Table 4: Evidence Supporting Hydroxyurea Treatment for Children with Sickle Cell Disease

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATIONS
Randomized controlled trial	The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), a randomized, double- blind, placebo-controlled clinical trial, found that hydroxyurea therapy ameliorated the clinical course of SCA in some adults with three or more painful crises per year. Reductions in the frequency of acute chest syndrome and transfusions were also noted. Long-term safety of hydroxyurea in patients with SCA is uncertain. The trial was stopped before treatment was completed because of the beneficial effects observed. (Note: adolescents were included among the participants, but not reported as a separate group.)	I	Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; 332(20):1317-1322.
Randomized controlled trial	The HUG-KIDS study was a Phase I/II trial of hydroxyurea in children, ages 5 to 15 years, with SCA. The study showed that hydroxyurea significantly increases hemoglobin concentration, mean corpuscular volume, HbF, and F-cell percentage above pretreatment values. In addition, study results showed that pediatric and adult patients had similar hematologic toxicities. Finally, no adverse effect on growth was observed during the treatment period.	I	Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: Results of the HUG-KIDS Study, a phase I/II trial. *Blood* 1999; 94:1550-1554.
Randomized controlled trial	The Hydroxyurea Safety and Organ Toxicity Study (HUSOFT) was an NIH-funded pilot trial in which very young children, ages 6 to 28 months old, with a median age of 15 months with SCA tolerated a liquid hydroxyurea formulation (20 mg/kg/day) and had improved blood counts and HbF concentrations compared with predicted age-specific levels.	I	Wang WC, Wynn LW, Rogers ZR, et al. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; 139(6): 790-796.
Randomized controlled trial	The Hydroxyurea to Prevent Organ Damage in Children with Sickle Cell Anemia trial (BABY HUG) was an NIH-funded multicenter randomized double-blinded trial of hydroxyurea in children aged 9 to 18 months at enrollment and receiving hydroxyurea or placebo for 2 years. While it failed to show significant differences in its primary endpoints of renal and spleen function, subjects receiving the drug had few episodes of pain, acute chest	I	Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide* in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; 377(9778): 1663-1672.*

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	syndrome, and dactylitis; less frequent hospitalizations and transfusions; plus higher hemoglobin and HbF levels and lower while blood cell and reticulocyte counts. It was not associated with significant toxicity other than expected mild to moderate neutropenia. Given the demonstrated benefits, clinicians should consider shifting their practice to prescribe hydroxyurea therapy to all very young children with SCA, rather than just treating only those most severely affected.		Thornburg CD, Files BA, Luo Z, et al. (2012). Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012; 120(22): 4304-4310. *Hydroxycarbamide is the British approved name for hydroxyurea.
Clinical guidelines (from agencies or groups)	NHLBI guidelines suggest that indications for hydroxyurea therapy in children and adolescents are HbSS (SCA) or SCD-S β^0-thalassemia and frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anemia. After baseline evaluation, hydroxyurea can be initiated at 10-15 mg/kg/day in a single daily dose for 6 to 8 weeks, with regular testing for complete blood count, percent Hb F, and serum chemistries. If no major toxicity occurs, dose may be escalated every 6 to 8 weeks until the desired endpoints are reached; regular blood counts should continue. Endpoints include less pain, an increase in HbF to 15%-20%, increased hemoglobin level if severely anemic, improved well-being, and acceptable myelotoxicity. Caution should be taken in patients with compromised hepatic or renal function. (p 165).	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.
Clinical guidelines (from agencies or groups)	The AAP sections on Hematology/Oncology and the Committee on Genetics suggest that daily oral administration of hydroxyurea increases HbF levels, decreases leukocyte counts, and decreases the frequency of episodes of pain and acute chest syndrome. Hydroxyurea may be appropriate for selected children and adolescents, accompanied by frequent monitoring for myelotoxicity and other drug-related complications by a physician with expertise in SCD and chemotherapy.	III	American Academy of Pediatrics Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. *Pediatrics* 2002; 109(3):526-535.
Clinical guidelines (from agencies or groups)	The NIH Consensus Development Conference stated that "Strong evidence supports the efficacy of hydroxyurea in adults to decrease severe painful episodes, hospitalizations, number of blood transfusions, and the acute chest syndrome. Although the evidence for efficacy of hydroxyurea treatment for children	III	Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment

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	is not as strong, the emerging data are encouraging." (p. 938) "… the evidence in children does not contradict the findings in adults that hydroxyurea improves hematologic variables and decreases hospitalization rates." (p. 933)		for sickle cell disease. *Ann Intern Med* 2008; 148(12): 932-938.
Comprehensive literature review	After synthesizing the published literature on the efficacy, effectiveness, and toxicity of hydroxyurea in children with SCD, the authors wrote, "Although not approved in children for the treatment of SCD, hydroxyurea is the only readily available agent that improves both hematologic and clinical outcomes. Its known and potential toxicities should be interpreted in this context, because it is indicated for treating a disease with tremendous morbidity and early mortality. Co-management by the primary care provider and a pediatric hematologist/ oncologist may be helpful in expanding access to hydroxyurea, because the distance to a referral center and need for frequent monitoring for hematologic toxicity may be a barrier to treatment." (p. 1338)	III	Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; 122(6):1332-1342.
Clinical overview and guidelines	"In lieu of curative therapy, one approach given considerable effort over the past 25 years has been the pharmacological induction of HbF beyond the fetal and infant periods. … Hydroxyurea … has a long and growing track record in inducing HbF in patients with SCD. In addition, hydroxyurea has a variety of salutary effects on other aspects of the pathophysiology of SCD, such as increased erythrocyte hydration, improved rheology, and reduced adhesiveness. Hydroxyurea also decreases leukocyte count, and releases nitric oxide. … Hydroxyurea may be an ideal therapeutic agent for use in children with SCD." (pp. 484-485)	III	Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Pediatr Clin North Am* 2008; 55(2):483-501.
Clinical overview and guidelines	Hydroxyurea can be offered to children with pain or acute chest syndrome as young as 2 years old. The drug should be considered for young patients with few acute clinical events but abnormal lab parameters. Another emerging category for treatment consideration is early evidence of organ dysfunction, such as hypoxemia, microalbuminuria, or elevated TCD velocities.	III	Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood* 2010; 115(26): 5300-5311.
Clinical overview	"… hydroxyurea should now be considered for every patient with SCA, regardless of symptoms, since we know that all patients with	III	McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: what have

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	SCA experience sickle-related vaso-occlusion and subsequent organ damage starting at a very early age. Ideally the time to intervene is early in life, just as fetal hemoglobin production declines in the first year." (p. 164)		we learned and what questions still remain? *Curr Opin Hematol* 2011; 18(3): 158-165.
Clinical guidelines	"Indications for hydroxyurea therapy are not universally agreed upon, but with greater evidence of long-term efficacy and safety, the threshold is lowering." (p. 368) The authors identify two strong potential indications for hydroxyurea therapy: frequent painful events and dactylitis. Moderate indications are acute chest syndrome, elevated transcranial Doppler velocities, stroke prophylaxis, and parental request.	III	Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. *Pediatr Blood Cancer* 2012; 59(2): 365-371.

Note: USPSTF criteria for assessing evidence at the individual study level are as follows: (1) Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs. (2) Well-designed cohort or case-control analytic study. (3) Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.