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REVIEW

Managing the Cerebrovascular Complications of Sickle Cell Disease: Current Perspectives

Jennifer Light*, Maria Boucher*, Jacquelyn Baskin-Miller*, Mike Winstead*

Pediatric Hematology-Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

*These authors contributed equally to this work

Correspondence: Mike Winstead, Division of Pediatric Hematology-Oncology, University of North Carolina at Chapel Hill, 101 Manning Drive, Chapel Hill, NC, USA, Tel +1 919-966-1178, Fax +1 919-966-7629, Email mwins@email.unc.edu

Abstract: The importance of protecting brain function for people with sickle cell disease (SCD) cannot be overstated. SCD is associated with multiple cerebrovascular complications that threaten neurocognitive function and life. Without screening and preventive management, 11% of children at 24% of adults with SCD have ischemic or hemorrhagic strokes. Stroke screening in children with SCD is well-established using transcranial Doppler ultrasound (TCD). TCD velocities above 200 cm/s significantly increase the risk of stroke, which can be prevented using chronic red blood cell (RBC) transfusion. RBC transfusion is also the cornerstone of acute stroke management and secondary stroke prevention. Chronic transfusion requires long-term management of complications like iron overload. Hydroxyurea can replace chronic transfusions for primary stroke prevention in a select group of patients or in populations where chronic transfusions are not feasible. Silent cerebral infarction (SCI) is even more common than stroke, affecting 39% of children and more than 50% of adults with SCD; management of SCI is individualized and includes careful neurocognitive evaluation. Hematopoietic stem cell transplant prevents cerebrovascular complications, despite the short- and long-term risks. Newer disease-modifying agents like voxelotor and crizanlizumab, as well as gene therapy, may treat cerebrovascular complications, but these approaches are investigational.

Keywords: stroke, silent cerebral infarction, moyamoya syndrome, transfusion, stem cell transplantation

Plain Language Summary

Sickle cell disease (SCD) is an inherited disease that affects the red blood cells (RBCs). A genetic mutation causes the RBCs to change from a flat, round shape into a long, curved "sickle" shape. Sickled RBCs disrupt blood flow and cause injury to the inner lining of the blood cells. Disrupting blood flow to the brain can lead to a stroke, where areas of the brain stop functioning. Strokes can be fatal or cause permanent difficulty speaking, moving, or learning. SCD can also cause silent infarctions or "silent strokes", which actually cause symptoms like difficulty learning. Previously, one-quarter of people with SCD had a stroke by age 45, and many of these strokes occurred in children. Today, strokes in children with SCD can be prevented by checking a transcranial Doppler (TCD) ultrasound every year and providing blood transfusions to children with abnormal blood flow on the TCD. If a person with SCD has a stroke, they need an emergency exchange transfusion to remove the "sickled" blood. Preventing stroke requires monthly blood transfusions for life, but there is interest in other treatments. For certain people with SCD, the medication hydroxyurea can prevent stroke. Stem cell or bone marrow transplantation can cure SCD but may not be possible for everyone. Researchers are studying newer medications and gene therapy, but the safety and effectiveness of these treatments are not yet known. Healthcare disparities also make it harder for many people with SCD to get treatment.

Introduction

Cerebrovascular complications of sickle cell disease (SCD) result from widespread vasculopathy. SCD is an autosomal recessive condition caused by a point mutation in the *HBB* gene, which causes a single amino acid substation in the β-globin chain.[1–4] The resulting hemoglobin S (HbS) variant polymerizes in its deoxygenated state, which causes the characteristic "sickle" shape change in erythrocytes when exposed to hypoxia.[5] Sickled

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erythrocytes interfere with the normal rheology of the microvascular circulation,[6] leading to vaso-occlusion and reperfusion injury.[7] Erythrocytes containing HbS also develop premature senescence[8] and have a shorted lifespan in the circulation, resulting in chronic intra- and extravascular hemolysis.[9] Other factors like sleep disordered breathing may contribute to intermittent erythrocyte sickling and tissue hypoxia.[10,11]

Ischemia-reperfusion injury and hemolysis contribute to an inflammatory milieu[12,13] and endothelial activation.[14] Hypercoagulability results from complex interactions between the coagulation system and the endothelium, including von Willebrand factor release, nitric oxide depletion, upregulation of vascular adhesion molecules like P-selectin,[15] interactions with microparticles, and alterations in the activity of intrinsic anticoagulants like protein C and protein S.[16–19] Chronic vasculitis and hypercoagulability in the carotid, vertebral, and cerebral arteries lead to acute infarctive and ischemic stroke, as well as chronic complications like carotid stenosis and moyamoya syndrome.[20]

Stroke and other complications of cerebrovascular disease represent significant sources of morbidity and mortality for people with SCD. In the longitudinal Cooperative Study of SCD, the estimated prevalence of stroke was 11% by age 19 years and 24% by age 45 years, with the highest risk and lowest age at first stroke among people with homozygous hemoglobin S (HbSS) disease and hemoglobin Sβ^0 (HbSβ^0) thalassemia.[21] Stroke risk is lower among people with hemoglobin SC (HbSC) disease[21,22] Hemoglobin Sβ^+ (HbSβ^+) thalassemia and other compound heterozygous forms of SCD have variable stroke risk, which may be related to degree of anemia and hemolysis.[23]

