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Hydroxyurea for the Treatment of Sickle Cell Disease: Efficacy, Barriers, Toxicity, and Management in Children

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Abstract

Hydroxyurea is the only approved medication in the United States for the treatment of sickle cell anemia (HbSS) and is widely used in children despite an indication limited to adults. We review the evidence of efficacy and safety in children with reference to pivotal adult studies. This evidence and expert opinion form the basis for recommended guidelines for the use of hydroxyurea in children including indications, dosing, therapeutic and safety monitoring, and interventions to improve adherence. However, there are substantial gaps in our knowledge to be addressed by on-going and planned studies in children.

Keywords

Hydroxyurea; sickle cell disease; efficacy; children

BACKGROUND

Hydroxyurea was approved by the Food and Drug Administration (FDA) for the treatment of adults with HbSS and frequent episodes of severe pain in 1998, but does not currently have a FDA approved indication for children. Hydroxyurea has multiple effects that may contribute to its efficacy in sickle cell disease (SCD). These include increased production of fetal hemoglobin (HbF) (1) with a concomitant reduction in the intracellular concentration of HbS, which affects the polymerization of deoxygenated HbS. This results in decreased hemolysis with the release of free hemoglobin (a contributor to endothelial dysfunction) and an increase in total hemoglobin concentration (2). Hydroxyurea also reduces the white blood count and the expression of cell adhesion molecules that contribute to vaso-occlusion and may serve as a nitric oxide donor (3, 4). The National Heart, Lung, and Blood Institute (NHLBI) issued recommendations in 2002 supporting the use of hydroxyurea in the treatment of children with SCD (5).

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NO CONFLICT OF INTEREST

Systematic Review and NIH Consensus Development Conference

As background for an NIH Consensus Development Conference in February 2008, a systematic review of the efficacy, effectiveness, toxicity, and barriers to the use of hydroxyurea in SCD was commissioned to include English primary publications through June 30, 2007 describing treatment in humans.(6) The review included 26 articles: 1 randomized controlled trial, 22 observational studies (11 with overlapping participants), and 3 cases reports of adverse events in children with SCD.(7) Most study participants had HbSS. Laboratory changes included increases in fetal hemoglobin (HbF) from 5 – 10 percent to 15 – 20 percent and hemoglobin concentration (about 1 g/dL) on hydroxyurea. Clinical effects of hydroxyurea included a decreased rate of hospitalization in the randomized controlled trial of 25 children and five observational studies by 56 – 87% and of pain crisis by 50 – 73% in 3 of 4 studies. Reports of three observational studies of hydroxyurea showed decreased recurrent neurological events compared to historical controls. Common adverse events were reversible mild to moderate neutropenia, mild thrombocytopenia, severe anemia, rash or nail changes (10%), and headache (5%). Severe adverse events were rare and not clearly attributable to hydroxyurea. This review concluded that there was strong evidence that hydroxyurea reduces hospitalization and increases total and fetal hemoglobin in children with severe HbSS, but there was inadequate evidence to assess efficacy in those with milder manifestations of SCD. The small number of children in long-term studies limited conclusions about late toxicities.

The NIH Consensus Development Conference concluded, “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 is not as strong, the emerging data are encouraging” (8).

ADDITIONAL STUDIES JULY 2007–APRIL 2011

Since the literature review for the NIH Consensus Conference, there have been many research publications on hydroxyurea for the treatment of SCD. We summarize this new information on efficacy, barriers and adherence to treatment, and toxicity.

