REVIEW ARTICLE

# Hydroxyurea for Sickle Cell Disease: A Systematic Review for Efficacy and Toxicity in Children

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## ABSTRACT

CONTEXT. Hydroxyurea is the only approved medication for the treatment of sickle cell disease in adults; there are no approved drugs for children.

OBJECTIVE. Our goal was to synthesize the published literature on the efficacy, effectiveness, and toxicity of hydroxyurea in children with sickle cell disease.

METHODS. Medline, Embase, TOXLine, and the Cumulative Index to Nursing and Allied Health Literature through June 2007 were used as data sources. We selected randomized trials, observational studies, and case reports (English language only) that evaluated the efficacy and toxicity of hydroxyurea in children with sickle cell disease. Two reviewers abstracted data sequentially on study design, patient characteristics, and outcomes and assessed study quality independently.

RESULTS. We included 26 articles describing 1 randomized, controlled trial, 22 observational studies (11 with overlapping participants), and 3 case reports. Almost all study participants had sickle cell anemia. Fetal hemoglobin levels increased from 5%–10% to 15%–20% on hydroxyurea. Hemoglobin concentration increased modestly (~1 g/L) but significantly across studies. The rate of hospitalization decreased in the single randomized, controlled trial and 5 observational studies by 56% to 87%, whereas the frequency of pain crisis decreased in 3 of 4 pediatric studies. New and recurrent neurologic events were decreased in 3 observational studies of hydroxyurea compared with 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.

CONCLUSIONS. Hydroxyurea reduces hospitalization and increases total and fetal hemoglobin levels in children with severe sickle cell anemia. There was inadequate evidence to assess the efficacy of hydroxyurea in other groups. The small number of children in long-term studies limits conclusions about late toxicities. *Pediatrics* 2008; 122:1332–1342

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**Key Words**
hydroxyurea, sickle cell disease, systematic review, efficacy, toxicity

**Abbreviations**
SCD—sickle cell disease
ACS—acute chest syndrome
HbSS—sickle cell anemia
HbF—fetal hemoglobin
RCT—randomized, controlled trial
AHRQ—Agency for Healthcare Research and Quality
MTD—maximum tolerated dose
HUSOFT—Hydroxyurea Safety and Organ Toxicity
TCD—transcranial Doppler
ANC—absolute neutrophil count
HPRT— hypoxanthine phosphoribosyl transferase

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SICKLE CELL DISEASE (SCD) is the most common disorder identified by newborn screening in the United States with >1600 confirmed cases reported in the National Newborn Screening Information System in 2006 and >200 000 new cases per year in Africa.[1,2] Mortality in children has decreased dramatically with newborn screening and better supportive care including prophylactic penicillin, empiric broad-spectrum antibiotics for fever, and better transfusion support for acute complications such as splenic sequestration and acute chest syndrome (ACS). However, children with SCD are still hospitalized frequently, most commonly for severe pain, fever, or ACS.[3]

Hydroxyurea was approved by the US Food and Drug Administration (FDA) for the treatment of adults with sickle cell anemia (HbSS) in 1998 but does not currently have an FDA-approved indication for children. Hydroxyurea has multiple beneficial effects that may contribute to its efficacy in SCD. These effects include the induction of fetal hemoglobin (HbF) production[4] with a concomitant increase in total hemoglobin and decrease in hemolysis with the release of free hemoglobin (a contributor to endothelial dysfunction).[5] Hydroxyurea may also be beneficial by reducing the white blood cell count and the expression of cell-adhesion molecules that contribute to vasoocclusion.[6] The National Heart, Lung, and Blood Institute issued recommendations in 2002 supporting the use of hydroxyurea for the treatment of children with SCD.[7]

To evaluate hydroxyurea in the treatment of SCD, the National Institutes of Health Office of Medical Applications of Research commissioned a systematic review of the efficacy, effectiveness, toxicity, and barriers to the use of hydroxyurea for SCD. In this article, we report our review of the efficacy, effectiveness, and toxicity of hydroxyurea in children (<18 years old) with SCD.

## METHODS

The methods for this systematic review are described in detail in another report.[8]

### Data Sources

We searched Medline, Embase, TOXLine, and the Cumulative Index to Nursing and Allied Health Literature through June 30, 2007, for English, primary publications that described treatment in humans. We identified additional publications by reviewing reference lists and consulting experts.

### Study Selection

We included randomized, controlled trials (RCTs), cohort studies with an untreated comparison group, and pre/post studies in which at least 20 participants were treated, because the studies of smaller size were of very low quality and were more likely to be biased. For evidence of toxicity, we also included the Center for the Evaluation of Risks to Human Reproduction review of hydroxyurea, smaller cohort studies, and case reports. We included studies of adults with SCD only if leukemia or lymphoma was described.

Two reviewers independently reviewed titles, abstracts, and full articles for eligibility.

### Data Extraction

A single reviewer abstracted data, and a coinvestigator verified accuracy. Reviewers were not masked to the journal or authors and their institutions.[9] Discrepancies were resolved through discussion and rereview.

Reviewers abstracted general study and participant characteristics and efficacy and toxicity outcomes onto Web-based forms. We abstracted select data from case reports (disease, subject age, duration of treatment, reported adverse event[s]) and assessed causality for each outcome by using the World Health Organization's causality assessment instrument described below.[10]

### Quality Assessment

We assessed the quality of randomized studies by using the scoring system developed by Jadad et al.[11] To assess quality of the observational studies, we developed a form to identify key elements for observational research as advocated by experts.[12–14] The form included 3 questions about the study population, 2 about the intervention, and 3 to identify potential confounders.[8] For our quality assessment of surveys, we adapted information from a review of the validity of evaluation instruments.[15,16] We included 2 questions that addressed data collection and the survey-completion rate, 3 about the study population, and 3 about the validity and reliability of the survey instrument.[8] Two reviewers completed quality assessments independently.

