American Society of Hematology 2020 guidelines for sickle cell disease: cerebrovascular disease in children and adults


ASH Clinical Practice Guidelines on SCD

1. Cardiopulmonary and Kidney Disease
2. Transfusion Support
3. Cerebrovascular Disease
4. Acute and Chronic Pain
5. Stem Cell Transplantation
How were these ASH guidelines developed?

**PANEL FORMATION**
Each guideline panel was formed following these key criteria:
- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of conflicts of interest

**CLINICAL QUESTIONS**
10 clinically-relevant questions generated in PICO format (population, intervention, comparison, outcome)

**EVIDENCE SYNTHESIS**
Evidence summary generated for each PICO question via systematic review of health effects plus:
- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

Example: PICO question
“Should automated red cell exchange vs simple transfusion or manual red cell exchange be used for patients with SCD receiving chronic transfusions?”

**MAKING RECOMMENDATIONS**
Recommendations made by guideline panel members based on evidence for all factors.
## How to use these recommendations

**STRONG Recommendation**  
(“The panel recommends...”)

<table>
<thead>
<tr>
<th>For patients</th>
<th>Most individuals would want the intervention.</th>
<th>A majority would want the intervention, but many would not.</th>
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<tbody>
<tr>
<td>For clinicians</td>
<td>Most individuals should receive the intervention.</td>
<td>Different choices will be appropriate for different patients, depending on their values and preferences. Use <strong>shared decision making</strong>.</td>
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Key terms in SCD stroke

• **Stroke**
  – acute neurologic injury of the brain, retina, or spinal cord that occurs as a result of ischemia or hemorrhage that last longer than 24 hours (World Health Organization Bull World Health Organ. 1980;58(1):113-130.)

• **Silent cerebral infarction (SCI)/silent stroke**
  – a lesion visible by magnetic resonance imaging (MRI) images with no associated findings on neurologic exam (American Heart Association/American Stroke Association, Stroke. 2019 Aug;50(8):e239.)
  – can be correlated with neurocognitive and behavioral deficits

• **Transient ischemic attack**
  – transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction seen on neuroimaging
Key terms in SCD stroke management

• Primary prevention
  – interventions to reduce the risk of a first stroke

• Secondary prevention
  – interventions to reduce the risk of recurrence in individuals who have already had a first stroke or SCI

• Transcranial Doppler (TCD)
  – noninvasive ultrasound-based method of measuring the flow rate of blood in
    • terminal internal carotid
    • proximal middle cerebral and intracranial arteries
Objectives

By the end of this session, you should be able to:

• Describe recommendations on primary stroke prevention for children with SCA in high-income settings
• Describe recommendations on the acute and timely treatment of suspected or confirmed stroke
  – transient ischemic attack
• Describe recommendations secondary prevention of ischemic strokes in children and adults with HbSS or HbSβ0
• Describe recommendations for screening silent cerebral infarcts for HbSS/HbSβ0 in children and adults
Objectives (cont’d)

– Describe recommendations on acute management of ischemic strokes using tissue plasminogen activator (tPA) for adults with SCD and stroke symptoms
Good Practice Statements

- **Good Practice Statement 1**
  - To adopt a health care system for tracking transcranial dopplers and their treatment

- **Good Practice Statement 2**
  - To consult with neurology/neuroradiology for all acute neurological events and timely and appropriate red blood cell transfusion

- **Good Practice Statement 3**
  - To discuss silent cerebral infarcts with patients/families, based on one non-sedation MRI and discussion about disease modifying therapy
Stroke is the most common permanent sequelae of SCD
Case 1

Primary stroke prevention for children with SCD living in low-middle- and high-income settings (Q 1, 2, 3)
Case 1: Screening and primary stroke prevention in a high-income country

A four-year-old male with HbSS living in the United States, presents to your clinic for an annual visit. In discussing plans for his disease surveillance, you note that the child has recently had two abnormal TCD measurements (high MCA velocity), what is the next best step?

