
Chapter 5: Hydroxyurea Therapy in the Management of Sickle Cell Disease

Introduction

This chapter addresses the use of hydroxyurea (also called hydroxycarbamide) in adults and children who have SCD. Hydroxyurea can reduce the frequency of sickle cell-related pain and the incidence of acute chest syndrome (ACS). A brief overview of these complications will be presented.

Pain is the most common symptom of SCD. Pain can be acute, chronic, or an acute episode superimposed on chronic pain. Smith and colleagues¹⁴⁵ collected daily pain diaries for 232 adults with SCD; pain was reported on 54.5 percent of the more than 30,000 days analyzed. However, people sought medical care for pain on only 3.5 percent of those days. These data suggest that many people who have SCD may be undertreated for their pain, may not perceive a benefit of treatment, or may have learned to self-manage their pain. Understanding of the processes that lead to an acute vaso-occlusive pain crisis and the pathophysiology of the chronic pain syndrome remains limited. It is known that rigid red blood cells (RBCs) obstruct the microvasculature; however, a full understanding of how these events start and what role other factors play in this process—such as vascular adhesion molecules, leukocytes, reticulocytes, endothelial cells, and platelets—has not been fully elucidated. With the exception of the joint pain of avascular necrosis, chronic pain syndromes in SCD have not been studied. In other chronic pain syndromes, central sensitization is thought to play a role.³⁶⁵ Hsieh and his colleagues³ described four people on chronic daily opioid medications for sickle cell pain who were weaned off these medications after successful stem cell transplants. This approach suggests the possibility that a reversible process may be responsible for the chronic pain that so frequently occurs in SCD.

Pulmonary complications are common in SCD. One of the most serious problems is ACS, which often follows an acute vaso-occlusive crisis (VOC) and can complicate many surgeries. The manifestations of ACS include fever, chest pain, hypoxemia, cough and/or dyspnea, and a new infiltrate evident on chest x ray involving at least one lung segment.²⁵¹ Potential etiologies of ACS include infection, bone marrow fat embolization, and *in situ* sickling with pulmonary infarction. ACS causes significant morbidity and is associated with higher risk of death. ([For additional discussion of ACS, refer to page 46](#) in the “Managing Acute Complications of Sickle Cell Disease” chapter)

Sickle cell anemia (SCA) refers to the clinically similar disorders HbSS or HbS β 0-thalassemia. Sickle cell disease (SCD) refers to all disease genotypes, including SCA and compound heterozygous disorders, such as HbSC, HbSD, and HbS β +thalassemia. The carrier state for hemoglobin S (HbAS or sickle cell trait) is not a form of SCD.

Multiple genetic and environmental factors influence the degree of hemolysis and the occurrence of vaso-occlusion in SCD. One of the best examples is the profoundly favorable effect that high fetal hemoglobin (HbF) levels have on preventing intra-erythrocytic hemoglobin S polymerization and vaso-occlusion. The beneficial effects of genetically determined, persistent elevations of HbF levels in people who have SCD throughout their lifespan were documented through carefully conducted cohort studies in the 1970s and 1980s.^{142,366} These observations supported the concept that therapeutic interventions to increase HbF levels could improve clinical outcomes, especially pain and ACS, in people who have SCD. For example, 5-azacytidine was found to be capable of inducing HbF production in cell cultures, an effect confirmed in an animal model³⁶⁷ and in a few people who had thalassemia or SCD. Other drugs capable of increasing HbF levels were sought to permit oral administration and more acceptable toxicity profiles.

Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as a promising drug candidate to increase HbF levels in people with SCD. Prior to its use in SCD, this medication has been in use for several decades to treat people with myeloproliferative disorders. Hydroxyurea is known to have rapid absorption and near-complete bioavailability and to be therapeutic with once-daily oral dosing. The initial clinical trial of hydroxyurea for the treatment of SCA involved two people. The study showed that short-term hydroxyurea therapy increased the number of HbF-containing reticulocytes and was not associated with short-term toxicities.³⁶⁸ This favorable result led to two carefully planned, extended studies testing the effects of hydroxyurea treatment in larger cohorts of people with SCA. Both of these clinical trials demonstrated that hydroxyurea was well tolerated and increased HbF levels in the majority of people.^{369,370} The results provided the necessary information to plan a major prospective phase III clinical trial to test the effects of hydroxyurea on clinical outcomes.³⁷¹ Subsequently, numerous observational studies and three randomized trials in people with SCA were conducted. Limited data from observational studies are available on hydroxyurea therapy in people with genotypes other than HbSS or HbS β^0 -thalassemia.

Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of action and benefits exist. For example, hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion.³⁷² Hydroxyurea also raises RBC volume (higher mean corpuscular volume (MCV)) and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion. In addition, nitric oxide released directly from hydroxyurea metabolism may contribute to local vasodilation.³⁷³

Methodology

Complete information about the methodology for these guidelines can be found in the [“Introduction and Methodology” chapter \(pages 1–9\)](#). The following information, specific to this chapter, supplements the standard methodology that was conducted for all clinical chapters of these guidelines.

For this chapter, all human studies in English published from 2007 to May 2010 that addressed the PICOS question were identified. Studies published prior to 2007 were obtained from the 2008 National Institutes of Health Consensus Conference on Hydroxyurea document, “Hydroxyurea for the Treatment of Sickle Cell Disease,”⁷ which included a systematic review. A total of 414 studies were included.ⁱ In some cases in this chapter, a literature search was not conducted, so the panel relied on their cumulative expertise and knowledge to make recommendations; these recommendations are labeled “Consensus–Panel Expertise.”

ⁱ An updated search was performed to span the time from June 1, 2010 through July 11, 2014. Two additional RCTs were identified, for a total of 414 studies, and a supplemental table reflecting these additions was added to the evidence table document.

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the Hydroxyurea for Sickle Cell Disease evidence table available at <http://www.nhlbi.nih.gov/guidelines/scd/index.htm>.

Summary of the Evidence

A comprehensive systematic review was conducted evaluating the efficacy, effectiveness, harms, and barriers associated with using hydroxyurea in SCD. Three randomized trials and 54 observational studies describing the use of hydroxyurea in adults ($n=21$) and children ($n=33$) were identified. Exhibit 11 describes participant characteristics for the randomized trials, and exhibit 12 includes the evidence profile of efficacy/effectiveness for hydroxyurea in patients with SCA.

Evidence of Efficacy/Effectiveness

Summary of Evidence in Adults With SCA

The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) was a randomized, double-blind, placebo-controlled trial involving 299 adults with SCA who had experienced three or more VOCs in the previous year. The clinical end point of three or more documented VOCs was chosen because of earlier data documenting that people who experience pain at that frequency had markedly lower survival rates.¹⁴² The MSH trial demonstrated that, compared to placebo, hydroxyurea therapy reduced the frequency of painful episodes and ACS events, as well as the need for RBC transfusions and hospitalizations.³⁷³ In 1998, based on the results of this trial, the U.S. Food and Drug Administration approved hydroxyurea for the treatment of clinically severe SCA in adults.

Summary of MSH Findings

- Lower annual rates of pain crises (median 2.5 crises per year vs. 4.5 crises per year)
- Longer time to a first crisis on study (3.0 months vs. 1.5 months) and longer time to a second crisis (8.8 months vs. 4.6 months)
- Lower incidence of ACS (25 patients vs. 51 patients)
- Reduced need for blood transfusions (48 patients vs. 73 patients)
- Increased total hemoglobin (0.6 g/dL) and HbF (from 5.0 to 8.6 percent in the intervention group), compared with a drop in the placebo group (from 5.2 to 4.7 percent)
- Lower costs for hospitalization for pain (\$12,160 in the hydroxyurea group versus \$17,290 in the placebo group)
- Differences in the effect on mortality and stroke outcomes were not statistically significant.