### Data Synthesis

We created detailed evidence tables for eligible studies. We did not quantitatively pool outcome data, because there were few RCTs, and qualitative heterogeneity among the observational studies made pooling these studies inappropriate.

### Grading of Evidence

We adapted an evidence-grading scheme recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[17] and modified in the Evidence-Based Practice Center manual.[18] We considered the evidence about efficacy and effectiveness together and toxicity separately. If an outcome was not evaluated in at least 2 RCTs, our evidence grade reflected data from the best available nonrandomized trials or observational studies because of the importance of replication of results.

We assessed the quality and consistency of evidence by evaluating the risk of bias (study quality scores), the applicability of the study population to the target population, and the strength and precision of the effect seen. Causality in case reports of toxicity was evaluated per the World Health Organization Collaborating Center for Drug Monitoring.[10,19] Two investigators graded the strength of the evidence for each question, and then all investigators reached consensus.

### Role of the Funding Source

This topic was nominated by the National Institutes of Health Office of Medical Applications of Research and selected by the Agency for Healthcare Research and Quality (AHRQ) for systematic review by an evidence-based practice center. A representative from the AHRQ served as a task order officer and provided technical assistance during the conduct of the full evidence report and provided comments on draft versions of the full evidence report. The AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis or interpretation, or preparation, review, or approval of the manuscript for publication.

### Data Synthesis

As shown in Fig 1, our search identified 12 555 potentially relevant citations and ultimately yielded 26 studies on the efficacy, effectiveness, or safety of hydroxyurea in children with SCD.

## IS HYDROXYUREA EFFICACIOUS AND EFFECTIVE FOR CHILDREN WITH SCD?

### Trial

A single RCT tested the efficacy of hydroxyurea in 25 children with HbSS at 2 centers in Belgium.[20] This was a small crossover study of moderate quality (Jadad score of 3 of 5, because the method of randomization was described incompletely and only the participants were masked to treatment assignment). The participants were

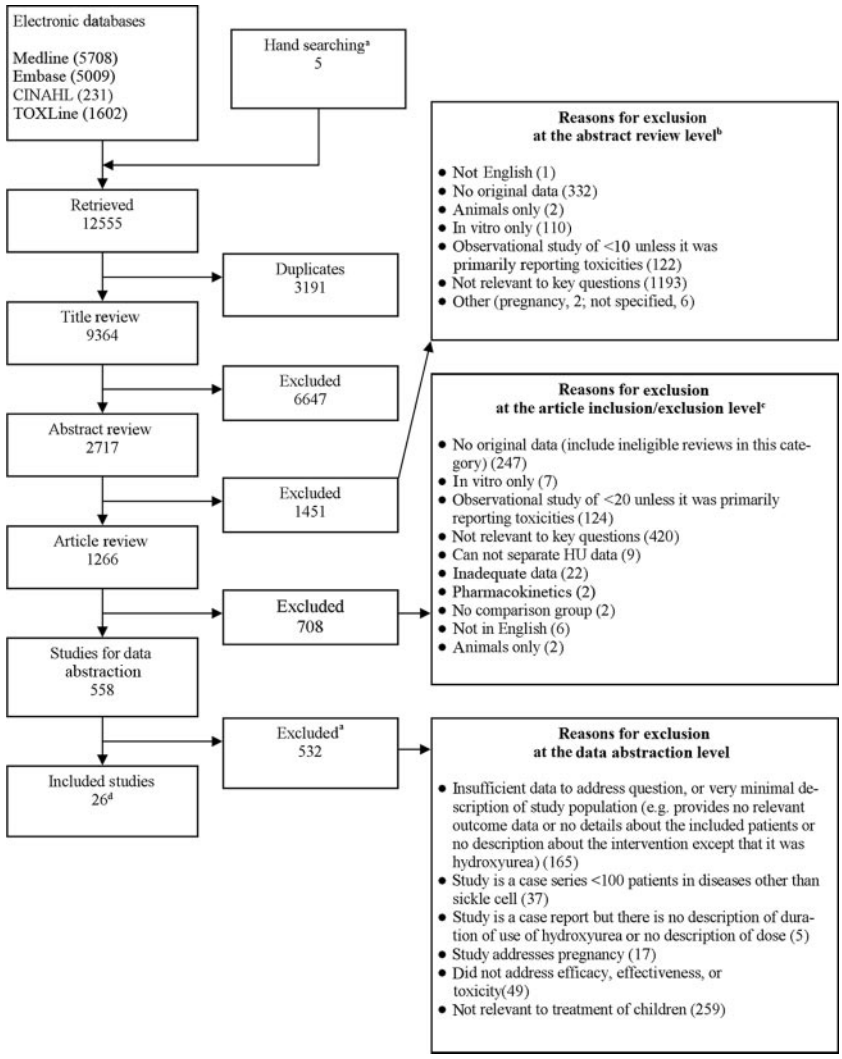


FIGURE 1
Summary of literature search and review process. [a] See "Methods" for details. [b] Total reasons for exclusion at the abstract level exceeds 1451 because reviewers were allowed to enter multiple reasons for exclusions. In addition, reviewers were not required to agree on the reason for exclusion. [c] Total reasons for exclusion at the article-review level exceeds 708 because reviewers were allowed to enter multiple reasons for exclusions. In addition, reviewers were not required to agree on the reason for exclusion. [d] Includes 3 case reports.