Acute complications

The efficacy of hydroxyurea to prevent acute complications of SCD was evaluated in the Hydroxyurea to Prevent Organ Damage in Children with Sickle Cell Anemia (BABY HUG), a Phase III multicenter randomized controlled trial of hydroxyurea (20 mg/kg/day) given for two years in 9 to 18 month old children with HbSS or sickle-β^0-thalassemia who were unselected for severity of disease. This study demonstrated the efficacy of hydroxyurea to reduce the rate of acute complications in very young children with HbSS including pain and dactylitis and some evidence for hospitalization, transfusion and acute chest syndrome (Table I) (9). Rates of acute complications were similar among groups in the randomized controlled Effects of Hydroxyurea and Magnesium Pidolate in Hemoglobin SC Disease (CHAMPS) trial. However, the CHAMPS trial was terminated by NHLBI for poor enrollment therefore the power of this study to detect a difference in acute complications was low (10).

Chronic Organ Dysfunction

The efficacy of hydroxyurea to prevent chronic organ dysfunction was recently evaluated in two randomized controlled pediatric studies. BABY HUG showed no difference between hydroxyurea and placebo for the primary outcomes [preservation of renal (glomerular filtration rate by ^{99m}Tc-TPDA clearance) or splenic function (qualitative uptake on 99Tc

spleen scan)]. Significant differences in the > 30 reported secondary outcomes included smaller increases in TCD velocity (20 vs. 32 cm/sec, p=0.0002) and kidney volume (30 cm^3 vs. 39 cm^3), and better splenic function as measured by quantitative uptake and Howell-Jolly body enumeration in the hydroxyurea compared to the placebo arm. As expected, total Hb, Hb F, and mean corpuscular volume were significantly higher, and the white blood cell and absolute reticulocyte count, and total bilirubin were lower in the hydroxyurea group. The Bayley Mental Development Index and Vineland score for communication, socialization, daily living and motor skills were similar. The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial compared the standard therapy to prevent recurrent stroke, chronic transfusions to hydroxyurea and phlebotomy with a combined endpoint of stroke and iron overload. There were more strokes in the hydroxyurea and phlebotomy arm (7 or 10%, 5.6 events per 100 patient-years) compared with no strokes in the transfusion arm. The study was stopped after about 80% of planned participant follow-up time when an analysis of exited subjects showed that liver iron concentration was not significantly different between the two groups, so the composite primary endpoint would not be reached and an increase in stroke risk was not considered acceptable (11).

Several publications have reported retrospective data on central nervous system complications in children with SCD treated with hydroxyurea. Hankins *et al.* described only one child with a new CNS injury, a punctuate hemorrhage in deep white matter, among 25 children (median age 11 years and 82 patient-years of follow-up) who were treated at the maximally tolerated dose (MTD) of hydroxyurea (12). Lefèvre and colleagues reported an average decrease in TCD velocity from 235 to 202 cm/sec in those treated with hydroxyurea vs. an average increase from 148 to 172 cm/sec in those untreated. They had a low rate of stroke 0.36 per 100 patient-years in the children treated for abnormal TCD and also a low rate of recurrence (2.9 per 100 patient-years) in those treated with hydroxyurea after a first stroke (13). This is similar to the rate of 4.6 per 100 patient-years reported from Duke University in 35 children treated with hydroxyurea for the secondary prevention of stroke (14).

To date, the only published reports of the effects of hydroxyurea on pulmonary hypertension in SCD have been observational. In a cross-sectional study of children and adolescents with SCD, Gordeuk *et al.* found no differences in the triscuspid regurgitant jet velocity between the 143 participants receiving hydroxyurea and the 227 not on hydroxyurea, after adjustment for age, sex, site, and chronic transfusion program (15).