Strokes in people with SCD frequently involve the distributions of median cerebral arteries, due to chronic narrowing of the internal carotid arteries, but strokes can also involve the vertebrobasilar arteries and other vessels along the Circle of Willis, potentially in association with vascular anomalies like moyamoya syndrome.[24–26] Neurocognitive and psychological complications of cerebrovascular disease affect children and adults with SCD,[27–30] requiring patients, families, and providers to be aware of screening practices and interventions to prevent life-threatening complications and improve quality of life.

Primary Stroke Prevention

Importance of Transcranial Doppler Screening

Primary stroke prevention identifies patients without a known prior stroke that are at high risk for an event. For people with SCD, the cornerstone of primary stroke prevention is routine screening with transcranial Doppler ultrasound (TCD). A landmark series of 283 TCDs in 190 patients with SCD found that stroke correlated with increasing blood-flow velocity in the median cerebral arteries, a marker of vascular narrowing; strokes occurred in 7 of 23 participants with elevated velocity, compared to none with normal velocity.[24] Identifying individuals at high risk allows effective preventive treatment with chronic transfusion therapy. The availability of effective intervention, as well as strong correlation between TCD and more complex studies like cerebral angiography and magnetic resonance imagine (MRI) with magnetic resonance angiography (MRA),[31–33] reinforce the utility, reliability, and importance of TCD as a screening technique.

For children with SCD, screening with TCD should be performed annually in patients aged 2 to 16 years with HbSS or HbSβ^0 thalassemia.[23] TCD is not currently recommended for children with HbSC.[23] For children with other forms of heterozygous SCD like HbSβ^+ thalassemia, TCD may be indicated if the clinical and laboratory phenotype resembles homozygous SCD.[23] TCD measures the time-averaged mean maximum velocity (TAMMV) of blood flow in the bilateral median cerebral arteries; velocities are generally interpreted as normal, conditional, or abnormal. A TAMMV ≥200 cm/s is associated with a 40% increased risk of stroke within 3 years and is the recommended cut-off for abnormal.[23,34] Velocities in the conditional range of 170–199 cm/s are at significant risk of rising into the high-risk range[35] and should be followed closely. Our usual practice is to repeat TCD within 3 months for velocities of 170–184 cm/s and within 1 month for velocticities of 185–199 cm/s.

These values were established by non-imaging TCD. Imaging TCD uses different technical methods and provides slightly different estimates of velocity.[36,37] Current guidelines recommend adjusting the threshold for chronic transfusion based on institutional TCD methods; for imaging TCD, high risk of stroke is indicated by two measurements ≥185 cm/s or any measurement ≥205 cm/s.[23]

Use of TCD may be limited by difficulty in obtaining adequate sonographic windows, inter-operator variability, and inability to obtain accurate readings in the vertebrobasilar arteries.[24,31] For children in whom adequate TCD readings cannot be obtained, despite multiple attempts by experienced operators, our practice is to obtain brain MRI and MRA. In young children these studies usually require sedation, so the treatment team must weigh the risks and benefits collaboratively with the patient's caregivers; pre-anesthesia transfusion is indicated. Healthcare disparities can also affect the availability of comprehensive care for people with SCD.[38] Providers must be aware of societal and racial inequities that affect healthcare for people with SCD.[39] At present, most strokes in children with SCD in the United States are associated with inadequate TCD screening or delayed initiation of chronic transfusion, gaps in care influenced by systemic inequity in healthcare resources.[25]

Even in those with no history of abnormal TCDs, screening MRI may identify silent infarctions. Based on current guidelines, a screening MRI of the brain is appropriate for asymptomatic adults with SCD and for asymptomatic children with SCD who are old enough to undergo MRI without sedation,[23] typically around age 10 years in our practice. It is also important to evaluate children for other treatable comorbidities like sleep disordered breathing, which is likely under-diagnosed and may be a risk factor for stroke.[10,11]

Initiation of Chronic Transfusions

For patients with elevated stroke risk, the standard of care is early initiation of chronic transfusion therapy. The landmark Stroke Prevention Trial in Sickle Cell Anemia (STOP) was a randomized controlled trial that showed the effectiveness of this management strategy. The benefit of chronic transfusion was pronounced, with a 93% reduction in the relative risk of stroke in the transfused group; the trial ended early due to clear evidence of benefit.[40,41] Chronic transfusions must be started in collaboration with the patient and family, including a clear discussion of the risks and benefits. Switching from chronic transfusion to hydroxyurea may be feasible for some patients (see "Duration of Transfusion Therapy and the Role of Hydroxyurea" below). For many patients, however, chronic transfusions are a lifelong intervention,[42] requiring long-term management of complications like iron overload.

