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Hydroxyurea for the Treatment of Sickle Cell Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Institutes of Health (NIH), Office of Medical Applications of Research (OMAR). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objective. To synthesize the published literature on the efficacy, effectiveness, and toxicity of hydroxyurea (HU) when used for treatment of sickle cell disease (SCD); and to review the evidence regarding barriers to its use.

Data Sources. Articles cited in MEDLlNE®, EMBASE, TOXLine, and CINAHL through June 30, 2007.

Review Methods. Paired reviewers reviewed each title, abstract, and article to assess eligibility. They abstracted data sequentially and then independently graded the evidence.

Results. In one small, randomized trial of HU in children with SCD; the yearly hospitalization rate was lower with HU than placebo (1.1 versus 2.8, p=0.002). The absolute increase in fetal hemoglobin (Hb F%*)* was 10.7 percent. Twenty observational studies of HU in children reported similar increases in Hb F%, while hemoglobin concentration increased by roughly 1 g/dl .

One large randomized trial tested the efficacy of HU in adults with SCD and found that after 2 years of treatment, Hb F% increased by 3.2 percent and hemoglobin increased by 0.6 g/dl, The median number of painful crises was 44 percent (p<0.001) lower among patients treated with HU. The 12 observational studies of HU enrolling adults with SCD supported these findings.

Panelists from the Center for the Evaluation of Risks to Human Reproduction reviewed the literature for potential toxicities of HU. They concluded that HU does not cause a growth delay in children 5-15 years old . There were no data on the effects on subsequent generations following exposure of developing germ cells to HU *in utero.* Some evidence supported impaired spermatogenesis with use of HU. Although we identified six patients taking HU who developed leukemia, the evidence did not support causality. Similarly, the evidence suggested no association between HU and leg ulcers in patients with SCD, although there was in patients with other illnesses. The literature supported neutropenia, skin rashes and nail changes associated with use of HU, but was sparse regarding skin neoplasms or other secondary malignancies in SCD.

Only two studies investigated barriers to use of HU. Perceived efficacy and perceived safety of HU had the largest influence on patients' (or parents') choice to use HU. Providers reported barriers to be patient concerns about side effects; and their own concerns about HU in older patients, patient compliance, lack of contraception, side effects and carcinogenic potential, doubts about effectiveness, and concern about costs.

Conclusions. HU is efficacious in children and adults with SCD; with an increase in Hb F%, and reduction in hospitalizations and pain crises. However, few studies have measured the effectiveness of HU for SCD in usual practice. The paucity of long-term studies limits conclusions about toxicities and about mortality. Future studies of interventions to overcome the barriers to use of HU in patients with SCD are necessary.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/hydscdtp.htm.

Executive Summary

Introduction

In February 1998, hydroxyurea was approved by the Food and Drug Administration (FDA) for use in adults with sickle cell disease. In 2002, The National Heart Lung and Blood Institute issued a recommendation that practitioners should consider using hydroxyurea daily in select patients with sickle cell disease. However, physicians are often non-adherent to practice guidelines and slow to change their practices in response to new data. To clarify the role of hydroxyurea in the treatment of patients with sickle cell disease and to improve physician adherence to guidelines regarding its use, the National Institutes of Health Office of Medical Applications of Research (OMAR) and the Agency for Healthcare Research and Quality (AHRQ) requested that the Evidence-based Practice Center (EPC) of the Bloomberg School of Public Health of the Johns Hopkins University prepare an evidence report. We were asked to address the following Key Questions:

1. What is the efficacy (results from controlled clinical studies) of hydroxyurea treatment for patients who have sickle cell disease?
2. What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?
3. What are the short- and long-term harms of hydroxyurea treatment?
4. What are the barriers to the use of hydroxyurea treatment (and other therapies) for patients who have sickle cell disease and what are the potential solutions?
5. What are the future research needs?[a]

Sickle cell disease is a genetic disorder that decreases life expectancy by 25 to 30 years and affects approximately 80,000 Americans. Individuals are diagnosed with sickle cell disease if they have one of several genotypes that result in at least half of their hemoglobin being hemoglobin S (Hb S). Sickle cell anemia refers specifically to the condition associated with homozygosity for the Hb S mutation (Hb SS). Several other hemoglobin mutations, when occurring with an Hb S mutation, cause a similar but often milder disease than sickle cell anemia. In addition to reduced life expectancy, patients with sickle cell disease experience chronic pain and reduced quality of life. Painful crises, also known as vaso-occlusive crises, are the most common reason for emergency department use and hospitalization, and acute chest syndrome is the most common cause of death.

Prior to the approval of hydroxyurea for use in sickle cell disease, patients with this condition were treated only with supportive therapies. These measures included penicillin in children to prevent pneumococcal disease, routine immunizations, and hydration and narcotic therapy to treat painful events. Red blood cell transfusions increase the blood's oxygen carrying capacity and decrease the concentration of cells with abnormal hemoglobin, but chronic transfusion therapy predictably leads to iron overload and alloimmunization. Therapies such as hydroxyurea

[a] The JHU EPC was not charged with conducting a separate review for Key Question 5 in the original task order; this question is addressed in the "Discussion" section of the report.

that raise fetal hemoglobin (Hb F, $\alpha_2\gamma_2$) levels are promising because they effectively lower the concentration of Hb S within a cell, resulting in less polymerization of the abnormal hemoglobin.

Hydroxyurea's efficacy in sickle cell disease is generally attributed to its ability to raise the levels of Hb F in the blood; however, the mechanisms by which it does so are unclear. Early studies suggested that hydroxyurea is cytotoxic to the more rapidly dividing late erythroid precursors, resulting in the recruitment of early erythroid precursors with an increased capacity to produce Hb F. One recent study supports a nitric oxide-derived mechanism for the induction of Hb F by hydroxyurea, and another study suggests that ribonucleotide reductase inhibition is responsible for this increase in Hb F. Alternatively, hydroxyurea may be of benefit in sickle cell disease for reasons unrelated to Hb F production, including its ability to increase the water content of red blood cells, decrease the neutrophil count, and alter the adhesion of red blood cells to the endothelium.

This interesting drug was first synthesized in 1869 in Germany by Dressler and Stein. A century later, phase I and II trials began to test its safety in humans with solid tumors. It was first approved by the FDA in 1967 for the treatment of neoplastic diseases and is presently approved for the treatment of melanoma, resistant chronic myelocytic leukemia (CML), and recurrent, metastatic, or inoperable carcinoma of the ovary.

Methodology

This review was conducted by a team from Johns Hopkins University with expertise in the management of sickle cell disease, clinical trial methodology (including clinical trials of hematological agents), systematic literature review, epidemiological studies, and ethics and adherence research. External technical experts, including academic and clinical experts and representatives of patients and public interest groups, provided input regarding the selection and refinement of the questions to be examined and the relevant literature to be considered. The core team worked with the technical experts, the OMAR Consensus Panel chairman, and the AHRQ to develop the Key Questions (see page 1). Literature inclusion criteria were tailored to each question, based on the availability and applicability of trial evidence and the relevance of other study designs.

In Key Questions 1 and 2, we addressed the efficacy and effectiveness of hydroxyurea in children and adults separately. Given the limited amount of evidence available from randomized controlled trials (RCTs), we also included non-randomized trials, cohort studies with a control population, and pre/post studies.

For Key Question 3, which addresses the toxicity of hydroxyurea, we reviewed studies (randomized and non-randomized, as well as observational studies) that addressed toxicities associated with this drug in patients with sickle cell disease. We also incorporated the findings of the experts at the Center for the Evaluation of Risks to Human Reproduction (CERHR); their detailed report, issued in 2007, reviewed toxicities in children and developing fetuses. We updated this information by including data from papers published since their report. In order to examine rare and long-term adverse effects, we also included observational studies, including case reports, together with indirect evidence from randomized trials, observational studies, case reports, and large cohorts of patients without sickle cell disease who had been treated with hydroxyurea.

For Key Question 4, we included information on barriers to the use of hydroxyurea, as well as those related to other therapies for the treatment of sickle cell disease. We included three types

of studies encompassing a broad range of study designs: 1) studies that tested an intervention aimed at overcoming barriers to accessing scheduled care, receiving medication prescriptions, or adhering to medications; 2) studies in which patients or providers or family members described what they perceived to be barriers to accessing scheduled care, receiving medication prescriptions, or adhering to medications; and 3) studies that tested whether supposed barriers were actually associated with accessing scheduled care, receiving medication prescriptions, or adhering to medications.

Literature Sources

We searched for articles using both electronic and hand searching. In March 2007, we searched the MEDLINE® and EMBASE databases. We repeated the search in May 2007, adding a supplemental search targeting thrombocythemia. On June 30, 2007, the MEDLINE® and EMBASE® searches were updated and additional searches were executed using TOXLine and CINAHL. All searches were limited to English-language articles involving treatment of humans. Review articles were excluded from the searches. Searches were not limited by date of publication or subject age.

Eligibility Criteria

An article was included if it addressed one of the key questions. An article was excluded if it was (1) not written in English, (2) contained no original data, (3) involved animals only, (4) was solely a report of an *in vitro* experiment, or (5) was a case series. We excluded studies with fewer than 20 patients unless the article was primarily reporting on toxicities in sickle cell disease. We excluded trials involving other diseases if fewer than 20 patients received hydroxyurea. We allowed cohort studies of diseases other than sickle cell disease only if they described more than 100 patients treated with hydroxyurea. Although we excluded case series because they do not provide sufficient data about the effectiveness of a medication we included case reports if they had information regarding the dose of hydroxyurea and the duration of treatment that could be use to assess a causal relationship with potential toxic effects.

Quality Assessment

We graded the included studies on the basis of their quality with regard to reporting relevant data. For the RCTs, we used the scoring system developed by Jadad et al.[b] For the observational studies (both cohort studies and controlled clinical trials), we created a quality form, based on those previously used by our EPC, that was aimed at capturing data elements most relevant to study design. We designed questions to evaluate the potential for selection bias (three items) and to assess the potential for confounding (five items). For our assessment of the quality of the qualitative studies we reviewed, we developed a nine-item form to identify key elements that should be reported when describing results from qualitative research, including a description of the population and subjects and transparency of the data collection procedures. Similarly, to assess the quality of the surveys we included, we created an eight-item form assessing

[b] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1-12.

information about the survey methods, population, and validity and reliability of the instruments used. A pair of reviewers each performed the quality assessment independently. In the case of the RCTs, a third reviewer reconciled the results of the first two reviewers; for the other study designs, the results of the two reviewers were averaged. The overall score was the percentage of the maximum possible score, ranging from 0 to 100 percent. The results for RCTs were reported as 0 to 5 points. We considered high-quality studies to be those with a Jadad score of 4 or 5, or those receiving 80 percent or more of available quality points. However, no study was excluded from review on the basis of its quality score.

Data Extraction

We used a sequential review process in which the primary reviewer abstracted all the relevant data into abstraction forms, and a second reviewer checked the first reviewer's forms for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. Differences were resolved by discussion. We then created detailed evidence tables containing information extracted from the eligible studies.

Grading of the Evidence

At the completion of our review, we graded the quantity, quality, and consistency of the best available evidence addressing Key Questions 1, 2, and 3 by adapting an evidence grading scheme recommended by the GRADE Working Group and the EPC guide that is was under development at the time of the review. We applied evidence grades to the bodies of evidence about the efficacy and/or effectiveness of hydroxyurea for the treatment of sickle cell disease in one assessment. In terms of the strength of the study designs, we considered RCTs best, followed by non-randomized controlled trials and observational studies. We assessed the quality and consistency of the best available evidence, including an assessment of limitations to individual study quality (using individual quality scores), certainty regarding the directness of the observed effects in studies, precision and strength of findings, and availability (or not) of data to answer the Key Question. We classified evidence bodies pertaining to each Key Question as shown in Table 1. The evidence from case reports was graded according to the criteria of the World Health Organization (WHO) Collaborating Center for Drug Monitoring.

Results

Efficacy and Effectiveness of Hydroxyurea in Children

A single, small, placebo-controlled randomized trial of hydroxyurea for 6 months in Belgian children with sickle cell disease reported that the rate of hospitalization and number of days hospitalized per year were significantly lower in the hydroxyurea group (1.1 admissions, $p=0.0016$ and 7.1 days, $p=0.0027$) than in the placebo group (2.8 admissions and 23.4 days). Hb F% increased by an absolute 10.7 percent from baseline in the treated group ($p<0.001$).

Among the cohort studies, Hb F% was reported as an outcome in 17 studies. The mean pre-treatment Hb F% ranged from 5 to 10 percent, and the on-treatment values were in the range of 15 to 20 percent. The percentage of F cells was less frequently reported, but it increased from

baseline in three of the four pediatric studies in which it was reported. Three of these cohort studies were retrospective; two reported increases in Hb F% comparable to those in the prospective studies. Hemoglobin concentrations increased modestly (roughly 1 gm/dL) but significantly across these studies.

The frequency of pain crises was reported as an outcome in five pediatric studies, with a reduction in frequency reported in three. In one retrospective cohort study in a resource-poor environment, the frequency of pain crises declined from a median of 3 per year to a median of 0.8 per year during treatment, with a median followup time of 24 months. Of note is the fact that these results were obtained using a fixed dose of hydroxyurea (15 mg/kg/day). A small, high-quality prospective study found a decrease in pain events, from 3.1 per year in the year prior to hydroxyurea therapy to 1.2 per year during the 18 months of therapy. Hospitalization rates decreased in all four studies describing this outcome. In the retrospective study described above, the hospitalization rates decreased to 0.5 per year during treatment, from a baseline rate of 4 per year. Within the Belgian Registry, hospitalization rates declined to 1.1 per patient-year during the third year of treatment, from 3.2 per patient-year.

One study assessed the impact of hydroxyurea on secondary stroke prevention by enrolling 35 children who needed to discontinue their chronic transfusion protocol. The average hydroxyurea dose was 27 mg/kg/day, and the children were treated for a mean of 42 months. The rate of recurrent ischemic events was 5.7 per 100 patient-years, which is better than was seen in another study in which children discontinued transfusions without starting hydroxyurea. One other study reported that brain images by magnetic resonance imaging (MRI) were stable during the course of treatment in 24 of 25 children. In the Belgian Registry, during 426 patient-years of hydroxyurea treatment, the rate of central nervous system events (stroke or transient ischemic attacks) was 1.3 per 100 patient-years, but no comparison rate was provided.

Based on one randomized trial in children and many observational studies, some of which were high-quality and most of which were consistent in their findings, we graded the evidence as shown in Table 1.

Efficacy and Effectiveness of Hydroxyurea in Adults

Only one randomized trial, the Multicenter Study of Hydroxyurea for Sickle Cell Anemia (MSH Study), tested the efficacy of hydroxyurea in adults with sickle cell anemia, with six additional analyses either based on this trial or on followup studies. The significant hematological effects of hydroxyurea after 2 years (as compared to the placebo arm) included a small mean increase of 0.6 g/dl in total hemoglobin and a moderate absolute increase in fetal hemoglobin of 3.2 percent. The median number of painful crises was 44 percent lower, and the time to the first painful crisis was 3 months, as compared to 1.5 months in the placebo arm. There were fewer episodes of acute chest syndrome and transfusions, but no significant differences in deaths, strokes, chronic transfusion, or hepatic sequestration. Use of hydroxyurea had no significant effect on annualized costs. It improved the quality of life, but only in those patients who experienced a substantial increase in Hb F%.

In all six prospective cohort studies in adults that reported hematological outcomes, Hb F% increased significantly. The mean baseline Hb F% ranged from 4 percent to 12 percent, and during hydroxyurea treatment, it ranged from 10 percent to 23 percent. As in the pediatric studies, there was a small increase in hemoglobin in most studies. The single retrospective study

Table 1. Summary of Evidence Relating to the Efficacy of Hydroxyurea in Sickle Cell Disease*

Outcomes	Evidence Grade	Basis for Grade
Key Question 1 and 2--Children		
Increase in fetal hemoglobin	High	One good RCT, plus consistent observational studies
Reduction in pain crises	Moderate	One good RCT; inconsistent observational studies
Reduction in hospitalizations	High	One good RCT, plus consistent observational studies
Reduction in neurological events	Low	Observational studies
Reduction in transfusion frequency	Insufficient	Few observational studies
Key Question 1 and 2 --Adults		
Increase in fetal hemoglobin	High	One good RCT, plus consistent observational studies
Reduction in pain crises	High	One good RCT, plus consistent observational studies
Reduction in hospitalizations	High	One good RCT, plus consistent observational studies
Reduction in neurological events	Insufficient	No studies
Reduction in transfusion frequency	High	One good RCT, plus consistent observational studies
Mortality	Low	Inconsistent observational studies

*****Evidence grades: "high" (high confidence that the evidence reflects the true effect; further research is very unlikely to change our confidence in the estimate of effect); "moderate" (moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate of effect and may change the estimate); "low" (low confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate); and "insufficient" (evidence either is unavailable or does not permit estimation of an effect); RCT=randomized controlled trial

reported hematological outcomes comparable to those seen in the prospective studies. The number of pain crises was described in three studies. In a study of Sicilians with Hb Sβ thalassemia, the frequency of crises decreased significantly, from a mean of 7 (median of 9) per year to a mean of 1.1 (median 1.8) per year. In the non-randomized study comparing patients receiving hydroxyurea to those receiving cognitive behavioral therapy, those receiving hydroxyurea had fewer pain crises (1.4 per year compared to 4.3 per year, $p \leq 0.05$) but this was not a strong study design for assessing such an outcome. Similarly, hospitalization rates decreased consistently in adults treated with hydroxyurea. In the study of Sicilians, the number of hospitalized days per year declined from 22.4 days to 1.2 days (SD =2.3) ($p<0.0001$). In a retrospective effectiveness study, the rates of hospitalization declined from baseline in the group treated for longer than 24 months (2.1 per year from 3.1 per year, $p=0.04$). However, in the group treated for fewer than 24 months, the hospitalization rates were not significantly different from baseline values.

Based on one high-quality randomized trial in adults and many consistent observational studies, we graded the evidence as shown in Table 1.

Toxicities of Hydroxyurea in Children and Adults

Our assessment of the strength of the evidence regarding the toxicity of hydroxyurea, when used in children, was generally derived from our review of the report by the panel of experts that

had been assembled by the National Toxicology Program (NTP)'s Center for the Evaluation of Risks to Human Reproduction (CERHR). The panel reviewed articles, published through January 2007, that pertained to the evaluation of adverse effects of hydroxyurea on development and reproduction in both humans and animals. Their review was not restricted to the use of hydroxyurea for sickle cell disease. The dosing of hydroxyurea for sickle cell disease is comparable to that in other diseases, although in the case of malignant disease, more drug is often given less frequently (such as 80 mg/kg every 3 days rather than 15-20 mg/kg daily).

The panel concluded that treatment of children aged 5 to15 years with hydroxyurea does not cause a growth delay. They felt there were insufficient data to allow them to evaluate the effects of hydroxyurea on pubertal development. The panel found no data regarding the effects on subsequent generations after exposure of germ cells to hydroxyurea, including exposure during fetal life, infancy, childhood, and adolescence. The CERHR report did not describe any studies on the long-term health effects, including carcinogenicity, of childhood exposure to hydroxyurea; we also found no such studies. The expert panel had concerns about the adverse effect of hydroxyurea on spermatogenesis in men receiving hydroxyurea at therapeutic doses; we also identified case reports of impaired spermatogenesis after hydroxyurea treatment in patients with sickle cell disease, as well as in patients with other illnesses. The CERHR report concluded that the use of hydroxyurea in pregnancy was not associated with adverse perinatal outcomes, but that there were no data on long-term outcomes in children who were exposed *in utero*. However, the panel expressed concern, based on minimal data from experimental studies, that hydroxyurea might increase the risk of congenital anomalies or abnormalities of fetal growth after exposure of pregnant women to the drug.

We found three cases of leukemia, described in observational studies, in patients with sickle cell disease who had been treated with hydroxyurea. We identified another three case reports of hydroxyurea-treated patients with sickle cell disease who developed leukemia, and one report of a child who developed Hodgkin's lymphoma. Toxicities in patients with sickle cell disease that are probably causally related to hydroxyurea are neutropenia, skin rashes, and nail changes.

We reviewed toxicity reports from hydroxyurea-treated patients with other illnesses and found many reports of leg ulcers and skin cancers. Among the randomized trials enrolling patients with other diseases, no trial demonstrated a greater number of cases of leukemia in the group treated with hydroxyurea. This parameter could not be assessed in the trials enrolling patients with chronic myelogenous leukemia (CML), as progression to acute leukemia was considered a poor response to the intervention and could not be considered a toxicity of treatment. We reviewed a case series of 26 patients with acute myelogenous leukemia (AML) with a unique t (3;21) chromosomal translocation. Among these 26 patients were 15 people with CML who had been treated with hydroxyurea. We found no other reports describing an association between this translocation and hydroxyurea.

We concluded that low-grade evidence suggested that hydroxyurea treatment in adults with sickle cell disease is not associated with an increased risk of leukemia. (Table 2)

Table 2. Summary of Evidence About the Toxicity of Hydroxyurea in Sickle Cell Disease*

Outcomes	Evidence Grade	Basis for Grade
Key Question 3--Children		
Leukemia (MDS/AML/Cytogenetic abnormalities)	Insufficient	CERHR report
Developmental toxicities (*in utero*)	Evidence of harm in animals	CERHR report
Leg ulcers	Insufficient	CERHR report
Growth delays	Evidence of no growth delay	CERHR report
Developmental toxicities in next generation	Insufficient	CERHR report
Key Question 3-- Adults		
Leukemia (MDS/AML/Cytogenetic abnormalities	Low	Indirect evidence and inconsistent results
Leg ulcers	High (absence of effect)	One good RCT, plus consistent observational studies
Skin neoplasms	Insufficient	No studies in sickle cell; high-grade evidence in other populations
Secondary malignancies	Insufficient	No studies in sickle cell; low-grade evidence in other populations
Adverse pregnancy outcomes	Insufficient	CEHER report
Spermatogenesis defects	Low	Case reports with evidence of causality

*Evidence grades as on Table 1; MDS = myelodysplastic syndromes; AML = acute myelogenous leukemia; CEHER = Center for the Evaluation of Risks to Human Reproduction.

High-grade evidence supported the assertion that hydroxyurea is not associated with leg ulcer development in patients with sickle cell disease, although high-grade evidence indicated that it is associated with leg ulcers in patients with other conditions. The evidence was insufficient in sickle cell disease to indicate whether hydroxyurea contributes to skin neoplasms, although high-grade evidence supported its involvement in patients with other illnesses. Similarly, there was insufficient evidence to establish whether hydroxyurea is associated with secondary malignancies in adults with sickle cell disease; the evidence in other diseases was only low-grade.

Barriers to the Use of Hydroxyurea and Other Treatments for Managing Sickle Cell Disease

Only two studies (one in patients and one in providers) investigated barriers to use of hydroxyurea; both used survey data. The study involving patients used a cross-sectional design and showed that the perceived efficacy and safety of hydroxyurea had the strongest association with patients' (or parents') choice of hydroxyurea therapy over other therapies. In the study of clinicians, the reported barriers to use of hydroxyurea for sickle cell disease included patient concerns about side effects and a variety of clinician concerns: the appropriateness of using hydroxyurea in older patients, patient compliance, a lack of contraception in premenopausal women, side effects and carcinogenic potential, doubts about effectiveness, and costs to patients.