2 to 22 years old (median: 9 years) and received hydroxyurea or placebo for 6 months followed by the other treatment. They were treated to the maximum tolerated dose (MTD) or a maximum of 25 mg/kg per day. Three (14%) participants were excluded after 4 to 5 months for failing to return for follow-up.

Hemoglobin levels increased by a mean of 0.4 g/dL ($P = .07$). The mean absolute increase in HbF levels was 10.7% ($P < .001$). Hospitalizations and the number of hospitalized days per year were lower during hydroxyurea treatment than during placebo treatment (1.1 vs 2.8 admissions [$P = .0016$] and 7.1 vs 23.4 days [$P = .0027$], respectively).[20]

### Other Study Designs

We identified 22 observational studies (Appendix 1) published between 1996[21] and 2007[22] that included 15 to 225 patients.[21,23] Sixteen were pre/post studies.[21,22,24–37] Two studies included historical controls.[27,33]

The study goals varied markedly (Appendix 1). Most studies reported both efficacy and toxicity data; however, 5 were primarily toxicity studies,[23,28,30,38,39] 8 were primarily efficacy studies,[20,21,24,27,29,31,33,34] and 9 were primarily effectiveness studies.[22,25,26,32,35,37,40–42]

#### *Patient Clusters*

Because we were concerned that some patients may have been described in more than 1 publication, we identified 4 clusters of studies. One cluster included articles from the Safety of Hydroxyurea in Children With Sickle Cell Anemia (HUG-KIDS) study,[28,34,37] and 1 cluster included the Hydroxyurea Safety and Organ Toxicity (HUSOFT) study.[27,33] In a third cluster, we included studies from the French Study Group on Sickle Cell Disease.[23,24,29,38] We suspect that children enrolled in their initial study were also described in the survey and follow-up study. The fourth cluster, from the Belgian Sickle Cell Group, described patients from their registry.[25,26]

#### *Interventions*

The initial dosage and titration schedule for hydroxyurea varied little. Most started at 15 or 20 mg/kg per day and increased by 5 mg/kg per day every 4 to 26 weeks until

TABLE 1 **Efficacy of Hydroxyurea in Observational Studies of Children With SCD**

| Outcome | Studies, *n* | Magnitude and Consistency of Effect | Evidence Grade |
|---|---|---|---|
| HbF% | 17 | 93%–366% increase | High |
| Hemoglobin | 16 | 5%–20% increase | High |
| Pain crises | 5 | Significant reductions in 3, no difference in 1, no baseline data in 1 | Moderate |
| Hospitalization | 5 | 56%–87% decline in yearly rate | High |
| Transfusions | 3 | Decreased in 3 small studies | Insufficient |
| Neurologic events | 3 | Comparable stroke rates as on chronic transfusion, stable brain images | Low |
| Splenic function | 3 | Improved in 14%–45% of children by scintigraphy; no change in pitted red cells in 1 study | Low |

toxicity or according to clinical response. One study specifically tested the efficacy of 15 mg/kg per day of hydroxyurea without titration,[32] and another used a fixed dose of 20 mg/kg per day.[33]

*Description of the Quality of the Studies*

The studies received between 31%[39] and 93%[21] of the possible points on a 16-point scale for assessing the quality of observational studies. There were 6 high-quality studies that received >80% of the quality points.[21,24,28,30,34,37] Most reports included objective outcomes and detailed interventions. The source of participants, inclusion criteria, and patient characteristics were less well described. The quality of reporting was poor regarding adherence and losses to follow-up, which can be an important bias in cohort studies.

There was only 1 high-quality study of the effectiveness of hydroxyurea for SCD.[37] The 3 survey-based studies provided little detail about the surveyed patients and providers and did not use validated instruments; however, they adequately collected toxicity data (their stated objective).[23,38,43]

*Description of Included Patients*

Included patients are summarized in the full evidence report.[8] The mean or median age of children in the 22 observational studies ranged from 1.3 to 14 years. One study included children and adults, but 94% of these participants were <20 years old at treatment initiation.[25] Few reports described the clinical severity of their cohorts on entry, although this information could often be inferred from the eligibility criteria. Most studies were limited to children with HbSS or sickle β-null thalassemia; a minority included a few participants with other genotypes.[23–26,37,38,42] The duration of observation varied both among and within studies. The longest median follow-up was 58.8 months in an extension study of the HUSOFT cohort.[27] Some individuals within each study were followed for longer, although they were not necessarily treated with hydroxyurea for the entire period.

*Efficacy and Effectiveness*

The observational studies more frequently reported hematologic than clinical outcomes. HbF% was reported in 17 studies (Table 1) and increased substantially from a mean of 5% to 10% at baseline to 15% to 20% during treatment. The percentage of F cells was reported less frequently, but it increased from baseline in 3 of 4 studies.[27–29] In the fourth study, the maintenance of a stable percentage of F cells and HbF% over 104 weeks of treatment, rather than the decline usually seen in young children, was attributed to hydroxyurea.[33] The 3 retrospective studies reported increases in HbF% comparable to that seen in the prospective studies.[32,37,41] Hemoglobin concentration increased modestly (~1 g/dL) but significantly across studies.

The frequency of pain crises decreased in 3 of 4 studies. In a retrospective study, pain crises declined from a median of 3 to 0.8 per year on treatment during a median follow-up of 24 months[32] using a fixed-dose of hydroxyurea (15 mg/kg per day) in a resource-poor environment (Central America and the Caribbean). A small, high-quality prospective study found a decrease in pain events from 3.1 per year before hydroxyurea to 1.2 per year during therapy.[30] In another study, pain frequency decreased from a median of 4 to 2 episodes per year during therapy ($P = .0009$).[31] Hankins et al[27] reported 17 children who had been enrolled in the HUSOFT trial during a 4-year extension study. Treated patients had 33.8 pain events requiring hospitalization per 100 patient-years, comparable to that of historical controls from the Cooperative Study of Sickle Cell Disease cohort (32.4 per 100 patient-years [$P = .87$]).