The usual approach to therapy is red blood cell (RBC) transfusion every 3 to 4 weeks, maintaining a hemoglobin concentration of at least 9 g/dl and a fraction of HbS <30% between transfusions.[23] This goal is based on the methodologies of STOP and its successor study, STOP2, as well as animal models and blood viscosity studies.[40,42–45] It is not necessary to maintain a normal hemoglobin concentration, as people with SCD adapt to chronic anemia and can be vulnerable to increased blood viscosity; our practice is to maintain a post-transfusion hemoglobin concentration of 10 to 11 g/dl.

Patients receiving chronic transfusion therapy may benefit from exchange transfusion, rather than simple transfusion (Table 1).[46,47] In exchange transfusion, a predetermined volume of blood is removed while RBCs are being transfused, either by apheresis (automated exchange) or by a medical provider (manual exchange).[47] Exchange transfusion provides greater control over the end-transfusion hemoglobin concentration and HbS and can also decrease iron overload, although patients receiving exchange transfusion still require long-term monitoring of iron status. Exchange transfusion is more resource-intensive than simple transfusion. Manual exchange (see "Management of Acute Stroke" below) requires one-to-one care for the duration of the procedure. Automated exchange requires an apheresis device and trained transfusion-medicine staff; priming the apheresis machine requires additional transfusion volume, and the procedure is generally not indicated for small children. Venous access for automated exchange transfusion may require an apheresis-compatible central venous access device; infection risk, MRI compatibility of the access device, and education for patients and caregivers are important in this context.

Transfusion Complications and Iron Overload

Chronic transfusion can be life-saving for people with SCD at high risk of stroke, but there are risks, particularly transfusion reactions and iron overload.[46] Immune-mediated transfusion reactions include acute and delayed hemolytic reactions, as well as alloimmunization. In people with SCD, severe delayed hemolytic transfusion reactions can involve reticulocytopenia and "bystander" hemolysis, leading to profound anemia and a risk of cerebral ischemia.[48,49] Close

Table 1 Approaches to Chronic Transfusion Therapy

Method	Simple Transfusion	Manual Exchange Transfusion	Automated Exchange Transfusion
Goal Hb	10–11 g/dl		
Goal HbS	<30%		
Procedure	Intravenous infusion of 10–15 mL/kg RBCs	Phlebotomize whole blood and transfuse aliquots of RBCs	Remove and infuse RBCs via apheresis
Access required	1 PIV (any size)	1–2 PIVs (moderate size for phlebotomy)	2 PIVs (large) or CVAD
Post-transfusion Hb	Always higher than pre-transfusion	Higher or equal to pre-transfusion	Better control than manual exchange
Likelihood of reaching goal HbS	Moderate	Moderately high	High
Iron loading	Rapid	Moderate	Slow
Time	2–3 hours	3–4 hours	1–2 hours
Availability	Widespread	Widespread	Limited
Cost	Low	Moderate	High

Note: CVAD for automated exchange must be apheresis-compatible and should be MRI-compatible.
Abbreviations: Hb, hemoglobin concentration; HbS, hemoglobin S fraction; RBCs, transfused red blood cells; PIV, peripheral intravenous catheter; CVAD, central venous access device.

collaboration between the patient, the hematology team, and the transfusion medicine service is essential for prompt recognition and management of transfusion reactions, as well as prevention.

Individuals with SCD receiving chronic transfusions are at high risk of alloantibody formation, due to repeated exposure to minor antigens on donor RBCs. Alloimmunization can occur to any minor RBC antigen, and it is essential that a person with a history of alloimmunization not be exposed to the mismatched antigen again. The antiglobulin tests of alloimmunized individuals may normalize over time, so it is essential that hematology and transfusion medicine carefully track transfusion reactions.

In addition to standard matching of the ABO antigens and the Rhesus-D antigen, people receiving chronic transfusions require more extensive matching of minor antigens. The most immunogenic antigens for people with SCD are in Rhesus group (C, c, E, e) and the Kell group (K).[50] All RBC transfusions for people with SCD should be matched at C, E, and K.[46,51] More extended matching of minor RBC blood groups like Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b), and MNSs may further reduce the risk of alloimmunization, but this practice limits the pool of blood donors, and the overall benefit is unclear.[44,46,52] For recently-transfused patients, molecular studies of the peripheral blood are not accurate indicators of the patient's RBC phenotype. In this situation, genetic studies are an alternative. There can be discrepancies between genotype and RBC phenotype.[53]

Iron overload is a ubiquitous complication of chronic transfusions, including exchange transfusion. Because the body does not have a physiological mechanism for eliminating large amounts of iron, the iron from transfused RBCs accumulates in the endocrine organs, liver, and myocardium, which can lead to life-limiting organ dysfunction.[54,55] Serum ferritin levels increase with iron burden[55,56] and should be monitored at least quarterly in patients receiving chronic transfusions. Ferritin levels alone, however, do not predict liver iron concentration (LIC) or other sequelae of iron overload.[56] Additional monitoring of iron burden should include MRI of the liver and of the heart with T2* sequences (which have generally replaced liver biopsy[57]) every 1 to 2 years, particularly in those with a ferritin concentration >1000 µg/l.[46] Chelation therapy is generally indicated for patients with evidence of cardiac iron loading (T2* <20 ms), LIC of at least 3.5 mg/g, or serum ferritin consistently above 1000 µg/l, although other thresholds may be considered.[54,55]