A. repeat test in six months
B. repeat test in one year
C. start transfusion/apheresis to reduce sickle hemoglobin level
D. no further action is needed
TCD screening and initiation of transfusion is necessary for primary stroke prevention

- Annual TCD screening should be performed for:
  - children with HbSS or HbSβ0 thalassemia (ages 2-16 years) (strong recommendation)
- For children with SCA or children who have compound heterozygous SCD, other than HbSC, who have evidence of hemolysis in the same range as those with HbSS, (ages 2-16 years) who have abnormal TCD velocities:
  - blood transfusion therapy every 3-4 weeks is recommended
  - blood transfusion for at least a year (vs no transfusion) with the goal of:
    - maximum HbS levels below 30%
    - hemoglobin levels at 9.0 g/dL (strong recommendation)
TCD screening with regular blood transfusions results in a reduction of stroke
Case 1 (continued)

The patient has now been on transfusion therapy for 18 months. The family is discussing options for possibly discontinuing transfusion therapy. Which of the following answers describes the next best course of action:

A. patient must continue transfusions indefinitely
B. patient can be put on MTD hydroxyurea
C. patient can be put on MTD hydroxyurea if he has a normal MRI/MRA
D. patient can discontinue transfusions
Hydroxyurea can replace blood transfusions in select cases in children with abnormal TCD values transfused for at least a year (Debaun et al. Lancet 2016 Feb 13;387(10019):661-70)

- Criteria for being able to stop indefinite monthly regular blood transfusion therapy for primary stroke prevention:
  - Red blood cell transfusion therapy for at least 1 year
  - No MRA defined vasculopathy
  - No silent cerebral infarct

- Alternative therapy to monthly blood transfusion: hydroxyurea
  - Hydroxyurea treatment at the maximum tolerated dose can be considered to substitute for regular blood transfusions.
Pooled analysis of the 10 studies documenting TCD measurements decrease after starting hydroxyurea therapy in children with HbSS
(Blood Advances 2020 Apr 28; 4(8): 1554–1588)
Case 2

Acute and timely treatment of suspected or confirmed ischemic stroke or TIA
Case 2

A 9-year-old female with HbSβ0 thalassemia presents to the ER with new onset hemiparesis and aphasia. Her hemoglobin is 9g/dL on presentation, and her symptoms started 35 minutes ago. What is the next best course of action?

A. admission to monitor for progression  
B. MRI/MRA  
C. simple transfusion  
D. exchange transfusion
SCD patients with neurological deficits should have prompt blood transfusion

- Prompt blood transfusion should be given upon recognition of symptoms without delay beyond 2 hours of acute neurological symptom presentation
- The type of transfusion (simple, modified exchange, or apheresis) is dependent on individual patient factors and local transfusion resources (strong recommendation)
- Optimal timing of intervention with blood transfusion therapy and brain-imaging modality has not been rigorously studied
- Exchange transfusion is preferred over simple transfusion
Management of acute neurological events

- Optimal timing of therapy is to have prompt (within 2 hours of presentation to medical care) transfusion in children and adults with SCD presenting within 72 hours of symptom onset.
- An assessment for anemia and percentage of sickle hemoglobin with consideration of transfusion on a case-by-case basis is suggested.
- For individuals with hemoglobin levels >8.5 g/dL presenting with focal neurological deficits or TIA, exchange transfusion therapy to decrease the possibility of hyperviscosity syndrome is suggested.
Multi-disciplinary management of acute ischemic stroke is recommended

- Close consultative interaction between hematologists, neurologists, and acute-care providers because the diagnosis of an acute ischemic stroke can be challenging
- If you do not work at a center capable of dealing with acute stroke, rapidly initiate low flow oxygen, IV fluids, complete blood count, and crossmatching and transfer to a facility that is adept at managing acute stroke
The final diagnosis of ischemic stroke or TIA is based on a complete neurological history, not MRI