Hospitalization rates decreased in all 5 studies that described this outcome. In the study of fixed-dose hydroxyurea described above, the hospitalization rate for patients on treatment decreased from a median of 4 to 0.5 per year.[32] Oliveri and Vichinsky[30] reported that hospitalizations declined from 6.7 to 1.7 per year with excellent adherence measured by an electronic monitoring device. In 2 studies from the Belgian Registry, hospitalization rates declined from 2.8 to 1.1 per patient-year and from 3.2 to 1.4 per patient-year.[25,26] Similarly, in a small study of severely ill children, hospitalization rates decreased from 7 to 3 per year.[21]

Only 3 studies described transfusion use in children. The transfusion rate decreased from 3.9 to 0.43 per year during treatment in 21 patients and from a median of 3 to 0 per year in 51 children.[31,32] Oliveri and Vichinsky[30] described a smaller but statistically significant decrease from 1.8 to 0.4 per year in 17 children.

Hydroxyurea for secondary stroke prevention was assessed in 35 children who discontinued chronic transfusions.[35] The rate of recurrent stroke was 5.7 per 100 patient-years. For comparison, this rate was higher than the 2.2 per 100 person-years reported in a retrospective cohort study of children who received ongoing transfusions[44] but lower than the 70% prevalence of recurrent stroke seen in the first year after discontinuing transfusion without alternative treatments.[45] Another study reported stable MRI of the brain during hydroxyurea

treatment in 24 of 25 children.[22] In the Belgian Registry, during 426 patient-years of hydroxyurea treatment, the rate of stroke or transient ischemic attacks was 1.3 per 100 patient-years, but no comparison rate was provided.[26]

Two studies reported transcranial Doppler (TCD) velocities, because elevated velocities are associated with an increased risk of stroke. Kratovil et al[41] described a decrease in the mean maximum velocity with hydroxyurea treatment from 125 to 111 cm/second. An untreated control group had an increase in velocity over the same time period of 4.7 cm/second. Zimmerman et al[42] prospectively studied 36 children who had repeat TCD after a mean of 10 months on hydroxyurea. Overall, velocities decreased significantly, and in 14 of 15 children with conditional baseline TCD velocities (170–199 cm/second), the values declined; in 5 of 6 with abnormal velocities (>200 cm/second), whose families declined transfusions, the velocities decreased to <200 cm/second.

Two of the 4 studies showed improved splenic function during hydroxyurea therapy.[22,31] Santos et al[31] reported that splenic function (as measured by scintigraphy) improved in 10 of 21 children, was stable in 8, and worsened in 3. In another prospective study of scintigraphy in 43 children, 6 (14%) completely recovered splenic function and 2 (5%) had preserved splenic function after a median of 2.6 years of hydroxyurea at the MTD. However, a small study found no difference in the number of pitted red cells (a marker of splenic function) in 12 children.[30] A cross-sectional study used flow cytometry for Howell-Jolly bodies (an automated procedure that is strongly correlated to the number of pitted red cells) as the outcome.[36] In patients with spleens, those taking hydroxyurea had more Howell-Jolly bodies than did those not taking the drug. This relationship was true as well for the patients without spleens, suggesting that Howell-Jolly bodies are increased by hydroxyurea irrespective of splenic function.

A retrospective study reviewed the efficacy of hydroxyurea for the prevention and treatment of microalbuminuria, a possible precursor to renal insufficiency.[46] Of the 17 treated patients without microalbuminuria at baseline, 16 remained free from microalbuminuria, and 4 of 9 patients with microalbuminuria had resolution during treatment with hydroxyurea.[40]

### Evidence

On the basis of 1 pediatric RCT of moderate quality and several observational studies, there is strong evidence that hydroxyurea increases HbF% and total hemoglobin, and reduces the frequency of hospitalization in children with SCD. There is moderate evidence (from 4 observational studies) that hydroxyurea decreases the frequency of painful crisis and weak evidence (from 3 observational studies) that it decreases neurologic events. There is insufficient evidence to comment on its effect on the frequency of transfusions and mortality in children (Table 1).

## ARE THERE PREDICTORS OF RESPONSE TO HYDROXYUREA?

### Baseline Predictors of Response

Children with SCD tended to have a larger increase in HbF% if they had a higher F reticulocyte count[29] or hemoglobin level[34] at baseline. The HbF% response was not predicted by age, gender, hematologic toxicities, or SCD haplotype.[29,34] Two studies from Belgium did not identify predictors of clinical response.[20,25] However, 1 study found that higher cerebral blood flow velocity at baseline was associated with a lower velocity on hydroxyurea.[41,42] In another study, recurrent stroke in children receiving hydroxyurea for secondary stroke prevention was associated with older age and initiation of hydroxyurea after chronic transfusion had been stopped.[35]

### Other Factors Associated With Response

In children with SCD on hydroxyurea, the HbF% response is associated with better adherence to treatment, higher dose,[27] increases in hemoglobin level and mean corpuscular volume from baseline, decreases in reticulocytes and white blood cell count, and lower reticulocyte and white blood cell counts at the MTD.[34] Recurrent stroke was associated with a higher absolute neutrophil count (ANC) during treatment.[35]

## ARE THERE TOXICITIES ASSOCIATED WITH USE OF HYDROXYUREA IN CHILDREN WITH SCD?

After a literature review (through January 2007) and expert panel discussion, the Center for the Evaluation of Risks to Human Reproduction of the National Toxicology Program and the National Institute of Environmental Health Sciences critically evaluated the effect of hydroxyurea on growth and development.[47,48] We briefly review their findings relevant to children and describe the additional nondevelopmental toxicities of hydroxyurea.

