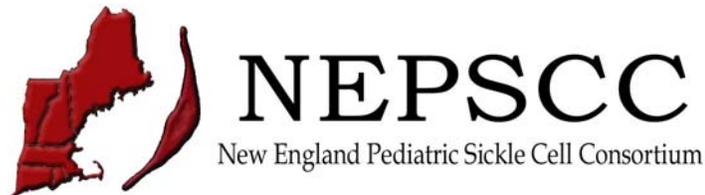


# New England Pediatric Sickle Cell Consortium



## Prevention and Treatment of Stroke for Pediatric Patients with Sickle Cell Disease

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### Disclaimer Statement:

- Hospital clinical pathways are designed to assist clinicians by providing an analytical framework for the diagnosis and treatment of specific medical problems. They may be used for patient education and to assist in planning future care. They are not intended to replace a physician's judgment or to establish a protocol for all patients with a particular condition. The ultimate decision regarding the care of any patient should be made in respect to the individual circumstances presented by the patient.
- Any specific medications and dosing must always be reviewed carefully for each patient in view of any history of drug allergy or adverse reactions.
- This document was based on available research and clinical experience at time of its compilation.
- The following protocol is a regional guideline, and may be adapted by individual institutions as needed.

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## I. Introduction

### A. Definitions

- Silent Stroke – MRI evidence of cerebral ischemic injury in the absence of focal neurologic deficits or history of overt stroke
- Stroke - “acute neurologic syndrome caused by vascular occlusion or hemorrhage with resultant ischemia and focal neurologic symptoms or signs lasting > 24 hours.”
- TIA – transient ischemic attack – above symptoms last < 24 hours
- TCD – transcranial Doppler ultrasound- non-invasive measurement of arterial blood flow velocity

### B. Background

- 10% of patients with sickle cell disease have stroke by age 20 years
- Risk depends upon genotype in Hb SS > Hb S-β thalassemia<sup>0</sup> > Hb S-β thalassemia<sup>+</sup> > Hb SC
- Increased risk ages 2 – 10 years
- Most commonly affects large arterial vessels
- Infarction more prevalent than hemorrhagic stroke in the pediatric population
- Screening for primary stroke risk with transcranial Doppler (TCD) is now considered standard care for patients with Hb SS disease and HbS- β thalassemia<sup>0</sup> disease
- Primary stroke risk can be decreased with chronic transfusion therapy in patients with Hb SS disease and HbS- β thalassemia<sup>0</sup> disease that have repeated TCD velocities >200
- No definitive data on role of MRI/MRA for screening for initial stroke prevention
- Unknown if TCD velocities are predictive of stroke in patients with other sickle syndromes (i.e. Hb SC Disease and HbS- β thalassemia<sup>+</sup> Disease)
- Not known what preventative therapy would be effective in preventing stroke in Hb SC Disease and HbS- β thalassemia<sup>+</sup> Disease patients
- If left untreated 90% of children with sickle cell disease who have a stroke will have recurrent stroke
- Patients with silent stroke have increased risk of subsequent infarctive stroke
- 17 – 23% of patients with sickle cell disease have silent stroke (2X the number who have stroke)

### C. Risk Factors

- TCD velocities > 200cm/sec on two consecutive exams
- Associate factors:
  - Low baseline hemoglobin
  - High leukocyte count
  - Prior TIA
  - Frequency and recency of acute chest syndrome
  - Elevated blood pressure
  - Stroke in sibling
  - Dactylitis in first 2 years of life
  - Absence of α-gene deletion

## II. Screening for Likelihood of Initial Stroke: Transcranial Doppler Screening

### A. Inclusion

- Hb SS disease and HbS-  $\beta$  thalassemia<sup>0</sup> disease between ages of 2 and 16 years

### B. Exclusion

- Hb SC disease and HbS-  $\beta$  thalassemia<sup>+</sup> disease
- Patients already on chronic transfusion program

### C. Screening

#### 1. Purpose

- Goal of TCD screening is to identify patients with increased risk of initial stroke in order to initiate preventative treatment