Chelation therapy must be individualized and carefully monitored for efficacy and tolerability. Deferoxamine is highly effective but must be given either intravenously or as a daily subcutaneous infusion, which makes it challenging for home use. Deferasirox is an oral chelating agent that has similar efficacy to deferoxamine and is often more feasible for chronic outpatient use.[58,59] Personal, social, and economic factors may interfere with a person's ability to take their chelating agent as prescribed, and careful follow-up is needed to ensure adherence.[60] Patients taking deferoxamine or deferasirox should be monitored for ocular, hepatic, or renal toxicity, and there is a small risk of opportunistic infection.[61,62] Deferiprone, another effective oral chelating agent, has been studied more recently in people with SCD, although its association with neutropenia may limit its use.[63,64]

Duration of Transfusion Therapy and the Role of Hydroxyurea

For people at high risk of stroke based on childhood TCD, primary stroke prophylaxis is a lifelong undertaking. In the STOP2 trial, stopping transfusion (without other prophylaxis) significantly increased the risks of rising TCD velocity and overt stroke.[42] More recently, the TCD with Transfusions Changing to Hydroxyurea (TWiTCH) trial found that hydroxyurea (hydroxycarbamide) can effectively stabilize TCD velocities in carefully selected patients (Table 2).[65] Participants in TWiTCH did not have a history of stroke, TIA, or severe vasculopathy (defined as carotid stenosis on MRA). All participants received chronic transfusion therapy for at least 12 months, and transfusions overlapped with hydroxyurea until reaching the maximum tolerated hydroxyurea dose. Although the TWiTCH trial included participants who had abnormal TCDs while receiving chronic transfusions, our practice is to only consider changing to hydroxyurea in patients whose TCDs have normalized.

When considering the transition from chronic transfusions to hydroxyurea, the care team must be cautious and partner with the patient and other caregivers. Like transfusion, primary stroke prevention with hydroxyurea must be continued lifelong. Because hydroxyurea is given at home, it is essential that the patient and family understand the need for strict adherence and also that the care team is aware of social factors that may complicate the patient's ability to obtain and

Table 2 Inclusions and Exclusions for Changing Primary Stroke Prevention from Chronic Transfusion to hydroxyurea[65]

Inclusion Criteria	
Diagnosis	Sickle cell anemia
Age	4 to 16 years
Transfusion duration	≥12 months
TCD velocity on chronic transfusion	Normal or abnormal
Required studies	Brain MRI and MRA
Exclusion Criteria	
Clinical history	Stroke
	Transient ischemic attack
	Prior severe vasculopathy
MRA findings	Moderate stenosis in 2 or more arteries
	Any severe arterial stenosis
TCD	Inadequate windows

Note: Our practice is to continue chronic transfusion therapy in patients with persistently abnormal TCDs.
Abbreviations: TCD, transcranial Doppler ultrasound; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography.

take their medication.[66–68] Continued TCD monitoring is necessary. Hydroxyurea appears to be safe for long-term use, but study of its secondary effects, such as infertility, is ongoing.[69–71]

In the randomized, controlled Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG) trial, starting hydroxyurea in early childhood was associated with a slower rise in TCD, compared to placebo.[72,73] An ongoing clinical trial is evaluating the up-front use of hydroxyurea for primary stroke prophylaxis in regions without access to chronic transfusion.[74]

Silent Cerebral Infarction

Silent cerebral infarction (SCI) is an abnormality on MRI that does not correlate with a permanent, focal neurological deficit.[75–77] Based on observational studies with surveillance MRI, the prevalence of SCI rises with age; around 39% of children and SCD and more than 50% of adults with SCD have silent infarctions.[23,76] Despite its name, SCI does manifest clinically as neurocognitive decline, difficulty with school and work performance, and other neuropsychological problems.[27,76] SCI is also a significant risk factor for overt stroke.[75] Recent reports suggest that SCI in people with HbSC disease may be more common than previously recognized.[78,79]

Once SCI is identified, it requires ongoing radiographic and clinical evaluation. Management of SCI is an individual process. The Silent Cerebral Infarct Multicenter Clinical Trial (SIT) showed that chronic transfusion therapy in children with SCI reduced the risks of overt stroke and extension of SCI, with 6% of transfused participants and 14% of control participants developing one of these outcomes.[77] Given the relatively high number needed to treat and the significant transfusion burden, the decision to initiate chronic transfusions for SCI must be individualized.[23] For children with SCI and significant schooling difficulty, for example, the benefits of chronic transfusion may outweigh the risks, although there is no standardized practice. Hydroxyurea may help prevent development and progression of SCI, although evidence is limited.[80–82]