Reduction of Mortality

Only a single abstract, a retrospective cohort study from Brazil, evaluated the effects of hydroxyurea on survival in children. It showed significantly improved overall survival in the hydroxyurea group (224 patients) of 99.4% at 10 years and 97.4% at 17.9 years versus 97.4% and 66.3% (p=0.03) in the untreated group (1419 patients). The treated patients were reported to have a more severe clinical course, but may have also differed from the untreated patients in other important unreported characteristics (e.g., socioeconomic status, adherence and access to care) (16). Two other adult studies also suggest a survival benefit of hydroxyurea. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) Follow-up Study, 16 years of observation after an 18 month randomized controlled trial, demonstrated reduced mortality in participants that continued on hydroxyurea for >10 years compared to those that received <10 years of hydroxyurea. The Laikon Study of Hydroxyurea (LaSHS) in Greece, a 17 year prospective study, compared 131 patients treated with hydroxyurea to 199 untreated patients. To qualify for hydroxyurea, patients had to be greater than 16 years old and have had 3 or more episodes of pain from SCD treated in the ED or hospital, the presence of jaundice, or complications of SCD including ACS or stroke in the last 5 years. Survival after 10 years was 86% for those treated with hydroxyurea vs.

65% for those not treated (P=0.001) with increased deaths in the untreated group from liver dysfunction, stroke, vaso-occlusive crisis, and acute chest syndrome. (17). Most participants had HbSβ^0 (40%) or HbSβ^+ (50%), but the difference in survival at 10 years was most striking for HbSS (100% vs. 10%). These three studies suggest a potential survival benefit of hydroxyurea, but are limited by potential confounding factors as highly motivated patients may have been more likely to seek out treatment with hydroxyurea.

Toxicity of Hydroxyurea

Hydroxyurea had an excellent safety profile in the BABY HUG Trial. Rates of significant cytopenia including severe neutropenia, thrombocytopenia, and anemia with reticulocytopenia were similar to the placebo group and there was no renal or liver toxicity. Children receiving hydroxyurea were more likely to have moderate neutropenia (ANC 500 to 1250/μl) with 107 events vs. 34 for placebo ($p<0.0001$), but no increase in bacteremia or sepsis. Also, no differences were found in genotoxicity measures including chromosome and chromatid breaks, variable-diversity-joining (VDJ) recombination events, or micronuclei assay results (9). Hydroxyurea was also reported to be safe in a small randomized controlled trial that enrolled children and adults with HbSC disease (Table II) (10). Several retrospective studies have reported abnormal sperm parameters, including decreased numbers, forward motility, abnormal morphology, and percentage living, in men with SCD before the initiation of hydroxyurea with a possible increase in oligospermia during and after treatment with hydroxyurea (18, 19). Another report of 4 adults continuously treated with hydroxyurea showed oligospermia in 2 and azoospermia in 2 (20). These studies raise concerns about the effects of hydroxyurea on male fertility, but the biased enrollment, small numbers treated with hydroxyurea, retrospective data collection, incomplete follow-up, and baseline abnormalities in men with SCD, limit the strength of these reports. In addition, long term follow-up of the MSH Trial, identified 51 pregnancies in participants and 41 pregnancies in the partners of male participants without teratogenicity or developmental delay in the offspring (21).

ONGOING AND PLANNED STUDIES

The Transcranial Doppler With Transfusions Changing to Hydroxyurea (TWiTCH) Phase III trial will compare 24 months of alternative therapy (hydroxyurea and phlebotomy) to standard therapy (transfusions) for pediatric subjects with HbSS and abnormal (≥200 cm/sec) TCD velocities. This NHLBI funded study will enroll participants who currently receive transfusions for the primary prevention of stroke. For hydroxyurea treatment to be declared non-inferior compared to transfusions, the hydroxyurea-treated group must have an average TCD change from baseline similar to the change observed with transfusion prophylaxis. The secondary endpoints include the rates of primary stroke, quantification of iron overload by liver MRI, quality of life, frequency of non-stroke neurological events, frequency of other sickle cell-related events, complications of phlebotomy, and growth and development

The Hydroxyurea to Prevent CNS Complications of Sickle Cell Disease in Children Study (HU Prevent) is a randomized controlled Phase II pilot study in children 12 to 48 months old with HbSS or HbSβ^0 and no prior stroke, silent cerebral infarct, or abnormal TCD velocities. Participants will be randomized to hydroxyurea or placebo for 36 months with a composite primary endpoint of stroke, silent cerebral infarct, or abnormal TCD velocity. Secondary endpoints will include the proportion of screened participants accepting randomization, the proportion with >90% adherence to study medication, and the rate of severe adverse events related to SCD and study procedures including sedation without transfusion for the required brain MRI.

