Managing Cerebrovascular Disease

An Educational Slide Set

American Society of Hematology 2020 Guidelines for Sickle Cell Disease

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Clinical Guidelines

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

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CLINICAL GUIDELINES

blood advances

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

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Background: Central nervous system (CNS) complications are among the most common, devastating sequelae of sickle cell disease (SCD) occurring throughout the lifespan.

Objective: These evidence-based guidelines of the American Society of Hematology are intended to support the SCD community in decisions about prevention, diagnosis, and treatment of the most common neurological morbidities in SCD.

Methods: The Mayo Evidence-Based Practice Research Program supported the guideline development process, including updating or performing systematic evidence reviews. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations.

Results: The panel placed a higher value on maintaining cognitive function than on being alive with significantly less than baseline cognitive function. The panel developed 19 recommendations with evidence-based strategies to prevent, diagnose, and treat CNS complications of SCD in low-middle– and high-income settings.

Conclusions: Three of 19 recommendations immediately impact clinical care. These recommendations include: use of transcranial Doppler ultrasound screening and hydroxyurea for primary stroke prevention in children with hemoglobin SS (HbSS) and hemoglobin Sβ^0 (HbSβ^0) thalassemia living in low-middle–income settings; surveillance for developmental delay, cognitive impairments, and neurodevelopmental disorders in children; and 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 HbSβ^0 thalassemia. Individuals with SCD, their family members, and clinicians should become aware of and implement these recommendations to reduce the burden of CNS complications in children and adults with SCD.

Summary of recommendations

Background

Stroke, silent cerebral infarcts (silent strokes), and cognitive morbidity are the most common permanent sequelae of sickle cell disease (SCD) in children and adults. Prior to 1990 in the United States, a large prospective cohort study demonstrated that by 40 years of age, ~20% and ~10% of adults with phenotype hemoglobin SS (HbSS) or hemoglobin SC (HbSC) had a cerebrovascular accident, respectively (Figure 1).[1] Over the last decades, screening with transcranial Doppler ultrasound (TCD)

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https://ashpublications.org/bloodadvances/article/4/8/1554/454384/American-Society-of-Hematology-2020-guidelines-for

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)

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?"

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

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

How to use these recommendations

	STRONG Recommendation ("The panel recommends…")	CONDITIONAL Recommendation ("The panel suggests…")
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use **shared decision making**.

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 HbSβ^0
- 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