We reviewed an additional 47 studies addressing barriers to the treatment of patients with sickle cell disease and interventions to overcome these barriers. In our review of barriers to adequate pain management, we found two factors that were identified as a barrier in more than two studies: negative provider attitudes and poor provider knowledge. Because of the quantity and consistency of these findings, we concluded that the evidence was high-grade that negative provider attitudes are barriers and moderate-grade that poor provider knowledge is a barrier to the use of pain medications in patients with sickle cell disease. The evidence for the remaining barriers to pain management was insufficient to allow us to draw any conclusions.

In our review of the barriers to other therapies for chronic sickle cell disease management, we concluded that the evidence was of a moderate grade that patient sex is not a barrier to use of therapies. Largely because of the paucity and inconsistency of the studies, we concluded that there was only low-grade evidence that patient/family knowledge, the number of hospital visits, and patient age are barriers to the use of therapies.

We identified three studies that tested interventions to improve patient adherence to established therapies for chronic disease management, but none of these three showed any effect on patient adherence. However, given the small sample sizes and the studies' diverse outcome measures, we concluded that there was only low-grade evidence that interventions did not improve patient adherence. In contrast, we identified nine studies that examined the impact of interventions to improve pain management during vaso-occlusive crises, and we concluded that there was moderate evidence that interventions can overcome barriers to the use of pain medications. We also identified one study that investigated the impact of an intervention to improve receipt of routine healthcare and, partly because of the strength of the effect found in the study, we concluded that there is moderate evidence to indicate that interventions can overcome barriers to the receipt of routine, scheduled healthcare for patients with sickle cell disease.

We found it informative that when researchers chose the barriers to investigate, they most often studied patient-related barriers. When patients were asked to identify barriers to the use of therapies, they most often cited provider-related barriers. The barrier to pain management that was most often identified by patients and providers was negative provider attitudes. However, only one of the nine pain management intervention studies addressed this issue directly through provider sensitivity training.

Limitations of the Evidence

The evidence base described here had significant limitations. Most notably, only two randomized trials addressed hydroxyurea efficacy and safety in patients with sickle cell disease. While the trial enrolling adults was a high-quality trial, it was not long, with only 2 years elapsing since randomization. Two years may be adequate for assessing short-term efficacy, but we had no trial data that made it possible to comment on the long-term efficacy of the drug. We also found no trial data to allow us to assess the effectiveness of this drug in a population who may be asked to take the medication for many years with less intense supervision and encouragement than is received in a trial. The trial conducted in children was a moderate-quality trial, but it was even shorter than the trial in adults, with only 6 months of treatment. Thus, this evidence base is limited by a lack of long-term effectiveness trials, even though the MSH trial may be considered a definitive trial of the short-term efficacy of the drug in adults. In addition, these trial results cannot be generalized to all patients with sickle cell disease, since the trials

included only patients with Hb SS; clinical response and toxicities are known to differ to some extent according to genotype.

The most frequently reported outcomes in the observational studies were hematological. The data convincingly demonstrated an increase in Hb F% with the use of this drug; however, there was far less evidence regarding the clinically relevant outcomes of hospitalization, stroke, pain crises, acute chest syndrome, and mortality. Furthermore, observational data may be plagued with issues of regression to the mean. If patients were started on hydroxyurea after a period of increased frequency of disease symptoms, it is expected that they would, in time, return to their usual disease severity, even without a change in therapy. This is a major concern in interpreting the pre/post data from many of these observational studies reporting clinical outcomes.

The evidence was scant regarding benefits for patients with genotypes other than Hb SS. Similarly, there was limited evidence about the use of doses other than the maximally tolerated dose (MTD). Also, there was little evidence to guide dosing based on clinical outcomes.

The evidence regarding toxicities had limitations as well. The relatively short clinical trials we found could not provide strong evidence for toxicities that may require many years of exposure to develop. The follow-up studies from these trials are important contributors to the literature, but they became observational studies after the period of randomization ended, and are thus subject to the limitations of any observational study. The losses to followup were substantial in the majority of the observational studies. Very few studies required active surveillance for toxicities, such as periodic skin examination or cytogenetic studies, with notable exceptions. The studies of toxicities suffered from a lack of control groups; for example, studies that describe impaired spermatogenesis would require a control of group of comparably ill men with sickle cell disease in order to determine whether this symptom was disease- or treatment-related.

In reviewing the evidence, we opted to include toxicity data from patients treated with hydroxyurea for conditions other than sickle cell disease. This approach provided only indirect evidence of toxicity, in that the patient populations were markedly different than patients with sickle cell disease.

Our investigation of barriers to the use of hydroxyurea was limited by the paucity of data regarding this question. Since there were only two studies specifically addressing barriers to the use of hydroxyurea, we needed to bring in supporting evidence from interventions that might have exhibited barriers comparable to those associated with hydroxyurea treatment. The majority of the potential barriers considered in the cross-sectional studies (i.e., those chosen by the researcher) were patient-related factors, which suggested a lack of attention to provider and societal-level contributions. Very few of these studies included adult patients. Only half of the cross-sectional studies used multivariate techniques to adjust for the effects of potential confounders, an omission that limited the value of these studies. Another concern was that many of the intervention studies used indirect outcomes, such as length of stay or total hospital costs, to assess improvement in pain management; these are not the best outcome measures for this question.

Future Research Needs

Several placebo-controlled trials in progress are expected to address some of the research gaps that remain: BABY-HUG is examining the safety and effectiveness of hydroxyurea in infants (results expected in late 2009), and the Stroke With Transfusion Changing to Hydroxyurea (SWiTCH) trial is examining hydroxyurea use for secondary prevention of stroke in patients with sickle cell disease. However, there is still a substantial need for research on the use of this drug.

The paucity of randomized trials suggests that additional randomized trials with other clinical outcomes may be appropriate, including trials that are aimed at preventing or treating other complications of sickle cell disease, including kidney disease, pulmonary hypertension, neurological events in adults, and psychiatric complications. Also, effectiveness trials are needed to assess the use of hydroxyurea in a regular care setting. These could be (1) clustered randomized trials in which some providers are randomized to use hydroxyurea in all patients and others are randomized to usual care, including the use of hydroxyurea when clinically indicated; or (2) effectiveness studies, in which one group of providers is actively encouraged to consider hydroxyurea when appropriate and another clinic is not targeted for education.

Longer studies are needed to assess the potential toxicities of this drug, particularly given its uncertain mechanisms of action. This would include studies in which patients are treated for longer periods of time, as well as studies in which patients are followed for longer periods of time after treatment is discontinued. This need is most relevant to outcomes with a long latency period, such as leukemia and secondary malignancies, including skin cancers. Randomized trials are not feasible for long periods, so a well-designed prospective study may be the optimal design. A registry of users of hydroxyurea could also be considered if the data collection and followup can be sufficiently rigorous and ongoing. Other toxicities requiring further study are the developmental toxicities and risk to subsequent generations that are described in detail in the CERHR report.

Many subgroups require further study, particularly patients with genotypes other than Hb SS. While there have been observational studies of patients with other genotypes, the randomized trials enrolled only patients with Hb SS. Patients with Hb SC are particularly understudied. Additional studies of hydroxyurea at doses other than the MTD are appropriate, particularly since the use of the MTD in resource-poor populations may be impractical. Effectiveness studies of hydroxyurea in resource-poor populations would be particularly beneficial. Other subgroups of interest are patients with comorbid illnesses, specifically HIV/AIDS and/or hepatitis C. More information is needed about the interactions between hydroxyurea and these underlying diseases, and between hydroxyurea and therapies for these diseases. Further research on the place of hydroxyurea in therapy and its comparative effectiveness is also indicated, since the existing studies have not defined the optimal time for initiation of hydroxyurea or identified the indicators that a patient has "failed" therapy with the drug. Other questions remain: Is there a role for rechallenge with the drug if there was no previous efficacy? Is there a role for hydroxyurea as an adjunctive therapy with other drugs? What are the best intermediate outcomes that will predict clinical response to the drug? Given the strong evidence that hydroxyurea reduces the frequency of pain and hospitalization in children and adults with sickle cell disease, some have questioned whether additional placebo-controlled trials of hydroxyurea are ethical. We suggest that additional trials are ethical in understudied subgroups (e.g., patients with genotypes other than

Hb SS), and in the evaluation of hydroxyurea for other indications (e.g., treatment of mild pulmonary hypertension or secondary prevention of stroke in adults).

Given that we have concluded that evidence supports the short-term efficacy of hydroxyurea in sickle cell disease, there is clearly a need for further research on the barriers to the use of this drug. These studies should aim to identify barriers at the level of the patient, at the level of the provider, and at a societal level, perhaps with special attention to adult patients. After these barriers are better characterized, interventions to overcome these barriers should be tested, including replication of the one promising study that demonstrated improved receipt of routine care in patients with sickle cell disease. The barriers and interventions that we identified as influencing the use of other treatments in sickle cell disease may provide an appropriate starting point for further study. Comparative effectiveness studies may be appropriate as well, in particular for testing established interve`ntions for improving pain control.

Evidence Report

Chapter 1. Introduction

Sickle Cell Disease

Sickle cell disease is a genetic disorder that decreases life expectancy by 25 to 30 years and affects approximately 80,000 Americans.[1,2] Sickle cell disease refers to a group of disorders in which the red blood cell undergoes sickling when deoxygenated. The existence of these abnormally shaped cells was first reported in 1910, when Herrick described their occurrence in a black dental student. The abnormality was subsequently identified as the result of an exchange of the amino acid valine for glutamine in the β-globin chain of the hemoglobin molecule. This abnormal hemoglobin becomes polymerized, causing the red blood cell to assume a sickle shape and making the cell both rigid and fragile. These distorted cells obstruct the blood vessels and may disrupt endothelial cell function, leading to tissue hypoxia and clinical complications. The fragile red cells have a markedly short life span, leading to the development of anemia and the release of free hemoglobin into the circulation, a phenomenon that is also injurious to the endothelium.

The term sickle cell anemia refers to the disease that occurs in patients who are homozygous for the Hb S mutation (SS disease). There are several other hemoglobin mutations that, when present in heterozygous form with an Hb S mutation, lead to the same disease but exhibit a milder phenotype. The most common of these other genotypes are Hb SC disease, sickle cell β thalassemia, and Hb SD disease. There is great variability in the clinical course of these various conditions, and it is not uncommon for patients with these Hb variants to experience frequent painful events and life-threatening complications.

Clinical Characteristics

Patients with sickle cell disease experience both chronic and episodic pain and have a reduced quality of life. [3] Painful crisis is the most common reason for emergency department use by patients with sickle cell disease. [4] The pathophysiology of a painful crisis is not entirely clear, and its determinants are uncertain. Some patients have frequent crises and severe disability, whereas others are able to lead relatively normal lives. Much of what we have learned about the incidence of complications in people with sickle cell disease comes from the Cooperative Study of Sickle Cell Disease (CSSCD).[5] (See list of acronyms.) This federally funded study, begun in 1979, was a large multi-institutional prospective study of the clinical course of sickle cell disease. In this study, the frequency of painful crises was variable: 0.8 episodes per person-year for sickle cell anemia, 1.0 episodes per person-year for Hb $S\beta^0$ thalassemia, and 0.4 episodes per person-year for Hb SC disease. [6] In a study of 1,056 patients with Hb SS disease in California, 70 percent of patients were admitted for a crisis; the overall rate of hospitalizations for crisis was 57 admissions per 100 years of observation. [7]

Acute chest syndrome is the most common cause of death and hospitalization in patients with sickle cell disease. [8] In a large multicenter study of acute chest syndrome, the working definition was a new pulmonary infiltrate in a patient with chest pain, with a temperature of more than 38.5°C and tachypnea, wheezing, or cough. [8] In the study in California, the incidence rate of acute chest syndrome was 14 per 100 years of observation. [7] In the CSSCD, acute chest

syndrome occurred in nearly 30 percent of 3,751 patients. Its incidence was highest in patients with Hb SS disease (12.8 per 100 patient-years). [9]

Stroke is another serious consequence of sickle cell disease and is seen more often in children than adults. In the CSSCD, the prevalence of stroke was 4 percent in those with Hb SS disease, with an incidence of 0.61 per 100 patient-years. [5] Investigators noted that stroke was associated with all the common genotypes. In the Powars[7] study in California, 11 percent of patients had suffered a stroke. Children who have had a stroke or who are at risk for stroke (as determined by transcranial Doppler [TCD] flow velocity) are typically treated with a chronic prophylactic transfusion regimen.

Another complication of sickle cell disease that affects patients' quality of life is the development of leg ulcers. In the Powars[7] study, 14 percent of the patients suffered from this complication. In the CSSCD, 25 percent of all patients had leg ulcers. [5] People with Hb SS disease or Hb $S\beta^0$ thalassemia are at higher risk of developing leg ulcers than are those with other genotypes. [10] The ulcers usually occur between the ages of 10 and 50 years and are more common in men than in women. [5] Therapy is supportive, involving local care of the ulcer, but many of these ulcers become chronic.

Established Treatments

Most of the therapies offered to patients with sickle cell disease are supportive and do little to change the underlying pathophysiology of the disease. These supportive measures include the use of penicillin prophylaxis in children to prevent pneumococcal disease, routine immunizations, and hydration and narcotic therapy to treat painful events. Some treatments, such as penicillin therapy, have improved both quality of life and survival. [11]

Transfusions are often used to increase the oxygen-carrying capacity of the blood and to decrease the concentration of cells with abnormal hemoglobin. In patients with repeated, severe complications of sickle cell disease, simple transfusions or exchange transfusions are often used to preserve organ function and prolong life. In the multicenter study looking at the treatment of acute chest syndrome, 72 percent of the patients received red cell transfusions to treat this acute event. [8] As mentioned above, children with a stroke history are treated with chronic transfusion therapy. [12] Despite the usefulness of chronic transfusion, its long-term effects include iron overload, which can damage the liver.

Currently, hydroxyurea is the only disease-modifying therapy approved for sickle cell disease. Hence, there is great interest in understanding more about its use in treating patients with this group of disorders.

A Brief History of Hydroxyurea

Hydroxyurea was first synthesized in 1869 in Germany by Dressler and Stein. [13] A century later, phase I and II trials began testing the safety of this drug in humans with solid tumors. It was first approved by the FDA in 1967 for the treatment of neoplastic diseases. [14] In subsequent years, clinical trials demonstrated the efficacy of this drug for the treatment of CML, psoriasis, and polycythemia vera. Although there have been reformulations of this drug, there were no labeling revisions until 1996. In February 1998, hydroxyurea received a new indication, for the treatment of sickle cell disease. [15] It is approved for use in reducing the frequency of painful crises and the need for blood transfusions in adult patients with recurrent moderate-to-severe

painful crises (generally at least three during the preceding 12 months). Hydroxyurea is also approved for use in the treatment of melanoma, resistant CML, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Mechanism of Action

The precise mechanism by which hydroxyurea produces its varied effects is unknown. Assays conducted in cell-free bacterial systems have demonstrated that its target is the enzyme ribonucleotide reductase, with hydroxyurea acting as a free radical that is specific for the tyrosyl groups of this enzyme. [16] Ribonucleotide reductase is essential for deoxyribonucleic acid (DNA) synthesis, and its inhibition by hydroxyurea results in S-phase cell cycle arrest. Other mechanisms may be responsible for the fact that this drug acts as a radiation sensitizer, inhibiting the repair of damaged DNA.

The efficacy of hydroxyurea in the treatment of sickle cell disease is generally attributed to its ability to boost the levels of fetal hemoglobin (Hb F,$\alpha_2\gamma_2$). This lowers the concentration of Hb S within a cell resulting in less polymerization of the abnormal hemoglobin. However, the mechanisms by which it increases Hb F are unclear. Early studies suggested that hydroxyurea is cytotoxic to the more rapidly dividing late erythroid precursors, an effect that leads to the recruitment of early erythroid precursors with an increased capacity to produce Hb F. Others have suggested that it acts directly on late precursors to reprogram them to produce Hb F. Alternatively, it may interrupt the transcription factors that selectively bind to promoter or enhancer regions around the globin genes, thereby altering the ratio of Hb A to Hb F (reviewed in Dover and Charache). [17] A recent study has provided evidence for a nitric oxide-derived mechanism for Hb F induction by hydroxyurea. [18] Another study has suggested that increases Hb F production by inhibiting ribonucleotide. [19] Alternatively, it may be of benefit in sickle cell disease for reasons unrelated to Hb F production, including its ability to increase the water content of red blood cells, decrease the neutrophil count, and alter the adhesion of red blood cells to the endothelium.

Pharmacokinetics

When used to treat sickle cell disease, hydroxyurea is administered orally and is readily absorbed. [15] Peak plasma levels are reached in 1 to 4 hr after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and areas under the curve are observed. The drug is distributed rapidly and widely in the body and concentrates in leukocytes and erythrocytes. Up to 60 percent of an oral dose undergoes conversion through metabolic pathways that are not yet fully characterized. One pathway is probably saturable hepatic metabolism, and another minor pathway may involve degradation by the urease found in intestinal bacteria. Excretion of hydroxyurea in humans is likely a linear first-order renal process.

Current Labeling

The current labeled dosing of hydroxyurea for sickle cell disease calls for the administration of an initial dose of 15 mg/kg/day in the form of a single dose, with monitoring of the patient's blood count every 2 weeks. [15] If the blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks until the MTD of 35 mg/kg/day is reached. If blood counts are between the acceptable range and the toxic range, the dose is not increased. If blood counts are found to be in the toxic range, treatment is discontinued until hematologic recovery. It may then be resumed after the dose is reduced by 2.5 mg/kg/day from the dose associated with hematologic toxicity. The drug may then be titrated up or down every 12 weeks in increments of 2.5 mg/kg/day until the patient is at a stable dose that does not result in hematologic toxicity. Counts considered to be acceptable are: neutrophils greater than or equal to 2500 cells/mm^3, platelets greater than or equal to 95,000/mm^3, hemoglobin greater than 5.3 g/dl, and reticulocytes greater than or equal to 95,000/ mm^3 if the hemoglobin concentration is less than 9 g/dl. Counts considered to be toxic are: neutrophils less than 2000 cells/ mm^3, platelets less than 80,000/ mm^3, hemoglobin less than 4.5 g/dl, and reticulocytes less than 80,000/ mm^3 if the hemoglobin concentration is less than 9 g/dl. [15,20]

In 1998, the FDA issued a Written Request for voluntary pediatric studies of many drugs[15]; included on this list was hydroxyurea. There is as yet no indication for the use of this drug in children.

Purpose of Evidence Report

In the pivotal randomized trial upon which the FDA based its approval of hydroxyurea, adult patients taking hydroxyurea were found to have fewer hospitalizations and fewer episodes of acute chest syndrome, and they required fewer transfusions than those who were not on hydroxyurea. [21] The authors projected an almost 50 percent reduction in hospitalizations if every eligible patient with sickle cell anemia in the United States was taking hydroxyurea, with a concomitant cost savings of 26 million dollars annually. [22]This study led to hydroxyurea's receiving an FDA indication for the treatment of patients with sickle cell disease, as well as the development of the National Heart, Lung, and Blood Institute recommendations for the use of the drug in this disease. [23] However, the response by physicians has been consistent with published studies that have shown high levels of physician non-adherence to a variety of clinical practice guidelines[24] and have demonstrated that physician practice is slow to change after the publication of a clinical study. Specifically, investigators have found that a lack of familiarity, lack of agreement with a treatment modality, and lack of outcome expectancy affect physician adherence to guidelines. [25]

To improve physicians' adherence to guidelines regarding the use of hydroxyurea and to clarify its role in the treatment of patients with sickle cell disease the Office of Medical Applications of Research (OMAR) at the National Institutes of Health (NIH) scheduled an NIH Consensus Development Conference: Hydroxyurea Treatment for Sickle Cell Disease, to be held in February 2008. The EPC of the Bloomberg School of Public Health of the Johns Hopkins University (JHU) was asked to prepare an evidence report for this conference in response to a request by the OMAR and AHRQ. We were asked to review and synthesize the evidence on the following questions, described in greater detail in Chapters 2 and 3:

1. What is the efficacy (results from clinical studies)of hydroxyurea treatment for patients who have sickle cell disease?
2. What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?
3. What are the short- and long-term harms of hydroxyurea treatment?
4. What are the barriers to the use of hydroxyurea treatment (and other therapies) for patients who have sickle cell disease and what are the potential solutions?
5. What are the future research needs?

Our goal was to provide the OMAR with a comprehensive review of the literature regarding these questions, so that this complex topic can be addressed with the available evidence.

Chapter 2. Methods

The objective of the report is to review and synthesize the available evidence regarding the efficacy and effectiveness of hydroxyurea treatment in patients with sickle cell disease, to assess the potential short and long-term harms of its use in patients with sickle cell disease and other diseases, and to discuss barriers to the use of hydroxyurea and other medications in the treatment of sickle cell disease. The results of this report will be presented to an NIH Consensus Panel in February 2008.

Recruitment of Technical Experts and Peer Reviewers

We assembled a core team of experts from JHU who have strong expertise in the management of and research in sickle cell disease, clinical trial methodology (including clinical trials of hematological agents), systematic literature review, epidemiological studies, and ethics and adherence research. We also recruited external technical experts from diverse professional backgrounds, including academic, clinical, and non-profit public interest groups. The core team asked the technical experts for input regarding key steps of the process, including the selection and refinement of the questions to be examined. Peer reviewers were recruited from various clinical settings. Bristol-Myers Squibb, maker of Droxia® and Hydrea®, was invited to review the draft report and declined in writing. In addition to Bristol-Myers Squibb, eight generic manufacturers of hydroxyurea were invited to serve as reviewers. The eight manufacturers declined in writing, were no longer manufacturing hydroxyurea, or did not reply to two or more written requests. (See Appendix F*.)

Key Questions

The core team worked with the technical experts, the OMAR Consensus Panel chairman, and the AHRQ to develop the Key Questions that are presented in the "The Purpose of This Evidence Report" section of Chapter 1 (Introduction). Before searching for the relevant literature, we clarified our definitions of these Key Questions and the types of evidence that we would include in our review.

Key Questions 1 and 2 addressed the efficacy (the therapeutic effect of an intervention in an ideal setting, such as a clinical trial) and effectiveness (the therapeutic effect of an intervention as demonstrated or observed in patients in their usual care setting) of hydroxyurea in patients with sickle cell disease. Based on discussion with our experts, we knew that limiting our search to randomized trials would yield an insufficient number of articles upon which to draw conclusions. Therefore, we opted to include RCTs, cohort studies with a control population, and pre/post studies. We planned to address efficacy outcomes in both children and adults. We chose not to include case series in our review of efficacy and effectiveness, since these studies would not yield strong evidence for efficacy. We opted to include studies of biomarkers as intermediary indicators of efficacy if they were of the appropriate study design (RCTs, controlled cohort studies, or pre/post studies) (Figure 1).