The panel concluded that hydroxyurea treatment of children aged 5 to 15 years does not cause growth delay but that there were insufficient data to evaluate its effects on puberty. They estimated, on the basis of a single study, that nursing infants of women taking hydroxyurea are exposed to 1 to 6 mg/day of hydroxyurea but did not comment on the effect of this exposure. The expert panel found no data on the effects of hydroxyurea on female human or animal reproductive processes or germ cells. However, they concluded that there is developmental toxicity in rat and mice fetuses with in utero exposure to hydroxyurea and male reproductive toxicity (decreased testis weight and sperm count in mice). The expert panel considered these data relevant to humans and had concerns about the adverse effect of hydroxyurea on spermatogenesis.

We reviewed the cases of leukemia in detail (including those identified from case reports) to evaluate the leukemogenic potential of hydroxyurea in SCD. There were 6 cases including 2 children and 4 adults. In France, a 10-year-old girl was treated with hydroxyurea for 1.5 months for bone pain before she was diagnosed with acute lymphoblastic leukemia.[23,38] The Belgian

TABLE 2 **Toxicities of Hydroxyurea Reported in Pediatric Studies**

| Author | *n* (Patient-Years) | Neutropenia | Platelets (<80 000/μL) | Anemia | Rash/Nail Changes | Other |
|---|---|---|---|---|---|---|
| Ferster et al[20] | 25 (12.5) | 0 | 2 | 0 | — | No clinically significant toxicity; no thrombocytopenia in placebo arm |
| Kinney et al[28] | 84 | 56, ANC < 2000/μL | 7 | 27 | 5 | No creatinine elevation; 12 headache; 11 ALT elevation |
| Zimmerman et al[37] | 122 (455) | – | HbSC 3/7<br>HbSBthal 1/7 | — | ~10% | No increase in VDJ rearrangements; 2 deaths (pneumococcal sepsis, acute hemolytic transfusion reaction) |
| Wang et al[33] | 28 | 17, ANC < 1500/μL<br>6, ANC < 500/μL | 1 | 7 | — | 2 accidental overdoses; 1 ALT elevation; 1 death (splenic sequestration) |
| Hankins et al[27] | 21 | 10 in year 3<br>9 in year 4 | 2 in year 5<br>1 in year 6 | 3 in year 3<br>1 in year 4 | — | 1 splenic sequestration; 1 death (pneumococcal sepsis) |
| de Montalembert et al[24] | 35 | 1 | 1<br>< 100 000/μL | – | 5 | 1 renal failure (from systemic lupus erythematosus); 1 secondary amenorrhea |
| de Montalembert et al[38] | 101 | 5, ANC < 1500/μL;<br>2, ANC < 1000/μL | 4<br>< 100 000/μL | — | 8 | 3 headache; 1 leukemia after 1.5 mo; 1 leg ulcer |
| de Montalembert et al[23] | 225 | 9 | 9 | 1 | — | 6 hypersplenism; 1 azoospermia; 1 leg ulcer (reported earlier)[38]; 1 leukemia (reported earlier)[38]; 1 death (asystolic cardiac arrest) |
| Gulbis et al[26] | 109 (426) | — | 2<br>< 100 000/μL | 5 < 60 g/L | — | 1 leukemia after 6 y; 1 death (splenic sequestration) |
| Scott et al[21] | 15 | 0 | 0 | 3/13 | 1 | 1 death (intracranial hemorrhage); 1 headache |
| Olivieri and Vichinsky[30] | 17 | 9 | 3 | 0 | 1 | 11 creatinine increase; 1 dyspepsia; 1 conjunctivitis |
| Hanft et al[39] | 38 | — | — | — | — | HPRT cloning efficiency and VDJ recombination events (see text) |

ALT indicates alanine aminotransferase; HbSC, sickle-hemoglobin C disease; HbSBthal, sickle β-thalassemia; —, data were not reported.

group reported a 21-year-old woman who developed acute promyelocytic leukemia after 8 years of hydroxyurea therapy.[26] A third case was described in a survey on cancer development in 16 613 patients with SCD. The survey included a 14-year-old who developed acute lymphoblastic leukemia 3 months after initiating hydroxyurea and 6 other cases of leukemia without previous hydroxyurea exposure. There was no description of the prevalence of hydroxyurea use in the patients without cancer.[43] The 2 case reports described a 25-year-old woman who developed acute myelocytic leukemia (FAB M1) after 2 years of hydroxyurea[49] and a 42-year-old woman diagnosed with acute myelocytic leukemia after 6 years of hydroxyurea for SCD.[50] An abstract described a 27-year-old woman who developed an acute nonlymphocytic leukemia after 8 years of treatment with hydroxyurea. The bone marrow aspirate suggested that leukemia developed in the setting of myelodysplasia.[51]

The single pediatric RCT reported thrombocytopenia in 2 of 25 children and no clinically significant toxicity.[20] Hematologic toxicities occurred in 10 of 11 observational studies that described toxicities (Table 2). Mild-to-moderate neutropenia was reported most frequently (4%–67% of the participants),[28,38] followed by thrombocytopenia (0%–18%)[21,30] and worsening anemia (0%–23%), defined as a 20% decrease or <50 g/L in most studies.[21,38] Severe neutropenia (ANC < 500/μL) was reported in only a single study in 6 of 28 infants during 2 years of treatment, but none of these episodes were associated with an invasive bacterial infection.[33] Elevations of alanine amino transferase were reported in 4% and 13% of the participants of 2 studies.[28,33]