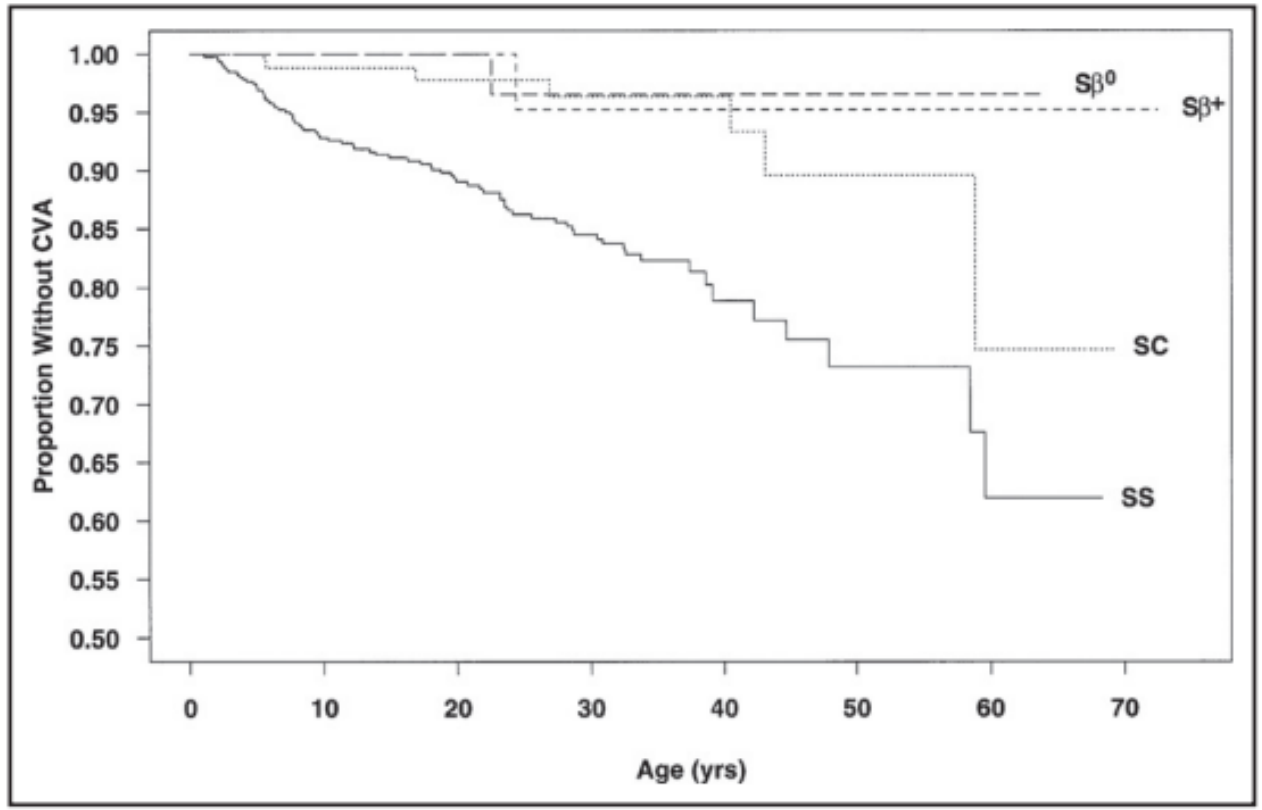
Good Practice Statements

- 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

BACKGROUND

Stroke is the most common permanent sequalae of SCD

(Ohene-Frempong et al Blood (1998) 91 (1): 288–294)



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?

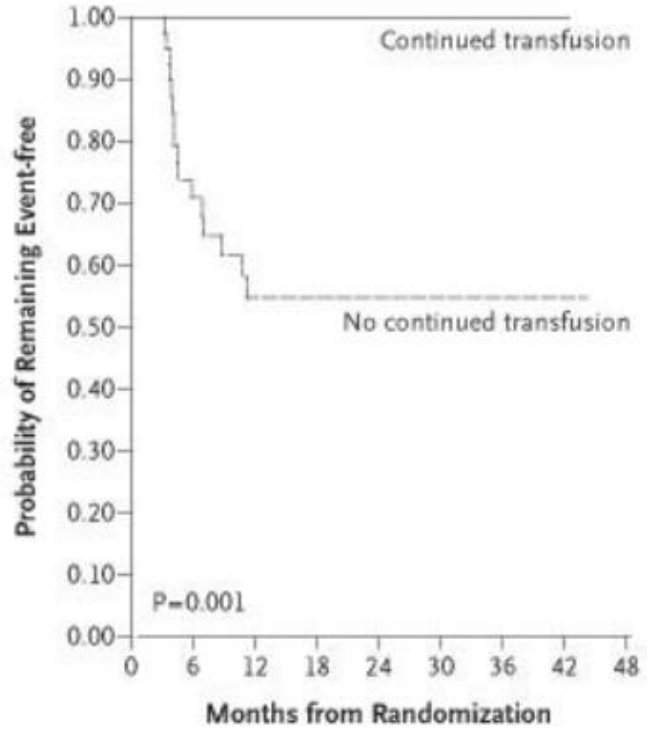
A. repeat test in six months
B. repeat test in one year
C. start transfusion/apheresis to reduce sickle hemoglobin level
D. no further action is needed

TCD screening and initiation of transfusion is necessary for primary stroke prevention

- Annual TCD screening should be performed for:
  - children with HbSS or HbSβ^0 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