#### 2. Population to Screen

- Age of patients to be screened: approximately 2-16 years
- Accurate measurements require:
  - Thin skull (need adequate bony windows)
  - Non-sedated, alert, cooperative child
- Do not sedate patients for TCD as it may alter results
- Consider repeating exam on any patient screened during acute illness

#### 3. Screening Schedule

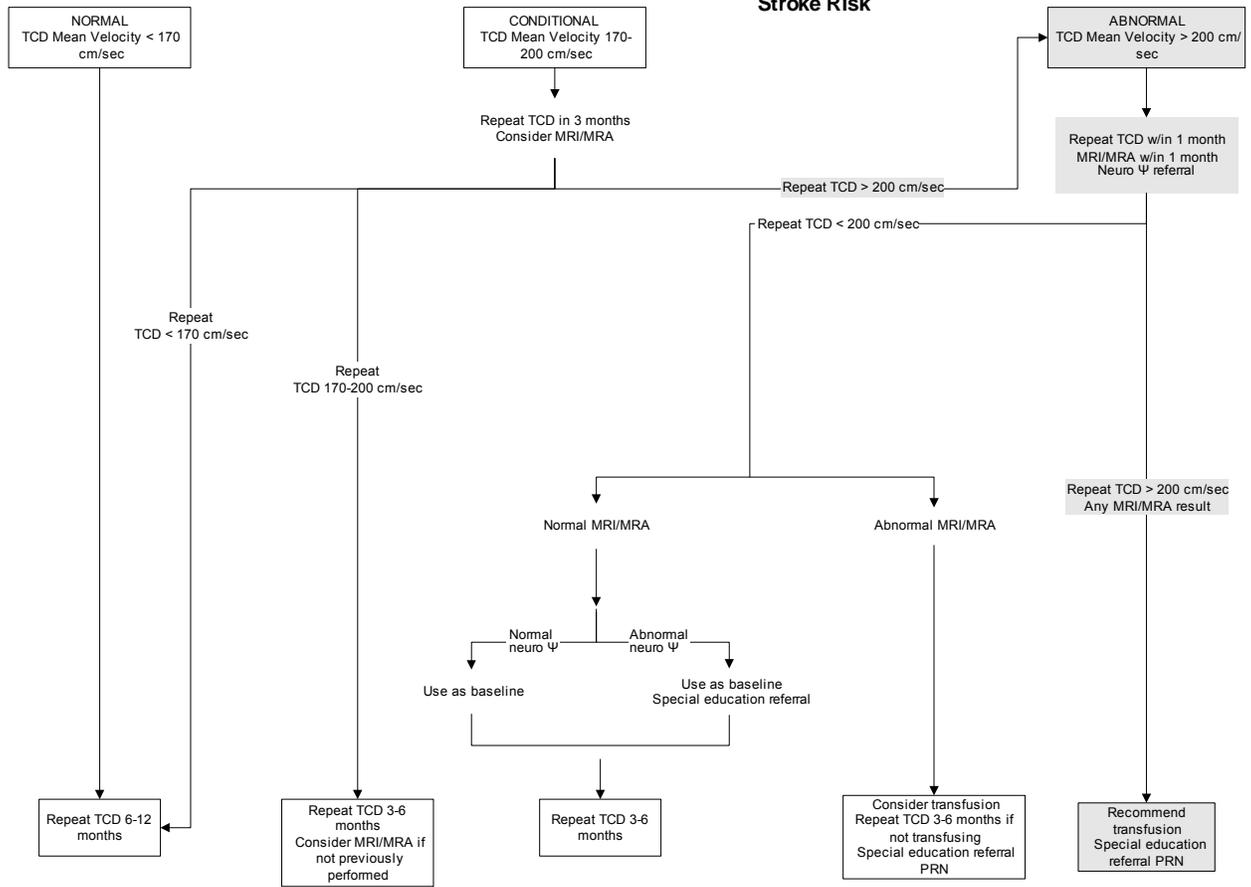
- See algorithm for details and definitions. Algorithm also contains decision tree including MRI/MRA and neuropsychology results.
  - Normal results (< 170 cm/sec) → repeat every 6-12 months
  - Conditional results (between 170 and 200 cm/sec) → repeat in 3 months. Consider MRI/MRA as clinically indicated. Consider other risk factors in determining need for chronic transfusion
  - Abnormal results (> 200 cm/sec) → repeat TCD and obtain MRI/MRA within 1 month; also obtain neuropsychological evaluation
- May consider repeat screenings based upon other factors:
  - New TIA → do 1 month after resolution
  - TCD showing significant change from previous exam → repeat in 3-6 months
  - Significant asymmetry → repeat in 3-6 months