Acute Stroke

Diagnosis

Because individuals with sickle cell disease (especially HbSS and HbSβ^0 thalassemia) are at high risk of stroke, it is important to have a high index of suspicion of stroke in this population. Clinicians should suspect a stroke or transient ischemic attack (TIA) in any patient with an acute neurological deficits, such as hemiparesis, ataxia, or dysphasia; altered consciousness, including new-onset seizures; or acute headache.[83–85] While an emergent, non-contrast-enhanced CT scan of the brain is necessary to evaluate for intracranial hemorrhage, the best evaluation of stroke is MRI with MRA, which can delineate the affected areas and also distinguish other conditions that mimic stroke.[86] Because strokes can arise from the vertebrobasilar circulation, MRA must include the vertebral arteries. Treatment should be initiated within 2 hours of symptom onset.[23] If emergent MRI and MRA are not available, treatment should not be delayed.

Management of Acute Stroke

Due to the pathophysiology of stroke in sickle cell disease, the treatment differs from stroke in other patients. The main goal is to decrease the fraction of HbS to less than 30% using emergent RBC transfusion. Ideally, this is done through an emergency exchange transfusion, which decreases the HbS fraction more efficiently than a simple transfusion and is associated with a five-fold lower risk of secondary stroke.[46,87,88] Emergent exchange transfusion may be complicated by the location and resources of the initial treating facility, as well as vascular access and patient acuity. Rather than delaying treatment, it may be necessary to perform an initial simple transfusion using C, E, and Kell-matched blood, targeting a hemoglobin concentration of 10–11 g/dl, followed by exchange transfusion as soon as possible.[43,46,86] Other medical therapies for stroke like tissue plasminogen activator are controversial in patients with SCD[23] and are not substitutes for transfusion.

Any patient with SCD and an acute stroke should be transferred to an intensive care unit equipped to manage neurological disorders as safely and quickly as possible. Exchange transfusion for acute stroke is best performed by automated apheresis.[46] Depending on local resources, however, manual exchange may be more feasible to avoid delays.

For a manual exchange, the volumes of blood to remove and transfuse can be calculated using the patient's body weight, starting hemoglobin/hematocrit, and starting HbS percentage (assume 100% if unavailable).

Our approach to manual exchange (Table 3) is to estimate the patient's total blood volume (Step 1) and then calculate the desired change in HbS percentage (Step 2) to reach 30% or less. Multiplying these values (Step 3) gives the volume of whole blood to remove. Because transfused RBCs are more concentrated than RBCs in vivo, the erythrocyte volume of the whole blood must be calculated, based on the patient's hematocrit (Step 4); this erythrocyte volume can then be converted to an equivalent transfusion volume using the hematocrit of transfused RBCs, typically around 60% (Step 5). To raise the final hemoglobin concentration requires adding approximately 5 mL/kg of transfused RBCs for every 1 g/dl change in hemoglobin concentration desired (Steps 6, 7). To prevent fluid shifts and cardiopulmonary decompensation, boluses of crystalloid are given before and after exchange, and blood is removed in aliquots over several hours, alternating with transfusion.

For acute ischemic stroke in patients with SCD, there is little role for surgical intervention. Neurosurgical or endovascular intervention may rarely be indicated for intracranial hemorrhage.[89] For patients with critical carotid stenosis or moyamoya syndrome, revascularization procedures may be indicated after recovery from the acute stroke (see "Surgical Revascularization" below).

Other Cerebrovascular Complications Presenting Similarly to Stroke

While emergent management of stroke is appropriate for patients with SCD and acute neurological findings, other disorders can present similarly. Recently, it has been reported that people with SCD are at increased risk of posterior reversible encephalopathy syndrome (PRES).[90] PRES involves altered mental status, headache, vision changes, and a characteristic finding on MRI of posterior cerebral white matter edema.[91] Risk factors for PRES are overrepresented

