Table 4: Evidence Supporting Chronic Transfusion Therapy and Hemoglobin S Monitoring in Children with Sickle Cell Disease

Type of Evidence	Key Findings	Level of Evidence (USPSTF Ranking*)	Citations
Randomized controlled trial	In the Stroke Prevention Trial in Sickle Cell Anemia (STOP), Adams et al. (1998) randomized 130 children with sickle cell disease (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 transcranial Doppler (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.
Clinical guidelines	One of the best evidence-based guidelines for SCD is the practice of using chronic transfusion to reduce HbS levels to 30% or less to prevent strokes in children with SCD with high central nervous system blood flow velocities. Once a decision has been made to begin chronic transfusion therapy, goals are set for the HbS percentage desired. A comprehensive transfusion protocol should include accurate records, including serial HbS percentages.	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.
Clinical guidelines	Severe manifestations of SCD warrant chronic transfusion as maintenance therapy. The goal is to suppress erythropoiesis sufficiently and provide enough normal red blood cells to reduce HbS to less than 30%. Chronic transfusion reduces the risk of stroke, vaso-occlusive pain, and acute chest syndrome. It may also prevent organ damage and possibly reverse some pre-existing organ damage. In children, it may also increase well-being, improve energy levels, exercise tolerance, growth velocity, and sexual development. Stroke is an indication for chronic transfusion therapy in all patients. In selected patients, the following are also indications: transient ischemia attack; abnormal transcranial Doppler ultrasonography readings; severe, recurrent	III	Lane PA, Buchanan GR, Hutter JJ, et al. Sickle cell disease in children and adolescents: diagnosis, guidelines for comprehensive care, and care paths and protocols for management of acute and chronic complications. 2001; Annual Meeting of the Sickle Cell Disease Care Consortium, Sedona, AZ. Nov. 10-12, 2001. http://txch.org/wp-content/uploads/sickle-cell-disease-guidelines-complications.pdf; accessed

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	acute chest syndrome; severe, debilitating pain; chronic organ failure; severe chronic anemia; and cardiac failure.		March 20, 2014
Clinical guidelines	The usual goal of transfusion is to suppress erythropoiesis and provide normal red blood cells to maintain the patient's HbS at less than 30%. Chronic transfusion therapy reduces the risk of recurrent stroke, vaso-occlusive pain, and acute chest syndrome.	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.
Clinical guidelines	Red blood cell transfusion therapy in SCD is an important life-saving treatment option, but it should not be taken lightly. Primary care providers should consult with a hematologist and blood bank physician when considering transfusion for patients with SCD. Transfusion therapy is indicated for complications associated with SCD such as symptomatic anemia, aplastic crises, acute chest syndrome, cerebrovascular accident, and acute splenic or hepatic sequestration. Many possible complications exist, including infection, alloimmunization, and iron overload.	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.
Clinical guidelines	Repeated transfusions reduce the risk of recurrent stroke in children with sickle cell anemia. About 50% of children with sickle cell anemia and stroke who do not receive transfusions have another stroke within 3 years, compared with about 10% of those who receive transfusions. The aim of transfusion is to reduce HbS concentration rapidly to less than 30% of the total hemoglobin concentration and to maintain this percentage for 3 to 5 years. Reducing the frequency of transfusion and permitting the HbS concentration to rise to 50% of the total hemoglobin concentration after 4 years of intensive transfusion appear to be reasonable. It is likely that an HbS concentration of less than 30% will prevent not only stroke but also other complications, although the amount of HbS reduction that strikes the best balance between therapeutic benefits and complications of transfusion has not been determined.	III	Steinberg MH. Management of sickle cell disease. *N Engl J Med* 1999; 340(13):1021-1030

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Clinical guidelines	Transfusion therapy is a key component of the comprehensive management of patients with SCD. It is effective treatment for many of the serious complications of SCD. Clear indications for therapy are acute chest syndrome, heart failure, multi-organ failure syndrome, stroke, splenic sequestration, and aplastic crisis. It is important that patients undergo transfusion only when clearly indicated. Transfusion should be considered in consultation with a hematologist.	III	Claster S, Vichinsky EP. Managing sickle cell disease. *BMJ* 2003; 327:1151-1155.
Research study	In preparation for the SWiTCH clinical trial, a survey of chronic transfusion practices at 23 medical institutions provided a mean pre-transfusion rate 35 ± 11% for 295 children with SCD. All institutions aimed for 30% initially, but seven eventually allowed for an Hb level of 50% or less. The 35% average applied to both children with and without a history of recurrent stroke. The only variable that had a substantial impact on the HbS percentage was whether transfusions were given on time.	III	Aygun B, McMurray MA, Schultz WH, et al. Chronic transfusion practice for children with sickle cell anemia and stroke. *Br J Haematology* 2009; 145: 524-528.
Research study	In a study looking at the efficacy of long-term transfusion, all patients were treated with a monthly regimen to maintain a pretransfusion HbS proportion of 30% and a hemoglobin value between 100 and 120 gm/L. Long-term transfusion therapy in patients with SCD reduced the rate of recurrence from up to 90% in patients not given transfusions to less than 10% in those in a long-term transfusion program. Study results demonstrate that transfusion markedly reduced the number of hospitalizations, including admissions for vaso-occlusive crisis, acute chest syndrome, and bacterial infections in patients with SCD. Pending the development of more definitive therapies, extended transfusion therapy may be an effective tool in the management of SCD and its complications.	III	Styles LA, Vichinsky E. Effects of a long-term transfusion regimen on sickle cell-related illnesses. *J Pediatr* 1994; 125(6):909-911.
Research study	In a study assessing the feasibility of a multicenter trial to reduce the risk of alloimmunization following repeated transfusions, the transfusion protocol required that each transfusion was preceded by the measurement of an HbS percentage, complete blood count, reticulocyte count, and red blood	III	Vichinsky EP, Luban NLC, Wright E, et al. Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusional trial. *Transfusion* 2001;

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	cell antibody screening.		41:1086-1092.

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.