#### 4. Compliance

- Family refusal to screen
  - Family refusal of transfusion therapy is not a true barrier to TCD screening
  - Inform family that chronic transfusion is standard of care for an abnormal TCD. Hydroxyurea is an unproven, although available, alternative.
- Non-compliance with TCD appointments is significant barrier to screening
- Provide education at clinic visits re: importance of TCD screening and risk of stroke in patients with sickle cell disease
- Inform family of results to encourage further compliance

*Adams RJ, McKie VC, Hsu L, Files B, et al. Prevention of a first stroke by transfusion in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonography. NEJM. 1998. 339(1):5-11.*

**Algorithm for TCD Screening for Stroke Risk**



### III. Evaluation and Treatment of Acute Change in Neurological Status

#### A. Inclusion

- all children and adolescents with sickle cell diseases with acute neurological symptoms

#### B. Diagnosis

- Clinical – focal neurologic change(hemiparesis, hemisensory deficit) AND/OR
- CT or MRI evidence of acute infarction

#### C. Management

##### 1. Purpose

- to initiate exchange transfusion therapy as soon as possible in the event of a suspected or probably acute infarctive stroke

##### 2. Initial Evaluation

- History and Physical exam, including thorough neurologic exam
- Obtain IV access, patient must be made NPO
- Labs and imaging studies
  - CBC, Type and Crossmatch (ensure extended phenotyping) electrolytes
  - If available immediately, neuroimaging with non-contrast CT to rule out hemorrhage
  - MRI/MRA with diffusion weighted images to detect early ischemia may be deferred until after exchange transfusion treatment
  - Consider LP after imaging if clinical indications of infection are present

\*DO NOT DELAY INITIATING TRANSFUSION THERAPY WHILE WAITING TO HAVE IMAGING STUDIES OR LP IF SIGNS ARE SYMPTOMS ARE CONSISTENT WITH STROKE\*

##### 3. Treatment

- Hematology, transfusion medicine/apheresis and neurology consults
- Admit to ICU for monitoring and venous access placement
- Suspected or confirmed infarctive stroke
  - Partial Volume exchange transfusion (manual exchange or erythrocytapheresis) with goal Hb 10g/dl, and % HbS < 30 %
  - If there is a delay in two way line placement or starting exchange transfusion strongly consider interim "simple/straight" transfusion if starting Hb allows
  - Target Hct <= 36 % or Hb <= 12
  - See Blood Transfusion for Pediatric Patients with Sickle Cell Disease CPG
- Hemorrhagic stroke
  - Neurosurgical evaluation with surgical/medical intervention as needed
- Other treatments
  - Antibiotics if evidence or concern for infection/meningitis.
  - IV + PO fluids at maintenance, may decrease rate if elevated ICP or if concern for cerebral edema
  - RX for elevated ICP if present
  - Consider pathophysiological role of dehydration in vaso-occlusion when treating with diuretics
  - Anti seizure meds if seizures are present or a potential complication
  - O2 to keep pulse ox > 95%
- MRI/MRA after exchange transfusion if not previously done

##### 4. Discharge criteria

- Clinically and neurologically stable for at least 24 hours.
- Refer to Section V: Prevention of Initial or Repeat Stroke
- Discharge planning completed:

- Arrange inpatient rehabilitation admission, if needed
- Arrange hematology and neurology follow-up
- Arrange neuropsychology follow-up
- Refer to public school or early intervention system for evaluation
- Arrange for other outpatient rehabilitation services (PT, OT, speech therapy)

#### **IV. Silent Stroke**

##### **A. Inclusion**

- All patients with sickle cell disease

##### **B. Diagnosis**

- Currently there are no recommendations for screening with MRI/MRA in patients with sickle cell disease to detect silent stroke