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

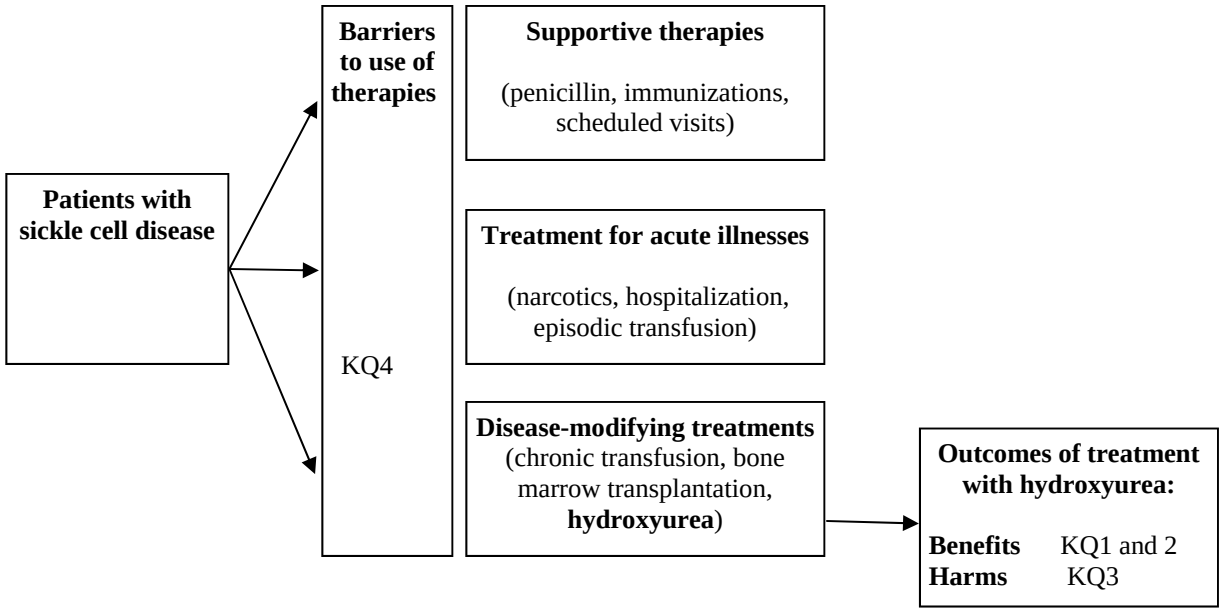

Figure 1. Analytic Framework

Key Question 3 addressed the toxicity of hydroxyurea in patients with sickle cell disease. To respond to this question, we chose to look for strong evidence of toxicity in patients with sickle cell disease by reviewing controlled studies (randomized, non-randomized, and pre/post studies) that had addressed toxicities in this population. Given that the CERHR[26] has recently reported in detail on toxicities to children and developing fetuses, we chose to update and confirm the findings presented in that report without producing our own detailed description of the developmental toxicities of hydroxyurea in children and fetuses.

Since we anticipated that the availability of strong evidence would be limited, we chose to also allow weaker forms of evidence such as case reports. We decided to exclude case series, since the level of detail in reports of cases series is generally insufficient to allow us to assess how the outcome is causally related to the exposure. To provide further information regarding the potential toxicities of this drug, we chose to also include indirect evidence of any toxicity in other patient populations treated with hydroxyurea. As noted above, we chose to include strong evidence of toxicities in other patient populations by reviewing controlled studies (both randomized and non-randomized and pre/post studies). We also included case reports in these populations, but not case series. The exception was the few very large case series (100 or more patients) reporting toxicities in patients with diseases other than sickle cell disease, excluding CML. Since we found no other source of published information on long-term exposure to hydroxyurea, we reasoned that these studies might provide useful, although indirect, evidence of particular toxicities.

Key Question 4 concerned barriers to the use of hydroxyurea. We anticipated finding little in the way of data that specifically addressed barriers to the use of this drug for sickle cell disease. Therefore, we sought information on barriers to the use of other therapies for treatment of sickle cell disease, including the receipt of routine, scheduled care; adherence to medications; and receipt of therapies, including pain control and prescriptions. We hypothesized that these barriers would be representative of barriers to the use of hydroxyurea. We opted to search for: (1) studies that tested whether supposed barriers were actual barriers to accessing scheduled care, receiving medication prescriptions, or adhering to medications; (2) studies in which patients, providers, or family members described what they perceived to be barriers to accessing scheduled care, receiving medication prescriptions, or adhering to medications; and (3) studies that tested an intervention aimed at overcoming barriers to accessing scheduled care, receiving medication prescriptions, or adhering to medications (Figure 2).

Literature Search Methods

Searching the literature involved identifying reference sources, formulating a search strategy for each source, and executing and documenting each search. For the searching of electronic databases, we used medical subject heading (MeSH) terms that were relevant to hydroxyurea, combined with sickle cell disease and with other hematologic diseases such as essential thrombocythemia. We used a systematic approach to searching the literature in order to minimize the risk of bias in selecting articles for inclusion in the review.

This strategy was used to identify all the relevant literature that applied to our Key Questions. We also looked for eligible studies by reviewing the references in pertinent reviews, by querying our experts, and by taking advantage of knowledge shared at core team meetings.

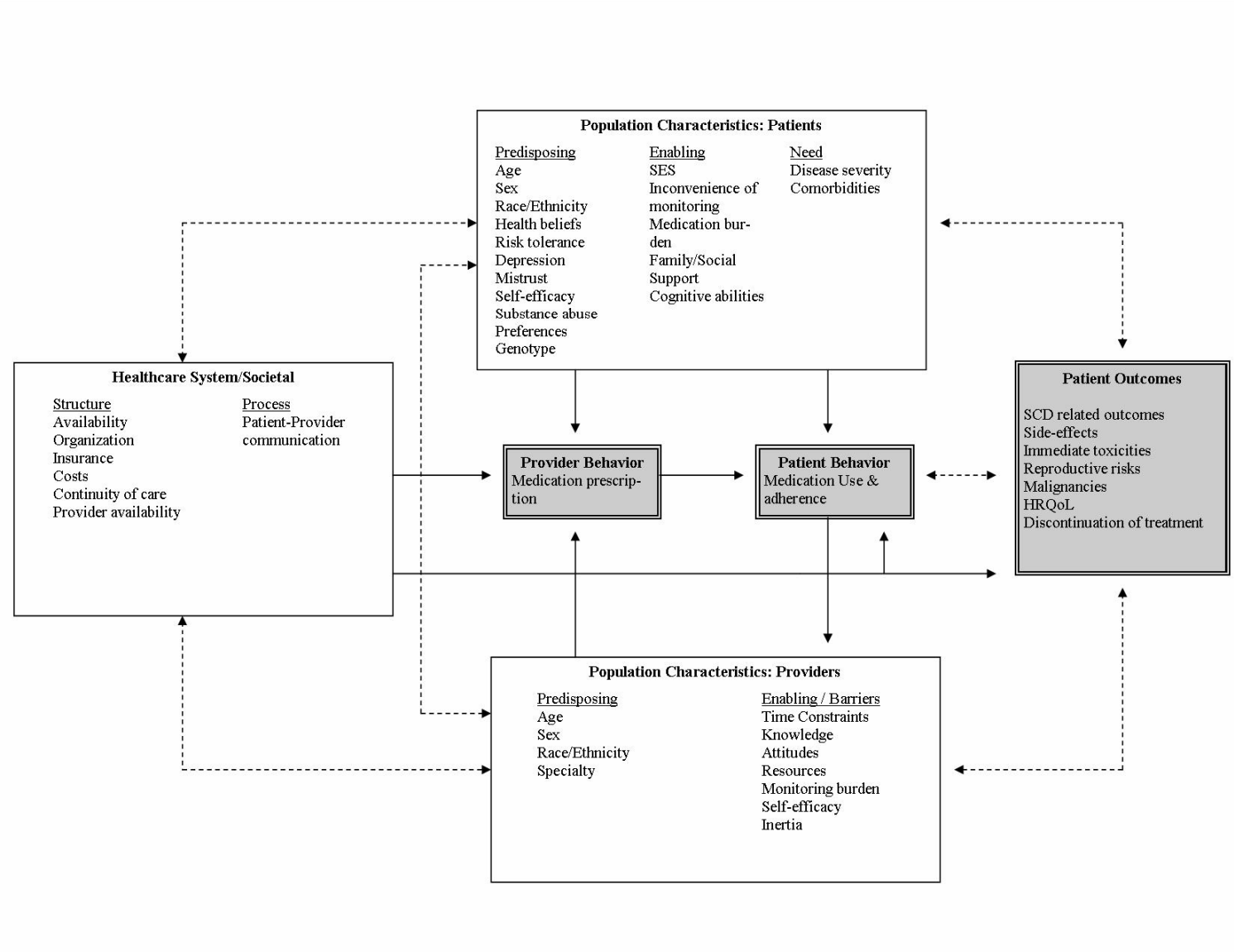

Figure 2.Conceptual Model: Hydroxyurea Treatment For Sickle Cell Disease (Adapted From The Aday & Andersen Expanded Behavioral Model)[26]

Sources

Our comprehensive search included electronic and hand searching. On March 15, 2007, we ran searches of the MEDLINE® and EMBASE® databases. A supplemental search targeting essential thrombocythemia was added to the MEDLINE and EMBASE searches on May 7, 2007. On June 30, 2007, the MEDLINE and EMBASE searches were updated, and additional searches were executed using TOXLine and CINAHL. All searches were limited to English-language articles involving treatment of humans. Review articles were excluded from the searches. Searches were not limited by date of publication or by subject age.

Search Terms and Strategies

Search strategies specific to each database were designed to enable the team to focus the available resources on articles that were most likely to be relevant to the Key Questions. We developed a core strategy for MEDLINE, accessed via PubMed, on the basis of an analysis of the MeSH terms and text words of key articles identified *a priori*. The PubMed strategy formed the basis for the strategies developed for the other electronic databases (see Appendix A*).

Organization and Tracking of the Literature Search

The results of the searches were downloaded into ProCite® version 5.0.3 (ISI ResearchSoft, Carlsbad, CA). Duplicate articles retrieved from the multiple databases were removed prior to initiating the review. From ProCite, the articles were uploaded to SRS 4.0 (TrialStat © 2003-2007). SRS is a secure, Web-based collaboration and management system designed to speed the review process and introduce better process control and scientific rigor. We used this database to store full articles in portable document format (PDF) and to track the search results at the title review, abstract review, article inclusion/exclusion, and data abstraction levels.

Title Review

The study team scanned all the titles retrieved. Two independent reviewers conducted title scans in a parallel fashion. For a title to be eliminated at this level, both reviewers had to indicate that it was ineligible. If the first reviewer marked a title as eligible, it was promoted to the next elimination level. If the two reviewers did not agree on the eligibility of an article, it was automatically promoted to the next level (see Appendix B, Title Review Form).

The title review phase was designed to capture as many studies as possible that reported on the efficacy and/or effectiveness of hydroxyurea treatment of hematologic diseases, the toxicity of hydroxyurea in the treatment of any disease, and the barriers to the treatment of sickle cell disease with hydroxyurea or other agents. All titles that were thought to address the above criteria were promoted to the abstract review phase.

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

Abstract Review

The abstract review phase was designed to identify articles that applied to our Key Questions. An abstract was excluded at this level if it did not apply to the Key Questions or for any of the following reasons: It was not written in English, contained no original data, involved animals only, was solely a report of an *in vitro* experiment, or was a case series of fewer than 10 patients, unless the article was primarily reporting on toxicities (Appendix B[*], Abstract Review Form).

Abstracts were promoted to the article review level if both reviewers agreed that the abstract could apply to one or more of the Key Questions and did not meet any of the exclusion criteria. Differences of opinion were resolved by discussion between the two reviewers.

Article Review

Full articles selected for review during the abstract review phase underwent another independent review by paired investigators to determine whether they should be included in the full data abstraction. At this phase of review, investigators determined which of the Key Question(s) each article addressed (see Appendix B, Article Inclusion/Exclusion Form). If articles were deemed to have applicable information, they were included in the data abstraction. Differences of opinion regarding article eligibility were resolved through consensus adjudication.

Once an article was included at this level, an additional level (filter) was added to further exclude articles that were found to be inapplicable once the data abstraction was underway. This process was used to eliminate articles that did not contribute to the evidence under review (see Appendix B, Triage Form). Articles could be excluded at this level for the following reasons: They contained insufficient data to address the question or only a very minimal description of a study population (e.g., they provided no relevant outcome data, no details about the included patients, or no description about the intervention except that it involved hydroxyurea). We excluded studies with fewer than 20 patients unless the article was primarily reporting on the toxicity of hydroxyurea in sickle cell disease. We excluded trials involving diseases other than sickle cell disease if fewer than 20 patients received hydroxyurea. We allowed case series if they described toxicities in more than 100 patients. We excluded case reports if there was no description of duration of use of hydroxyurea or no description of the dose(s) used, or if the study addressed pregnancy. A list of the articles excluded at this level is included in Appendix D.

Data Abstraction

After applying the criteria described above, we used a sequential review process to abstract data from the remaining articles. In this process, the primary reviewer completed all the relevant data abstraction forms. The second reviewer checked the first reviewer's data abstraction forms for completeness and accuracy. Reviewer pairs were formed to include personnel with both clinical and methodological expertise. The reviews were not blinded in terms of the articles' authors, institutions, or journal. [27] Differences of opinion that could not be resolved between the reviewers were resolved through consensus adjudication.

[*] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

For all articles, excluding case reports, reviewers extracted information on general study characteristics: study design, location, disease of interest, inclusion and exclusion criteria, and description of administered therapies (see Appendix B*, General Form). Participant characteristics were also abstracted: information on intervention arms, age, race, genotype and haplotype, substance abuse, socioeconomic status, and related data on the disease under study.

Outcome data were abstracted from the articles that were applicable to the Key Questions regarding hydroxyurea's efficacy and/or effectiveness and its toxicity. Reviewers abstracted data on both categorical and clinical outcomes and toxicities (see Appendix B, Key Questions 1-3). Case reports on hydroxyurea toxicity were abstracted using a separate form. The reviewers abstracted data on disease, subject age, the reported adverse event(s), and causality using the WHO's causality assessment instrument described below[28] (see Appendix B, CR Tox).

Separate forms were developed to abstract data for Key Question 4 (see Appendix B, Key Question 4 Form). For each study, we determined the extent to which the measured study outcomes were likely to be true measures of the outcome of interest (e.g., provision of appropriate pain management or receipt of routine, scheduled care). For example, in the pain management interventions, we considered utilization outcomes (e.g., hospital length of stay or costs) and descriptive comments from patients (without explicit qualitative methodology to analyze those comments) to be forms of indirect evidence, and we considered variables abstracted by chart review (e.g., ratings of patient-controlled analgesia, pain consults, or patient pain ratings) to be forms of direct evidence.

For Key Question 4, we categorized each study as providing "direct" or "indirect" evidence. Studies in which there was at least one outcome that was considered to be a true measure of our outcome of interest were considered to provide "direct" evidence. We categorized the study as providing "indirect" evidence if either (1) only indirect outcomes were measured or (2) both direct and indirect outcomes were measured, but only the indirect (and not the direct) outcome demonstrated an effect.

For each study designed to test interventions to overcome treatment barriers, we determined by consensus of two reviewers whether there was "improvement," "partial improvement," "no improvement" or a "detrimental" effect. We categorized intervention studies as indicating "improvement" if some, most, or all measured outcomes showed statistically significant improvement and no outcomes worsened. We categorized intervention studies as indicating "potential improvement" if the authors implied that some, most, or all measured outcomes had improved and they gave data to suggest that their conclusions were correct but did not perform statistical tests. We categorized intervention studies as indicating "partial improvement" if our main outcome of interest did not improve as a result of the intervention, but there were other positive effects. We categorized intervention studies as showing "no improvement" if there was no improvement in any outcome and no outcomes worsened. We categorized intervention studies as "detrimental" if some, most, or all measured outcomes worsened and no outcomes improved.

Quality Assessment

We assessed the included studies on the basis of the quality of their reporting of relevant data. For the randomized controlled trials, we used the scoring system developed by Jadad et al.[29]: (1) Was the study described as randomized (this includes the use of words such as

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

"randomly," "random," and "randomization")? (2) Was the method used to generate the sequence of randomization described, and was it appropriate? (3) Was the study described as double-blind? (4) Was the method of double-blinding described, and was it appropriate? (5) Was there a description of withdrawals and dropouts?

For the observational studies (both cohort studies and controlled clinical trials), we created a quality form based on those previously used by our EPC. This form was aimed primarily at capturing data elements most relevant to study design. We designed questions to evaluate the potential for selection bias, which might limit internal validity and generalizability, as well as questions to assess the potential for confounding, which could bias the estimates of the treatment effect. [30-32] For our assessment of the quality of the qualitative studies we reviewed, we developed a form to identify key elements that should be reported when describing the results of qualitative research, as advocated by leaders in the field. [33-35] For our quality assessment of the surveys reviewed, we adapted information from Ratanawongsa et al. [36] The quality assessments were done independently by paired reviewers. A third reviewer reconciled the results of the first two reviewers in the case of the randomized trials. [29] For the other study designs, the results of the two reviewers were averaged. The quality assessment instruments are included in Appendix B, Quality Forms.

Data Synthesis

We created a set of detailed evidence tables containing information extracted from the eligible studies. We stratified the tables according to the applicable Key Question(s). Once evidence tables were created, we re-checked selected data elements against the original articles. If there was a discrepancy between the data abstracted and the data appearing in the article, this discrepancy was brought to the attention of the investigator in charge of the specific data set, and the data were corrected in the final evidence tables.

We did not quantitatively pool the data for any of the outcomes because there was a paucity of RCTs addressing any of our outcomes of interest. The substantial qualitative heterogeneity among the observational studies (with different populations, different dosage schedules, and different durations of follow-up) made pooling these studies inadvisable.

Data Entry and Quality Control

Data were abstracted by one investigator and entered into the online data abstraction forms (see Appendix B, Forms). Second reviewers were generally more experienced members of the research team, and one of their main priorities was to check the quality and consistency of the first reviewers' answers.

Grading of the Evidence

At the completion of our review, we graded the quantity, quality, and consistency of the best available evidence, addressing Key Questions 1 and 2 together and Key Question 3 alone, by adapting an evidence grading scheme recommended by the GRADE Working Group[37] and modified in Chapter 11 of the EPC Manual currently under development. We separately

considered the evidence from studies of children and studies of adults. In rating the strength of the study designs, RCTs were considered to be best, followed by non-RCTs and observational studies. If an outcome was evaluated by at least two RCTs as well as observational studies and case reports, our evidence grade was based only on the RCTs evaluating that outcome. If an outcome was evaluated by one or no RCTs, our evidence grade was based on the single RCT (if any) in addition to the best available non-RCT or the best available observational studies (cohort studies considered best, followed by cross-sectional studies and studies with a pre/post observational design). The results of case reports were incorporated into the grading of Key Question 3 as described below.

We assessed the quality and consistency of the best available evidence, including an assessment of the risk of bias in relevant studies (using individual study quality scores), whether the study data directly addressed the Key Questions, and the precision and strength of the findings of individual studies. We classified evidence bodies pertaining to each Key Question into four basic categories: (1) “high” grade (high confidence that the evidence reflected the true effect; further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (moderate confidence that the evidence reflected the true effect; further research may change our confidence in the estimate of effect and may change the estimate); (3) “low” grade (low confidence that the evidence reflected the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate); and (4) “insufficient” (evidence was either unavailable or did not permit the estimation of an effect) (Appendix E).

The evidence regarding the case reports was graded according to the WHO Collaborating Center for Drug Monitoring. [28,38] A reaction was rated as “certain” if all four criteria for causality were fulfilled: (1) a plausible time relationship between drug administration and an event; (2) an absence of a concurrent disease that might have caused the event; (3) a reasonable response to drug withdrawal; and (4) existence of a rechallenge or a demonstrated biological explanation. A reaction was rated as "probable" if criteria 1, 2, and 3 were fulfilled, and "possible" if only criterion 1 was met and information on criterion 3 was lacking or unclear. A reaction was rated as "unlikely" if criterion 1 was not met and if other drugs, chemicals, or underlying disease provided a plausible explanation for the reaction. We rated a reaction as “possible” if only criterion 1 was met and the reaction did not meet criteria for “certain.” After these causality assessments, we assigned a level of evidence to each reported potential adverse event: Level 1 evidence had to have at least one certain case report, level 2 evidence had to have at least one probable report but no certain report, and level 3 evidence had to have at least one possible report but no certain or probable case report. The level 1 evidence was used as supportive evidence when assigning an evidence grade to the whole body of evidence for Key Question 3.

We graded the evidence for Key Question 4 using two instruments: The sub-question regarding interventions to overcome barriers was graded using the instrument described above. We graded the evidence regarding the existence of barriers using a modification of this instrument that addressed similar domains: the quantity of studies, protection against bias in the studies (quality), and consistency (Appendix E).

For each outcome of interest, two investigators graded each Key Question, and then the entire team discussed their recommendations and reached a consensus.

Peer Review

Throughout the project, the core team sought feedback from the external technical experts and the OMAR panel. A draft of the report was sent to the technical experts and peer reviewers, as well as to representatives of the AHRQ and the NIH (OMAR). In response to the comments from the technical experts and peer reviewers, we revised the evidence report and prepared a summary of the comments and their disposition that was submitted to the AHRQ.

Chapter 3. Results

Literature Search /Abstract/Article Review

The literature search process identified 12,550 citations that were deemed potentially relevant to the Key Questions. An additional 5 articles were found by hand searching, as described in Chapter 2; thus, the total number of citations retrieved was 12,555 (see Figure 3). We excluded 3,191 duplicate citations. Most duplicates came from concurrently searching MEDLINE® and EMBASE. The search strategy used in EMBASE was modeled on that which we used in MEDLINE, with similar search terms (see Appendix A[*]). Also, the EMBASE search engine allows the user to search the MEDLINE database as well as EMBASE, a strategy that often yields many duplicates between the two search sites. This EPC employs this strategy in order to improve the sensitivity of the search.

In the title review process, we excluded 6,647 citations that clearly did not apply to the Key Questions. In the abstract review process, we excluded 1,451 citations that did not meet one or more of the eligibility criteria (see Chapter 2 for details). At article review, we then excluded an additional 708 articles that did not meet one or more of the eligibility criteria. An additional 223 were excluded during article review when we discovered that necessary information was not provided in the text. This exclusion process left us with 335 articles that were eligible for inclusion in the review of one or more of the Key Questions.

Description of the Types of Studies Retrieved

Forty-seven studies, described in 53 articles, applied to Key Questions 1 or 2. There were 2 randomized controlled trials, described in 8 publications, and 37 observational studies that directly addressed the efficacy and/or effectiveness of hydroxyurea in the treatment of sickle cell disease. Eight articles described data on biomarkers as intermediate indicators of efficacy in hydroxyurea-treated patients with sickle cell disease. Sixty-four articles, many of which also included efficacy data, applied to Key Question 3: 2 RCTs of hydroxyurea in sickle cell disease described in 5 publications, 20 observational studies of hydroxyurea in sickle cell disease, 20 randomized controlled trials of hydroxyurea in other diseases, and 19 observational studies of hydroxyurea in other diseases. We reviewed 194 publications that described case reports about the toxicity of hydroxyurea. We identified 49 studies that applied to Key Question 4 concerning barriers to the care of patients with sickle cell disease.