- An MRI of the brain may facilitate a diagnosis of acute cerebral ischemia, but cannot replace a history and examination
- The absence of abnormality seen on the diffusion weighted image on MRI of the brain does not definitively exclude the diagnosis of an ischemic stroke.
- If a patient with SCD presents with an acute-onset focal neurological deficit and the health care provider believes that the patient has had an ischemic stroke or TIA, intervention should be the same to minimize the potential risk of ongoing ischemic brain injury
Increasing hemoglobin with a transfusion improves oxygen delivery to the brain

\[ DO_2 = CO \times (1.39 \times [Hb]) \times SaO_2 + (0.003 \times PaO_2) \]

Rate of oxygen delivery (ml per minute)

Haemoglobin concentration (grams per litre)

Cardiac output (litres per minute)

Oxygen binding capacity of haemoglobin: 1.39 ml per gram

Haemoglobin oxygen saturation expressed as a fraction (i.e. 97% is expressed as 0.97)

Amount of dissolved oxygen in the blood, in ml. For every 1 mmHg of oxygen tension, 0.003ml of oxygen gas is dissolved in 100ml of blood.
Oxygen delivery to the brain is also dependent on the HbS%  
(Stroke, 19(12), pp.1466-1469)

- Thresholds for postapheresis HbS percentage and hemoglobin level are typically set at 15% to 20% and 10g/dL, respectively.
- When the HbS level is 20%, the total hemoglobin level can generally be 10 g/dL, up to 12 to 13 g/dL, without concerns for viscosity related complications, and the optimal recommended range of hemoglobin level postapheresis is 10 to 12 g/dL.
- When the hemoglobin level is 5.0 g/dL, a simple transfusion to increase the total hemoglobin to 10.0 g/dL may be required.
Case 3

Acute management of ischemic strokes and the use of tPA for adults with SCD presenting with stroke symptoms (Question 7)
Case 3

A 41-year-old female with HbSβ0 thalassemia presents with new aphasia and hemiparesis that started two hours ago. Her hemoglobin is 8.5 g/dL. Imaging confirms that there is no hemorrhage. What is the next best course of action:

A. tPA only
B. exchange transfusion only
C. exchange transfusion and tPA if consistent with institutional guidelines
D. no further management
Administration of tPA should never delay prompt blood transfusion

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

- For all patients, the administration of tPA should not delay prompt simple or exchange blood transfusion therapy
- Patients may be evaluated for IV tPA based on its established inclusion and exclusion criteria detailed in stroke management algorithms
tPA treatment in adults with SCD must be balanced with timely treatment with prompt transfusions

- Evidence does not exist as to which treatment option should be provided first (tPA or blood transfusion)
- Given the increased overall survival of adults with SCD into middle and old age with the cumulative effect of traditional cardiovascular risk factors leading to stroke
- Offering emergent treatment with tPA to older adults with SCD presenting with acute ischemic strokes within 4.5 hours of symptom onset is advised
The evidence for the benefit of tPA in SCD is scant, and the potential harm associated with tPA is significant

- One study of tPA for hyperacute stroke compared outcomes of adults with and without an SCD diagnosis using administrative data from a large US health provider.
- There was no difference in efficacy or safety outcomes between the 2 groups, but the study was limited by lack of confirmation of SCD phenotype and probable inclusion of individuals with sickle cell trait.
- The panel suggests that adults with SCD and acute ischemic stroke be considered for IV tPA following established guidelines because of the strong evidence for improved outcomes in the general population.
Acute presentation of neurological event in a child with SCA requires transfusion within 2 hours of presentation.
Acute presentation of neurological event in adults with SCD requires transfusion within 2 hours of presentation.
Onset 4-5 hours; initiate simple transfusion; noncontrast head CT

- Hemorrhage on head CT: Consult hematology and neurosurgery
  - No hemorrhage on head CT: Consider IV-tPA according to established inclusion/exclusion criteria. Evidence of moyamoya on vascular imaging?
    - No moyamoya vasculopathy and large vessel occlusion: Evaluate for thrombectomy
      - Simple transfusion to achieve Hb 10 g/dL
        - Exchange transfusion to reach Hb 5 level 15–20%
    - Moyamoya vasculopathy: simple transfusion to achieve Hb 10 g/dL
      - Exchange transfusion to reach Hb 5 level 15–20%
Onset 4.5-24 hours: initiate simple transfusion. Evidence of moyamoya on vascular imaging?
Symptom onset or worsening of deficit within 24-72 hours?