##### **C. Treatment**

- Patients with abnormal TCD (>200 cm/sec) and silent stroke have a high risk of infarctive stroke and should be started on chronic transfusion regimen
- Currently there are no treatment recommendations for patients with isolated finding of silent stroke, but Algorithm for TCD Screening for Stroke Risk should be followed

## V. Prevention of Initial or Repeat Stroke

### A. Inclusion

- Hb SS disease and HbS-  $\beta$  thalassemia<sup>0</sup> disease needing chronic transfusion therapy for stroke prevention
  - Prevention of initial stroke for patients determined to be at high risk
  - Prevention of recurrent stroke in patients with history of stroke

### B. Exclusion

- Hb SC Disease and HbS-  $\beta$  thalassemia<sup>+</sup> Disease\*
- \*Their management must be individualized

### C. Management

#### 1. Purpose

- Maintain % Hb S to <30% to prevent initial or recurrent stroke

#### 2. Chronic transfusion regimen – standard of care to prevent stroke recurrence

- Blood product: Leukocyte-reduced and sickle hemoglobin negative packed red blood cells (PRBCs). Extended phenotyping is highly recommended, (especially for Kell). Exact blood product may depend upon institutional guidelines
- Transfusion Volume
  - The amount of PRBCs used should be calculated to raise the patient's hematocrit to 30% (target range 28-33% or Hb to 10g/dl; calculate as follows:
    - Hematocrit
 
$$\text{ml of PRBC transfuse} = \frac{(30\% - \text{current hct}) \times (\text{Patient weight in kg} \times 80)}{(\text{hct PRBC (use 60\%)})}$$
    - Hemoglobin
 
$$\text{mL of PRBC to transfuse} = \frac{((\text{desired Hb} - \text{actual Hb}) \times (\text{weight} \times 75\text{mL/kg}))}{(\text{Hb of PRBC (use 22.5)})}$$
- Rate of transfusion: Blood can be given at the following rates for patients not acutely ill:
  - Patient without history of fluid intolerance or heart failure  
4-5 ml/kg per hour
  - Patient with history of fluid intolerance or heart failure  
3 ml/kg per hour, or slower if clinically appropriate
- Transfusion frequency:
  - Repeat Q 3-6 weeks to maintain post-transfusion Hb > 12g/dl and % Hb S < 30%.
  - Two years after initial stroke may consider relaxing parameters to maintain % Hb S < 50%
  - May need to have a single exchange/phoresis if patient has missed scheduled transfusions in order to reduce %S
- May be more difficult to suppress reticulocytosis in certain patients, especially those with lung disease.
- If unable to suppress reticulocyte account consider a sleep study
- Labs and imaging studies
  - Monthly CBC with clot
  - Hb electrophoresis as needed to monitor %S and determine transfusion frequency, at least q3-4 months
  - Monitor LFTs and ferritin q3-4 months
  - HIV and hepatitis screen yearly
  - Neuroimaging studies as indicated for any acute event
  - Consider repeating baseline studies before any change in treatment, including the discontinuation of transfusion therapy
- Start Desferal therapy as per Iron Overload CPG

- Duration of chronic transfusion is not well studied. Recommend treatment until at least 18 years of age. Need to also consider allo-immunization status, and chelation compliance in determining continuation of transfusion therapy.

#### D. Alternatives to chronic transfusion therapy

##### 1. Erythrocytapheresis (automated exchange transfusion)

- Can be used as alternative to chronic simple PRBC transfusion when available
- Avoids problem of iron overload
- May require specialized venous access
- Exposes patient to increased number of units of blood

##### 2. Stem Cell Transplant

- Consider HLA-typing in patients with stroke who have a full siblings
- Educate family re: cord blood collection for new siblings, this does not obligate family to go forth with transplant

##### 3. Hydroxyurea

- No current recommendations for using hydroxyurea as stroke prevention.
- Anecdotal reports of success
- May be alternative for family refusing transfusion or patient who cannot be transfused (allo-immunization, symptomatic iron overload not compliant with chelation)
- Overlap initiation of hydroxyurea with chronic transfusions for 6 months
  - Multiple considerations when transitioning from transfusions to hydroxyurea
  - Recommend consulting with hematologist experienced in the process

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