Clinical adverse events could rarely be directly attributed to hydroxyurea. Common mild toxicities included rash and nail changes (reported in ~10% of participants in 6 studies)[21,24,28,30,35,38] and headache (3%–15% in 3 studies).[21,24,28] Hypersplenism and/or splenic sequestration was uncommon (1%–5% in 4 studies).[23,26,27,33] Other rare adverse events in the observational studies included 2 accidental overdoses of hydroxyurea in toddlers,[33] hyperbilirubinemia (2),[37] secondary amenor-

rhea,[24] conjunctivitis (1),[30] dyspepsia (1),[30] intracranial hemorrhage (1),[21] leg ulceration (1),[38] renal failure attributed to systemic lupus erythematous (1),[24] and death (7).[21,23,26,27,33,35] The 2 deaths from splenic sequestration were possibly attributable to treatment with hydroxyurea, because improved splenic function may increase the risk of hypersplenism and splenic sequestration.[26,33] The French studies reported a variety of clinical toxicities, but only 19 of 225 participants discontinued hydroxyurea because of toxicity.[23]

Two studies addressed the mutagenicity of hydroxyurea in children. Hanft et al[39] used 2 established in vitro assays of acquired somatic mutations: the hypoxanthine phosphoribosyl transferase (HPRT) assay (which measures the frequency of mutations in the selectable HPRT gene locus) and the VDJ assay (which detects illegitimate recombination events between the $V_\gamma$ and $J_\beta$ gene loci). They reported a similar frequency of HPRT mutations in 21 children without hydroxyurea exposure and 17 children after a median of 7 and 30 months' exposure and a slight increase in VDJ events from 1.06 per $\mu$g DNA (no hydroxyurea exposure) to 1.58 per $\mu$g DNA (after 7 months) to 1.82 per $\mu$g DNA (after 30 months) ($P = .04$). The same laboratory reported a similar number of illegitimate VDJ recombination events in a group of 26 children after an average of 4 months (1.36 per $\mu$g of DNA) and 57 months (1.15 per $\mu$g of DNA) of treatment with hydroxyurea.

We reviewed 4 published case reports that described toxicities associated with hydroxyurea use in 5 children with SCD. Two of these reports described the same Greek child who developed Hodgkin's lymphoma.[52,53] The additional cases were nail hyperpigmentation[54] and avascular necrosis (1).[52]

We conclude, on the basis of our review of toxicities, that there is moderate evidence to support an increased risk of reversible, usually mild, cytopenias and rash or nail changes in children with SCD treated with hydroxyurea. There is insufficient evidence to estimate the risk of leukemia or other secondary malignancies, splenic sequestration, and leg ulcer development in children.

## ARE THERE PREDICTORS OF TOXICITY FROM HYDROXYUREA?

Only 1 study specified what predicted toxicity from hydroxyurea in children. Patients with hemoglobin SC disease had more frequent cytopenias with dose increases than children with other genotypes.[37]

## DISCUSSION

The published evidence supports that hydroxyurea increases HbF and decreases the rate of hospitalization in children with HbSS. There is far less evidence for many of the clinically important outcomes including painful crises, ACS, stroke, and cognitive development in children, but a methodologically rigorous RCT demonstrated significant reductions in painful crisis, ACS, and the number of transfusions in adults.[55] The limited pediatric evidence suggests that hydroxyurea may improve splenic function and decrease stroke risk.

Much of the data are from observational studies (often without a comparison arm) and may be confounded by regression to the mean for clinical outcomes. Patients are often started on hydroxyurea after a period of increased disease activity, so it is expected that the patient may return to their usual disease severity even without an efficacious therapy.

Hydroxyurea does not seem to affect the growth and development of children aged 5 to 15 years, but it has concerning developmental toxicity in rat and mice fetuses and reproductive toxicity in male mice. These and limited human data[56] imply adverse effects of hydroxyurea at therapeutic doses on spermatogenesis.

The underlying evidence for this review has limitations. Foremost, only a single RCT of 25 children evaluated efficacy, and the only effectiveness studies had single-arm observational designs. The results from the trial are not widely generalizable to the United States, because it occurred in a different health care system and mostly included patients with HbSS with frequent hospitalizations. These results may not apply to other genotypes of SCD and children with less frequent hospitalizations.

The evidence for adverse effects is limited as well. Observational studies (without control groups) are inadequate for evaluating the risk of adverse events that are complications of SCD, such as splenic sequestration (the cause of 2 of the 7 deaths reported in these studies). In addition, follow-up was often too short to identify adverse events that may require many years of exposure, such as leukemia, and losses to follow-up were substantial in most studies, potentially introducing additional bias.

Many subgroups require additional study. Patients with hemoglobin SC, nearly 30% of newborns with SCD,[57] were particularly understudied. Additional studies of hydroxyurea at doses other than the MTD are essential, because the monitoring required to determine the MTD may be a barrier to treatment, particularly in resource-poor regions. Additional research is needed to determine the optimal time for initiation of hydroxyurea to identify the criteria for treatment failure and surrogate outcomes for predicting clinical improvement. Also needed are randomized trials designed to prevent other complications of SCD, including renal insufficiency and pulmonary hypertension, and more rigorous effectiveness studies to evaluate hydroxyurea in a regular care setting.

## CONCLUSIONS

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. Comanagement 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.