Table 3 Sample Calculations for Manual Exchange Transfusion

Phlebotomy and tranfusions volumes		**Example: 30-kg child with HbS 90%, Hb 7 g/dl, HCT 21%**
1. Estimate the patient's **total blood volume** (TBV). $TBV = Weight\ (kg) \times 75\frac{ml}{kg}$	1. _____ ml	$30\ kg \times 75\frac{ml}{kg} = \mathbf{2250\ ml}$
2. Calculate the desired **change in HbS** (ΔHbS). $\Delta HbS = 1 - \left(\frac{Goal\ HbS\ (\%)}{Starting\ HbS\ (\%)}\right)$	2. _____	$1 - \left(\frac{30\%}{90\%}\right) = \mathbf{0.67}$
3. Calculate the **whole-blood volume to remove** (WBV). $WBV = TBV \times \Delta HbS$	3. _____ ml	$2250\ ml \times 0.67 = \mathbf{1500\ ml}$
Infuse 10–20 ml/kg of crystalloid before starting. Remove this volume in 4-6 aliquots, 15–30 minutes apart.		Infuse 300-600 ml crystalloid. Remove **300 ml** every 30 minutes for 5 cycles.
4. Calculate the **erythrocyte volume to remove** (EV). $EV = \frac{WBV \times Patient\ HCT}{100}$	4. _____ ml	$\frac{1500\ ml \times 21}{100} = \mathbf{315\ ml}$
5. Convert the EV to a **base RBC volume** to transfuse. $Base\ RBC\ volume = \frac{EV \times 100}{HCT\ of\ transfused\ RBCs}$	5. _____ ml	$\frac{315\ ml \times 100}{60} = \mathbf{525\ ml}$
6. **Add RBC volume** to raise the hemoglobin concentration. $Added\ RBC\ volume = Weight\ (kg) \times (Goal\ Hb - Starting\ Hb) \times 5$	6. _____ ml	$30\ kg \times (10 - 7) \times 5 = \mathbf{450\ ml}$
7. Calculate the **total RBC volume** to transfuse. $Total\ RBC\ volume = Base\ volume + Added\ volume$	7. _____ ml	$525\ ml + 450\ ml = \mathbf{975\ ml}$
Transfuse in 4–6 aliquots, between phlebotomy cycles. Infuse 10–20 ml/kg of crystalloid after completion.		Transfuse **195** ml every 30 minutes for 5 cycles. Infuse 300–600 ml crystalloid.

Notes: There are multiple equations to estimate TBV. Assume a starting HbS of 100% if the patient's HbS is not available. Hematocrit of RBC units and the expected rise in Hb per mL transfused may vary by institution; consult local blood bank.
Abbreviations: HbS, hemoglobin S; HCT, hematocrit; Hb, hemoglobin concentration (g/d); RBC, transfused red blood cells.

among people with SCD, including hypertension, renal disease, immunosuppressant therapy, and blood transfusion,[92,93] Sickle cell disease is a hypercoagulable state,[19] with protein C and protein S dysregulation, and individuals with SCD may also be at an increased risk of cerebral venous sinus thrombosis or thrombotic complications of hospitalization.[94,95]

Stroke Aftercare

Secondary Stroke Prevention

Secondary prophylaxis refers to the prevention of subsequent strokes in patients with a history of stroke. Without preventive treatment after a first stroke, 67% of people with SCD in one series had an additional stroke.[83] The earliest reports of chronic transfusion therapy in SCD were for secondary stroke prevention in the 1970s,[96] an approach supported by subsequent studies.[97,98] Due to the lack of equipoise and the danger of withholding prophylaxis, this practice has not been the subject of controlled trials.[99] As with primary prevention, chronic transfusion for secondary stroke prevention is generally performed every 3 to 4 weeks, maintaining a hemoglobin >9 g/dl and an HbS <30% between transfusions.[23] Even with chronic transfusions, there is a significant risk of subsequent strokes, as well as other neurocognitive complications.[98]

In contrast to primary prophylaxis, hydroxyurea alone cannot be used for secondary stroke prevention. The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial, a randomized controlled trial of hydroxyurea versus chronic transfusion for secondary stroke prevention, studied stroke risk and iron overload.[100] The trial was closed due to futility, after interim analysis found a 10% prevalence of stroke in the hydroxyurea group, compared to 0% in the transfused group, with no difference in iron burden. Chronic transfusion remains the standard of care for secondary stroke prevention in people with SCD.

Meeting the Needs of Stroke Survivors

Overwhelmingly, the evidence points to a consistent cognitive decline among stroke survivors.[30] Routine neurocognitive evaluations are necessary for all patients with a prior stroke,[23] and for children it is important to monitor school performance. Children can succeed in school after strokes, but they may require individualized education plans, and their caregivers may require advocacy and support from the medical team. For young adults with SCD, the transition from pediatric to adult care is associated with a significant risk of worsening disease and death.[101] While death rates from SCD have consistently declined among children, they have risen among adults, likely reflecting socioeconomic obstacles to obtaining access to care.[102]

Adult stroke survivors require continuity of high-quality SCD care, including secondary prophylaxis. Cognitive deficits and psychological comorbidities are associated with greater risk during the transition period[101,103] Recognizing that the transition to adult care is not a single event but an ongoing process that begins during adolescence and continues through early adulthood,[104,105] it is essential that stroke survivors, their caregivers, and their providers actively collaborate to ensure continuity of care, regular neurocognitive assessment, continuation of chronic transfusions, and management of iron overload.