The Long Term Effects of Hydroxyurea Therapy in Children With Sickle Cell Disease (HUSTLE) is a prospective observational cohort study of children with SCD to evaluate the long-term cellular and molecular effects of hydroxyurea. It includes a biospecimen repository for two cohorts, those currently treated with hydroxyurea and those initiating therapy at study entry. Primary outcome measures are repeated assessments of DNA damage (from VDJ recombination events, chromosomal breakage studies with quantification of microdeletions, percentage of HJB in immature [CD71+] erythrocytes) and pharmacokinetics. Secondary outcome measures will include end organ functional assessments of brain (, spleen, kidneys, lung, heart and growth.

Initial results on potential genotoxicity were recently reported. After in-vivo hydroxyurea exposure there was a significantly increased number of circulating micronuclei-containing reticulocytes; however this was observed early in therapy and did not accumulate over time (22). There was substantial inter-patient variability in hydroxyurea-induced micronuclei levels and interestingly, the observed increases were positively correlated to markers of efficacy. Baseline chromosomal damage and the repair of DNA damage induced by ionizing radiation were also examined (23). These reports did not identify evidence of cumulative genetic damage with long-term hydroxyurea treatment, and suggest low *in vivo* mutagenicity and carcinogenicity.

TREATMENT GUIDELINES FOR CHILDREN

We now have close to 30 years of clinical experience since the first report of hydroxyurea treatment in SCD (24) and there are several published consensus and personal guidelines for initiating and managing hydroxyurea in children with SCD (25–29).

Indications for treatment

Indications for hydroxyurea therapy are not universally agreed upon, but with greater evidence of long-term efficacy and safety, the threshold is lowering. Each clinician must weigh the evidence and determine a threshold in conjunction with the patient and family. A list of potential indications is included in Table III. In addition to the laboratory and clinical profile, one must consider the neurocognitive status of the child, the psychosocial milieu of the family and previous adherence with outpatient visits and laboratory monitoring as hydroxyurea taken sporadically is unlikely to result in significant benefit.

Initiation and Dose escalation to Maximally Tolerated Dose (MTD)

Based on data from the BABYHUG (9), HUG-KIDS (30), HUSOFT (31), Toddler HUG (32), and other studies (33, 34), 85 to 90% of children with HbSS will tolerate an initial hydroxyurea dose of approximately 20 mg/kg/day given as a single dose. Unless there is concomitant renal dysfunction, reticulocytopenia, thrombocytopenia, or relative neutropenia, there is no reason to start at a lower dose. Hydroxyurea is available commercially in the United States in 200 mg, 300 mg, 400 mg, and 500 mg capsules, but some centers choose to use only 500 mg capsules, and achieve desired weekly dosing using an ‘asymmetric’ dosing schedule. For children who cannot swallow capsules, a liquid hydroxyurea formulation (100mg/mL) can be compounded from capsules by an experienced local or institutional pharmacy (Table IV). Such liquid formulations are stable for weeks to months with refrigeration or at room temperature (35). In addition, multiple generic formulations appear to be functionally equivalent (36).

Beneficial effects of hydroxyurea can begin within weeks of commencing therapy (37), however, the primary laboratory effects (e.g., HbF induction, lowering of white blood count (WBC) and ANC), are dose-dependent and may take 4 to 6 months to reach maximal effect (33, 38).