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**APPENDIX 1 Observational or Single-Arm Studies of Hydroxyurea in SCD**

| Author (Year) and Design | General Study Information | Arm, *n* | HbF%[a] | Hemoglobin, g/L | Other Outcomes |
|---|---|---|---|---|---|
| Pediatric Hydroxyurea Safety Trial (HUG-KIDS) | | | | | |
| Kinney et al[28] (1999), prospective pre/post | Inclusion: age 5–15 y, HbSS, pain ≥3 or ACS in last year, 6 heights and weights in 2 y | HU, 84 | 17.8 (7.2)[b] | 90 (14)[b] | Effects by 6 mo |
| | Follow-up: up to 24 mo | Pre, 84 | 7.3 | 78 | |
| Ware et al[34] (2002), prospective pre/post | Inclusion: age 5–15 y, HbSS, pain ≥3 or ≥3 pain and ACS episodes in past year, ACS ≥3 in past 2 y | HU, 68 | 17.6 [2.9–32] | — | |
| | Follow-up: 11.7 mo (mean) | Pre, 68 | 6.7 | 77 | |
| Zimmerman et al[37] (2004), retrospective pre/post | Inclusion: on HU for ≥6 mo, SCD | HU, 122 | 19.7 (8.5)[c] | 97 (13)[c] | Efficacy maintained |
| | Follow-up: 45 mo (mean) | Pre-HU, 122 | 7.6 | 82 | |
| HUSOFT trial | | | | | |
| Wang et al[33] (2001), cohort with historic comparison arm | Inclusion: infants (age not specified), HbSS, HbS$\beta^0$thal | HU, 21 | 20.3 (4.9) | 88 (12) | |
| | Follow-up: 24 mo | Pre-HU, 28 | 21.8 (7.8) | 85 (12) | |
| | Comment: investigators matched 3 patients from the CSSCD to enrolled patients by diagnosis, gender, and age | CSSCD | 10.9 (7.9) | 77 (10) | |
| Hankins et al[27] (2005), prospective pre/post | Inclusion: enrolled in the HUSOFT trial[d] | HU, 17 | 23.7 (7.4)[c] | 91 (14)[c] | Pain crisis 33.8/100 patient-years |
| | Follow-up: 58.8 mo (25–72) | Pre-HU, 21 | 21.8 (7.8) | 85 (12) | |
| | Comment: investigators matched 3 patients from the CSSCD to enrolled patients by diagnosis, gender, and age | CSSCD | — | — | 32.4/100 patient-years |
| French cluster | | | | | |
| de Montalembert et al[24] (1997), prospective pre/post | Inclusion: age 4–20 y, HbSS, HbS$\beta^+$thal, HbS$\beta^0$thal, S$\alpha+$ thal, SC, pain hospitalization ≥3/y | HU, 35 | 13.7 [3.2–27.0][b] | 9 (14)[e] | Decreased painful crises in 32/35 |
| | Follow-up: 32 mo (12–59) | Pre-HU, 35 | 4 [0.85–13.9] | 84 (12) | |
| Maier-Redelsperger et al[29] (1998), prospective pre/post | Inclusion: SCD, pain ≥3/y | HU, 29 | 13 (9.4) | 91 (9) | |
| | Follow-up: 22 mo (12–26) | Pre-HU, 29 | 4 [0.85–13.9] | 84 (12) | |
| de Montalembert et al[38] (1999), survey | Inclusion: 2–20 y when starting HU | HU, 101 | — | — | HU stopped in 17 |
| | Follow-up: 22 mo (0.5–93) | Pre-HU, 101 | — | — | |
| de Montalembert et al[23] (2006), survey | Inclusion: Pain ≥3 hospitalizations, untransfused stroke, ACS, hemoglobin < 6–7, high TCD velocity, cardiac ischemia | HU, 225 | — | 82 (15)[f] | HU stopped in 82 |
| | Follow-up: 46 mo (0–152) | Pre-HU, 225 | — | 66 (5)[f] | |
| Belgian cluster | | | | | |
| Ferster et al[25] (2001), prospective pre/post | Inclusion: children and young adults, pain ≥2 hospitalizations/y, stroke, TIA, ACS, priapism, or AVN | HU, 93 | 16.7 (10.6)[g] | 88 (12)[g] | Hospitalizations 1.06 (1.9)/patient-year,[h] ACS 3.5/100 patient-years |
| | Follow-up: 42 mo | Pre-HU, 93 | 7.3 | 82 | Hospitalizations 2.76 (2.3)/patient-year |
| Gulbis et al[26] (2005), prospective pre/post, other | Inclusion: children and young adults, pain ≥2 hospitalizations/y, stroke, TIA, ACS, priapism, or AVN | HU, 70 | 14 g/L (HbF)[c] | 87 [67–120][e] | Hospitalizations 1.38 (2.2)/patient-year[e] ACS 3.3/100 patient-years, stroke/TIA 1.3/100 patient-years |
| | Follow-up: 47 mo, 426 patient-years | Pre-HU, 109 | 3 g/L (HbF) | 82 [67–100] | Hospitalizations 3.2 (2.7)/patient-year |