[*] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

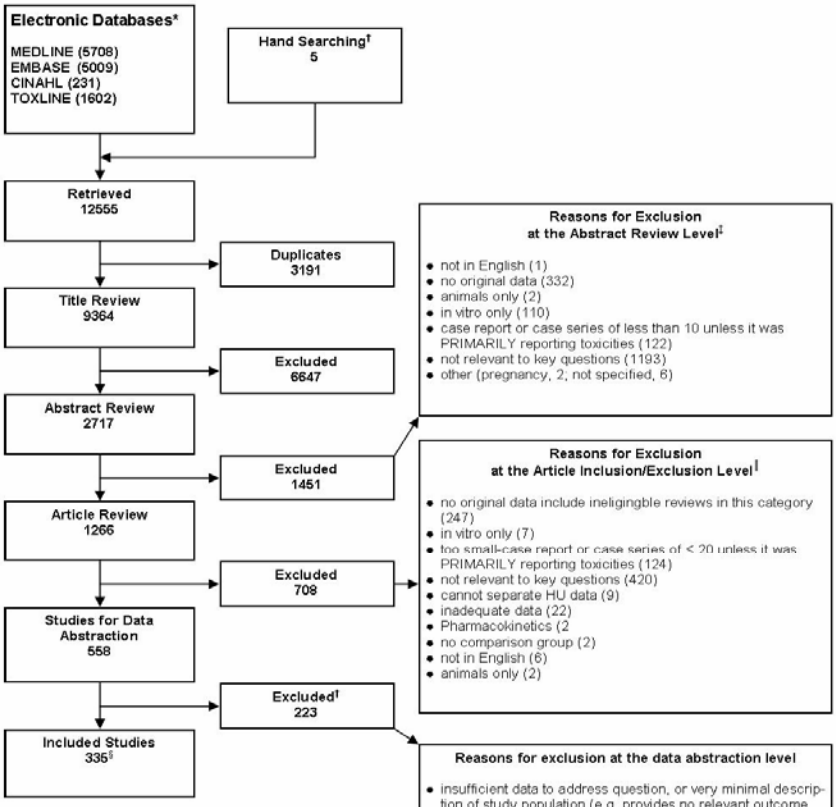

Figure 3. Summary of literature search and review process.

* See Appendix C for detailed search strategies
† See methods section for details
‡ Total reasons for exclusion at abstract level exceeds 1451 because reviewers were allowed to enter multiple reasons for exclusions. Additionally, reviewers were not required to agree on the reason for exclusion.
‖ Total reasons for exclusion at Article Review level exceeds 708 because reviewers were allowed to enter multiple reasons for exclusions. Additionally, reviewers were not required to agree on the reason for exclusion.
§ includes 194 case reports.

Key Question 1: What is the Efficacy (results from clinical studies)of Hydroxyurea Treatment for Patients who have Sickle Cell Disease?

Key Question 2: What is the Effectiveness (in everyday practice) of Hydroxyurea Treatment for Patients who have Sickle Cell Disease?

Description of Randomized Trials

We identified eight published reports describing results from two randomized controlled trials of hydroxyurea for the treatment of sickle cell disease (Appendix C, Evidence Table 1). These reports presented the results from the MSH, [21,22,39-42] an extended followup of the participants in the MSH, [43] and a pediatric study in Belgium. [44] The MSH began enrollment at multiple centers in North America in 1992, and the results were published in 1995. This study enrolled 299 adults. The Belgian study began enrollment in 1992 at two centers in Europe, and the results of this study were published in 1996 after enrollment of 25 patients. The Belgian study had a crossover design; patients were randomized to receive hydroxyurea or placebo for the first 6 months and then to receive the other treatment for the next 6 months. Hematological outcomes were reported as the change from baseline after 6 months of hydroxyurea, and clinical outcomes were compared between the placebo and hydroxyurea arms. The methods used for dose escalation and monitoring for toxicity were similar in the two studies, except the maximum dose was 35 mg/kg/day in the MSH and 25 mg/kg/day in the Belgian study.

Description of the quality of the studies. Both trials had rigorous eligibility criteria designed to select patients with severe sickle cell anemia or sickle α-thalassemia and minimize the risk of known toxicities. The methodological quality of the MSH was excellent (Jadad score of 5, out of a maximum of 5) and that of the Belgium study was moderate (Jadad score of 3), because the method of masking was not described (Appendix C, Evidence Table 2). Both the MSH and the Belgian study provided a placebo control with masking of patients, but only the MSH study masked the providers and the endpoint adjudication panel. In the MSH, 53 patients (18 percent) had permanent or extended cessation of the study medication: 21 percent in the hydroxyurea group and 14 percent in the placebo group. Frequent reasons for discontinuation were pregnancy (n=16), inactivity (n=18), myelotoxicity at 2.5 mg/kg/day or "simulated toxicity" (n=5), and a need for long-term transfusion therapy (n=5). [39] The Belgian investigators excluded three patients (14 percent) after 4 to 5 months for failing to make the required monthly visits.[44]

Description of the included patients. A description of the patients is given in Appendix C, Evidence Table 3. The MSH included only adults (mean age, 30.5 years), and approximately half of the participants were male. The Belgian study included mostly children (median age, 9 years; range, 2 – 22 years), and approximately half were male. The majority of patients in both studies were African or African American and had sickle cell anemia. The β-globin haplotype was reported only in the MSH study; about 40 percent were homozygous for the Benin haplotype, 20

percent were heterozygotes with the Benin/Central African Republic (CAR) haplotype, and the remainder had other combinations.

Description of Observational Studies (Pre/Post Design or Non-Randomized Control Group)

Design. Our analyses included the results of 37 observational studies of hydroxyurea use in patients with sickle cell disease: 19 in North America, 11 in Europe, 2 in the Middle East, and 3 in Central or South America (Appendix C*, Evidence Table 4). The earliest studies we identified were published in 1992, [45,46] and one-quarter of the studies were published in the past 2 years. The studies ranged in size from only 8 patients in a cytotoxicity study [47] to 225 patients in the large French cohort. [48] More studies were designed to enroll children only (n=20) than adults only (n=12).

The majority of the studies are best described as pre/post studies in which the patients' clinical parameters were described prior to starting hydroxyurea and again after they had been on the drug for a period of time. Nine of the studies were retrospective, [45,48-55] two were cross-sectional, [56,57] and the rest were prospective studies. Three studies described comparison groups of patients who were not treated[58,59] with hydroxyurea. [60-62]

The study goals varied markedly (described in Evidence Table 4)**.** The majority aimed to assess the long-term safety and efficacy of hydroxyurea. Some studies, however, were more specialized, including two that assessed the effect of the drug on transcranial Doppler (TCD) velocities, [62,63] one that assessed the efficacy of a low dose of hydroxyurea, [50] three that specifically assessed splenic function, [56,64,65] one that focused on cutaneous adverse effects, [66] one that assessed albuminuria, [49] one that assessed secondary stroke, [67] and several that looked at malignancy and cytotoxic effects of the drug. [47] Most studies reported both efficacy and toxicity data; however, 8 were primarily toxicity studies, [47,48,53,57,66 55,64,68]18 were primarily efficacy studies, [45,62,63,69 46,50,59-61,70-78] and 11 were primarily effectiveness studies, [49,51,52,56,58,65,67,79-82] although the designs of the efficacy and effectiveness studies were often similar. Toxicity studies without efficacy data are not included in Evidence Table 8**.** [53,57]

Patient Clusters. We identified four clusters of studies based on the patient populations examined; this approach was taken because of our concern that some patients might have been described in more than one publication. One cluster was comprised of manuscripts related to the Safety of Hydroxyurea in Children with Sickle Cell Anemia (HUG-KIDS) study. HUG-KIDS was a high-quality phase I/II study that began recruiting children in December, 1994 and continued through March, 1996. The first of these studies that we included in this cluster was primarily a toxicity study. [68] The second included efficacy data from the children who reached the MTD during the study. [73] The third study was a pre-post effectiveness study that included 15 of the children who had been enrolled in HUG-KIDS. [81]

The second cluster was the Hydroxyurea Safety and Organ Toxicity (HUSOFT) cluster, which consisted of two studies. [60,72] The first was the HUSOFT study itself, which was a cohort study of hydroxyurea use in young children with Hb SS. [60] In this publication, the CSSCD cohort was described as a comparison group. The second study was an extension of HUSOFT study, in which investigators followed the patients for a longer time. [72]

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

In our third cluster, we grouped studies from a group of investigators in France. The patients were recruited from centers participating in the French Study Group on Sickle Cell Disease. The first study was a pre-post efficacy study; [76] the second study was also an efficacy study that included some (or all) of the patients who had been described in the first study. [75] The third publication was a survey of French physicians treating children with hydroxyurea to assess toxicity. [55] We expect that those children who were enrolled in the first study were also described by their physicians in the survey. [76] Finally, the most recent study was a cohort study[48] to explore toxicity, which involved recruiting patients who had been in the earlier studies and those identified by the survey. [55]

The fourth cluster consisted of two publications from the Belgian Sickle Cell Group. [58,82] Both publications described the experiences of patients in their registry, with the latter study including more patients. [82] To our knowledge, the studies outside these four clusters included no overlapping patients.

Interventions. The initial dosage and titration schedule for hydroxyurea varied little across studies, with most starting at 15 or 20 mg/kg and titrating upward by 5 mg/kg at some interval (ranging from every 4 weeks to every 6 months) or according to clinical response. One study specifically tested the efficacy of the drug without up-titration, [50] and the HUSOFT study did not involve titration. [60] A number of the observational studies did not include any description of the dosages received by the patients.

Description of the quality of the studies. The studies that were evaluated with our 16-point scale for assessing the quality of observational studies received between 27 percent [47] and 93 percent[77] of the possible points (Appendix C, Evidence Table 5). There were eight high-quality studies that received more than 80 percent of the quality points. [46,64,68,70,73,76,77,81] There was a small but significant decline in quality score over the years (p=0.01). Most of the studies appropriately chose objective outcomes to report, and most described their interventions with adequate detail. Studies were less complete in their description of their source population, i.e., the population from which their participants were drawn; they were also less complete in their description of the inclusion criteria for their study and in their description of the characteristics of the included patients. Authors did a particularly poor job of describing how complete the adherence to the intervention was and of describing losses to followup. For cohort studies, inadequate description of losses to followup can be an important source of bias. There were no high-quality studies that directly addressed the effectiveness of treatment with hydroxyurea for sickle cell disease, an important issue for the implementation of a therapy. The two studies that used a survey design were not considered high-quality because they provided little detail about the surveyed patients and providers and did not use any validated instruments for collecting information; however, they were probably adequate for their purpose, which was to collect toxicity data from providers. [53,55]

Description of the included patients. A description of the included patients is given in Appendix C, Evidence Table 6. Although not all studies reported the sex of the enrolled patients, for those that did, the percentage of males ranged from 40 percent[77] to 74 percent. [76] The majority of the studies included patients with Hb Sβ thalassemia and with Hb SC disease in addition to Hb SS.

HUSOFT was a study of very young children (mean age of 1.3 years, with a range from 0.5 to 2.3 years). [60] The 20 pediatric studies had mean or median ages ranging from 1.3 to 14 years, and the 12 adult studies had mean or median ages from approximately 21 to 33 years. Two studies included adults and children, [58,70] and two did not describe the age range. [69,79] Three of

the studies from Europe were exclusively of Caucasian patients. [71,74,78] Few studies described the clinical activity of their cohorts upon entry, although this information could often be inferred from the inclusion and exclusion criteria. The duration of observation of the enrolled patients varied markedly both across studies and within studies. The studies with the longest median followup times were in the range of 36 to 45 months. Some individuals within each study were followed for much longer, although they were not necessarily treated with hydroxyurea for the duration of their followup.

Efficacy and Effectiveness of Hydroxyurea in Children

The Belgian RCT, a small placebo-controlled study, reported hematological outcomes as the change from baseline after 6 months of treatment with hydroxyurea (Appendix C, Evidence Table 7). In the hydroxyurea group hemoglobin increased by a mean of 0.4 g/dl, and the absolute mean increase in Hb F was 10.7 percent ($p<0.001$). [44] For these children, the rate of hospitalization and number of days hospitalized per year were significantly lower for the hydroxyurea group (1.1 admissions, $p=0.0016$ and 7.1 days, $p=0.0027$) than for the placebo group (2.8 admissions and 23.4 days).

Among the observational studies, more reported hematological outcomes than reported clinical outcomes. Hb F% was reported as an outcome in 17 studies (Table 1; Appendix C, Evidence Table 8). In all the studies that reported Hb F% before and during treatment with hydroxyurea, the HbF% increased substantially while patients were being treated. The mean pre-treatment Hb F% ranged from 5 to 10 percent, and the post-treatment values were in the range of 15 to 20 percent. The percentage of F cells was less frequently reported, but it increased from baseline in three of the four pediatric studies in which it was reported. [68,72,75] In the fourth study, the maintenance of a stable percentage of F cells and Hb F% over 104 weeks of treatment, rather than the decline usually seen in young children, was attributed to hydroxyurea therapy. [60] Three of these observational studies were retrospective. [49-51] Of these, two reported increases in Hb F% that were comparable to those in the prospective studies. [49,50] One brief report described 226 patients who had taken hydroxyurea and compared the 38 patients who died to the remainder who survived. [51] The Hb F% increase was greater in the patients who died than among those who survived, but these two groups were substantially different before treatment. The authors concluded that not all patients benefit from hydroxyurea. Hemoglobin concentration increased modestly (roughly 1 gm/dl) but significantly across these studies.

Table 1. Efficacy of Hydroxyurea in Observational Studies of Children with Sickle Cell Disease

Outcome	Number of Studies Reporting	Magnitude and Consistency of Effect
Hb F%	17	93% to 366% increase*
Hemoglobin	16	5% to 20% increase
Pain Crises	4	No difference in 1; no baseline data in 1; and significant reductions in 2
Hospital Admissions	4	56% to 87% decline in yearly rate
Transfusions	1	Decreased for 3.9/ year to 0.43/ year
Mortality	4	Very rare events
Neurological Events	3	Comparable stroke rates as on chronic transfusion, stable brain images

The frequency of pain crises was reported as an outcome in five pediatric studies. [50,59,64,72,82] In the retrospective study by Svarch et al., the frequency of pain crises declined from a median of 3 per year to a median of 0.8 per year while patients were on treatment, with a median followup time of 24 months. [50] It is particularly important to note that these results were obtained in a resource-poor environment (Central America) and used a fixed dose of hydroxyurea of 15 mg/kg/day. Another study reporting pain outcomes was a small study by Hankins et al. [72] that prospectively followed 17 children who had been enrolled in HUSOFT during a 4-year extension study. The authors reported 33.8 pain events requiring hospitalization per 100 patient-years while their patients were on treatment, a rate that did not differ from that reported for untreated patients in the CSSCD cohort (32.4 per 100 patient-years, p=0.87). The authors felt that differences in the methods of collecting pain data in their study and in the CSSCD may have biased the results toward a finding of no difference. They observed fewer episodes of acute chest syndrome than were seen in the CSSCD. A small, high-quality study found a decrease in pain events from 3.1 per year in the year prior to hydroxyurea therapy to 1.2 per year during 18 months of therapy. [64] Similarly, in a 12-month study by Santos et.al, pain frequency decreased from a median of four episodes per year to two per year during the year of therapy (p=0.0009). [59] In the most recent study from the Belgian Sickle Cell Registry, patients had 2.2 pain crises per year that required hospitalization while on treatment, although it is not clear what the baseline rate was for their population. [82]

Hospitalization rates were reported in four studies. Again, in the retrospective Central American study, the hospitalization rates decreased to 0.5 per year while on treatment from a baseline rate of 4 per year. [50] In the study by Oliveri, rates declined by 75 percent, to 1.7 per year from 6.7 per year; [64] compliance with medication use was very high in this study. Similarly, in a small study of severely ill children, the hospitalization rates dropped to 3 per year from 7 per year. [77] In the Belgian Registry, hospitalization rates declined to 1.1 per patient-year from 3.2 per patient-year after 3 years. [82]

Two studies reported TCD velocities. [62,63] In the study by Kratovil et al., the mean maximum velocity decreased on treatment to 111 cm/sec from a mean maximum of 125 cm/sec. [62] A control group that was not treated with hydroxyurea had an increase in velocity over the same time period of 4.7 cm/sec. In the recent prospective study by Zimmerman et al., 37 children had TCD measurements prior to starting hydroxyurea. [63] The children (n=36) reached a stable MTD of 27.0 mg/kg/day and had repeat Doppler studies after a mean of 10 months. Velocities decreased significantly in the right and left middle cerebral arteries, right and left anterior cerebral arteries, and left posterior cerebral artery. In 14 of 15 children with conditional baseline TCD velocities, the values improved; in 5 of 6 with abnormal velocities, whose families refused transfusions, the velocities decreased to less than 200 cm/sec.

One study assessed the impact of hydroxyurea on secondary stroke prevention by enrolling 35 children who needed to discontinue their chronic transfusion protocol. [67] The average dose of the drug was 27 mg/kg/day, and the children were treated for a mean of 42 months. Seven children had recurrent ischemic events, for a rate of 5.7 per 100 patient-years. We noted, for comparison, that this rate was higher than the 2.2 per 100 person-years reported in a retrospective cohort study of children who received ongoing transfusions, [83] but it was better than the 70 percent prevalence of recurrent stroke seen in the first year after discontinuing transfusion without alternative treatments. [84] One other study reported that brain images obtained by MRI were stable during the course of treatment in 24 of 25 children. [65] In the Belgian Registry, during 426 patient-years of hydroxyurea treatment, the rate of central nervous system

events (stroke or transient ischemic attacks) was 1.3 per 100 patient-years, but no comparison rate was provided. [82]

Four studies assessed splenic function during hydroxyurea therapy. [56,59,64,65] One found no difference in the 12 children in whom the number of pitted red blood cells was counted. [64] A cross-sectional study used Howell-Jolly bodies as the outcome: [56] In the group of patients with spleens, patients on hydroxyurea therapy had a greater number of Howell-Jolly bodies than did those in the group not taking the drug. This relationship was true as well for the patients without spleens, suggesting that Howell-Jolly bodies are not simply a measure of splenic function. In a prospective study of 52 children, of whom 43 had had spleen function measured with scintigraphy both at baseline and on therapy, 6 patients (14 percent) completely recovered splenic function, and 2 (5 percent) had preserved splenic function after a median of 2.6 years of hydroxyurea at the MTD. [65] In the study by Santos et al., splenic function as measured by scintigraphy improved in 10 of 21 children was stable in 8, and worsened in 3. [59] A retrospective study reviewed the efficacy of hydroxyurea in reducing the progression of microalbuminuria[49] : Of the 17 treated patients without microalbuminuria at baseline, 16 remained free from microalbuminuria; 4 of 9 patients with baseline microalbuminuria normalized their urinalysis during treatment. The study by Santos and coworkers was the only one to describe transfusion use in children, reporting that the transfusion rate decreased from 3.9 per year to 0.43 per year in their 21 treated patients. [59]

Efficacy and Effectiveness of Hydroxyurea in Adults

In the MSH RCT, significant hematological effects of hydroxyurea after 2 years (relative to the placebo arm) included a small mean increase in total hemoglobin (0.6 g/dl) and moderate increases in fetal hemoglobin (3.2 percent) and mean corpuscular volume (MCV; 10.1 fl) (Appendix C, Evidence Table 7). [21,39,40] The median number of painful crises was 2.5 per year for those receiving hydroxyurea, as compared to 4.5 per year (a 44 percent decrease, $p<0.001$), and the time to first painful crisis was 3 vs 1.5 months ($p<0.01$). There were fewer episodes of acute chest syndrome (25 vs 51, $p<0.001$), transfusions (55 vs 79 patients, $p=0.002$, and 423 vs 670 units, $p=0.002$), but no significant differences in deaths (2 vs 6), strokes/chronic transfusion (2 vs 3), or hepatic sequestration (1 vs 3). [39] In the long-term followup study, which was observational after the initial period of randomization, the mortality rate was 40 percent lower ($p=0.04$) when patients were taking hydroxyurea (1.5 per 3-month period) than when taking placebo or no treatment (2.6 deaths per 3-month period). However, the long-term mortality, when analyzed according to the initial treatment assignment in the 2-year randomized trial, was similar for the hydroxyurea (3.1 per 100 person-years) and placebo (3.6 per 100-person-years) groups. The rates of stroke, sepsis, and renal and hepatic failure were also similar between the two groups. [43]

The MSH trial also included an evaluation of costs and quality of life. Annualized total costs were $16,810 for the hydroxyurea group and $22,270 for the placebo group ($p=0.21$), with significantly lower costs for hospitalization for pain in the hydroxyurea group ($12,160, $p<0.05$) than the placebo group ($17,290). [22] The hydroxyurea and placebo groups were similar in terms of all the quality of life measures, but participants with the greatest increase in Hb F (upper half of the change in Hb F) had significantly better "general health now" ($p<0.001$), decreased pain by 4-week recall ($p=0.004$), and better general health ($p=0.001$). [42] A sub-study of the MSH, completed at a single institution, evaluated exercise capacity; which increased in the

hydroxyurea group when compared to the placebo group. This improvement was accompanied by an increase in weight and decrease in the resting heart rate in the hydroxyurea group (3.2 kg and -14 beats/min, as compared to the placebo group's 1.8 kg and -4 beats/min). [41]

In the six prospective, observational studies of adults that reported hematological outcomes, Hb F% increased significantly in all six studies (Table 2; Appendix C*, Evidence Table 8). [45,46,71,74,78,80] The mean baseline Hb F% ranged from 4 percent to 12 percent, and during hydroxyurea treatment it ranged from 10 percent to 23 percent. The greatest increase was seen in the study by Voskaridou et al., [78] which was a prospective study of Caucasian patients with Hb $S\beta^+$ thalassemia and Hb $S\beta^0$ thalassemia who were treated with high doses of hydroxyurea, up to 2.5 g/day. These 14 patients had an increase from a mean of 3.6 percent (standard deviation [SD]=2.1) to 23 percent (SD=7.7). The smallest increase in Hb F% was seen in the study from Brazil, which reported outcomes by haplotype. This was a study of 22 patients; the greatest increase was among patients who had a homozygous Bantu haplotype (n=9 patients), from 4 percent to 9 percent (p=0.003). [80] As in the pediatric studies, there was a small increase in hemoglobin in most studies. The retrospective study by Loukopoulos reported hematological outcomes very comparable to those seen in the prospective studies. [74]

The number of pain crises was described in three studies. [46,61,71] The frequency of crises experienced by the 32 patients who completed the study by Charache et al. decreased from 4 per 6 months (range 0 to 20) to 1.3 per 6 months (range 0 to 9), although this difference was not statistically significant. In a study of Sicilians with Hb $S\beta^+$ thalassemia and Hb $S\beta^0$ thalassemia, the frequency of crises decreased from a mean of 7 (median of 9) per year to a mean of 1.1 (median 1.8) per year ($p<0.0001$). [71] These results included all crises, not just pain crises. In a non-randomized study comparing patients receiving hydroxyurea to those receiving cognitive behavioral therapy, those receiving the drug had fewer pain crises (1.4 per year compared to 4.3 per year, $p\leq0.05$), although this was not a strong design on which to base such an outcome. [61]

Hospitalization rates also decreased for adults treated with hydroxyurea. In the study of Sicilians, the number of hospitalized days in a year declined from 22.4 days to 1.2 days (SD =2.3; $p<0.0001$). In a retrospective effectiveness study by Ferguson et al., the rates of hospitalization declined from baseline in the group that was treated for longer than 24 months (to 2.1 per year from 3.1 per year, p=0.04). [52] For the group treated for fewer than 24 months, however, the investigators did not find a significant difference in hospitalization rates from baseline. In the study comparing hydroxyurea to cognitive behavioral therapy, the patients receiving the drug and those receiving behavioral therapy had similar hospitalization rates (1.1 per year [SD= 2.4] versus 0.9 per year [SD=1.2]). [61]

Table 2. Efficacy of Hydroxyurea in Observational Studies of Adults with Sickle Cell Disease

Outcome	Number of Studies Reporting	Magnitude and Consistency of Effect
Hb F%	6	68% to 536% increase
Hemoglobin	5	0% to 66% increase*
Pain Crises	3	68% to 84% decline in yearly rates
Hospital Admissions	3	18% to 32% decline in yearly rates
Transfusions	None	
Mortality	None	
Neurological events	None	

*The population in the study with no increase in hemoglobin was entirely composed of patients with $HbSB^0$ or SB^+thalessemia, but these patients had a large increase in Hb F% (536%).