(New England Journal of Medicine 353, no. 26 (2005): 2769-2778)



No. at Risk							
Continued transfusion	31	28	24	21	18	9	0
No continued transfusion	21	13	11	10	8	5	1

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

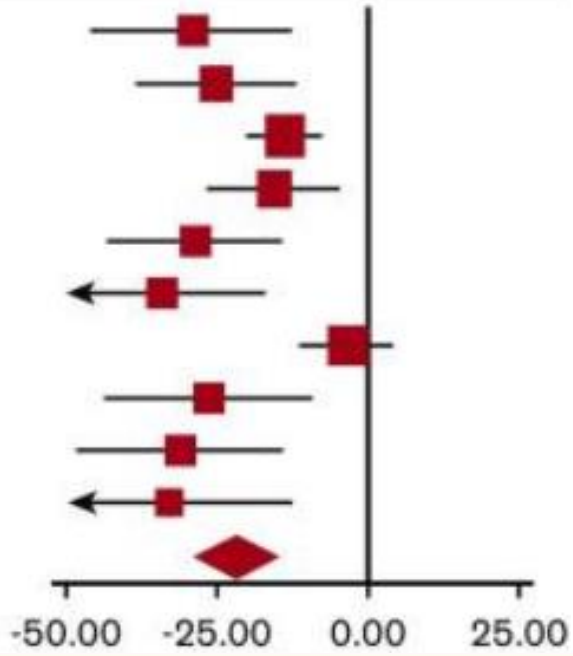
(Debaun et al. Lancet 2016 Feb 13;387(10019):661-70)

- 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)

Study Name	Mean time on Hydroxyurea (months)	Mean dose of Hydroxyurea
Lagunju, 2019	3.0	25.0
DeBaun, 2016	3.0	20.0
Kratovil, 2006	6.0	23.3
Hankins, 2015	10.1	25.0
Zimmerman, 2007	12.0	27.9
Lagunju, 2015	12.0	24.0
Adegoke, 2018	17.6	15-35
Thornburg, 2009	25.0	MTD
Gulbus, 2005	33.6	<=20
Lefevre, 2008	37.2	Low to moderate
Pooled analysis, random		



Case 2

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

Case 2

A 9-year-old female with HbSβ^0 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

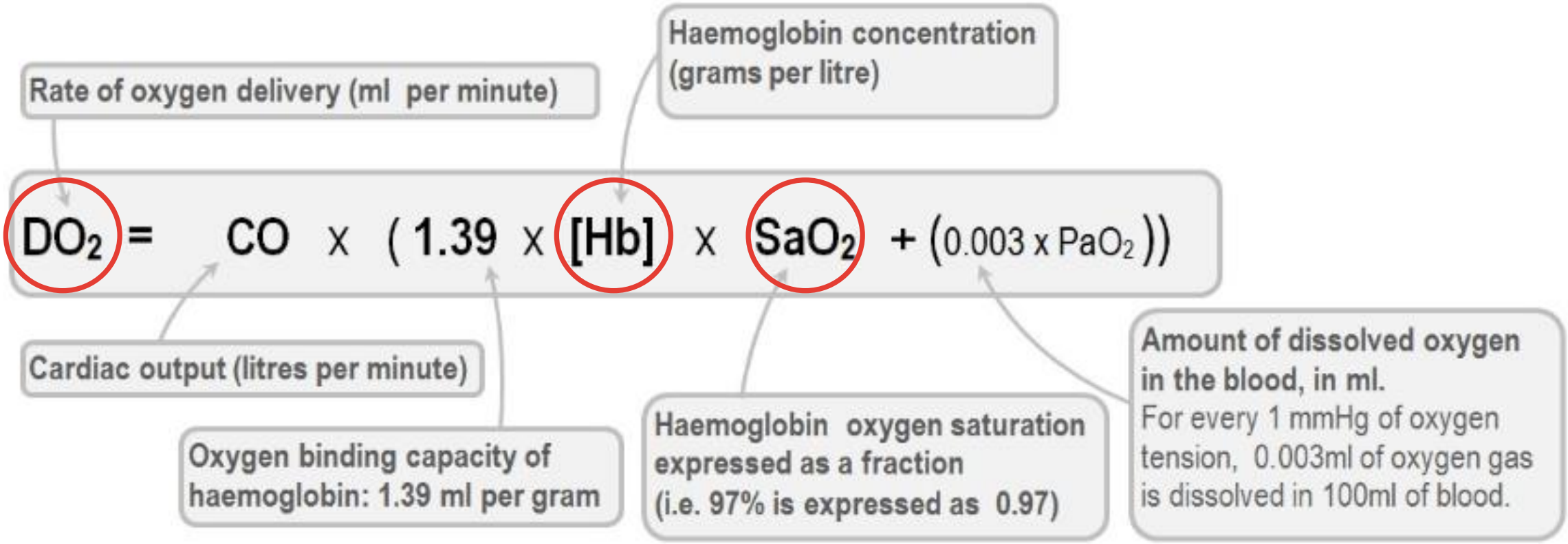
Multi-disciplinary management of acute ischemic stroke is recommended

