Table 4: Evidence Supporting Anticipatory Guidance of the Identification, Prevention and/or Management of Strokes and Silent Infarcts in Children with Sickle Cell Disease

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATION(S)
Clinical guidelines	• Prevention of a first stroke (primary prevention): Children with sickle cell disease (SCD) ages 2 to 16 years old should be screened for stroke risk using transcranial Doppler ultrasonography (TCD). Chronic transfusion should be strongly considered in those with confirmed abnormal TCD. If TCD is unavailable or technically inadequate, or if TCD results do not meet criteria for treatment in the presence of other strong indications of high risk, consideration should be given to intervention on an individualized basis unless enrollment in appropriate treatment trials is an option. (p. 93) • Children with ischemic stroke should undergoing acute evaluation with computed tomography (CT) scanning followed by intravenous hydration and exchange transfusion to reduce Hb S to less than 30% total hemoglobin. In most cases, this should be followed by chronic transfusion. (p. 93) • Children with intracranial hemorrhage should be evaluated for a surgically correctable lesion. Following this, chronic transfusion is recommended in cases of severe vasculopathy or unrepaired aneurysm. Acute hydration and short-term exchange transfusion may be beneficial as well. (p. 93) • Prevention of recurrent stroke (secondary prevention) involves chronic blood transfusion, with the target of reducing Hb S to less than 30% of total hemoglobin. The reduction in recurrent strokes is significant, but patients may still have a stroke despite adequate transfusion and low Hb S levels. (p. 88) • Current recommendations are that transfusion should be continued for at least 5 years or at least until the child reaches the age of 18. Chronic transfusion induces iron overload, which must be managed along with the transfusions. (p. 88) • For a child in whom a transient ischemia attack (TIA) is observed or strongly	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.

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	suspected, the presence of significant large vessel disease on imaging indicates the need for transfusion. Any other indication of significant risk to the brain should be followed by prophylactic treatment with transfusion. If a child's brain blood supply has failed once, even transiently, the patient is at significant risk of further deterioration. (p. 86) • The presence of silent brain lesions, assessed by magnetic resonance imaging (MRI), is associated with increased risk of clinical stroke. These lesions are evidence of brain injury and should prompt evaluation of the child for learning and cognitive problems; the cerebral vessels should be evaluated for primary stroke prevention. (p. 89) • While hemiparesis typically improves, cognitive deficits are often significant and long-lasting; formal testing should be carried out to identify rehabilitation and educational needs. (p. 85)		
Clinical guidelines	Any acute neurological symptoms other than mild headache should be evaluated immediately. Symptoms include weakness, impaired ability to communicate, seizures, loss of motor function, severe headache, stupor, and coma. • Initial evaluation should include a complete blood count, reticulocyte count, noncontrast CT or MRI to exclude hemorrhage. • Treatment includes anticonvulsants, if necessary; other supportive care for seizure or increased intracranial pressure, if present; and a program of chronic transfusions, usually initiated acutely by partial exchange transfusion or erythrocytapheresis. • Ischemic central nervous system injury can also present with nonfocal or soft signs, such as developmental delays or poor school performance. • Children at highest risk of stroke can be identified by screening with TCD ultrasonography. Those with positive findings may be candidates for primary stroke prevention and chronic transfusion.	III	American Academy of Pediatrics Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. Pediatrics. Mar 2002;109(3):526-535.

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATION(S)
	(all information, p.530)		
Randomized controlled trial	In the Stroke Prevention Trial in Sickle Cell Anemia (STOP), Adams et al. (1998) randomized 130 children with SCD and high stroke risk to receive either standard care or transfusions. The trial was ended early when the authors found that the risk of first stroke decreased by 92% when abnormal TCD screening results were followed by blood transfusions.	I	Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998; 339(1):5-11.
Randomized controlled trial	Adams et al. (2005) randomized 79 children with SCD and high stroke risk who had received transfusions for ≥ 30 months to receive either continued transfusions or no continued transfusions. The trial was ended before the planned enrollment of 100 children because discontinuation of transfusion was found to result in high rates of reversion to abnormal TCD results and subsequent stroke.	I	Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005; 353(26):2769-2778.
Secondary analysis	Abboud et al. (2004) looked back at the STOP study data to determine the utility of magnetic resonance angiography (MRA) to predict stroke risk in children with SCD. The results suggested that TCD often detects flow abnormalities before stenotic lesions on MRA become evident.	II	Abboud MR, Cure J, Granger S, et al. Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study. Blood 2004; 103(7):2822-2826.
Prospective cohort study	Siebert et al. (1998) followed 117 children with SCD over a period of 8 years. The authors found nine TCD factors that were significant for clinical disease. They recommended that TCD be used as initial screening for cerebrovascular disease in children with SCD.	II	Seibert JJ, Glasier CM, Kirby RS, et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8-year study. Pediatr Radiol1998; 28(3):138-142.
Clinical guidelines	• Children with conditional TCD screening results between 170 and 200 cm/second should get a second screen within 3 months. • Children with abnormal TCD results greater than 200 cm/second should have a confirming TCD and start transfusion therapy	III	Wang CJ et al. Quality-of- care indicators for children with sickle cell disease. *Pediatrics* 2011; 128:484-493.

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATION(S)
	within 1 month. • Children who experience a stroke, silent infarct, or TCD results of 170 cm/seconds or more should have an age-appropriate neurocognitive evaluation by a psychologist. • Children with SCD presenting with first time clinical stroke should be transfused.		
Clinical guidelines	Reducing the frequency of transfusion and permitting the Hb S concentration to rise to 50% of the total hemoglobin concentration after 4 years of intensive transfusion appear to be reasonable.	III	Steinberg MH. Management of sickle cell disease. *N Engl J Med* 1999; 340(13):1021-1030.
Clinical guidelines	Silent infarcts are strongly associated with increased risk of stroke in children with SCD SS (sickle cell anemia). A normal finding on MRI is reassuring. Performing MRI at an early age and in combination with TCD should improve the usefulness of silent infarct as a stroke predictor.	III	Miller ST, Macklin EA, Pegelow CH, Kinney TR, Sleeper LA, Bello JA, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr* 2001; 139(3):385-390.
Clinical guidelines	Caretakers of young children with SCD should be educated about signs of TIA and advised to report them.	III	Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998; 91(1):288-294.
Clinical guidelines	Primary care providers should consult with a hematologist or sickle cell specialist and neurologist at a comprehensive sickle cell center for optimum management of patients who are at risk for CVA as documented by an abnormal TCD measuring greater than 170 cm/second or a previous history of stroke.	III	Pack-Mabien A, Haynes Jr J. A primary care provider's guide to preventive and acute care management of adults and children with sickle cell disease. *J Am Acad Nurse Pract* 2009; 21:25-257.

Note: USPSTF criteria for assessing evidence at the individual study level are as follows: I) Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs. II) Well-designed cohort or case-control analytic study. III) Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.