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

Several of the studies reported additional efficacy outcomes. In the study by Loukopoulus et al., a mean clinical severity score was calculated based on an arbitrary scale that quantified pain and duration of pain. [74] Over 12,018 patient-weeks of treatment, the severity score declined to 81.7 from 1182. In comparing the group receiving hydroxyurea to the group receiving cognitive behavioral therapy, the investigators reported a significant improvement in General Health Perception from the SF36 Health Survey among those receiving the drug. [61]

Ferster et al. enrolled children and young adults in their study, [58] while Al-Jam'a et al. enrolled adults and children older than 5 years. [70] Ferster et al. demonstrated hematological benefit, with an increase in Hb F% from a mean of 7.3 to 16.7 percent ($p<0.01$) and an increase in hemoglobin from 8.2 g/dl to 8.8 g/dl ($p<0.01$). [58] Also, none of the patients had a stroke during the study, despite the fact that this was a sick population, with 9 of the 93 having a history of prior stroke and 19 having a history of acute chest syndrome. The rate of hospitalization for those receiving hydroxyurea was 1.1 per patient-year, and the rate of acute chest syndrome was 3.5/100 patient-years. In the study of Saudi Arabian patients, Al-Jam'a et al. demonstrated good hematological outcomes, with an increase in Hb F% from 12.6 percent to 25.7 percent ($p<0.05$), as well as clinical benefit, with a decrease in hospitalization to a mean of 0.93 per year ($p<0.0001$) and a decrease in hospital days to 5.1 per year from 34 per year ($p<0.05$).

Predictors of benefit from hydroxyurea treatment. Many studies have explored predictors of benefit from hydroxyurea (Table 3); one was designed specifically to address this question. [73] Predictors of the fetal hemoglobin response to hydroxyurea were most frequently reported. In the MSH study, Hb F% increased to a greater extent in participants with a lower rate of painful events and, at baseline, reticulocytes greater than 300,000/µl, F reticulocytes greater than 12 percent, absolute neutrophil count (ANC) greater than 7500/µl, and fetal hemoglobin greater than 7.5 percent. Hb F% increased less in men, to a lesser degree in those with the CAR haplotype, with less than 80 percent adherence to therapy, or with fewer than two episodes of hematological toxicity during treatment. [21] In a Phase II study from the same group, Hb F was associated with the most recent plasma level of hydroxyurea, as were Hb F and white blood cell counts at baseline. [46] Similarly, in children, an increase in Hb F% was associated between higher F reticulocyte counts at baseline[75] and adherence to therapy, [52]as well as increases in hemoglobin and MCV from baseline, decreases in reticulocytes and white blood count from baseline, and lower reticulocyte and white blood counts at the MTD. [73] A pediatric study also identified an association with a higher baseline hemoglobin and greater response. [73] Neither adult nor pediatric studies found that Hb F% was predicted by age; [40,46,73,75]; the pediatric studies did not find that gender, hematological toxicities, [73] or haplotype[75] predicted response.

Clinical responses to hydroxyurea, i.e., a decreased rate of painful episodes, were associated with the baseline rate of painful episodes, decreases in the absolute neutrophil count and absolute reticulocyte count, and increases in MCV. [21] Men treated with the drug had greater absolute increases in aerobic power ($p<0.05$) than did women. [41] Two pediatric studies from Belgium did not identify any predictors of clinical response; [44,58] however, other observational studies did do so. Hospital admissions were significantly decreased in adults with at least 2 years of hydroxyurea treatment with no interruptions exceeding 2 weeks, when compared to those with a shorter duration of therapy or interruptions. [52] In children, an increasing dose of hydroxyurea was associated with a decrease in cerebral blood flow velocity. [62] Recurrent stroke in children receiving hydroxyurea for secondary stroke prevention was associated with older age, initiation of hydroxyurea after chronic transfusion had been stopped, and a higher ANC during treatment.[67]

Table 3. Predictors of Benefit from Hydroxyurea in Studies of Sickle Cell Disease

Author, year	Predictors of Benefit from Hydroxyurea Treatment	Outcome
Trials		
Steinberg, 1997[40]	Lower baseline crisis rates, baseline reticulocyte count (>300,000/ul), women, absence of CAR haplotype, F reticulocytes > 12%, absolute neutrophil count >7500/µl, Hb>7.5%, >80% adherence, and >2 hematological toxicity episodes during treatment	Hb F%
Ferster, 1996[44]	Not associated with the initial Hb F level, white blood cell count, or platelet count	Hb F%
Ballas, 2006[42]	Higher Hb F%, higher baseline quality of life, lower baseline daily pain, baseline crisis rate <6/year	Quality of life
Hackney, 1997[41]	Men compared to women	Aerobic power
Charache, 1995[21]	Prior crisis rate, lower absolute neutrophil count, higher reticulocyte count, and MCV	Painful episodes
Observational Studies		
Charache, 2992[46]	Last plasma HU level, higher initial Hb F%, and higher white blood count	Hb F%
Hankins, 2005[72]	Dose increase	Hb F%
Loukopoulous, 1998[69]	Females	Hb F%
Loukopoulous, 2000[74]	Low Hb F at baseline; great similarity in response between siblings	Hb F%
Maier-Redelsperger, 1998[75]	Increase in MCV and higher initial F reticulocytes; not age, gender, haplotypes; Hb F% at 6 months did not predict maximum	Hb F%
Vicari, 2005[80]	Not age, not sex	Hb F%
Ware, 2002[73]	Positively associated with Hb F% at baseline, Hb at baseline, and MTD achieved. Negatively associated with # of pills returned. Not age, not sex, not hematologic toxicities. Other predictors: change in Hb from baseline to MTD, MCV change from baseline to MTD, decline in reticulocytes from baseline and number at MTD, white count decline from baseline and white count at MTD	Hb F%
Ferguson, 2002[52]	Duration and completeness of therapy	Hospital admissions
Ferster, 2001[58]	Not predicted by hematological values	Hospital admissions
Zimmerman, 2007[63]	Higher TCD velocity at baseline predicted response	Cerebral blood flow velocity
Ware, 2004[67]	Lower recurrence for those who initiated HU therapy before discontinuation of transfusion therapy	Recurrent stroke
Kratovil, 2006[62]	Dose of HU	Cerebral blood flow velocity

CAR = Central African Republic; Hb F%=fetal hemoglobin percentage; MCV = mean corpuscular volume; HU = hydroxyurea; MTD = maximum tolerated dose; TCD=transcranial Doppler

Response to hydroxyurea treatment according to genotype. As described above, studies were generally stratified by age (adult or pediatric); however, other subgroups were less thoroughly investigated. While the majority of patients studied were homozygous for Hb S, most of the studies had some patients with other genotypes. Five studies reported outcomes stratified by genotype (Table 4). The most detailed study was that by Loukopoulous et al., which described all of the hematological outcomes in their small patient sample, stratifying them by sex and genotype. [74] Only a single study reported specific outcomes for patients with Hb SC disease; this study demonstrated less improvement with hydroxyurea treatment in this subgroup, and these

seven children were less able to tolerate dose increases. [81] In general, patients with Hb $S\beta^0$ thalassemia or Hb $S\beta^+$ thalassemia responded to treatment in a manner comparable to that of patients with Hb SS.

Studies of biomarkers suggesting a drug effect. We identified eight studies that compared potential surrogate markers of disease severity or response in patients treated with or without hydroxyurea. [85-92] These studies were all cross-sectional or cohort studies with at least one comparison group (Appendix C*, Evidence Tables 9-11). The studies enrolled patients from North America (5), Europe (2), or Central and Latin America (1). The description of the eligibility criteria was often quite limited, and the majority of studies were of moderate to poor quality. There was only limited information regarding patient characteristics and the starting dose, monitoring, and titration of hydroxyurea.

Four studies included a report of hemoglobin and Hb F levels among groups and reported increases in total and fetal hemoglobin that were comparable to those of the other observational studies in sickle cell disease after treatment with hydroxyurea. [86,87,90,92] In three studies, treatment with hydroxyurea was associated with significantly increased levels of nitric oxide metabolites, [87,91] cyclic guanosine monophosphate, [87] and nitric oxide synthase and with reduced levels of arginase. [86] Another study identified lower levels of endothelin-1, a potent vasoconstrictor, in children treated with hydroxyurea for more than 12 months, when compared to untreated patients. [88] These molecules may be biomarkers of abnormal vasoreactivity in sickle cell disease that may contribute to vaso-occlusive complications. Other potential biomarkers of vaso-occlusion were the significant decreases in rigidity and rates of elastic shear in patients with sickle cell disease who had been treated with hydroxyurea, when compared to those in untreated sickle cell disease patients. [85] However, these values were still significantly higher than those in controls without sickle cell disease. A small study failed to show differences in tumor necrosis factor-α in adults with Hb SS treated with and without hydroxyurea, [89]while a study with similar design (comparing adults with Hb SS with and without vaso-occlusive complications and treated with and without hydroxyurea) described a higher percentage of oxyhemoglobin and a lower percentage of reduced hemoglobin in patients on hydroxyurea, with or without vaso-occlusive complications. [91] The higher percentage of oxyhemoglobin may reflect decreased adhesion and

Table 4. Outcomes of Hydroxyurea Use in Sickle Cell Disease Reported by Genotype

Author, year	Comments
Santos, 2002[59]	More marked improvement in splenic function in patients with Hb SS than in patients with HbSβ0-thalassemia. Thought to be due to less severely impaired splenic function at baseline in patients with Hb $S\beta^0$-thalessemia
Loukopoulos, 2000[93]	No increase in Hb among patients with Hb $S\beta^+$-thalassemia; increase in the Hb SS and $HbS\beta^0$-thalessemia groups. The β-thalassemia genotype did not affect Hb F response; substantial increase in all groups.
Zimmerman, 2004[81]	Hb F % increased from baseline in all genotypes except those with Hb SC disease. Patients with severe forms of SCD (Hb SS, HbS/β^0, and Hb S/OArab) had significant increases in hemoglobin concentration, whereas patients with Hb SC or $HbS\beta^{+/-}$thalassmia had minimal changes in Hb concentration. Patients with Hb SC tolerated less HU before toxicity developed.
el-Hazmi, 1992[45]	Increase in Hb F% for patients with Hb SS and patients with $HbS\beta^0$-thalessemia
Maier-Redelsperger, 1998[75]	All patients in study were homozygous SS; no difference in response to HU by β-globin gene haplotypes.

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

more rapid transit of the cells through the capillary beds. A final pediatric study demonstrated significant decreases in total bilirubin (most likely secondary to decreased hemolysis and release of heme) after treatment with hydroxyurea. [90] The baseline level and absolute decrease in bilirubin were strongly correlated with promoter polymorphisms of uridine diphosphoglucuronate glucuronosyltransferase 1A (UGT1A). The lowest levels of bilirubin, both before and during treatment, were seen in children with the UGT1A 6/6 genotype; intermediate levels were seen in the heterozygotes (6/7), and the highest levels were seen in those with the UGT1A 7/7 genotype. These diverse studies of biomarkers suggest possible mechanisms for hydroxyurea's clinical benefits in addition to its ability to increase Hb F and reduce hemoglobin polymerization.

Strength of the evidence regarding the efficacy and effectiveness of hydroxyurea. Based on one RCT in children and many observational studies, some of which were of high quality and most of which were consistent in their findings, we graded the evidence as follows: We concluded that there was a high grade of evidence to support the contention that hydroxyurea raises Hb F in children, and subsequent research is unlikely to change our estimate of that effect, except perhaps in unique populations (such as infants or patients with Hb SC). There was moderate evidence to support the claim that hydroxyurea reduces the frequency of pain crises, and a high grade of evidence to support the contention that treatment reduces the frequency and/or duration of hospitalization in children. There was only a low grade of evidence to support the claim that hydroxyurea reduces neurological events in children and insufficient evidence to allow any conclusions regarding transfusion frequency.

Based on one high-quality RCT in adults and many observational studies, we concluded that there was a high grade of evidence to support the conclusion that hydroxyurea raises Hb F in adults with sickle cell disease, and future research is unlikely to substantially alter these conclusions. There was also high-grade evidence that the drug reduces the frequency of pain crises and that it reduces the frequency and/or duration of hospitalization in adults. There was also high-grade evidence that it reduces transfusions, but only low-grade evidence, from the observational followup of patients in MSH, that it reduces mortality. The evidence base was insufficient to allow us to comment on neurological events in adults (Table 5).

Key Question 3: What are the Short- and Long-term Harms of Hydroxyurea Treatment?

Report by The Center for the Evaluation of Risks to Human Reproduction (CERHR)

The National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS) established the NTP's CERHR in June 1998. The stated purpose of the CERHR was "to provide an unbiased, scientific evaluation of human and experimental evidence of the adverse effects on reproduction and development caused by agents to whom humans may be exposed." Hydroxyurea was selected for study by the Center in 2006; we briefly review their findings here, as they are relevant to our review of the toxicities of hydroxyurea. CERHR researchers searched databases that included REPROTOX, HSDB, IRIS, DART, PUBMED, and Toxline, through January 2007, to identify articles pertinent to the evaluation of adverse effects on development and reproduction in both humans and animals. The articles were reviewed in

Table 5. Summary of the Evidence

Outcomes	Evidence Grade	Basis for Grade
Key Question 1 and 2--Children		
Increase in fetal hemoglobin	High	One good RCT, plus consistent observational studies
Reduction in pain crises	Moderate	One good RCT; inconsistent observational studies
Reduction in hospitalizations	High	One good RCT, plus consistent observational studies
Reduction in neurological events	Low	Consistent observational studies
Reduction in transfusion frequency	Insufficient	Few observational studies
Key Question 1 and 2 --Adults		
Increase in fetal hemoglobin	High	One good RCT, plus consistent observational studies
Reduction in pain crises	High	One good RCT, plus consistent observational studies
Reduction in hospitalizations	High	One good RCT, plus consistent observational studies
Reduction in neurological events	Insufficient	No studies
Reduction in transfusion frequency	High	One good RCT, plus consistent observational studies
Mortality	Low	Inconsistent observational studies
Key Question 3--Children		
Leukemia (MDS/AML/Cytogenetic abnormalities)	Insufficient	CERHR report
Developmental toxicities (*in utero*)	Insufficient; evidence of harm in animals	CERHR report
Leg ulcers	Insufficient	CERHR report
Growth delays (children 5 to 15 years)	Evidence of no growth delay	CERHR report
Developmental toxicities in next generation	Insufficient	CERHR report
Key Question 3--Adults		
Leukemia (MDS/AML/Cytogenetic abnormalities	Low (absence of effect)	Indirect evidence and inconsistent results
Leg ulcers	High (absence of effect)	One good RCT, plus consistent observational studies
Skin neoplasms	Insufficient	No studies in sickle cell; high-grade evidence in other populations
Secondary malignancies	Insufficient	No studies in sickle cell; low-grade evidence in other populations
Adverse pregnancy outcomes	Insufficient	CERHR report
Spermatogenesis defects	Low	Case reports with evidence of causality

Table 5. Summary of the Evidence (continued)

Outcomes	Evidence Grade	Basis for Grade
Key Question 4--Barriers		
Negative provider attitudes are barrier to use of pain medication	High	More than one study, consistent finding
Poor provider knowledge is a barrier to use of pain medication	High	More than one study, consistent finding
Patient sex is **not** a barrier to use of therapies	Moderate	Few studies, but consistent
Patient/family knowledge is a barrier to use of therapies	Low	Few studies, and inconsistent
Number of hospital visits is a barrier to use of therapies	Low	Few studies, and inconsistent
Patient age is a barrier to use of therapies	Low	Few studies, and inconsistent
Key Question 4--Interventions		
Interventions do **not** improve adherence to therapies for chronic disease management	Low	Small studies, diverse outcome measures
Interventions can overcome barriers to use of pain medications	Moderate	High quality studies, but few
Interventions can overcome barriers to the receipt of routine, scheduled care.	Moderate	High quality studies, but few

RCT = Randomized controlled trial; CERHR = Center for the Evaluation of Risks to Human Reproduction; MDS/AML = myelodysplastic syndromes/acute myelogenous leukemia

advance by an expert panel, which then prepared a document describing the strength of the evidence that hydroxyurea is a reproductive or developmental toxicant. [26] The 13-member expert panel discussed the data and finalized their opinions about the toxicity ofhydroxyurea, identified areas of knowledge gaps, and identified future research priorities. Given this detailed report and acceptable methodology, this EPC opted not to duplicate their effort, and we instead report here a summary of their findings regarding the developmental and reproductive toxicities of hydroxyurea.

Scope and findings.

Summary of the General Toxicology and Biological Effects of Hydroxyurea. The expert panel concluded, based on a single study, that nursing infants of women taking the drug may have an exposure to hydroxyurea of 1 to 6 mg/day, but that this dose would be dependent on the infant's nursing schedule, the mother's dose, and the volume of the infant's feeds.

Summary of the Developmental Toxicity Data. The panel concluded that hydroxyurea treatment of children aged 5 to15 years does not cause a growth delay. The panel felt that there were inadequate data regarding growth effects in infants and children younger than 5 years of age, as well as insufficient data to allow them to evaluate the effects of the drug on pubertal development. The expert panel also concluded that there were no data on the effects on subsequent generations following exposure of germ cells to hydroxyurea, including exposure during fetal life, infancy, childhood, and adolescence. The CERHR report described no studies of the long-term health effects, including carcinogenicity, from childhood exposure to hydroxyurea. The expert panel found sufficient data to conclude that there is developmental toxicity in rat and mice fetuses that are exposed to hydroxyurea *in utero*. The manifestations of this toxicity include decreased body weight, increased malformation rate, and a decrease in the number of live births. The expert panel felt that the experimental animal data were relevant to the assessment of risk in

humans. Thus, the expert panel had concerns that hydroxyurea may increase the risk of congenital anomalies or abnormalities of fetal growth and postnatal development after exposure of pregnant women to the drug.

Summary of the Reproductive Toxicity Data. The expert panel found no data on the reproductive effects of hydroxyurea in humans. Similarly, the panel concluded that there were insufficient data to be able to draw conclusions about female reproductive toxicity in animals. However, they concluded that hydroxyurea produces reproductive toxicity in male mice, as evidenced by decreased testis weight and sperm count. They also felt that the experimental animal data were relevant to the assessment of risk in humans. Therefore, they expressed concerns about the adverse effect of hydroxyurea on spermatogenesis in men receiving the drug at therapeutic doses.

Summary of Pregnancy Outcomes. The CERHR report identified 21 relevant papers. The report reviewed studies examining pregnancy outcomes in women who had sickle cell disease or essential thrombocythemia and were taking hydroxyurea. However, there were no controlled studies on the use of the drug during pregnancy. The largest case series described outcomes in 32 pregnancies in 31 patients treated with hydroxyurea for essential thrombocythemia (n=22), CML (n=6), chronic myeloid splenomegaly (n=2), or sickle cell disease (n=1). [94] The authors concluded that the two cases of intrauterine fetal growth restriction and the nine patients with preterm deliveries constituted an increase over the rates expected for this population, but it was not possible to attribute causality in these cases.

The remaining 20 articles were case reviews or small case series, and there was no clear evidence for causality in the case of any of the 10 abnormal outcomes described in the report. These outcomes were: elective abortion (n=3), stillbirth (n=2), preterm delivery (n=2), intrauterine growth restriction (n=2), and one unknown event. Based on the case series described above and these case reports, the CERHR report concluded that the use of hydroxyurea in pregnancy does not appear to be commonly associated with adverse perinatal outcomes and that there are no data on long-term outcomes in children who were exposed *in utero*. Given the publication of animal data indicating that hydroxyurea produces congenital anomalies and abnormalities of fetal growth in multiple experimental species, the expert panel did express a concern that hydroxyurea might increase the risk of congenital anomalies or abnormalities of fetal growth and postnatal development after exposure of pregnant women to the drug.

We identified one additional article related to hydroxyurea in pregnancy that was not included in the CERHR report. [95] This report was a case series of 21 pregnancies in 18 patients with a hematological malignancy. Only one patient, a 22-year-old woman with CML, received hydroxyurea during her pregnancy. At 28 weeks of gestation, she was admitted for vaginal bleeding, underwent emergency cesarean delivery for placental abruption, and delivered a male infant weighing 1800 grams, with normal hematological values. The patient died on post-operative day 1, and the infant developed respiratory distress and died as a result of intracranial bleeding.

Results of Randomized Trials in Sickle Cell Disease

The toxicity data reported from randomized trials of hydroxyurea in sickle cell disease have mainly been limited to short-term toxicities. Only four publications from the MSH study reported toxicities in adults. [21,39,40,43] The investigators described lower absolute neutrophil counts (4900/µl vs 6400/µl) in the hydroxyurea group than in the placebo group, but both groups had

similar numbers of other adverse events, including thrombocytopenia, thrombocytosis, malignancy, aplastic crisis, aseptic necrosis, lymphadenoathy, and bleeding tendency. The proportion of patients with hair loss, fever, rash and/or nail changes, or gastrointestinal disturbance reported at three or more followup visits was similar for both groups (Table 6; Appendix C*, Evidence Table 12)**.** [21] The one publication describing long-term followup of the MSH participants described only two malignancies, one in each group. [43] In the study of Belgian children, white blood cell counts decreased from baseline by 3570/µl ($p<0.001$), but changes in the absolute neutrophil count were not reported. [44]

Results of Observational Studies in Sickle Cell Disease Including Case Reports

Observational Studies. Although studies that lack comparison arms are not optimal for attributing causality to an observed event, observational studies are useful for describing events in people exposed to a drug outside of a randomized trial (Table 6; Appendix C, Evidence Table 13). We first describe the observational studies reporting cases of leukemia.