After initiating hydroxyurea therapy at 20 mg/kg/day, monitoring clinic visits every 4 weeks during dose escalation is adequate. At each interval visit, interval history, reinforcement of daily adherence, a physical examination focused on potential toxicities are performed. A complete blood count (CBC) with WBC differential and reticulocyte count should be performed at each interval visit. Liver and kidney function tests as well as a hemoglobin electrophoresis should be obtained every 3–6 months. Ideally, no medication is dispensed until the weight and blood counts are available. Hydroxyurea dose is most frequently limited by neutropenia, but also by reticulocytopenia, and more rarely by thrombocytopenia. Based on comparison of standardized and maximum tolerated dose (MTD) (26, 33), it is advisable to escalate the daily hydroxyurea dose by ~5 mg/kg/day every 8 weeks. The 4-week interval is too short for most dose adjustments, since hematological toxicity can accumulate. The target ANC for MTD is generally accepted to be 2–3 × 10^9/L (2000–3000 / μL). It is critical to review the trends in peripheral blood counts at each visit so as to reinforce the beneficial effect of the medication with families and to anticipate slowly cumulative toxicity over several visits.

Most children with HbSS require a dose of 25–30 mg/kg/day to reach this MTD (33, 39, 40). The MTD, measured in mg/kg/day, is typically established within 6 months, but should be assigned only after tolerating a particular dose for at least 8 weeks. The MTD of hydroxyurea should not exceed 35 mg/kg/day (or 2500 mg/day) because failure to achieve marrow suppression at these doses strongly suggests non-adherence.

Monitoring Frequency and Dose Modifications

When a stable MTD is reached it is often appropriate to decrease the frequency of monitoring visits to bimonthly; and depending on the patient and family, extending to quarterly visits may be possible without a drop in adherence. Frequent dose modifications are generally unnecessary although periodic dose increases due to regular weight gain are appropriate.

The most frequent reason to modify the hydroxyurea dose, especially during the escalation to MTD, is hematological toxicity. Early clinical trials of hydroxyurea in children with SCD used appropriately conservative,(30) but with more clinical experience a somewhat more liberal approach can be safely used in the majority of children. Practical toxicity definitions and thresholds for erythrocytes, reticulocytes, neutrophils, and platelets are listed in Table V. Traditionally, hydroxyurea toxicity guidelines also include thresholds for hepatic or renal toxicity (e.g., transaminases >3–5X the upper limit of normal or a doubling of creatinine) but such organ toxicity is almost never related to hydroxyurea treatment. Indeed, significant increases in ALT or creatinine without accompanied hematological toxicity should prompt investigations for alternative etiologies.

When a hematological toxicity occurs on hydroxyurea therapy, the medication should be held until the cytopenia resolves. Almost all hematological toxicities are dose-dependent, reversible, and recover within 1 week of drug interruption, although severe toxicity (sometimes associated with bone marrow suppression from viral infections) may cause pancytopenia and take 2–3 weeks until recovery. When the counts recover the dose can either be resumed at the previous amount or modestly decreased, (e.g., reduced by 2.5 – 5.0 mg/kg/day). MTD usually remains quite stable unless there is substantial weight gain, development of splenomegaly, or change in renal function. If the ANC is > 3000 / μL for 2 visits at a stable dose, the MTD dose can be increased by a small amount, approximately 2.5 mg/kg/day. However, before increasing the hydroxyurea dose beyond a previously established stable MTD, the likelihood of diminished medication adherence should be strongly considered. If a child is admitted or treated for an acute sickle complication hydroxyurea should not be held unless there is evidence of hematological toxicity.

Maximizing Adherence and Minimizing Failure

Poor adherence is the primary reason that hydroxyurea therapy is ineffective in children with SCD. Medication non-adherence is perhaps the best documented but least understood health-related behavior.(41) Anticipation of barriers to adherence for individual patients combined with the development of creative solutions will promote adherence and optimal beneficial drug effects. It is clear that children and their family members will be more adherent to therapy and the relatively frequent clinic visits if they believe that treatment will be beneficial. A very effective way to personalize the tangible benefits of hydroxyurea therapy is to show the beneficial trends in laboratory values, and review the erythrocyte changes on peripheral blood smear that occur with good adherence and treatment response.