APPENDIX 1 **Continued**

| Author (Year) and Design | General Study Information | Arm, *n* | HbF%[a] | Hemoglobin, g/L | Other Outcomes |
|---|---|---|---|---|---|
| Other | | | | | |
| Scott et al[21] (1996), prospective pre/post | Inclusion: age 10–17 y, HbSS, Hb Sβ$^0$thal, S α+ thal, ≥3 hospitalizations/y for pain, ACS, or priapism | HU, 13 | 15.2[h] (9.8) | 95[g] (15) | Hospitalizations 3/y (4) |
| | Follow-up: 43.6 mo [24–63] | Pre-HU, 15 | 6.9 (6.2) | 82 (10) | Hospitalizations 7/y (2.4) |
| Olivieri and Vichinsky[30] (1998), prospective pre/post | Inclusion: HbSS, pain ≥3 or ACS in the previous year | HU, 17 | 16.7[b] (1.8) | 102[b] (36) | Hospital (d) 8.1/y (2.8),[h] VOC 1.2/y (0.4),[e] ACS 0.2/y (0.1),[e] transfusion 0.4/y (0.2)[e] |
| | Follow-up: 18 mo | Pre-HU, 15 | 7.6 (1.6) | 89 (43) | Hospital (d) 29.1/y (4.8), VOC 3.1/y (0.5), ACS 1.3/y (0.5), transfusion 1.8/y (0.4) |
| Ware et al[35] (2004), prospective pre/post | Inclusion: age pediatric, HbSS, transfusion, stroke | HU, 35 | 18.6 (6.6) | 92 (14) | Stroke recurrence rate 5.7/100 patient-years |
| | Follow-up: 29 mo [12–49] | | | | |
| Kratovil et al[41] (2006), retrospective case-control | Inclusion: HbSS, pain >5/y, stroke and not transfused, severe ACS, TCD examination before and during HU | HU, 24 | 11.8[b] | 82[i] [59–106] | CBF velocity 111.2 cm/sec[c] |
| | Follow-up: 6–48 mo | No HU, 24 | 4.6 | 78 [52–106] | CBF velocity 124 cm/sec |
| Svarch et al[32] (2006), retrospective pre/post | Inclusion: age 4–18 y, HbSS, pain ≥3 in past year or sepsis ≥1 in past 2 y | HU, 51 | 12.4[b] (7.9) | 85[b] (10) | Hospitalizations 0.5/y [0–4], VOC 0.8/y [0–2], transfusions 0/y [0–3] |
| | Follow-up: 24 mo | Pre-HU, 15 | 6.4[b] (5.3) | 78[b] (10) | Hospitalizations 4/y[0–6], VOC 3/y [0–6] transfusions 3/y, [0–8] |
| Zimmerman et al[42] (2007), prospective pre/post | Inclusion: children, HbSS, HbSO | HU, 37 | 22.7 (7.9)[c] | 94 (10)[c] | CBF velocity 135 cm/sec (27)[c] |
| | Follow-up: 10 mo (5) | | | | |
| | Comment: stroke rate was 0.52/100 patient-years | Pre-HU, 37 | 10.3 (6.6) | 78 (11) | CBF velocity 166 cm/sec (27) |
| McKie et al[40] (2007), retrospective cohort | Inclusion: age >2 and <21 y, HbSS | HU, albumin + 19 | 11.8 [4–25.4] | — | 16/17 without microalbuminuria |
| | | HU, albumin + 9 | 19.8 (21.5) | 86 (10) | 4/9 normalized microalbuminuria |
| | Follow-up: 21.8 mo | Pre-HU, + albumin 9 | 8.6 (1.0) | 80 (14) | |
| | | Pre-HU, 154 | 8.5 (1.1) | — | |
| Harrod et al[36] (2007), cross-sectional | Inclusion: age <20 y | HU/no splenectomy, 46 | | | HJB/10$^6$ RBC 3533 (2665) |
| | | No HU/no splenectomy 58 | | | 1263 (1193) |
| | Follow-up: NR | HU/splenectomy 11 | | | 4984 (2037) 2101 (945) |
| | | No HU splenectomy 10 | | | |
| Hankins et al[22] (2008), retrospective pre/post | Inclusion: children, HbSS, HbSβ$^0$thal | HU, 52 | — | 95 (17) | Splenic function increased 6/40, stable brain MRI 24/25 |
| | Follow-up: 29 mo (2–103) | | | | |
| | Comments: splenic function measured by scintigraphy | Pre-HU, 52 | — | 85 (15) | |
| Santos et al[31] (2002), prospective pre/post | Inclusion: age 3–22, HbSS, HbSβ$^0$thal, ≥2 episodes of priapism or ACS, ≥6 painful crises | HU, 21 | 20 | — | VOC 1.81/y, transfusions 0.43/y, splenic function increased in 10 |
| | Follow-up: 12 mo | — | 4.8 | — | VOC 5/y, transfusions 3.9/y |

HU indicates hydroxyurea; NR, not reported; HbSβ$^+$thal, sickle β$^+$ thalassemia; HbSβ$^0$thal, sickle β-null thalassemia; HbSC, sickle-hemoglobin C disease; HbSO, hemoglobin SO Arab; CSSCD, Cooperative Study of Sickle Cell Disease; AVN, avascular necrosis; VOC, vasoocclusive crisis; CBF, cerebral blood flow; HJB, Howell-Jolly Body; TIA, transient ischemic attack; RBC, red blood cell; —, data were not reported.

[a] Mean (SD) [range] unless otherwise noted.

[b] $P < 0.0001$.

[c] $P < 0.001$.

[d] This is the extension study of the HUSOFT trial; 17 completed 4 years, and 11 completed 6 years from start.

[e] $P < 0.05$.

[f] Hemoglobin values from 20 patients treated for severe anemia.

[g] $P < 0.01$.

[h] $P < 0.005$.

[i] $P$ was not significant.

[@] Uses data from the phase I/II HUG-KIDS study, but analyses only include children who reached the MTD.

[!] Includes patients who were in the HUG-KIDS study ($n = 15$) and in the HUSOFT trial ($n = 7$) and 33 patients in stroke study.

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