In the observational studies we reviewed, three cases of leukemia were reported in people with sickle cell disease who were treated with hydroxyurea. In a study from the French group, a 10-year-old girl was treated with the drug for 18 months. She was admitted with pain and fever; bone marrow examination disclosed ALL, with the Philadelphia chromosome. [48,55] Thus, this group noted a single case among 225 treated patients in this well-characterized cohort whose investigators paid careful attention to losses to followup. The Belgian group reported on a 21-year-old woman who developed acute promyelocytic leukemia after 8 years of hydroxyurea therapy. [82] Researchers for the International Association of Sickle Cell Nurses and Physician Assistants collected data about cancer development in 16,613 patients with sickle cell disease. Cancer was diagnosed in 49 patients, including seven cases of leukemia. Three of the 49 had been using hydroxyurea, including one 14-year-old who developed ALL 3 months after initiation of the drug. There were no data on the prevalence of hydroxyurea use among this population of 16,613 people (Appendix C, Evidence Table 13). [53]

Another study described a related toxicity, acquired DNA mutations, in hydroxyurea-treated patients with sickle cell disease. [57] In this study, two assays were used to quantify acquired somatic DNA mutations in peripheral blood mononuclear cells (PBMCs) after *in vivo* exposure to hydroxyurea: The HPRT assay measures hypoxanthine phosphoribosyl transferase (HPRT) mutations, while the VDJ assay identifies ‘‘illegitimate’’ T-cell receptor Vγ-Jβ interlocus recombination events. The authors looked at PMBCs from three groups: patients with sickle cell disease who were treated with hydroxyurea, patients with myeloproliferative diseases who had been exposed to hydroxyurea, and normal controls. They found that adults with sickle cell disease and adults with myeloproliferative diseases had a comparable number of mutations when compared to controls; however, children with sickle cell disease having 30 months of hydroxyurea exposure had more VDJ mutations (1.82 +/- 1.2) than did children with 7 months of exposure (1.58 +/- .87) or no exposure at all (1.06 +/- 0.45, $p=0.04$). HPRT mutations were similar in the two exposed groups. The authors interpreted this result as a slight increase in recombination events and suggested that this increase does not directly portend the development of leukemia. Similarly, 26 adult patients with sickle cell disease who had been exposed to

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

hydroxyurea for at least 5 years at the MTD were found to have no increase in illegitimate VDJ rearrangements, when assessed using similar methodology. [81] Karotypic analysis in one study

Table 6. Major Toxicities of Hydroxyurea in Other Diseases

Disease	Total studies: N	Leukemia†, n	Leg ulcer, n	Skin neoplasms, n	Secondary malign-nancies, n	Comments
HIV	RCT: 6 Other: 0	0	0	0	RCT: 1	4 cases of Kaposis' sarcoma in the retroviral + HU arm, compared to 1 in the arm with retroviral therapy and no HU; this was not statistically significantly different
CML	RCT: 5 Other: 4	NA	0	RCT: 0 Other: 1	RCT: 1 Other: 0	5/158 patients examined in one study for skin manifestations while on HU had skin cancer; RCT there were a total of 5 malignancies but no difference between arms in the incidence of malignancy (HU v. IFN v. Bu)
Solid tumor	RCT:2 Other: 0	0	0	0	0	
MPD*	RCT: 0 Other: 5	RCT: 0 Other: 5	RCT: 0 Other:2	0	RCT: 0 Other: 1	One cohort study with a comparison arm: There was no statistical difference in the incidence of AML between those patients treated with HU alone and those who did not receive any drug therapy (p=0.64). An additional 16 cases of leukemia were reported in the remaining observational studies that included a total of 400 patients.
PV	RCT: 1 Other: 5	RCT: 1 Other: 5	RCT: 1 Other: 0	RCT: 1 Other: 0	RCT: 1 Other: 2	The actuarial risk of leukemia in the RCT was 10% at 13 years in the HU-alone arm. In the RCT, there was a slight, but not significant, increase in skin cancers for subjects in the HU arm (4 versus 1). In the observational studies with comparison arms, there was no statistical difference in leukemia when HU was compared to arms with no myelosuppresive therapy.
ET	RCT: 2 Other: 4	RCT: 2 Other: 4	0	0	RCT: 1 Other: 0	The RCT showed no significant difference in leukemia incidence between arms. When the patients that had received Bu in the randomized trial were removed from analysis, there was no significant difference in the incidence of malignancies between those treated with HU and the untreated group. In the observational studies, after controlling for other risk factors in multivariate analysis, HU was not associated with a statistically significant increase in the risk of leukemia.

* Studies that combined different MPDs
† Number of studies reporting toxicity

HU = hydroxyurea; CML = chronic myelogenous leukemia; MPD = myeloproliferative disorder; PV = polycythemia vera; ET = essential thrombocythemia; IFN = interferon; Bu = busulfan; AML = acute myelogenous leukemia; RCT = randomized controlled trial

revealed no difference in the percentage of abnormal chromosomes before and after treatment with hydroxyurea. [46] In a similar, although smaller study, there was no significant difference in chromosomal aberrations ($p>0.05$) pre- and post-treatment and no difference in the mitotic index (Appendix C*, Evidence Table 13). [47]

The more frequent toxicities are described in Appendix C, Evidence Table 13. Toxicities were described in 22 of the 35 observational studies; 8 of these were studies designed to primarily report toxicities from hydroxyurea. [47,48,53,55,57,64,66,68] Additional articles described moderate decreases in platelet counts on therapy; this observation is not included in the table, since this is an known effect of the drug and is generally not considered to be an adverse event. Rare deaths were reported. In one study with 455 patient-years of followup, one child died of pneumococcal sepsis despite a normal absolute neutrophil count, and another child died from an acute transfusion reaction. [78] Neither death was thought to be related to hydroxyurea. There were single deaths reported in five other studies[48,60,72,77,82]; all of the deaths were from expected complications of sickle cell disease, and none were thought to be due to myelosuppression (Appendix C, Evidence Table 13).

Neutropenia was a frequently reported adverse event. In the HUSOFT study, 17 of the 28 children had an absolute neutrophil count of less than 1500/µl, including 6 with an absolute neutrophil count of less than 500/µl. [60] In the extension of the HUSOFT study, there were 21 episodes of neutropenia in 10 children in the third treatment year and 21 episodes in 9 patients in the fourth year. [72] In the HUG-KIDS study, 56 of 84 patients had an absolute neutrophil count of less than 2000/µl. Thrombocytopenia was less frequently reported.

Leg ulcers were only reported as occurring in three studies and were infrequent. [55,66,74] Prior leg ulcer was associated with the development of leg ulcer during hydroxyurea treatment in the study that reported the highest incidence of ulcers (5 of 17 treated patients). [66] Rash and nail changes were moderately common.

The other even rarer toxicities are described in Appendix C, Evidence Table 14. The number of individuals experiencing these toxicities was low in all studies. No study reported any secondary malignancies.

Case Reports. We identified 19 published case reports about toxicities associated with hydroxyurea use in patients with sickle cell disease (Appendix C, Evidence Table 15). Two of these reports described the same Greek child who developed Hodgkin's lymphoma. [96,97] The 18 unique case reports included four reports of low sperm count or decreased sperm motility, two cases of avascular necrosis, two cases of skin hyperpigmentation, and one case each of leg ulcer, cytopenia, splenomegaly, cryptosporidium infection, intracerebral hemorrhage, acute myocardial infarction, and the case of Hodgkin's lymphoma previously mentioned. All of these toxicities were described in adults, except for the case of Hodgkin's.

In addition, leukemia was reported in three young women with sickle cell anemia who had been treated with hydroxyurea. We describe these three cases in detail here: One was the 21-year-old woman mentioned above who was treated as part of the Belgian Registry of Sickle Cell Disease. [98] She had been taking hydroxyurea for 8 years but stopped for 2 years while pregnant and nursing. She resumed hydroxyurea therapy, and 8 months later was diagnosed with AML (M3v). Another report was of a 25-year-old Saudi Arabian woman who was treated with hydroxyurea for 2 years with good response. She was subsequently diagnosed with AML (FAB M1); cytogenetic studies revealed no abnormal clone. [99] Interestingly, this patient had splenomegaly, without explanation, at the time that she began hydroxyurea therapy and also had

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

hepatitis C infection. The final case report described a 42-year-old woman with Hb SS who was treated for 6 years with hydroxyurea. She was diagnosed withAML; she had no cytogenetic analysis. [100] We are aware of one other case report of leukemia in a patient with sickle cell anemia treated with hydroxyurea. This case was reported in abstract form and described a 27-year-old woman who developed an acute non-lymphocytic leukemia after 8 years of hydroxyurea therapy. Her bone marrow aspirate suggested that the leukemia developed in the setting of myelodysplasia. [101]

Each of these toxicities had only Level 3 evidence for causality (at least one "possible" report of an adverse event, but no "certain" or "probable" case report), with the exception of cytopenia, which was considered to have Level 2 evidence (at least one "probable" report of an adverse event, but no "certain" report) because there was one case report that demonstrated probable causality. Reports of leukemia are difficult to score with the WHO causality scale because there is no possibility for regression of disease with removal of the putative causal agent (leukemia cannot spontaneously remit), so the case reports of leukemia cannot be described as showing probable or certain causality.

Results of Studies of Other Diseases

Given that the number of patients with sickle cell disease who were treated for long durations with hydroxyurea is few, we opted to review toxicities in patients with diseases other than sickle cell disease in order to gather additional evidence regarding the potential toxicities of this drug.

Randomized trials and large observational studies. We found 39 publications (20 randomized and 19 observational studies) that examined the toxicity of hydroxyurea in diseases other than sickle cell disease. (Appendix C*, Evidence Tables 16, 17, 18, 19, 20, and 21). Included among these were studies of the addition of hydroxyurea to other often-used therapies, enabling us to describe the additive toxicity attributable to hydroxyurea. These publications included studies examining the effects of adding hydroxyurea to standard antiretroviral therapy in patients with HIV/AIDS and the addition of hydroxyurea to interferon, as these drugs may be used in patients with sickle cell disease and comorbid illnesses. There were eight publications about hydroxyurea use in patients with HIV, nine in patients with CML, five in patients with a variety of myeloproliferative diseases, two in patients with solid tumors, eight in patients with polycythemia vera, and six in patients with essential thrombocythemia. We present the results for the RCTs, followed by those for the observational studies.

Description of the quality of the studies. The quality of the RCTs was evaluated using the Jadad criteria. The study scores ranged from 1[102,103] to 4[104] (Appendix C, Evidence Table 22), with most of the studies scoring a 2 or 3. The studies were all randomized, but most did not describe the method of randomization, and they also lost points for not describing the blinding of the participants. A majority of the studies also provided at least some information about the subjects that were withdrawn from the study.

The observational studies were evaluated with our 16-point scale for assessing the quality of these studies. These studies received between 28 percent [105] and 73 percent[106] of the available points (Appendix C, Evidence Table 23). Thus, none of these studies reached our cutoff of more than 80 percent, which we judged to indicate high quality. Only one of these studies reported on

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

adherence. [107] The scores were also diminished because most of them did not describe the subjects that were lost to followup.

Scope and findings.

HIV/AIDS. The eight publications related to HIV examined the addition of hydroxyurea to antiretroviral therapy in randomized trials. The number of patients per arm of the study ranged from 21 to 72. The addition of hydroxyurea to other antiretroviral therapy was associated with a significantly increased risk of neutropenia and thrombocytopenia in two of the three studies in which this toxicity was reported. [102,104,108-110] Three of the publications described the same patient cohort. [102,109,110] None of these studies, however, examined the exact same drug regimen. In the study by Frank et al., [104] the thrombocytopenia was seen only in the group on the high dose of hydroxyurea (1500 mg/day). Two studies showed that the addition of the drug increased the risk of gastrointestinal (GI) upset. [110,111] Swindells et al. demonstrated that about twice as many patients on hydroxyurea had neurological or psychiatric issues and endocrinological or metabolic side effects, when compared to patients receiving an antiretroviral agent alone. [111]

The cluster of papers by Rutschmann et al. included three papers with results from three different time points for the same 144 randomized study patients. [102,109,110] Twenty-four patients crossed over to hydroxyurea after 12 weeks, and 19 remained in the non- hydroxyurea arm. This series of studies demonstrated a significant increase in fatigue, paraesthesias, and neuropathy in the treatment arm with hydroxyurea added to ddI/stavudine, when compared to the arm with antiretroviral therapy alone. The maximum followup was 24 months (range, 24 weeks to 24 months). This is the only study that reported any incidence of malignancy. There were four cases of Kaposi's sarcoma in the hydroxyurea arm, as compared to one case in the non-hydroxyurea arm (p=0.2). There were no reports of leukemia in any of these studies.

There were no observational studies of hydroxyurea use in HIV treatment that met our inclusion criteria.

Chronic Myelogenous Leukemia (CML). There were five randomized trials of hydroxyurea use in CML. In these studies, hydroxyurea was compared to interferon, to the combination of hydroxyurea and interferon, and to busulfan. The number of patients per arm ranged from 24 to 308. The maximal followup for these studies was approximately 4 years. There were three articles from the German CML group. [112-114] The first of these articles compared hydroxyurea with busulfan in 441 patients. [112] The median followup was 2 years. Patients were allowed to cross over to the other arm of the study, depending on their response. Little toxicity was reported in this paper, although the authors noted that there was less bone marrow aplasia and lung fibrosis in the hydroxyurea arm, and they felt that hydroxyurea was better tolerated than busulfan. The second study from the German CML group enrolled 513 patients in three arms: hydroxyurea versus interferon versus busulfan. [113] The median followup in this study was 3.4 years. Eighteen percent of the patients on interferon had an adverse effect that required discontinuation of therapy, as did 10 percent in the busulfan group and only 0.5 percent in the hydroxyurea group. The authors reported the development of five malignancies, one in the hydroxyurea arm and two each in the interferon and busulfan arms. Most differences in toxicities were seen in the final German study, which followed patients for over 7 years. [114] This study compared outcomes in 534 patients treated with either hydroxyurea alone or with hydroxyurea and interferon. There was more dermatologic, gastrointestinal, and bone marrow aplasia in the interferon plus hydroxyurea arm than in the hydroxyurea-alone arm (no p values given). This study and the one by the Benelux Chronic Myelogenous Leukemia Study Group[115] also showed increased flu-like and psychiatric illness in the interferon plus hydroxyurea arm. No secondary

malignancies were reported in either of these studies or in an additional small study comparing hydroxyurea and interferon. [116] The studies did report progression to blast crisis, since this was considered an outcome and not a toxicity.

To help address the question of the possible association between hydroxyurea and the risk of malignancy, we included a case series of 26 patients with AML who had a unique t(3;21) chromosomal translocation. [117] This group included 15 patients with CML who had been treated with hydroxyurea, along with one patient with CML who had received imatinab. Another six of the patients with AML had received a mixture of prior chemotherapies for other malignancies prior to developing AML, and two patients had *de novo* AML and had no prior chemotherapy exposure. The patients treated with hydroxyurea had been on therapy for 2 weeks to 31 months before progressing to AML.

There were two additional case series involving patients with CML. One of these was an evaluation of skin manifestations in 158 patients treated with hydroxyurea for a median of 38 months. [118] Thirteen percent of the patients developed skin toxicity while on the drug, and five patients developed skin cancer. The racial makeup of the patients in this study was not reported. The other case series examined the effectiveness of hydroxyurea in 134 patients with CML and mentioned only minor adverse effects in a total of 3 patients. [119] The final observational study in CML was a cohort study comparing hydroxyurea to busulfan for treating CML. [120] The median duration of followup in this study was 32 months for hydroxyurea and 31 months for busulfan. There was no mention of the development of secondary malignancies in either the busulfan- or hydroxyurea-treated patients in this publication.

Solid Tumors. There were two controlled trials of hydroxyurea use in patients with solid tumors. [121,122] In a study of hydroxyurea versus adriamycin use in advanced prostate cancer, more patients in the hydroxyurea arm developed leukopenia (no p values were given). [121] We found no observational studies of hydroxyurea use for the treatment of solid cancers.

Polycythemia Vera. There were two publications describing randomized trials involving polycythemia vera, [103,123] both of which were part of the same large trial by Najean et al. comparing hydroxyurea and pipobroman. The first trial reported on subjects who were treated from 1 to 17 years. [123] The second study reported toxicities after subjects had a mean exposure of 14 years to hydroxyurea and of 11 years to pipobroman. [103] The first study did not report leukemia incidence by arm but reported an actuarial risk of 10 percent at 13 years for both arms. The second study described 15 subjects in the hydroxyurea arm who developed leukemia, with 40 percent of the disease occurring after the 12th year of followup; in the pipobroman arm, 25 subjects developed leukemia, with 44 percent of the disease occurring after the 12th year of followup. Only the first publication reported the incidence of other malignancies. The hydroxyurea arm had 10 subjects with malignancies, with an incidence of 1.1 percent per year; in the pipobroman arm, there were 6 subjects who developed a malignancy, with an incidence of 1.1 percent per year. The authors noted a slight, but not significant, increase in skin cancers among subjects in the placebo arm (four versus one).

There were six observational studies examining the outcomes of patients with polycythemia vera. The largest of these studies described 1,638 patients who were followed for a median of 2.8 years (maximum, 5.3 years). [124] In this study, three treatment groups were described: (1) those treated with hydroxyurea, (2) those treated with any other cytoreductive drug alone or in combination, and (3) those treated with no drug or α-interferon alone. Twenty-two cases of myelodysplastic syndrome (MDS)/AML occurred in these patients at a median of 8.4 years (range, 2.2-19.8 years) after the diagnosis of polycythemia vera. There were 6 cases in the

hydroxyurea-alone arm, 11 cases in the other cytoreductive arm, and 5 in the no drug/interferon arm. As compared to patients treated with phlebotomy or interferon, patients receiving hydroxyurea as the only cytoreductive drug had no increased risk of developing MDS/AML, whereas those treated with pipobroman, busulfan, chlorambucil, or ^{32}P alone or in combination were at significantly higher risk (hazard ratio [HR], 5.46; 95% confidence interval [CI], 1.84-16.25; p=0.0023). Patients in this study who received hydroxyurea plus alkylating agents or ^{32}P had a significantly increased risk of developing MDS/AML (HR, 7.58; 95% CI, 1.85-31.00; p=0.005) when compared to patients treated with phlebotomy or interferon. This study also examined other associations with an increased risk of developing MDS/AML. The authors found that women were at increased risk of progressing to MDS/AML, after controlling for age and drug exposure (HR, 2.93; 95% CI, 1.18-7.26; p = 0.0205), and low blood cholesterol levels at recruitment were associated with progression to MDS/AML (HR, 6.58; 95% CI, 2.08-20.86; p = 0.0014).

The second-largest cohort study involving polycythemia vera had 597 patients. [105] These patients were analyzed in four treatment groups; (1) hydroxyurea alone, (2) pipobroman, (3) ^{32}P and hydroxyurea maintenance therapy, and (4) ^{32}P without hydroxyurea maintenance. The patients treated with ^{32}P had longer followup than those in the other groups receiving pipobroman or hydroxyurea alone (10.5 years vs 6.7 years, respectively). The rate of MDS/AML or lymphoma was 19 percent after 10 years for the ^{32}P arm receiving maintenance hydroxyurea, versus 10 percent at 10 years for the ^{32}P arm without hydroxyurea maintenance. This difference was reported as significant, but no p-value was given. In the other two arms, the actuarial incidence of MDS/AML or lymphoma was estimated at 13 percent in the hydroxyurea-alone arm and 14 percent in the pipobroman arm, but the authors noted that few patients had actually been followed for more than 10 years. The authors also reported the actuarial risk of developing a malignancy. The actuarial risk of malignancy for the ^{32}P group who received maintenance hydroxyurea was 29 percent at 12 years of followup; it was 15 percent at 12 years for those who received ^{32}P but no hydroxyurea maintenance. The actuarial risk for malignancy in the other two arms could not be calculated, but the observed risk was 9 percent in each of the two arms. Finally, this study examined the actuarial risk of developing myelofibrosis. The risk did not differ for the arm receiving ^{32}P with maintenance versus the arm receiving ^{32}P without maintenance (16 percent at 10 years and 23 percent at 14 years, vs 10 percent at 10 years and 19 percent at 14 years). No patients in the pipobroman arm developed myelofibrosis, and the actuarial risk in the hydroxyurea-alone arm was 17 percent at 12 years. The authors did not feel they could conclude much about the long-term effect of hydroxyurea alone in this study, given the short period of followup. This study was not analyzed by intention to treat. The authors justified the lack of such analysis by stating that in their experience “intended treatment is modified in more than 3/4 of cases before the tenth year, so that actuarial "intention to treat” analysis is probably not valid in the long-term.” They felt that by excluding patients who might have switched therapy from their analysis of long-term followup data, they might remove those patients at the highest risk of a poor outcome. In their study, for example, 12 patients originally assigned to the hydroxyurea arm were switched to pipobroman, and five patients on the pipobroman arm were switched to the hydroxyurea arm.

There were two articles in this series that described outcomes in the same set of patients. [125,126] The original publication[125] in 1986 compared the outcomes in 51 patients with polycythemia vera who had been treated with hydroxyurea and phlebotomy in the Polycythemia Vera Study Group 08 study (PVSG-08), and they compared this group to a historical control

group from the PVSG-01 study in which 134 patients were treated with phlebotomy alone. The maximum followup in this study was 389 weeks (7.5 years). Three patients (5.9 percent) in the hydroxyurea /phlebotomy arm developed leukemia, as compared to two (1.5 percent) in the phlebotomy group (p=0.25). The authors concluded from this original study that this drug did not increase the risk of leukemia at followup of 378 weeks. The followup study by Fruchtman et al. extended the followup of these patients to a median of 8.6 years and a maximum of 15.2 years. [126] The incidence of AML in the hydroxyurea /phlebotomy arm was 9.8 percent and 3.7 percent in the control arm; this difference was not statistically significant (p=0.0973). Thirty-one percent of the patients in the hydroxyurea arm died, as compared to 40 percent in the control arm (p=0.07).

Another study that looked at outcomes in patients with polycythemia vera was a study in which the authors compared outcomes in patients treated with hydroxyurea who had received prior myelosuppressive therapy and those in patients treated with hydroxyurea who had not received any prior drug treatment. [127] Followup for this study ranged from 15 months to 48 months. There were no statistically significant differences in the incidence of AML between the two groups.

Another observational study was a description of a single-center experience with 100 patients with polycythemia vera who had been treated with hydroxyurea over a 20-year period. [128] The mean duration of therapy was 64.9 months (5.4 years). Two patients developed AML, one patient with a 100 pack-year smoking history developed lung cancer, and six patients developed myelofibrosis.

Essential Thrombocytosis. Of the three randomized studies evaluating the use of hydroxyurea in essential thrombocytosis, two were from the same clinical trial. This study compared hydroxyurea to no myelosuppressive therapy. The original publication by Cortelazzo et al. did not report toxicity. [129] In the 6-year followup study, [130] seven subjects in the hydroxyurea arm developed a malignancy (four MDS/AML, one chronic lymphocytic leukemia, two lung cancers), as compared to one patient (breast cancer) in the no-treatment arm. There was a significant difference in cancer-free survival (p=0.0321). Of note, five of the eight patients with secondary malignancies had received busulfan as cytoreductive therapy before randomization into this study. When the patients who had received busulfan were removed from the analysis, there was no significant difference in the incidence of malignancies between those treated with hydroxyurea and the untreated group. One additional trial was a study of over 800 patients randomized to either hydroxyurea and aspirin or anagrelide and aspirin. [131] After a median of 39 months of drug exposure, there was no statistical difference in the incidence of leukemia between the two groups. There was a significantly higher number of patients who developed myelofibrosis in the anagrelide arm than in the hydroxyurea arm (p=0.01), but there was no difference between the two groups in the number of subjects who died from progression of their disease.

There were four observational studies that examined the outcome of patients with essential thrombocytosis. The largest of these studies included 605 patients followed for a median of 84 months (range, 0-424). [106] This study looked at the incidence of leukemic transformation and described the study participants in six treatment groups that are outlined in Appendix C, Evidence Table 21. Leukemic transformation occurred in a total of 20 patients (3.3 percent). Five patients in the hydroxyurea-alone arm developed leukemia, as compared to four in the no-treatment arm. In multivariate analyses, older age, abnormally low hemoglobin, and a platelet count greater than or equal to 1000 $x10^9$/l were predictors of leukemic transformation. In

univariate analysis, the incidence of leukemic transformation was highest among those receiving cytotoxic therapy (p=0.03). However, there was not a significant risk associated with any therapy in multivariate analysis after controlling for the risk factors identified in prior analysis (p=0.15).