- 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



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 HbSβ^0 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

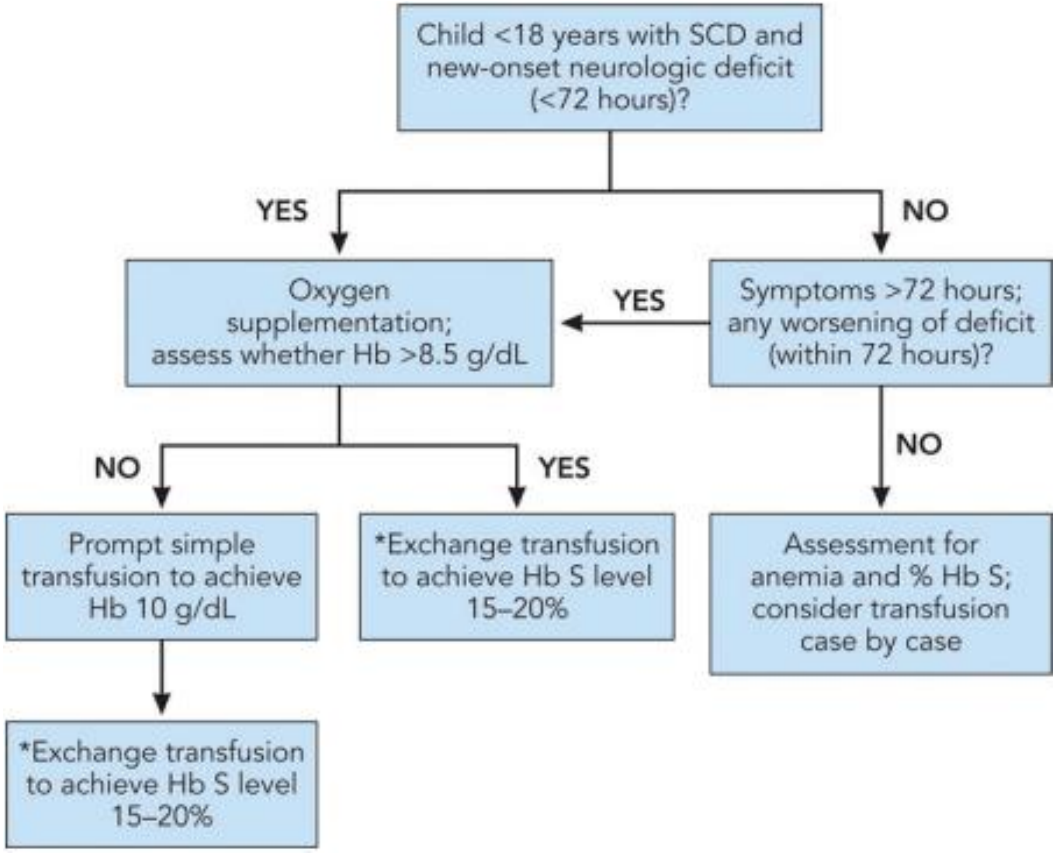
tPA treatment in adults with SCD must be balanced with timely treatment with prompt transfusions