Over 2 years of treatment, the benefit of hydroxyurea on quality of life was limited to people who maintained increased HbF levels. These restricted benefits occurred in social function, pain recall, and general health perception. Annualized total costs were similar between the intervention group and the placebo group. The trial had low risk of bias but was stopped early for benefit, which may exaggerate the observed benefit. Supporting evidence from 21 observational studies involving 3,378 adults, with followup periods of 24–96 months, was consistent in showing a reduction in pain crises (60–90 percent), hospitalizations (90–100 percent), and an increase in HbF (4–20 percent).

A 9-year followup analysis of MSH participants indicated a reduction in mortality for the group of people who took hydroxyurea compared to those who did not take the medication.³⁷⁴ When the cohort was followed for up to 9 years, people taking hydroxyurea had 40 percent reduced mortality (analysis according to cumulative

hydroxyurea exposure, not the original randomization). Survival was related to HbF levels and frequency of vaso-occlusive crises. More recently, extension of the followup analysis to 17.5 years for nonrandomized people indicated continued safety and benefit of hydroxyurea, including reduced mortality.³⁷⁵ Results were published from another prospective clinical study of hydroxyurea therapy with 17-year followup analysis.³⁷⁶ This prospective, nonrandomized study was conducted in Greece and enrolled people older than 16 years who had HbSS or HbSβ⁰-thalassemia, and HbSβ⁺-thalassemia. Similar to the results of the MSH trial, the results from this study showed that hydroxyurea therapy reduced the frequency of painful episodes and ACS events and the need for RBC transfusions and hospitalizations. Hydroxyurea therapy also significantly improved survival when compared to conventional therapy.

With randomized trials, both stopping the trial early and imprecision (single trial with <300 events) can affect the quality of the evidence. However, the overall quality of the evidence is considered high because the supporting observational evidence and the large treatment effect that follows hydroxyurea administration strengthen inference.

Summary of Evidence in Children With SCA

For infants, children, and adolescents who have SCA, hydroxyurea treatment results have closely and consistently mirrored those of adults. The first large, prospective, multicenter phase I/II trial (HUG KIDS) of school-aged children who were treated with hydroxyurea escalated to the maximum tolerated dose demonstrated laboratory efficacy, few short-term toxicities, and lack of toxicity for childhood growth and development.³⁷⁷ Soon after, a prospective phase I/II trial of infants with SCA who were treated with a liquid hydroxyurea formulation at a fixed dose of 20 mg/kg/day generated favorable short-term safety data and evidence suggesting prevention of sickle cell-related organ damage.³⁷⁸ Subsequently, several groups in the United States and Europe published open-label data regarding the laboratory and clinical efficacy of hydroxyurea for young people with SCA, with evidence of sustained laboratory and clinical responses but without apparent long-term toxicities. Taken together, these trials provide almost 15 years of pediatric data on both the safety and efficacy of hydroxyurea for young people (reviewed in Ware 2010).³⁷² Most recently, the phase III double-blinded, placebo-controlled infant hydroxyurea study “Pediatric Hydroxyurea phase III Clinical Trial”³⁷⁹ had equivocal results for preservation of organ function, but confirmed the improvements in laboratory parameters such as total hemoglobin level and HbF level, and decreased numbers of sickle-related acute clinical events such as pain and ACS.³⁸⁰ Long-term observational studies suggest sustained beneficial effects of hydroxyurea for young people without excessive myelotoxicity, deleterious effects on growth and development, altered fertility, accumulation of mutations, or increased carcinogenicity.³⁸¹⁻³⁸⁴

Exhibit 11. Participant Enrollment Criteria for Placebo-Controlled Randomized Controlled Trials of Hydroxyurea Therapy in Sickle Cell Disease

Publication	Age Range	Clinical Characteristics
Charache et al. 1995 (MSH) ³⁷³	>18 yr	≥3 crises in 12 mo
Ferster et al. 1996 ³⁸⁵	2 yr–22 yr	>3 crises in 12 mo
Wang et al. 2011 (BABY HUG) ³⁸⁰	9 mo–18 mo	No restriction based on clinical severity

Exhibit 12. Evidence Profile—Evidence of Efficacy/Effectiveness for Children and Adults With Sickle Cell Anemia (Hydroxyurea Versus Usual Care)