Other Therapies to Modify Stroke Risk

Surgical Revascularization

Neurosurgical consultation is indicated for patients with evidence of a severe vasculopathy, including critical arterial stenosis or moyamoya syndrome on MRA. Moyamoya syndrome is a complication of chronic internal carotid artery occlusion, in which friable collateral vessels develop along the base of the brain; cerebral angiography demonstrates the characteristic “wisp of smoke” enhancement in the collateral vessels.[106] Even with chronic transfusion therapy, the rate of stroke and TIA in people with moyamoya was 41% in one series.[107]

Indirect revascularization procedures like encephaloduroarteriosynangiosis (EDAS) mobilize blood vessels from the scalp into the calvarium to perfuse areas distal to the stenotic vessels; published experience suggests a low risk of serious surgical complications like hemorrhage, perioperative stroke, or functional impairment.[23,108,109] As an adjunct to chronic transfusion therapy, surgical intervention may decrease stroke risk, and a recent review of pediatric patients found that

EDAS facilitated return to school.[110] However, there are no controlled studies of neurosurgical intervention, and the specific revascularization procedure used typically depends on institution and surgeon preference. Any consideration of neurosurgical intervention requires a multidisciplinary collaboration between hematology, neuroradiology, neurosurgery, and the patient.[23]

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) for SCD decreases stroke risk, and a history of stroke is a strong indication to evaluate for HSCT.[111,112] HSCT replaces the patient's hematopoietic progenitor cells and immune system with those of a related or unrelated donor. Cerebrovascular benefits are established by multiple studies, with improved stenosis scores, improved TCDs, and reduction in strokes post-transplant.[113,114] Given the availability of effective disease-modifying therapy, however, the risks of HSCT must be carefully considered.[115–117]

Complications of HSCT include effects of pre-HSCT conditioning therapy, infection, graft rejection, and acute or chronic graft-versus-host disease (GVHD).[118] Late effects of conditioning agents like busulfan and cyclophosphamide include infertility and organ dysfunction.[111] GVHD, which involves tissue destruction by donor lymphocytes, can be life-threatening or interfere considerably with quality of life, especially after unrelated-donor HSCT.[119] Research is ongoing to mitigate these risks, including the use of lower-intensity conditioning regimens and enhanced GVHD prophylaxis with agents like abatacept.[120] Interim analysis from an ongoing clinical trial (Clinicaltrials.gov identifier NCT04018937) of HSCT with reduced-intensity conditioning for young children with SCD and matched sibling donors has reported 100% disease-free survival and no severe GVHD,[121] emphasizing the viability of early HSCT for SCD.

Risks of HSCT are higher among adolescents and adults with SCD, compared to young children. Data from the Sickle Cell Transplant to Prevent Disease Exacerbation (STRIDE) study, however, found that related- or unrelated-donor HSCT is feasible in adults with SCD and severe comorbidities, with 82% event-free survival in this exceptionally high-risk population.[122] The ongoing STRIDE2 trial (Clinicaltrials.gov identifier NCT02766465) will compare the long-term outcomes of HSCT to standard therapy.[123] For adults with matched sibling donors, the National Institutes of Health and other centers successfully piloted HSCT with very low-intensity conditioning, which was associated with 87% to 92% disease-free survival.[124,125] This approach is currently being studied in children (ClinicalTrials.gov Identifier NCT03587272).[126] Regardless of the approach taken, any patient with SCD and a history of stroke or other cerebrovascular disease should be evaluated for HSCT at a center with experience treating SCD.

Investigational Therapies

Voxelotor and Crizanlizumab

Ongoing clinical trials are evaluating voxelotor and crizanlizumab, disease-modifying drugs recently approved in the United States for SCD management, for their effects on cerebrovascular complications (Table 4). Crizanlizumab (SelG1) downregulates endothelial expression of P-selectin, thereby reducing inflammation-mediated cell adhesion.[15,127,128] In the Study to Assess Safety and Impact of SelG1 with or Without Hydroxyurea Therapy in Sickle Cell Disease Patients

Table 4 Active Trials of Disease-Modifying Therapy for Cerebrovascular Disease in the United States

ID	Drug	Design	Outcome	Ages (Years)	Sponsor
NCT04218084	Voxelotor	RCT	TCD	2 to 14	Global Blood Therapeutics
NCT05228834		RCT	Neurocognition	8 to 17	Global Blood Therapeutics
NCT02850406		Single-arm	Pharmacokinetics, hemoglobin, TCD	0.5 to 17	Global Blood Therapeutics
NCT05018728		Single-arm	Hemodynamics	4 to 17	Robert Clark Brown
NCT05334576	Crizanlizumab	Single-arm	SCI	16 and older	Andria Ford

Abbreviations: ID, ClinicalTrials.gov Identification Number; RCT, randomized controlled trial; TCD, transcranial Doppler; SCI, silent cerebral infarction.