A study published in 1998 reported the outcomes of 357 patients with essential thrombocytosis who had been treated with therapies that included hydroxyurea, ^{32}P, pipobroman, and busulfan. [132] The median followup was 98 months. Seventeen patients developed MDS/AML or lymphoma. There were no differences in the incidence of MDS/AML or lymphoma between groups when the drugs were used as single agents. However, progression to MDS/AML was less frequent in patients treated with hydroxyurea alone (7 of 201) than in patients treated with hydroxyurea combined with other agents (7 of 50, p =0.01), or than in patients in whom hydroxyurea was used after one of the other agents (3 of 76, p = 0.04). Of the 13 evaluable patients, 7 had 17p deletional chromosomal abnormalities when they developed MDS/AML or lymphoma. All of them had received hydroxyurea either alone (n=3) or in combination with other drugs (n=4).

One study looked at the outcomes of 231 Chinese individuals with essential thrombocytosis over a median followup of 10 years. [133] Five patients developed leukemia; three of these patients had been treated with hydroxyurea alone, and two had been exposed to hydroxyurea and melphalan. The use of melphalan was significantly associated with the development of leukemia (p=0.002). Seven patients developed myelofibrosis, six in the hydroxyurea-alone group and one in the hydroxyurea /melphalan group.

The final observational study of essential thrombocytosis was a retrospective analysis of 155 patients treated for essential thrombocytosis in Pavia, Italy from 1985-1995. [107] The median followup was 104 months (8-240). In this study, 4 of 23 patients treated with hydroxyurea, 4 of 106 patients treated with pipobroman, and none of the 26 patients who received no therapy developed MDS/AML. The incidence rate ratio for progression was 6.15 for hydroxyurea versus pipobroman (p=0.019). Of note, three of the patients who developed MDS/AML or lymphoma while on hydroxyurea had 17p deletional chromosomal abnormalities.

Myeloproliferative Disorders. The first study we describe was a cohort study comparing several patient populations listed in Appendix C, Evidence Table 19. [134] The mean followup period in this study for any patient on hydroxyurea was 7.8 years. Thirteen patients developed MDS/AML or lymphoma, including five patients treated with hydroxyurea alone, seven patients treated with hydroxyurea plus another agent, and one patient that had not received any chemotherapy. There was a significantly increased risk of MDS/AML or lymphoma in the group of patients who received hydroxyurea (either alone or in combination with other agents) when compared to those who were not exposed to any chemotherapy (p=0.033). There was no statistical difference in the incidence of AML or lymphoma between those patients treated with hydroxyurea alone and those who did not receive any drug therapy (p=0.64) Another study was a prospective cohort study that began in 1976 and followed patients with polycythemia vera, essential thrombocytosis, and idiopathic myelofibrosis, all treated with hydroxyurea. [135] All patients were followed for at least 5 years. Three of 30 patients with polycythemia vera, 1 of 10 with essential thrombocytosis, and 3 of 10 with myelofibrosis developed MDS/AML or lymphoma. Four of 11 patients with polycythemia vera, 1 of 5 with essential thrombocytosis, and 2 of 3 with myelofibrosis developed chromosomal abnormalities; none of these patients had had any chromosomal abnormalities prior to therapy.

There were two studies that examined outcomes in patients with a variety of myeloproliferative disorders. The first followed 152 polycythemia vera or essential

thrombocytosis patients on hydroxyurea for a median duration of 4.3 years. [136] In this study, three patients (1.97 percent) developed MDS/AML or lymphoma, and four (2.6 percent) developed leg ulcers. In a retrospective study of 75 patients with essential thrombocytosis and 54 with polycythemia vera treated with hydroxyurea and followed for a median of 7.18 years, three patients developed AML or lymphoma, and one developed pancreatic cancer. [137] All four of these patients had received treatment with busulfan prior to therapy with hydroxyurea. In addition to these toxicities, four patients developed leg ulcers, three developed skin rashes, and two developed significant anemia. The final study we reviewed examined the outcomes of 34 patients with polycythemia vera who had been treated with hydroxyurea, 30 with essential thrombocytosis who had been treated with hydroxyurea, 1 with polycythemia vera who had been treated with busulfan, and 4 with essential thrombocytosis who had been treated with interferon. Of the 34 polycythemia vera patients treated with hydroxyurea for a mean of 86 months, 2 (5.7 percent) developed AML or lymphoma. Of the 30 essential thrombocytosis patients exposed to hydroxyurea for a mean of 79 months, 1 developed AML or lymphoma.

Case Reports. We identified 235 case reports in 175 publications. The underlying conditions in the patients experiencing toxicities may have merely reflected the relative proportions of patients taking hydroxyurea, with the proportions of patients having CML or essential thrombocythemia being highest, despite a lack of FDA approval of this drug for the treatment of essential thrombocythemia (Appendix C, Evidence Table 24).

The most frequently reported complication was leg ulcer (66 reports), followed by dermatologic changes (34 reports), including hyperpigmentation, rashes consistent with dermatomyositis, and others. There were 27 reports of skin neoplasms, including epitheliomas, actinic keratoses, basal cell cancers, and, most frequently, squamous cell cancers. Nail changes were also frequently reported (nine case reports). There was one report of alopecia and six reports of oral ulcers or Behcet's disease. Level 1 evidence supports a causal role for hydroxyurea in leg ulcers and in skin neoplasms.

Fever was also a frequently reported event (15 reports), with Level 1 evidence to support a role for hydroxyurea. Similarly, there was Level 1 (at least one "certain" case report of an adverse event) evidence to support a role for this drug in causing hepatitis (often accompanied by fever). The reported pulmonary complications included two reports of alveolitis, with Level 2 evidence supporting causality; one report of pulmonary fibrosis with only Level 3 evidence; and five reports of interstitial pneumonitis, with Level 1 evidence, supporting the causality of hydroxyurea in this complication.

Leukemia was reported 33 times. Among the patients developing leukemia, 57 percent had essential thrombocythemia, 24 percent had polycythemia vera, 6 percent had an MPD, and 6 percent had a hypereosinophilic condition. The mean age of these patients was 32 years (range, 43 to 87 years), and 45 percent were female. The mean length of of hydroxyurea treatment was almost 6 years, with a range of 12 weeks to 17 years. As discussed above, it was impossible to describe the causality as being certain or probable in this scoring system, given a condition that cannot regress.

The other toxicities with Level 1 evidence included azospermia or a decrease in sperm motility, limbal stem cell deficiency (a corneal condition), and pruritis.

Predictors of toxicity. Few studies specified what factors predicted toxicity from hydroxyurea (Table 7). In the MSH trial, the patients having the greatest response in terms of Hb F% were more likely to have two or more episodes of hematological toxicity, [40] although it may

be the case that hematological toxicity was predicting the Hb F response. The few other findings we noted were that leg ulcers at baseline were associated with leg ulcers while on therapy, [66] and

Table 7. Predictors of Toxicity from Hydroxyurea in Studies of Sickle Cell Disease

Author, year	Predictors of toxicity
Trials	
Steinberg, 1997[40]	Patients with higher Hb F response were more likely to have two or more episodes of hematological toxicity
Observational Studies	
Bakanay, 2005[51]	Lower Hb and higher BUN, 2 BAN alleles, and 1 CAM allele are predictive of being in the deceased group on multivariate analysis
Wang, 2001[60]	Presumed viral infections associated with neutropenia while on HU
Charache, 2992[46]	HU clearance was not predictive of toxicity.
Chaine, 2001[66]	Prior history of leg ulcer was associated with leg ulcer on treatment (p<0.005).

Hb = hemoglobin; HU = hydroxyurea; BUN = blood urea nitrogen

viral-like infections were associated with neutropenia while on hydroxyurea. [60] As described above, patients with Hb SC disease tolerated dose increases less well than did patients with other genotypes. [81] Charache et al. found no association between hydroxyurea clearance and toxicity. [46]

The strength of the evidence regarding the toxicity of hydroxyurea. As described in the Methods, we reviewed the CERHR report as part of our assessment of developmental toxicities. Based on this panel's findings, we concluded that there was insufficient evidence to comment on the risk of leukemia in children treated with hydroxyurea or to conclude that this drug contributes to developmental toxicities in the next generation (offspring of treated patients). Similarly, there was insufficient evidence to allow us to assess whether exposure *in utero* causes developmental defects, although there was low-grade evidence that the use of hydroxyurea in pregnancy is not commonly associated with adverse perinatal outcomes. There was low-grade evidence, including the efficacy studies that we reviewed, that hydroxyurea is not associated with growth delays in children and adolescents. The CERHR report stated that the animal data, which were reviewed for their report, are relevant to humans, and the panel found evidence of developmental toxicities in rats and mice exposed *in utero.*

We graded separately the evidence regarding toxicities of hydroxyurea in adults in the case of patients with sickle cell disease and those with other diseases. We used the evidence from other diseases as indirect evidence regarding toxicities that could be potentially expected in patients with sickle cell disease.

Low-grade evidence based on the results of the MSH suggested that hydroxyurea treatment in adults with sickle cell disease is not associated with leukemia. The evidence from patients with other diseases also provided low-grade evidence that the drug is not associated with leukemia. High-grade evidence supported that hydroxyurea is not associated with leg ulcers in patients with sickle cell disease, although high-grade evidence supported the claim that it is associated with leg ulcers in patients with other conditions. The evidence was insufficient in sickle cell disease to indicate whether hydroxyurea contributes to skin neoplasms, although high-grade evidence in other conditions supported the possibility that it does. Similarly, there was insufficient evidence to indicate whether hydroxyurea is associated with secondary malignancies in adults with sickle cell disease, and the evidence in other diseases was only low-grade. There was also insufficient evidence regarding pregnancy outcomes in treated patients with sickle cell disease, and the evidence from patients with other diseases was low-grade but supported a lack of adverse effects. Low-grade evidence supported the possibility that hydroxyurea is associated

with spermatogenesis defects in patients with sickle cell disease, and this relationship was supported by low-grade evidence from other conditions (Table 5).

Key Question 4. What are the Barriers to the Use of Hydroxyurea Treatment (and other therapies) for Patients who have Sickle Cell Disease and what are the Potential Solutions?

Characteristics of Studies Addressing Barriers to the Use of Therapies for Sickle Cell Disease

Of the studies that addressed this key question, 15 employed a cross-sectional study design to test an association between a patient, provider, or system factor and the use of therapy; [138-152] 18 described patient and/or provider-reported barriers to therapy; [93,153,153-168] and 3 used both methods. [155,169,170] Studies employing cross-sectional designs to assess the association between a patient, provider, or system factor and the use of therapies are shown in Appendix C*, Evidence Table 25, and studies describing patient and/or provider-reported barriers to therapy are shown in Appendix C, Evidence Table 26**.**

Cross-sectional studies testing associations. Of the 18 studies using a cross-sectional design (Appendix C, Evidence Table 25), only 1 addressed barriers to the use of therapies to increase Hb F, [138] 8 addressed barriers to the use of established therapies for management of sickle cell disease, [139-144,169,170] 3 addressed barriers to the use of appropriate pain medication during vaso-occlusive crises, [145,146,155] and 6 addressed barriers to the use of routine, scheduled care for sickle cell disease. [147-152]

The one study that dealt with therapies to increase Hb F examined factors associated with patient (or parent) decisions to initiate therapy. [138] Of the eight studies that addressed barriers to the use of established therapies, one focused on patient adherence to chelation therapy, [139] while the remainder focused on patient adherence to antibiotic prophylaxis. [140-144,169,170] Of the three studies that that dealt with the use of appropriate pain medications during vaso-occlusive crises, two addressed providers' provision of pain medications to patients, [145,155] and one addressed patients' use of pain medications. [146] Of the six studies that dealt with routine, scheduled care, three directly addressed the use of routine health services, [147,148,150] one addressed the transition to adult care, [149] one addressed appointment-keeping, [152] and one addressed general adherence. [151]

Two-thirds of the cross-sectional studies were published in the past 5 years (2002-2007), while the remainder were published in the previous decade (1992-2001). Three of the 18 cross-sectional studies focused on health professionals as study subjects, [140 145,155]while the remainder studied patients. Adult patients with sickle cell disease were the targeted patient population of interest in only 1 of the 18 cross-sectional studies. [152] In four of the cross-sectional studies, children and adults were the targeted patient population of interest.[147,149,150,155] The remainder focused on children (or parents/caregivers). The majority were conducted in the United States, while one was conducted in Saudi Arabia[170]and five did not specify a location.

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

Descriptive studies of reported barriers. Of the 20 descriptive studies of patient- and provider-reported barriers to the use of therapies for sickle cell disease (Appendix C, Evidence Table 26), 1 addressed barriers to the receipt of treatment to increase Hb F, [93] 2 addressed barriers to patient adherence to established therapies for disease management, [169,170] 13 addressed barriers to the receipt of pain medications, [153-155,159-168] 1 addressed barriers to bone marrow transplantation, [158] and 3 addressed barriers to generic healthcare quality. [156,157,171]

About half of the descriptive studies were published in the past decade (1998-2007), with the remainder published in the preceding decade (1988-1997). Most (n=13) descriptive studies occurred in the United States; however, 6 were conducted in the United Kingdom, [154,159,161,163,166,168] and one was conducted in Saudi Arabia. [170]

Of the 20 descriptive studies, 9 used primarily quantitative descriptive methods (e.g., questionnaires), [93,153-158,169,170] 10 used primarily qualitative methods (e.g., focus groups and in-depth individual interviews), [153,159-167] and 1 used mixed quantitative and qualitative methods. [168] The majority of the descriptive studies included patients as a study population, [154,158,159,161,162,164-167,169,170] while others included providers, [93,155-158] and some included both patients and providers. [160,163,168,171] Of the 15 descriptive studies that included patients as the study population, 12 were focused on adults, [154,159-168,171] and 3 were focused on children. [158,169,170]

Results of Studies Addressing Barriers to the Use of Therapies for Sickle Cell Disease

Results of cross-sectional studies testing associations. The results of the cross-sectional studies are summarized in Table 8. Each of the potential barriers and facilitators below was identified in only one study. The factors in each category that were examined but not associated with use of therapies are included in Table 8 but not detailed below.

The one study that addressed barriers to the use of therapies to increase Hb F (specifically, hydroxyurea) found that the perceived efficacy and perceived safety of hydroxyurea had the largest influence on patients' (or parents') choice of hydroxyurea therapy over other therapies. [138]

The eight studies that addressed potential barriers to the use of established therapies for disease management found two potential patient-related barriers (family stress and having more children in the home), and one potential system-related barrier (being seen in an academic medical center). [139-144,169,170] These eight studies also identified 11 potential patient-related facilitators of the use of established therapies for disease management (private insurance, sharing of responsibilities between parent and child, more hospital visits, more adults in the home, having a car, no child prior history of transfusion, younger patient age, more caregiver knowledge, greater intent to adhere, greater perceived benefits, and family employment) and two potential provider-related facilitators (provider female gender and pediatric specialty).

The three studies that addressed barriers to the use of appropriate pain medication during vaso-occlusive crisis found one patient-related barrier (an increased number of hospital visits was associated with less optimal pain management) and one provider-related barrier (negative provider attitudes). [145,146,155] These studies also found one potential patient-related facilitator (dispositional optimism being associated with better patient use of pain medications) and two potential provider-related facilitators (provider female sex and fewer years in practice).

Table 8. Patient, Provider, and Societal Barriers and Facilitators Shown to be Associated with Treatment for Patients with Sickle Cell Disease

Type of Treatment		Barriers and Facilitators (n Studies)		
		Patient	**Provider**	**Societal/ System**
Treatments to increase hemoglobin F	*Barriers*		NR	NR
	Facilitators	Perceived efficacy (1) Perceived safety (1)	NR	NR
	Neither	Parental age (1) Parental sex (1) Number of children (1) Parent's rating of child's HRQOL (1) Frequency of VOC (1)	NR	NR
Established therapies for disease management	*Barriers*	Family stress (1) More children at home (1)	NR	Academic medical setting (1)
	Facilitators	Private insurance (2) Caregiver knowledge (2) Parent and child share responsibility (1) Hospital visits (1) More adults in home (1) Having a car (1) No prior child history of transfusions (1) Younger patient age (1) Intent to adhere (1) Perceived benefits (1) Family employment (1)	Provider knowledge (1) Provider specialty [pediatrics] (1)	NR
	Neither	Behavioral/psychological adjustment (1) Patient/caregiver knowledge (2) Satisfaction with regimen (1) Patient sex (3) Patient age (3) Urban residence (1) Non preventive outpatient care visits (1) Parental education (1) SCD type (1) Number of children (1) Years on therapy (1) History of stroke (1) Hospital visits (2) **Established therapies for disease-management** Child cognitive disability (1)	Provider years in practice (1) Provider gender (1)	Convenience of the regimen (1) Cost sharing (1)
Pain management during vaso-occulsive crisis	*Barriers*	Hospital visits (1)	Negative attitudes (1)	
	Facilitators	Dispositional optimism (1)	Female sex (1) Fewer years in practice (1)	NR
	Neither	Patient age (1) Patient sex (1) Parental education (1)	Provider attitudes (1) Professional experience and training (1)	NR

Table 8. Patient, Provider, and Societal Barriers and Facilitators Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Type of Treatment		Barriers and Facilitators (n Studies)		
		Patient	**Provider**	**Societal/ System**
Receipt of routine scheduled care	*Barriers*	Greater community socioeconomic distress (1)	NR	NR
	Facilitators	Greater parental/family knowledge (2) Rural geographic region* (2) Self-efficacy (1) Female patient sex (1) Family problem-solving effort (1) Higher family income (1) Illness-related stress (1) Social support (1)	NR	NR
	Neither	Community socioeconomic distress (1) Physical functioning (1) Number of medical problems (1) Parent adolescent relationship (1) Disease severity (1) Stressful life events (1) Clinical mal-adjustment (1) Receipt of preparation for the transfer to adult care (1) Interference of disease in daily life (1) Level of medical problems (1)	NR	Distance to a clinic (2)

*After adjustment for distance to clinic. Bivariate results in one of the two studies suggested that rural patients have less utilization when travel distance is not controlled. VOC = vaso-occlusive crisis; SCD = sickle cell disease; NR = not reported.

The six studies that addressed barriers to use of routine, scheduled care for sickle cell disease[147-152] found one potential patient-related barrier (greater community socio-economic distress) and eight potential patient-related facilitators (greater parental knowledge, rural geographic region, higher self-efficacy, female patient sex, higher family problem-solving effort, higher family income, greater illness-related stress, and greater social support). Of note, the studies that found rural location to be a potential facilitator controlled for distance to the clinic, which may have eliminated the typical reason for decreased access by rural patients.

Results of descriptive studies of reported barriers. The results of studies employing descriptive methodologies to identify patient and provider-reported barriers to the use of therapies are summarized in Table 9.

Table 9. Summary of Barriers to the Treatment of Sickle Cell Disease Reported by Patients and Providers

Type of Treatment	Study Subjects (n studies)	Barriers (n studies identifying barrier)		
		Patient	Provider	Societal/ System
Treatments to increase hemoglobin F	Providers (1)	Patient anticipation of side effects (1)	Concern about patient compliance (1) Concern about side effects/ carcinogenic potential (1) Doubts about effectiveness (1) Concerns about use in older patients (1) Concern about lack of patient contraception (1)	Cost (1)
Established therapies for disease-management	Patients (2)	Forgetting medicine (2) Disliking taste (1) Concern about side effects (1) Caregiver being busy (1) Child falling asleep (1) Running out of medicine (1)	NR	NR
Pain management during vaso-occulsive crisis	Patients (8) Providers (2) Mixed (3)	Race (1)	Negative attitudes (13) Lack of knowledge (5) Lack of time (2) Inadequate pain assessment tools (2)	NR
Receipt of routine scheduled care	NR	NR	NR	NR
Bone marrow transplantation	Providers (1)	Lack of donor (1) Lack of psychosocial or financial support (1) Parental refusal (1) History of noncompliance (1)	Physician refusal (1)	NR
Non-specific 'treatment' or healthcare 'quality'	Providers (1) Mixed (2)	Race (2) Older age (1) Male sex (1)	Lack of knowledge (1)	NR

NR = not reported.

The one study that explored barriers to the use of treatments to increase Hb F (specifically, hydroxyurea) for patients with sickle cell disease found that providers reported the barriers to be patients' concerns about side effects and the providers' own concerns about the use of hydroxyurea in older patients, about patient compliance, about a lack of contraception, about side effects and carcinogenic potential, doubts about effectiveness, and concern about the costs to patients. [93]

The two studies that addressed barriers to the use of established therapies for disease management both examined patient (caregiver)-reported reasons for missing doses of prophylactic antibiotic medication and found that caregivers reported missing doses as a result of forgetting, being too busy, running out of medication, having the child fall asleep, and the child not liking the taste of the medication. [169,170]

All of the 13 studies that addressed barriers to the receipt of pain medications during vaso-occlusive crises found that both patients and providers reported that some type of negative provider attitude affected the quality of the pain management for patients with vaso-occlusive crisis. [153-155,159-168] Other barriers identified by patients and providers included poor provider knowledge of sickle cell disease (mentioned in five studies), lack of time (mentioned in two studies), inadequate pain assessment tools (mentioned in two studies), and race (mentioned in one study).

The one study that addressed barriers to bone marrow transplantation found that providers from bone marrow transplant centers reported that the major barriers to bone marrow transplantation for patients with sickle cell disease were lack of a donor, lack of psychosocial or financial support, a history of patient noncompliance, parental refusal, and physician refusal. [158]

The three studies that addressed barriers to general healthcare quality found that patients and providers reported that three patient-related factors (patient race, older patient age, and patient male sex) may affect the quality of care provided to patients with sickle cell disease. [156,157,171]

Strength of the evidence of the existence of barriers to the use of therapies in sickle cell disease. There was insufficient evidence to allow us to identify barriers to the use of hydroxyurea. Regarding barriers to the use of established therapies for sickle cell disease, four items were identified as either barriers, facilitators, or neither in more than two studies and thus were eligible for evidence grading. These were patient/family knowledge, number of hospital visits, patient age, and patient sex.

We concluded that the evidence that sex is not a barrier to the use of therapies was of a moderate grade. Largely due to the relative paucity of studies and their inconsistency, we concluded that there was only low-grade evidence that patient/family knowledge, the number of hospital visits, and patient age are barriers. The evidence for the remaining barriers to the use of established therapies was insufficient to allow us to draw any conclusions.

Regarding barriers to pain management, we identified two factors that were identified as a barrier in more than two studies and were thus eligible for evidence grading. These were negative provider attitudes and poor provider knowledge. Because of the quantity and consistency of these findings, we concluded that the evidence was high-grade that negative provider attitudes are barriers and moderate-grade that poor provider knowledge is a barrier to the use of pain medications for patients with sickle cell disease. The evidence for the remaining barriers to pain management was insufficient to allow us to draw any conclusions. There was insufficient evidence to allow us to identify barriers to the use of routine health services and bone marrow transplantation for sickle cell disease (Table 5).