- 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

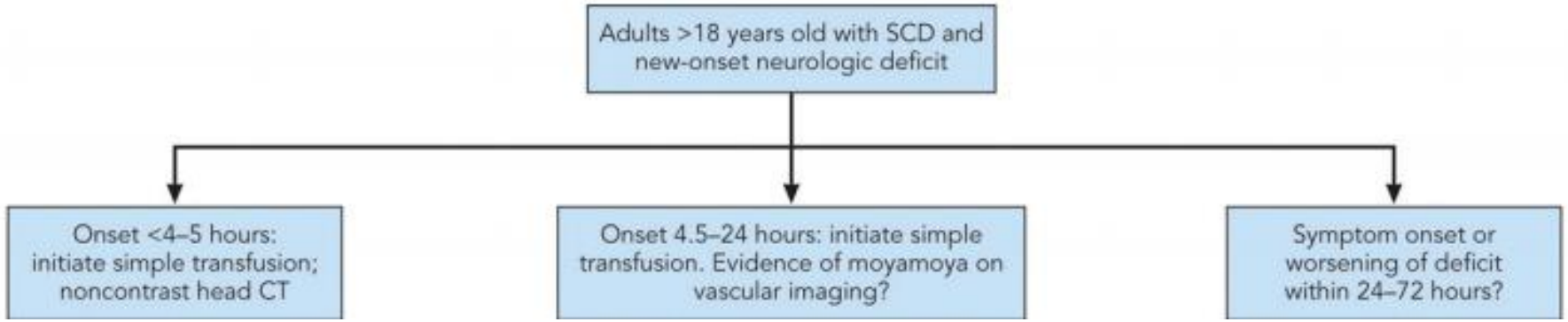
The evidence for the benefit of tPA in SCD is scant, and the potential harm associated with tPA is significant

- 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

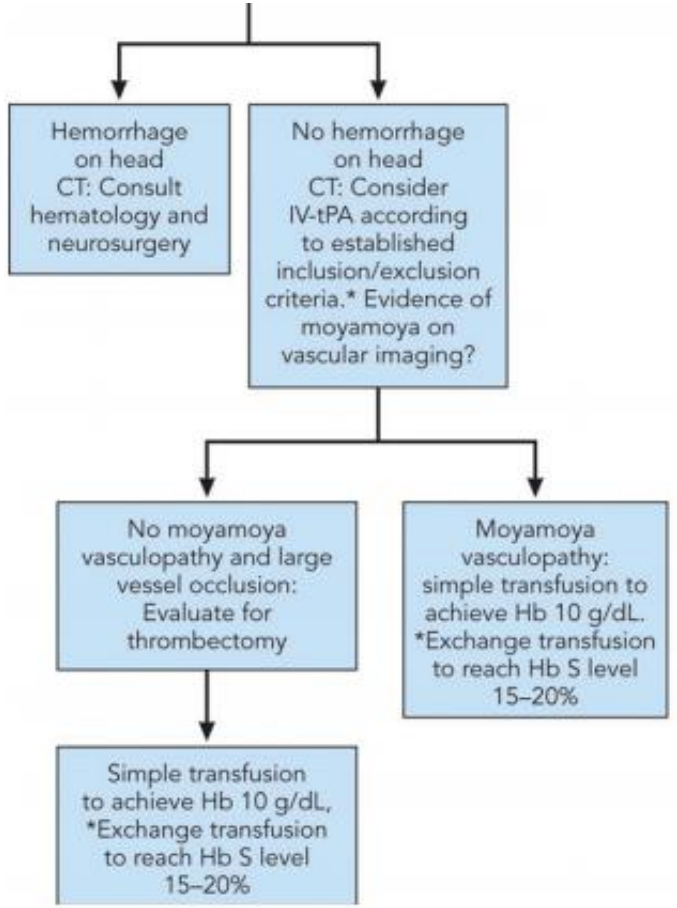
Acute presentation of neurological event in a children with SCA requires transfusion within 2 hours of presentation