Table 5 Active Trials of Gene Therapy for Sickle Cell Disease in the United States

ID	Type	Ages (Years)	Cerebral Vasculopathy	Sponsor
NCT04293185	Gene insertion	2 to 50	Excluded	Bluebird bio., Inc.
NCT05353647		13 to 40	Excluded	David Williams, NHLBI, CIRM, BMTCTN
NCT02247843		≥18	Included	Donald B. Kohn, CIRM
NCT04819841	Gene editing	12 to 40	Included	Graphite Bio, Inc.
NCT04853576		18 to 50	Excluded	Editas Medicine, Inc.
NCT05456880		18 to 35	Excluded	Beam Therapeutics, Inc.
NCT05329649		2 to 11	Included	Vertex Pharmaceuticals, Inc.
NCT05477563		12 to 35	Excluded	Vertex Pharmaceuticals, Inc.
NCT04443907		2 to 40	Excluded	Novartis Pharmaceuticals

Abbreviations: ID, ClinicalTrials.gov Identification Number; NHLBI, National Heart, Lung, and Blood Institute; CIRM, California Institute for Regenerative Medicine; BMTCTN, Bone Marrow Transplantation Clinical Trials Network.

with Pain Crises (SUSTAIN), crizanlizumab decreased vaso-occlusive episodes and acute chest syndrome; there was one stroke in the study group, but cerebrovascular complications were not a primary or secondary endpoint.[129]

Voxelotor stabilizes HbS in the oxygenated state, which inhibits polymerization and erythrocyte sickling.[127,130] Voxelotor is approved in the United States for patients with SCD at least 12 years of age; the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) study did not measure stroke incidence.[131] Stroke was a concern during the development of the drug, due to initial concerns that increasing oxygen affinity would reduce oxygen extraction in sensitive tissues like the brain.[132] The HOPE trial did not report any strokes in the control or voxelotor groups, nor did interim analysis of HOPE Kids (ClinicalTrials.gov Identifier NCT02850406), an ongoing pediatric voxeloator trial that includes TCD velocity as a primary endpoint.[133] TCD velocity is also the primary study question of the HOPE Kids 2 study (ClinicalTrials.gov Identifier NCT04218084).

Gene Therapy

As a monogenic disorder caused by a point mutation, SCD has long been an appealing target for gene therapy.[134] Current approaches to gene therapy involve collecting a patient's hematopoietic progenitor cells via marrow harvest or apheresis; genetically modifying the cells ex vivo by inserting a new transgene or, more recently, direct gene editing; and reinfusing the genetically-modified progenitors after high-dose chemotherapy conditioning.[135] In contrast to allogeneic HSCT, there is no need for a donor and no risk of GVHD. Although gene therapy figures prominently in recent media coverage of SCD,[136,137] this approach to treatment is investigational, and its risks and benefits are still being established. As of November, 2022 multiple publicly- and privately-funded studies of gene therapy for SCD were actively recruiting in the United States; most of these studies exclude people with cerebrovascular disease (Table 5).

Ongoing research will be necessary to evaluate the potential risk and benefits of gene therapy for reducing stroke risk. The largest clinical trial of gene therapy for SCD to date was conducted by the biotechnology corporation bluebird bio, using transgene insertion.[138] Among 35 participants, there was sustained improvement in hemoglobin concentrations, with decreased vaso-occlusive events and no strokes after treatment, including participants with a prior history of stroke. Two participants subsequently developed worsening anemia and cytogenetic abnormalities, and one participant developed leukemia five years after gene therapy.[138,139] In addition to short- and long-term toxicities of conditioning chemotherapy, gene therapy can potentially lead to "genotoxicity", or malignant transformation of the genetically-modified progenitors,[140,141] emphasizing the imperative for long-term follow-up research in this promising field.

Conclusion

Stroke is a devastating contributor to mortality, disability, and loss of neurocognitive function for people with SCD. With access to effective TCD screening and chronic transfusion therapy, which can be substituted for hydroxyurea in selected cases, people with SCD can avoid these complications. Stroke prophylaxis contributes to the overall burden of illness, requiring lifelong management of secondary complications like iron overload, as well as monitoring for neurocognitive complications, vascular malformations, and SCI. People with SCD and cerebrovascular disease can have complex medical and social needs, which require lifelong, comprehensive, patient-centered, multidisciplinary care. Screening and prophylaxis are not available to all people with SCD, due in part to structural disparities in healthcare that must be addressed through policy and advocacy.

There is an ongoing need for research into cerebrovascular complications of SCD, both to address the burdens and limitations of standard treatment and to develop new treatments in a safe but expeditious manner. The past several years have seen a sharp increase in new therapies for SCD, and ongoing clinical trials will evaluate the efficacy of medications like voxelotor and crizanlizumab for stroke prevention. Concurrently, clinical trials in HSCT have the potential to further increase the availability of safe, effective, curative therapy for people with SCD. Gene therapy is a promising area of research and development, which is drawing attention from the media and public; both the long-term benefits of gene therapy for people with cerebrovascular complications of SCD and the long-term risks of genetically modifying marrow progenitors require ongoing study.

As we look toward the future of SCD management, we must not lose sight of the immense suffering caused by cerebrovascular disease for people with SCD and their families; the racial, economic, and geographic barriers to equitable management of these complications; and, above all, the fact that collaboration between policymakers, non-governmental organizations, industry, researchers, medical providers, and people with SCD can overcome this devastating burden of illness.

Disclosure

Dr Maria Boucher reports personal fees from Forma, personal fees from GBT, outside the submitted work. The authors report no conflict of interest in this work.

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