Adherence is also optimized when the same dose is administered every day at a consistent time convenient for the patient and family without dividing the daily dose to BID or TID. Emphasis should be placed on choosing a time that will lead to reliable dosing more so than an exact time as varying the time by several hours between days is not problematic. Occasional patients (aproximately 5%) will mention gastrointestinal symptoms such as abdominal pain or nausea after taking hydroxyurea in the morning; in these instances changing to evening dosing usually leads to resolution of symptoms. At each clinic visit the importance of daily administration should be emphasized and specific questions regarding adherence should be asked (e.g., Who gives the dose? What time is it administered? How many doses are missed per week?). The parent must be reminded they are in charge of ensuring that the medication is swallowed each day. It is imperative to anticipate that occasionally children will miss a dose of hydroxyurea without any immediate ill effect. Actively reminding the patient that billions of blood cells are produced every day and hence the medication must be taken every day for maximal benefit is logically appealing, even to young patients.

The use of simple adherence aids or mnemonic devices (e.g., preloaded pill cases, medication scorecard/calendar, daily cell phone alarm, centralized texting reminders, keeping the pill bottle in plain sight, associating pill taking with a daily event) can significantly improve adherence (14). The best strategy for adherence must include a thorough understanding of the rationale for treatment, continuity of providers, and regular clinic visits to engender trust and loyalty, emphasize the need for daily adherence, and demonstrate the tangible benefits of treatment.

Failure of hydroxyurea to produce clinical and/or laboratory benefit seems quite rare in children who successfully take the medication with adequate dosing and schedule. Response rates to hydroxyurea in adults may be lower and one could hypothesize is related to the decreased cellularity or health of the adult marrow, early renal disease, hesitation to push to MTD, or poorer adherence (23, 42).

GAPS IN KNOWLEDGE

Other Genotypes of SCD

The published experience with hydroxyurea is almost entirely limited to HbSS, HbSβ^0 thalassemia, or Italian and Greek patients with HbSβ^+ thalassemia. Compound heterozygous variants of severe SCD are uncommon and rarely eligible or enrolled in clinical trials. There remains a need for rigorous evaluation of hydroxyurea in patients with HbSC and the typically more mild HbSβ^+ thalassemia seen in people of African ancestry. However, there are substantially fewer people with these genotypes with severe disease manifestations and therefore identifying and enrolling suitable participants is very challenging. Thus the effects of HU in compound heterozygous sickle variants are not well known. HbSC represents 25–30% of cases of SCD in the United States, but remains the ignored stepchild in clinical trials

of SCD. (43) There is still a need for a Phase II trial of the safety and efficacy of hydroxyurea in patients with HbSC after the early closure of the CHAMPS trial due to poor enrollment. (10) Enrollment is likely to remain an issue for future clinical trials of treatments for HbSC, as many patients have more mild disease and are therefore less willing to participate in time-intensive studies. For this reason, inclusion and exclusion criteria should be designed to maximize potential enrollment and other endpoints should be considered (e.g., blood viscosity, sickle cell retinopathy).

Fixed dose vs. MTD

There has been no direct comparison of fixed dose to MTD in children or adults with SCD. However, the indirect comparison of multiple studies that escalated to MTD compared to fixed dose or escalation to clinical effect, supports greater improvement in beneficial laboratory measures (increased total Hb concentration, Hb F, decreased WBC) in children treated at the MTD (33, 44, 45). However, fixed dose hydroxyurea may require less frequent or no laboratory monitoring and cause fewer episodes of cytopenia as seen with 20 mg/kg/day dose used in the BABY HUG Study. This may be particularly valuable in regions with limited resources for health care.