Outcome	Quality of the Evidence	Treatment Effect
Pain crises	High	Statistically significant benefit
Acute chest syndrome	Moderate	Statistically significant benefit
Hemoglobin level, fetal hemoglobin level, need for blood transfusions	Moderate	Statistically significant benefit
Mortality	Low	Imprecise estimate
Stroke	Low	Imprecise estimate

Summary of Evidence in People With Genotypes Other Than HbSS or HbSβ⁰-Thalassemia

There have been no phase III trials of hydroxyurea therapy in people with SCD having genotypes other than HbSS or HbSβ⁰-thalassemia. The prospective, nonrandomized study from a major clinical center in Greece referred to earlier enrolled 165 people with HbSβ⁺-thalassemia.³⁷⁶ Only 44 people were receiving hydroxyurea. Data analysis was based on all subjects enrolled in the study, with the majority receiving hydroxyurea therapy represented by people with SCA. The overall 10-year survival for the subset of people with HbSβ⁺-thalassemia receiving hydroxyurea was not significantly different from those receiving conventional therapy. A phase II study of children and adults with HbSC evaluated the effects of hydroxyurea and magnesium pidolate on laboratory parameters.³⁸⁶ The study was closed due to slow enrollment, and only 36 people were evaluable for the primary outcome of proportion of hyperdense cells after 8 weeks; no difference was seen for people receiving hydroxyurea. In addition, people receiving hydroxyurea had favorable hematological effects with increased HbF and RBC MCV, which were not observed for people receiving only magnesium pidolate.

Evidence of Side Effects

The evidence for hydroxyurea toxicity in people with SCD is derived from three RCTs that enrolled 517 people and from 47 observational studies that enrolled more than 3,000 people. In people who do not have SCD, toxicity evidence is derived from 21 RCTs that enrolled more than 4,800 individuals and 35 observational studies that enrolled more than 7,500 individuals (see exhibit 13). (For more information, see the evidence table at <http://www.nhlbi.nih.gov/guidelines/scd/index.htm>).

Exhibit 13. Evidence Profile—Evidence of Side Effects in Sickle Cell Anemia

Potential Toxicity	Quality of the Evidence	Treatment Effect
Bone marrow suppression	High	Reversible cytopenias associated with hydroxyurea
Leukemia	No supporting evidence in SCD populations/Very low	The available evidence does not support the association of hydroxyurea treatment with the development of leukemia in adults or children
Leg ulcers	Adults: Moderate Children: Low	The available evidence does not support the association of hydroxyurea treatment with leg ulcers
Other side effects	Very low	Numerous other side effects were reported in the literature with low frequency and none with certain causality
Reproductive effects	Very low	Minimal human data exist on potential harmful reproductive effects of hydroxyurea in males and females

Evidence Supporting Use of a Treatment Protocol

Although the literature does not compare different implementation protocols for hydroxyurea, the expert panel was concerned that not using a protocol could lead to inadequate dosing or poor monitoring. Hence, to maximize the benefits and safety of hydroxyurea treatment, the expert panel strongly recommends adopting a standardized protocol based on the available evidence. The expert panel developed a suggested protocol based on (1) protocols used in published clinical trials and observational studies, (2) indirect evidence derived from basic science and pharmacokinetics of hydroxyurea, and (3) a consensus process. Although the protocol contains several technical remarks and recommendations needed to implement hydroxyurea therapy safely and effectively, it should be considered as guidance and modified to fit an individual patient's clinical situation (see [“Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy”](#)).

Additional Considerations

Guideline developers consider what is known in the literature about people's values and preferences and make assumptions about values demonstrated by people encountered in clinical practice. In the area of SCD, the evidence supporting the nature and distribution of people's values is not strong. However, the expert panel has considered patients' values in their decisionmaking process. In one study of pediatric patients and their caregivers, parents and children indicated a preference for hydroxyurea over other therapies such as routine RBC transfusions or stem cell transplantation. The benefit/harm balance seems to be the driving determinant of treatment choice in this study.³⁸⁷ In developing these recommendations, the expert panel placed high value on preventing SCD morbidity (specifically, VOCs and ACS) and low value on cost, burden, and the potentially unknown long-term adverse effects of hydroxyurea therapy.