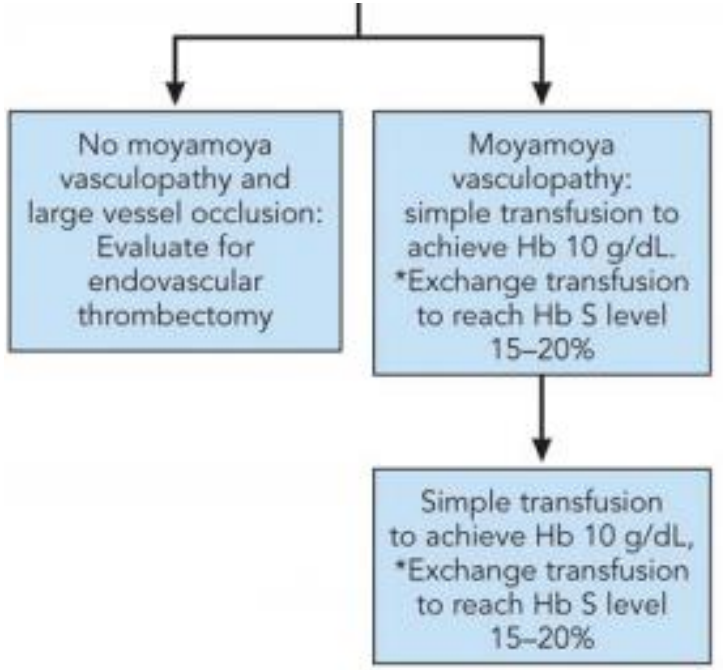
Acute presentation of neurological event in adults with SCD requires transfusion within 2 hours of presentation



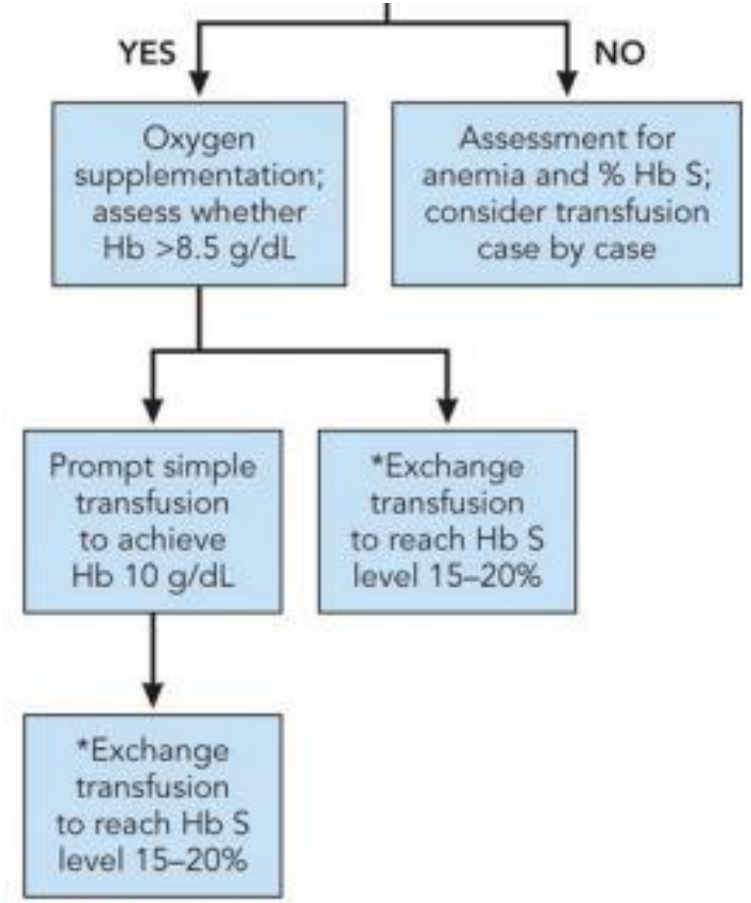
Onset 4-5 hours; initiate simple transfusion; noncontrast head CT