Use in Resource Poor Countries

It is estimated that more infants with SCD are born each year in Africa alone (~200,000) than the size of the entire North American sickle cell population (46). The greatest improvements in North American pediatric sickle cell mortality coincided with widespread newborn screening, early initiation of penicillin prophylaxis, and use of conjugated vaccines against encapsulated bacterial pathogens. (47) The impact of more recent screening (e.g., TCD) and treatments (e.g., Hydroxyurea) may have had a more modest effect on pediatric mortality. The large clinical trials of HU in pediatric SCD have occurred almost exclusively in the US and Europe that together represent <1% of the global burden of SCD. (46) Focusing on developing infrastructure in the resource poor setting (newborn screening, infection prevention, controlling co-morbid disease) is likely to provide more ‘bang for the buck’ initially. The once daily oral dosing of hydroxyurea therapy makes it an attractive possible therapeutic intervention. Given that it is unlikely for there to be widespread access to facilities to perform laboratory monitoring, studying fixed dosing without monitoring may be appropriate.

CONCLUSION

In conclusion, this is an exciting time for clinicians that treat children with SCD and the children and families with disease. We have compelling evidence that hydroxyurea can reduce painful events and hospitalizations in children of all ages with HbSS. Fixed-dose hydroxyurea in young children and with dose escalation in older children is safe with monitoring for myelosuppression. However, the evidence is not sufficient to convince us to start hydroxyurea in all children with SCD (those children with a mild phenotype of HbSS and other genotypes). Evidence of the efficacy of hydroxyurea to prevent end-organ damage from HbSS and to prevent acute complications of HbSC and HbSβ^+ would expand the indications for use in children with HbSS with milder phenotypes and other genotypes of SCD.

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Abbreviations

FDA	Food and Drug Administration
HbSS	sickle cell anemia
SCD	sickle cell disease
HbSC	hemoglobin SC disease
HbSβ^0	hemoglobin S-β-null thalassemia
HbSβ^+	hemoglobin S-β-plus thalassemia
HbF	fetal hemoglobin
ACS	acute chest syndrome
MTD	maximum tolerated dose
RCT	randomized controlled trial

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Table I

Recently Completed Randomized Controlled Trials of Hydroxyurea in Children with Sickle Cell Disease

Study, Year	Entry Criteria	N	Treatment	Length	Primary Outcomes		Secondary Outcomes				
					Spleen	Renal-GFR	Pain	Dactylitis	ACS	Transfusion	TCD
BABY HUG 2011(9)	Age 9–18 months HbSS, HbSβ^0, No growth failure, developmental delay, or abnormal TCD	96 97	HU 20 mg/kg Sucrose placebo	2 yrs	27% 38% p=0.2	+23 ml/min +21 ml/min p=0.84	177 375 p=0.002	24 123 p<0.0001	8 27 p=0.02	35 63 p=0.03	+20 cm/sec +32 cm/sec p=0.0002
SWiTCH 2010(11) Abstract	HbSS, age 5–19 yrs with previous stroke and iron overload	67 66	Phlebotomy + HU 20–35 mg/kg Transfusions + chlelation	2.5 yrs	Stroke	Fe overload	TIA	Death			
					11% 0% NR	NR NR NS	9% 13%	1% 1%	Study stopped for futility after 80% of total patient follow-up time		
CHAMPS 2011(10)	HbSC,≥5 years, ≥1 vasocclusive event in last year, Hb 8–12.5 g/dl, >3% dense RBC No HU, Mg, or transfusion	36	HU 20 mg/kg HU+ placebo HU + Mg Mg + placebo Placebo	44 weeks	Dense RBC (>41 g/dl) 9% 12% 10% 13%		MCV 89 fl 76 fl p<0.01	HbF 5.2% 2.2% p<0.01	Closed for poor accrual 73% of participants <18 years old HbF and MCV ↑ more in children No difference in clinical events		

