCD has declined greatly since TCD screening and treatment programs have been more widely adopted. However, CTT must be continued indefinitely as the risk of stroke rises with discontinuation. Ongoing studies are assessing if alternative treatments, such as hydroxyurea, can be utilized.

Patients with SCD who have had an ischemic stroke have a very high risk of recurrence without prophylactic therapy. CTT as secondary stroke prevention following an initial stroke has been shown to be effective, but must also be continued indefinitely. CTT in pediatric patients requires adequate venous access and patient and parent compliance. Chronic transfusions may also result in alloimmunization, infection and iron overload, so alternative therapies are needed. Unfortunately, a trial of hydroxyurea for secondary stroke prevention was stopped early due to an increased risk of stroke without a benefit of superior reduction in iron burden. BMT with a matched sibling donor or matched unrelated donor is an alternative therapy for lasting protection from further CNS events.

Silent cerebral infarcts occur in approximately a third of children with SCD-SS. These infarcts are not benign, as the nomenclature suggests, but rather are associated with neurocognitive abnormalities and an increased risk of developing overt stroke. The optimal treatment of silent infarcts remains unknown, but ongoing research is addressing this problem.

Five-year view

The results of several large, ongoing studies in SCD will likely transform the treatment of this disease in pediatric patients over the next 5 years. The BABY HUG study has already demonstrated that TCD velocities are lower in subjects who received hydroxyurea compared with placebo. As these subjects age, it should become more clear whether these lower TCD values translate into a lower risk of stroke. Information on the role of hydroxyurea in primary stroke prevention following a period of CTT will be available with the TWiTCH trial analysis.

In the next 5 years, therapies to prevent silent infarcts or halt progression of CNS injury in patients who already have silent infarcts will be tested. The ongoing SIT trial will determine whether CTT is a suitable therapy for the prevention of progression of silent infarcts and neurological injury. Hydroxyurea and other treatments will probably also be tested. Once a therapeutic option is available, recommendations for screening with brain MRI/MRA will be made. Hopefully, as more patients are identified, additional educational and therapeutic services will become available to mitigate the sequelae of silent infarcts. Newer MRI techniques such as blood oxygen-level-dependent imaging and other CNS imaging techniques, such as PET, will potentially be able to identify patients at risk of CNS injury perhaps allowing for earlier intervention.

Novel targeted therapies for prevention and treatment of stroke should become available as the pathways and mechanisms of damage that contribute to cerebral infarcts are elucidated. As BMT in this population becomes safer and more donor sources become available, increased numbers of patients will receive this treatment, perhaps earlier in the course of the disease prior to the development of significant organ toxicity. Gene therapy trials will also offer insight into this curative treatment option.

Key issues

- Ischemic, hemorrhagic and 'silent' infarcts cause significant morbidity and mortality in pediatric patients with sickle cell disease (SCD)-SS.
- Clinical risk factors associated with increased risk of ischemic stroke include prior transient ischemic attack, prior silent infarct, frequent or recent acute chest syndrome, increased systolic blood pressure, nocturnal hypoxemia and abnormal transcranial Doppler (TCD).
- Screening children with SCD-SS with TCD ultrasound is an effective method to identify patients at highest risk of developing ischemic strokes and then initiate a primary prevention strategy. Since the implementation of TCD screening, the rate of first stroke in patients with SCD has decreased.
- Brain MRI/magnetic resonance angiography evaluations for evidence of 'silent' infarcts and/or vasculopathy should be considered for SCD-SS patients with conditional or abnormal TCD, family history of stroke in SCD or evidence of neurocognitive abnormalities.
- The mainstay of primary and secondary stroke prevention is chronic transfusion therapy.
- Currently, research supports indefinitely continuing chronic transfusion therapy as no studies have demonstrated a safe alternative.
- Bone marrow transplant is an alternative for those patients with SCD and a high risk of stroke who have a matched sibling bone marrow donor or significant sequelae from SCD.

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Website

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Medscape EDUCATION Stroke in patients with sickle cell disease

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing a 2-month-old male infant with sickle cell disease (SCD) and an SS genotype. His father also has SCD and has a history of 2 prior strokes. The parents are concerned regarding their son's risk of stroke. What can you tell them regarding the epidemiology of stroke in SCD?
   - ☐ **A** The overall prevalence of stroke among all patients with SCD exceeds 25%
   - ☐ **B** The highest incidence of stroke in childhood is between the ages of 2 and 5 years who have SS disease
   - ☐ **C** Genotype has little influence on the risk of stroke among patients with SCD
   - ☐ **D** Silent infarcts generally do not occur among children under 2 years of age

2. What can you tell these parents regarding risk factors for stroke among patients with SCD?
   - ☐ **A** A recent episode of acute chest syndrome is a risk factor for stroke
   - ☐ **B** A time-averaged mean of the maximum (TAMM) velocity on transcranial Doppler ultrasound (TCD) of 160 cm/s is an important risk factor for stroke
   - ☐ **C** Higher hemoglobin levels can predict an increased risk of hemorrhagic stroke
   - ☐ **D** Abnormal TCD velocity is most effective in predicting the risk of silent infarcts

3. Which of the following options should be part of your primary stroke prevention plan for this child?
   - ☐ **A** The child should be evaluated with MRI now
   - ☐ **B** The child should be evaluated with TCD now
   - ☐ **C** The child should be evaluated with imaging TCD (TCDi) now
   - ☐ **D** TCD should be initiated at age 2 years

4. The patient does well for years but presents with vertigo and fatigue at age 16 years. A workup reveals probable ischemic stroke. Which of the following statements regarding the acute and ongoing treatment of this patient is most accurate?
   - ☐ **A** He should receive an evaluation for acute treatment with tissue plasminogen activator
   - ☐ **B** Acute treatment should include clopidogrel and heparin
   - ☐ **C** Chronic transfusion therapy (CTT) should be considered as a lifelong treatment
   - ☐ **D** Hydroxyurea has replaced chronic transfusion therapy as the best secondary prevention measure against recurrent stroke