Onset 4.5-24 hours: initiate simple transfusion. Evidence of moyamoya on vascular imaging?



Symptom onset or worsening of deficit within 24-72 hours?



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

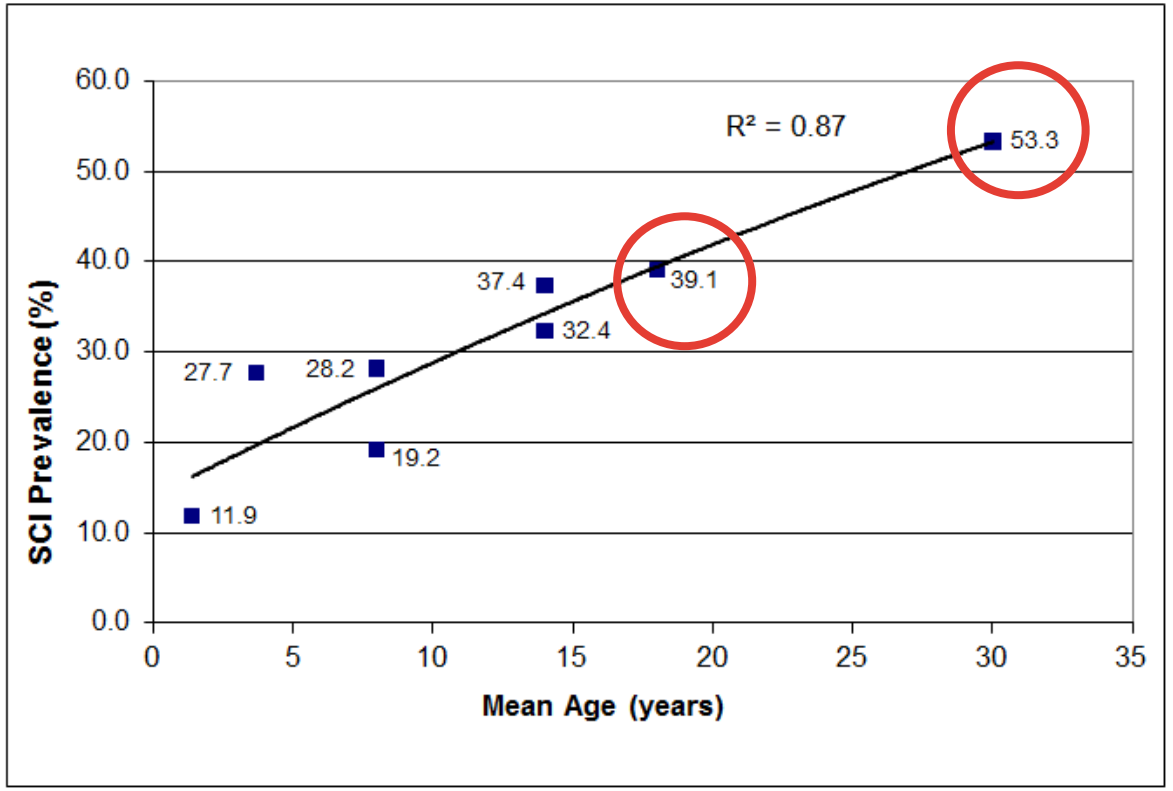
C. MRI surveillance every 12 to 24 months

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 HbSß^0 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 HbSβ^0 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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- ASH support team: Starr Webb, Kendall Alexander, Robert Kunkle

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