Although the hydroxyurea clinical trials cited in this chapter used very restrictive definitions for chronic, acute, and recurrent pain, the panel has chosen to broaden the definitions by using information from people in observational studies and clinical trials. For example, for this document, the expert panel defined recurrent SCD-associated pain to include daily pain requiring the use of opioid medication. In addition, the expert panel also includes those people who have episodes of pain, which, in the view of the patient and provider, significantly affect activities of daily living and quality of life.

It is the nature of most efficacy clinical trials to restrict enrollment to people with substantial clinical severity. Unfortunately, this limits data on the majority of people who do not fit easily into the restrictive clinical trial definitions—that is, the people who are seen in everyday practice. Notably, the pediatric phase III trial (BABY HUG)³⁷⁹ did not have specific inclusion criteria based on clinical severity; even infants with no previous clinical VOCs were eligible for enrollment. This was intentional and designed to allow the findings to be generalized to all infants and toddlers with SCA.³⁸⁰

The panel deliberated extensively on using data from clinical trials alone, which in most cases would limit the use of hydroxyurea to people who have had three or more pain crises in the last year. However, the panel felt that this would prevent the use of hydroxyurea in some adults who have chronic, acute, and recurrent pain, and for whom observational studies have generally shown a benefit from the medication. Therefore, in an effort to include the broad range of pain syndromes that affect the ability of people with SCD to participate in their desired daily activities, the panel's definitions of chronic, acute, and recurrent pain and their recommendations for the use of hydroxyurea have been expanded beyond the eligibility criteria used in the clinical trials. Thus, the expert panel believes that the use of hydroxyurea is indicated in a broader range of individuals than those described in the inclusion criteria for MSH and hopes to encourage use of the medication in people who have acute and/or chronic pain that regularly interferes with their quality of life.

In addition, when issuing recommendations for adults, the expert panel occasionally used data from the pediatric SCD literature and data from populations without SCD who were treated with hydroxyurea. In particular, this occurred in the areas of evidence of harm and treatment initiation and monitoring. The panel acknowledges that this indirect evidence is of lower quality and associated with weaker inferences.

Hydroxyurea Treatment Recommendations

Recommendations

1. Educate all patients with SCA and their family members about hydroxyurea therapy. (See [consensus treatment protocol on page 145](#)).
(Consensus–Panel Expertise)
2. In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea.
(Strong Recommendation, High-Quality Evidence)
3. In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea.
(Strong Recommendation, Moderate-Quality Evidence)
4. In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea.*
(Strong Recommendation, Moderate-Quality Evidence)
5. In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea.
(Strong Recommendation, Moderate-Quality Evidence)
6. In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia).
(Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children >42 months and adolescents).
Note: The panel intentionally used the term “offer” realizing that patients’ values and preferences may differ particularly considering treatment burden (e.g., laboratory monitoring, office visits), availability of drug in a liquid form, and cost. Therefore, the panel strongly encourages shared decisionmaking and discussion of hydroxyurea therapy with all patients.
7. In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia.
(Weak Recommendation, Low-Quality Evidence)
8. In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy.
(Moderate Recommendation, Very Low-Quality Evidence)
9. To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol.
(Strong Recommendation, High-Quality Evidence)
10. In people with HbSβ⁺-thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy.
(Moderate Recommendation, Low-Quality Evidence)
11. In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert.
(Moderate Recommendation, Very Low-Quality Evidence)

* For more information, see the [ACS section of the “Managing Acute Complications of Sickle Cell Disease”](#) chapter.

Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.
- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count $\geq 2,000/\mu\text{L}$; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/ μL .
- Maintain platelet count $\geq 80,000/\mu\text{L}$
- If neutropenia or thrombocytopenia occurs:
 - Hold hydroxyurea dosing
 - Monitor CBC with WBC differential weekly
 - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
 - Increase by 5 mg/kg/day increments every 8 weeks
 - Give until mild myelosuppression (absolute neutrophil count 2,000/ μL to 4,000/ μL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include:
 - CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
 - Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.