- **YES**
  - Oxygen supplementation; assess whether Hb >8.5 g/dL
  - Prompt simple transfusion to achieve Hb 10 g/dL
  - *Exchange transfusion to reach Hb S level 15-20%*

- **NO**
  - Assessment for anemia and % Hb S; consider transfusion case by case
  - *Exchange transfusion to reach Hb S level 15-20%*
Case 4

Screening for silent cerebral infarcts in children and adults with HbSS or HbSβ^0 thalassemia (Question 10)
Case 4

A 6-year-old female with HbSS is evaluated with a non-sedation screening MRI and found to have a silent cerebral infarct. She is on hydroxyurea therapy. Which of the following is the best next action?

A. discussion about secondary prevention with regular blood transfusions and HSCT
B. cognitive screening assessment
C. MRI surveillance every 12 to 24 months
D. all of the above
Silent cerebral infarcts are very common in sickle cell anemia (Kassim et al. Blood. 2016 Apr 21;127(16):2038-40.)

Before completing high school 39% of the students with SCA will have silent cerebral infarcts and 53% of young adults with SCA
Minimum of 6 reasons to screen at least once for silent cerebral infarcts in children and adults with HbSS or HbSβ⁰ thalassemia

1. High pre-test probability of the disease
   - Approximately 39% in students
   - Approximately 50% in adults
2. Associated with decreased FSIQ of at least 5-point drop
3. May provide evidence for additional services (education and employment)
4. Is associated with higher infarct recurrence without any treatment
5. May include executive dysfunction which has specific evidence based cognitive strategies to overcome (American Congress of Rehabilitation Medicine)
6. Efficacious therapy demonstrated to decrease the rate of new cerebral infarcts in children with pre-existing cerebral infarcts
After a silent cerebral infarct is identified, panel recommends tangible steps to inform family

- Neurological evaluation to assure that infarcts are classified as a silent cerebral infarct rather than overt stroke.
- A discussion regarding:
  - Secondary prevention options including regular blood transfusions and HSCT.
  - Cognitive screening assessment
- MRI surveillance every 12 to 24 months to assess for cerebral infarct progression.
  - If new infarcts are present, then a discussion with the patient and family regarding the pros and cons of a step-up in therapy intensity to prevent cerebral infarct recurrence
Summary

• The responses to the remaining PICO questions were based on review of all available observational studies, including cerebral hemodynamic studies in SCD (Only 3 RCTs)
• The panel did not include the role of HSCT for primary and secondary stroke prevention, an emerging treatment strategy in high-income settings.
Recommendations that immediately impact clinical care in high-resource settings

1. use of transcranial Doppler ultrasound screening in children with HbSS and HbSβ⁰ thalassemia (and hydroxyurea for primary stroke prevention living in low-middle-income settings)

2. surveillance for developmental delay, cognitive impairments, and neurodevelopmental disorders in children

3. use of magnetic resonance imaging of the brain without sedation to detect silent cerebral infarcts at least once in early-school-age children and once in adults with HbSS or HbSb0 thalassemia
Limitations of imaging definition of silent cerebral infarct

- A definition of silent cerebral infarcts that requires a 5-mm size with corresponding T1-weighted hypointensity on MRI, instead of 3-mm only, will lead to a large misclassification bias with fewer children being identified with silent cerebral infarcts.
- A minimum size for silent cerebral infarct of 3 mm has been used in adult SCD studies and is predictive of infarct recurrence.
- The diagnosis of a silent cerebral infarct can be challenging if the radiologist is unfamiliar with the definition of silent cerebral infarct in SCD.
- The definition of silent cerebral infarct cannot be extrapolated to include the common definition of lacunar strokes in the general population, which includes a T1 hypointensity in addition to a 5-mm FLAIR hyperintensity.
Acknowledgements

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• See more about the ASH SCD guidelines: https://hematology.org/SCDguidelines