N indicates number of participants; GFR, glomerular filtration rate; ACS, acute chest syndrome; TCD, transcranial Doppler ultrasound; HU, hydroxyurea; HbSS, sickle cell anemia; HbSβ^0, sickle β-null thalassemia; Fe, iron;, TIA, transient ischemic attack, HbSC, sickle hemoglobin C disease; Hb, hemoglobin; RBC, red blood cell; Mg, magnesium pidolate; MCV, mean corpuscular volume; HbF, percentage of fetal hemoglobin; yrs, years, NR, not reported

Table II

Toxicity Results in Recent Studies of Hydroxyurea for Sickle Cell Disease

Study, Year	Drug	ANC 500–1250/ul	ANC <500/ul	Platelets <80,000/ul	Rash/nail changes	Sepsis or bacteremia	Other
BABY HUG 2011 (9)	HU	107 events in 45participants ↓ dose in 9 P<0.00001	5 in 5 P=0.26	12 in 11 P=0.32	122 in 62 P=0.08	3 in 2 P=0.26	Reticulocytopenia, chromosome and chromatid breaks, VDJ recombination events, and micronuclei assay results were similar in both groups
	Placebo	34 events in 18 participants ↓ dose in 5	2 in 2	8 in 7	165 in 69	6 in 5	
CHAMPS 2011(10)	HU	1	0	0	NR	NR	No difference in diarrhea and abdominal pain among groups
	Placebo	1	0	0	NR	NR	

HU indicates hydroxyurea; ANC, absolute neutrophil count.

Table III

Potential Indications and Strength of Recommendation* for Hydroxyurea Therapy in Children with HbSS

Category	Indication	Strength of Recommendation
Acute vaso-occlusive	Frequent Painful Events Dactylitis Acute Chest Syndrome	Strong Strong Moderate
Laboratory markers of severity	Low Hb Concentration Low HbF Elevated WBC Elevated LDH	Weak Weak Weak Weak
Organ Dysfunction Brain Lungs Renal	Elevated TCD velocities Silent MRI, MRA changes Stroke prophylaxis	Moderate Weak Moderate
	Hypoxemia Comorbid Asthma	Weak Weak
	Proteinuria	Weak
Miscellaneous	Sibling on hydroxyurea Parental Request	Weak Moderate

Hb indicates hemoglobin; HbF, hemoglobin F; WBC, white blood cell count; LDH, lactate dehydrogenase; TCD, transcranial Doppler ultrasound; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography;

*Strength of recommendation based on published data and expert opinion when data are unavailable (sibling on hydroxyurea, parental request)

Table IV

Instructions for compounding Hydroxyurea Syrup (100 mg/mL, 120 mL volume)

Ingredients:	Hydroxyurea 500mg capsules # 24 Sterile Water Syrpalta® or simple syrup vehicle
Procedure:	Empty the contents of the capsules into large beaker (or mortar if not using a magnetic stirring rod and plate). Add 60 mL of sterile water and stir vigorously until dissolved. Note: this may take several hours and the excipients in the powder will remain undissolved. The hydroxyurea will descend to the bottom of the beaker while the excipients will float on the top. Do not heat. The use of a magnetic stirring rod and stirring plate will help the dissolution process Once the hydroxyurea has completely dissolved, filter the solution to remove the excipients. Add sufficient quantity of flavored vehicle to a final volume of 120mL. (final concentration = 100 mg/mL)

Table V

Hematological toxicity thresholds requiring hydroxyurea dose modifications

Neutrophils	absolute neutrophil count (ANC) < 1.0×10^9/L (1000/μL
Hemoglobin	<7.0 gm/dL with low reticulocytes, e.g., absolute reticulocyte count < 100×10^9/L (100,000/μL) Decrease by >20% from previous value, with low reticulocytes as above
Reticulocytes	<80×10^9/L (80,000/μL) unless the hemoglobin concentration is >8.0 gm/dL
Platelets	<80×10^9/L (80,000/μL)