Characteristics of Studies Addressing Interventions to Overcome Barriers to the Appropriate Use of Therapies

Thirteen studies addressed interventions to increase the appropriate use of therapies. [172-184] None of these studies focused on interventions to increase the appropriate use of hydroxyurea. Nine focused on provider interventions to increase the appropriate provision of pain medications for patients with vaso-occlusive crisis, [172-180] three focused on patient interventions to improve adherence to therapies (desferoxime, [181] antibiotics, [182] and general adherence to health-promoting activities[183]), and one focused on a patient intervention to improve the receipt of routine, scheduled health care for sickle cell disease (Appendix C, Evidence Tables 27 and 28). [184]

The majority of these interventions were assessed using observational (e.g., pre/post) study designs, but there were two RCTs[182,183] and three studies that had a concurrent control group.[173,175,176] The majority of the studies were conducted in the United States, with two taking place in the United Kingdom[177 179]and one in Canada.[182]

The majority of the provider interventions to improve pain management involved clinical protocols/pathways,[172-175,178,180] while one primarily involved audit and feedback,[177] and two involved changing the structure of care through the use of a day hospital[176] or a fast-track admission process.[179] In addition, one of the clinical protocol/pathway interventions included staff sensitivity training.[174]

The effect of interventions to improve pain management was measured directly in terms of its impact on pain management quality, as assessed by medical record review in six studies[173,175-177,179,180] and patient ratings in three studies;[174,179,180] the effect of such interventions was also assessed indirectly through healthcare utilization in five studies[175 172,174,176,178]and healthcare costs in two studies.[174,175] No study examined the impact of an intervention directly on patient-reported levels of pain.

Results of Studies Addressing Interventions to Overcome Barriers to the Appropriate Use of Therapies

A summary of the results of studies addressing interventions to increase the appropriate use of therapies is provided in Table 10 (see also Appendix C*, Evidence Tables 27 and 28).

Four of the studies that measured the impact of an intervention to improve the quality of pain management during vaso-occlusive crisis showed improvement in one or more direct outcomes,[173,179,180,185] while the remaining five studies showed potential improvement either through the suggestion of an improvement on a direct outcome (without a statistical test) or a statistically significant improvement in one or more indirect outcomes.

Two of the three studies that focused on patient interventions to improve adherence to therapies showed no effect of the intervention on patient adherence to desferoxime[181] or to antibiotic prophylactic therapy.[182] One of the studies that focused on patient interventions to improve adherence to therapies showed no increase in health-promoting activities as a result of the intervention but did show some improvements in child health-related quality of life and child-parent relationships.[183]

The one study that evaluated a patient intervention to improve receipt of routine, scheduled health care for sickle cell disease demonstrated a substantial and significant reduction in the percent of patients who had not attended clinic over the past 2 years.[184]

The strength of the evidence addressing interventions to overcome barriers to the use of therapies. The evidence was insufficient to allow us to identify interventions to overcome barriers to the use of hydroxyurea and bone marrow transplantation.

None of the three studies testing interventions to improve patient adherence to established therapies for chronic disease management showed any effect on patient adherence. However, due to the small sample sizes and diverse outcome measures, we concluded that there was only low-grade evidence that interventions cannot improve patient adherence.

We concluded that there was moderate evidence that interventions can overcome barriers to the use of pain medications and moderate evidence to support the contention that interventions

* Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

can overcome barriers to the receipt of routine, scheduled healthcare for patients with sickle cell disease (Table 5).

Table 10. Results of Studies That Evaluated the Effect of a Patient or Provider Intervention to Improve Patient Adherence and Provider Provision of Appropriate Therapy for Patients with Sickle Cell Disease

Type of Therapy	Patient interventions Outcome: Adherence to therapy	Provider Interventions: Outcome: Provision of appropriate therapy
Treatments to increase hemoglobin F	NR	NR
Established therapies for disease-management	Partial Improvement (1) No Improvement (2)	NR
Pain management during vaso-occulsive crisis	NR	Improvement (4) Potential Improvement (5)
Bone marrow transplantation	NR	NR
Receipt of scheduled care	Improvement (1)	NR
Non-specific “treatment” or healthcare quality	NR	NR

NR = not reported.

Chapter 4. Discussion

Since its approval for the treatment of sickle cell disease in 1998, hydroxyurea has been under intense study. The body of evidence supporting its use is large but is mainly based on observational data. There have been only two randomized controlled trials of the use of this drug in sickle cell disease, although an additional large trial is nearing completion. The other studies of this drug have included several controlled studies comparing patients receiving hydroxyurea to patients receiving another intervention or usual care, but the vast majority of the studies have been observational studies, including well-described prospective cohorts and many small studies reporting patient experiences pre- and post-treatment with hydroxyurea. In addition, the literature is replete with case reports describing toxicities ascribed to hydroxyurea, although the majority of these reports concern diseases other than sickle cell disease. Few studies have specifically identified barriers to the use of hydroxyurea in patients with sickle cell disease. No studies have tested an intervention to improve patient acceptance of this medication or patient adherence. For this report, we opted to review the literature related to barriers to the use of other medications and treatments in patients with sickle cell disease, since we believe that the barriers may often be similar.

In this section, we describe key findings from our literature review, describe the limitations of this body of literature, and discuss the limitations of our report. We also describe studies that are in progress and make suggestions, based on the gaps in the current evidence, with regard to studies that should be undertaken in the future.

Summary of the Key Findings

Key Questions 1 and 2

Efficacy and Effectiveness of Hydroxyurea in Children

A single, small RCT investigated the efficacy of hydroxyurea in children. In this Belgian study, the rate of hospitalization and number of days hospitalized per year were significantly lower in the hydroxyurea group than in the placebo group. [44] The small size of this study and the short duration of treatment with the drug (6 months) did not provide adequate data to permit assessment of the long-term responses to hydroxyurea. The results of this trial are supported by data from 20 observational studies in children. Interpretation of many of these observational studies is complicated by their incomplete description of losses to followup. The HUSOFT was the only study of very young children, with a mean age of 1.3 years; [60] this Phase I/II study also had a published followup study. [72] Hb F% was reported as an outcome in 16 of these observational studies. In the studies that reported Hb F% before and during treatment with hydroxyurea, the Hb F% increased substantially while patients were on treatment, with results comparable to those reported in the RCT. The mean pre-treatment Hb F% ranged from 5 to 10 percent, and the post-treatment values were in the range of 15 to 20 percent. In the study of infants, hydroxyurea therapy prevented the expected decline in Hb F% that is usually seen in this

age group. Hemoglobin concentration increased only modestly (roughly 1 gm/dl) but significantly across studies.

The frequency of pain crises decreased in three of the five studies in which this variable was assessed; in one study without a comparison group, it was unclear how the rate differed from an untreated group. Hospitalization rates declined in all studies in which this was assessed. Two studies reported TCD velocities and demonstrated decreased velocity while the children were being treated. [62,63] One study included a control group that showed an increase in velocity over the treatment period. [62] One other study demonstrated rates of recurrent stroke in patients receiving hydroxyurea to be comparable to the rate typically seen in children on chronic transfusion therapy. [67]

Based on one RCT in children and on many observational studies, some of which were of high quality and most of which were consistent in their findings, we concluded that there was a high grade of evidence to support the claim that hydroxyurea raises Hb F in children. There was moderate evidence to support the contention that hydroxyurea reduces the frequency of pain crises, and a high grade of evidence that it reduces the frequency and/or duration of hospitalization in children. There was a low grade of evidence to support that claim that hydroxyurea reduces neurological events in children, and insufficient evidence to allow us to draw any conclusions regarding transfusion frequency.

Efficacy and Effectiveness of Hydroxyurea in Adults

Only one randomized trial tested efficacy in adults with sickle cell disease, the MSH Study. [39] Six additional analyses based on this trial or on followup studies have also been published. [21,22,40-43] In the MSH, 18 percent of patients had permanent or complete cessation of the study medication during the trial. The significant hematological effects of hydroxyurea after 2 years (when compared to the placebo arm) included a small increase in total hemoglobin of 0.6 g/dl and a moderate absolute increase in fetal hemoglobin of 3.2 percent. [44] The results of the MSH study included significant differences in several critical clinical outcomes between the hydroxyurea arm and placebo. The median number of painful crises was 44 percent lower in the hydroxyurea arm, and the time to the first painful crisis was 3 months, as compared to 1.5 months for those in the placebo arm. There were fewer episodes of acute chest syndrome and transfusions, but no significant differences in deaths, strokes/chronic transfusion, or hepatic sequestration. The MSH study also included an evaluation of costs and quality of life, both of which favored the use of hydroxyurea.

The results of the 12 observational studies enrolling only adults supported the findings in the MSH study. In all six studies of adults that reported hematological outcomes, Hb F% was significantly higher for those receiving hydroxyurea. [45 46,71,74,78,80]The number of pain crises was given in three studies, all of which demonstrated a significant decline in frequency with drug treatment. [46,61,71] Similarly, hospitalization rates decreased for adults treated with the drug. In a group of patients treated for fewer than 24 months, however, the investigators did not find a significant difference in hospitalization rates from baseline, [52] although patients who discontinue before 24 months may represent a different population than those who are able to tolerate a longer duration of therapy.

There was only one study that assessed responses in patients with Hb SC, although many studies included at least some patients with Hb $S\beta^{0/+}$ thalassemia. The results appeared to be

comparable for patients with Hb SS and Hb S$\beta^{0/+}$ thalassemia. Sex and age had little influence on outcomes.

Several interesting studies have described potential biomarkers of the response to hydroxyurea. One study identified significantly decreased rigidity and rates of elastic shear in patients with sickle cell disease treated with hydroxyurea, when compared to untreated sickle cell disease patients, but the values were still significantly higher than those for controls without sickle cell disease. [85] Another study described lower rates of arginase activity in those treated with hydroxyurea, but again the rates were lower in controls without sickle cell disease. Similarly, increased nitric oxide metabolites and cyclic GMP were reported in patients treated with hydroxyurea. [87] Levels of endothelin-1 were significantly lower in children with Hb SS on hydroxyurea at steady-state when compared to an untreated group, [88] but the levels of tumor necrosis factor-1 were similar for untreated patients with Hb SS and those receiving a single dose of hydroxyurea. [89] These studies suggest that other mechanisms may contribute to the benefit resulting from hydroxyurea in addition to the anti-sickling effect produced by an increase in Hb F concentration in red blood cells.

Based on one high-quality RCT in adults and many observational studies, we concluded that there was a high grade of evidence to support the claim that hydroxyurea raises fetal hemoglobin in adults with sickle cell disease and that future research is unlikely to substantially alter these conclusions. There was also high-grade evidence that hydroxyurea reduces the frequency of pain crises and that the drug reduces the frequency and/or duration of hospitalization in adults. There was also high-grade evidence that hydroxyurea reduces transfusions, but only a low grade of evidence that it reduces mortality. The evidence base was insufficient to allow us to comment on neurological events in adults.

Key Question 3

Toxicities of Hydroxyurea in Children and Adults

Our assessment of the strength of the evidence regarding the toxicity of hydroxyurea when used in children came largely from our review of the report by the panel of experts assembled by the CERHR. This panel reviewed articles, published through January, 2007, that were pertinent to the evaluation of adverse effects of hydroxyurea on development and reproduction in both humans and animals.[26]

The panel concluded that treatment of children aged 5 to15 years with hydroxyurea does not cause a growth delay. They felt that there were insufficient data to allow them to evaluate the effects of the drug on pubertal development. The expert panel also concluded that there were insufficient data regarding the effects on subsequent generations following exposure of germ cells to hydroxyurea, including exposure during fetal life, infancy, childhood, and adolescence. The CERHR report did not describe any studies on the long-term health effects, including carcinogenicity, of childhood exposure to hydroxyurea; we were also unable to find any such studies. The expert panel had concerns about the adverse effect of hydroxyurea on spermatogenesis in men receiving the drug at therapeutic doses, and we also identified relevant case reports in both patients with sickle cell disease and patients with other illnesses who had been treated with hydroxyurea. The CERHR report concluded that the use of the drug in pregnancy was not commonly associated with adverse perinatal outcomes and that there were no data on long-term outcomes in children who were exposed *in utero*.

Three cases of leukemia were described in the observational studies we reviewed that dealt with patients with sickle cell disease who had been treated with hydroxyurea; [53,55,82] we also identified another three case reports of hydroxyurea-treated patients with sickle cell disease who developed leukemia, and one report of a child developing Hodgkin's lymphoma. Without knowing how many patients had been treated with hydroxyurea, it was impossible to calculate whether this rate of leukemia was higher than the baseline rate for young adults with sickle cell disease. In one study, a higher rate of VDJ recombination events was reported in patients treated for 30 months than in those treated for 7 months; [57] another study found this not to be the case. [81] Two studies found no increase in chromosomal abnormalities in the treated patients. [46,47] Other toxicities associated with hydroxyurea in patients with sickle cell disease that appeared likely to be causally related to its use were neutropenia, skin rashes, and nail changes. The other toxicities reported were rare.

We reviewed toxicity reports from patients with other diseases who were treated with hydroxyurea and found additional toxicities, including a high number of leg ulcers and skin cancers. Of the RCTs enrolling patients with polycythemia vera, MPD, HIV, and essential thrombocytosis, none demonstrated a greater number of cases of leukemia in the group treated with hydroxyurea as a single agent. This parameter could not be assessed in the trials enrolling patients with CML, since acute leukemia was evaluated as an outcome rather than as a medication-related toxicity. To further address this potential relationship between hydroxyurea and the risk of malignancy, we reviewed a case series consisting of 26 patients with AML who had a unique t(3;21) chromosomal translocation. [117] Among these 26 patients were 15 with CML who had been treated with hydroxyurea. We found no other reports describing an association between this translocation and the use of this drug.

In our analysis of patients with diseases other than sickle cell disease, we also found evidence from case reports that hydroxyurea could cause fever, hepatitis, and interstitial pneumonitis. The hematological toxicities (cytopenias) seen were often intensified when patients were receiving other myelotoxic drugs such as antiretroviral therapies.

We concluded, based on our review of toxicities in both patients with sickle cell disease and patients with other diseases, that there was low-grade evidence that hydroxyurea treatment in adults with sickle cell disease is not associated with leukemia. High-grade evidence supported the claim that hydroxyurea is not associated with leg ulcers in patients with sickle cell disease, although high-grade evidence also indicated that hydroxyurea is associated with leg ulcers in patients with other conditions. We hypothesized that the improvement in rheology offsets any increase in leg ulcer risk associated with the drug.

The evidence was insufficient with regard to sickle cell disease to allow us to determine whether hydroxyurea contributes to skin neoplasms, although high-grade evidence in other conditions suggested that it does. The other populations studied were largely light-skinned populations, so we were not surprised that the skin cancer risk was notably different across populations. Likewise, there was insufficient evidence to indicate whether hydroxyurea is associated with secondary malignancies in adults with sickle cell disease, and the evidence in other diseases was only low-grade.

Key Question 4

Barriers to the Use of Hydroxyurea and Other Treatments for Managing Sickle Cell Disease

We anticipated finding few data that specifically addressed barriers to the use of hydroxyurea. Indeed, only two studies explored barriers to use of this drug, [93,138] and no study tested interventions to overcome such barriers. Given the scarcity of the data, we sought information on barriers to the use of other therapies for the treatment of sickle cell disease, including the receipt of routine, scheduled care; adherence to medications; and receipt of therapies, including pain control and prescriptions.

As expected, we found insufficient evidence to allow us to directly identify barriers to the use of hydroxyurea. Of the 18 cross-sectional studies we reviewed that tested whether hypothesized barriers affected the use of therapies, only one investigated barriers to hydroxyurea use. [138] This study found that the perceived efficacy and perceived safety of the drug had the largest influence on patients' (or parents') choice of hydroxyurea therapy over other therapies.

The one descriptive study that explored barriers to the use of hydroxyurea in patients with sickle cell disease found that providers reported such barriers to be patients' concerns about side effects, as well as the providers' own concerns about the use of the drug in older patients, about patient compliance, about a lack of contraception, about side effects and carcinogenic potential, doubts about effectiveness, and concern about the costs to patients. [93]

Largely because of the relative paucity of relevant studies and their inconsistency, we concluded that there was only low-grade evidence that patient or family knowledge, the number of hospital visits, and patient age are barriers. We concluded that the evidence was of a moderate grade that sex is not a barrier to use of therapies. The evidence about the remaining barriers to the use of established therapies was insufficient to yield any firm conclusions.

Regarding barriers to adequate pain management that were identified in both cross-sectional studies and descriptive studies, we identified two barriers that were cited in more than two studies: negative provider attitudes and poor provider knowledge. Because of the quantity and consistency of these findings, we concluded that the evidence was high-grade that negative provider attitudes are barriers and moderate-grade that poor provider knowledge is a barrier to the use of pain medications for patients with sickle cell disease. The evidence for the remaining barriers to pain management was insufficient to allow us to draw any conclusions.

None of the three studies testing interventions to improve patient adherence to established therapies for chronic disease management showed any effect on patient adherence. [181-183] However, because of the small sample sizes and diverse outcome measures in these studies, we concluded that there was only low-grade evidence that interventions cannot improve patient adherence. We concluded that there was moderate evidence that interventions can overcome barriers to the use of pain medications, and moderate evidence supported the possibility that interventions can overcome barriers to the receipt of routine, scheduled healthcare for patients with sickle cell disease.

We found it informative that when researchers chose barriers to investigate, they most often studied patient-related barriers. When patients were asked to identify barriers to use of therapies, they most often identified provider-related barriers. The barrier to pain management that was most often identified by patients and providers was negative provider attitudes. However, only

one of the nine pain management intervention studies addressed this issue directly through provider sensitivity training. Although the barriers related to the use of pain medications during vaso-occlusive crisis may not seem immediately relevant to the use of hydroxyurea, we concluded that it is likely that patients who have bad experiences when seeking healthcare may lose trust in the healthcare system and be less willing to take recommended medications, including hydroxyurea.

Limitations

This evidence base described here has significant limitations. Most notably, there were only two RCTs addressing hydroxyurea efficacy and safety in patients with sickle cell disease. [21,44] While the trial enrolling adults was a high-quality trial, it was not long, with only 2 years elapsing since randomization. [21] Two years may be an adequate duration for an assessment of efficacy. However, we had no trial data available to allow us to comment on the effectiveness of this drug in a population that may be asked to take the medication for many years with less intense supervision and encouragement than is received in an RCT. The trial conducted in children was a moderate-quality trial, but it was even shorter than the trial in adults, involving only 6 months of treatment. [44] Thus, the evidence base here was limited by a lack of effectiveness trials and a paucity of trials of efficacy, even though the MSH trial may be considered a definitive efficacy trial of this drug in adults. [21]Also, these trial results cannot be generalized to all patients with sickle cell disease because they included only patients with Hb SS, and clinical response and toxicities appear to differ to some extent by genotype.

The most frequently reported outcomes in the observational studies were hematological outcomes. The data convincingly demonstrated an increase in Hb F% with use of this drug; however, there was far less evidence regarding the clinically relevant outcomes of hospitalization, stroke, pain crises, acute chest syndrome, and mortality. Furthermore, we are concerned that the observational data may have been plagued with issues of regression to the mean; if patients are started on hydroxyurea after a period of worsening of symptoms, it is expected that they would, in time, return to their usual disease severity, even without a change in therapy. This is a major concern in interpreting the pre/post data from many of these observational studies reporting clinical outcomes.

We note also that the evidence was scanty regarding benefits for patients with genotypes other than Hb SS. Many of the studies included mixed genotypes, although predominantly Hb SS, without separately reporting outcomes by genotype. There were notable exceptions, [45,59,74,75,81] with several of these being high-quality studies. [75,81] Similarly, there was only limited evidence about the use of doses other than the MTD. Most of the observational studies described titration of the dose either on a schedule or according to patients' hematological parameters, although the HUSOFT investigators used a fixed dose in their infants, [60] and one study specifically assessed the response to a fixed dose. [50] Thus, there was little evidence to guide the choice of dose based on clinical outcomes.

The evidence regarding toxicities had limitations as well. Again, the relatively short clinical trials we found could not provide strong evidence for toxicities that may require many years of exposure. The followup studies from these trials are important contributors to the literature, but they became observational studies after the period of randomization ended and were subject to the limitations of any observational study. The losses to followup were substantial in the majority of the observational studies. Approximately half of the observational studies carefully

described the reasons for these losses, while the others did not. We cannot draw conclusions about the magnitude of risks and benefits of this drug without knowing whether patients left a study because of inadequate response to the drug or because of the development of adverse events or complications. As noted above, many of the observational studies were too short to adequately address the most critical toxicities, such as leukemia and other secondary malignancies. Very few studies required active surveillance for toxicities, such as periodic skin examination or cytogenetic studies, again with notable exceptions. [46,57] The studies of toxicities suffered from a lack of control groups; for example, studies that describe impaired spermatogenesis would require a control of group of comparably ill men with sickle cell disease in order to make it possible to determine whether this is symptom is disease- or treatment-related.

In reviewing the evidence, we opted to include toxicity data from patients treated with hydroxyurea for conditions other than sickle cell disease. We appreciate that this approach provides only indirect evidence of toxicity, in that the patient populations were markedly different than patients with sickle cell disease. The populations were substantially older and predominantly comprised of light-skinned individuals, and many of the patients had an underlying disease of the bone marrow. We still believe that these studies were useful in providing some evidence regarding potential toxicities of hydroxyurea, although the indirect nature of this evidence was an acknowledged limitation of this body of data.

Our investigation of barriers to the use of hydroxyurea was limited by the paucity of data regarding this question. Since there were only two studies specifically addressing barriers to the use of this drug, we again needed to bring in supporting evidence related to interventions that might have been associated with barriers comparable to those related to hydroxyurea treatment. The majority of the potential barriers considered in the cross-sectional studies (i.e., those chosen by the researcher) were patient-related factors, which suggested a lack of attention to provider and societal-level contributions. Very few of these studies included adult patients. Only half of the cross-sectional studies used multivariate techniques to attempt to control for the effects of potential confounders, an omission that notably reduced the quality of the evidence provided by these studies. Another concern was that many of the intervention studies used indirect outcomes, such as length of stay or total hospital costs, to assess improvement in pain management. We are not certain that these are the best outcome measures for this question.

We acknowledge that there are also limitations to our report. In particular, we restricted our literature review to studies published in English because of the limited resources available. Also, although we used a previously validated scale for assessing the quality of the randomized trials, we created our own quality assessment tools for the other study designs, based on recommendations in the literature. While these tools have not been formally validated (e.g., shown to correlate with outcomes), we used items in our scales that have been used previously and are widely thought to be indicators of high-quality reporting. We chose to consider publications that were letters to the editor and therefore not peer-reviewed, although they were reviewed by the editorial staff. We made this decision because of our familiarity with several unique studies that provided information that was not available elsewhere in the published literature and because we wanted to be very inclusive in our search for reports of malignancies. We opted not to exclude studies based on their quality scores, although this may have been a valid choice. Given our interest in identifying toxicities, we chose to include even the lowest-quality studies. We had some difficulty in clearly notating the duration of followup of patients in these studies, as the data were often reported within a single study in many different forms, with

results reported separately for patients with different lengths of followup. We chose not to quantitatively pool these data because there was marked qualitative heterogeneity between studies, and pooling data from observational studies is even more problematic than combining results from trials. We do not consider this a limitation of our approach, but it did make the results more challenging to report in a succinct fashion.

Research in Progress

We identified eight studies that are in progress by searching www.clinicaltrials.gov, which is a service of the National Institutes of Health. These studies are detailed in Appendix C[*], Evidence Table 29. Six of these studies are interventional, and two are observational. The BABY-HUG study is a Phase III randomized trial treating children from 9 months to 18 months old with hydroxyurea or placebo in order to look for a reduction in rates of damage to the major organs during followup. Study recruitment began in October, 2003 and ended in June, 2007. The study was designed to enroll 200 randomized participants. As of October 4, 2007, 233 patients had entered the screening process, 191 were eligible to begin study treatment, 191 had started study treatment, and 59 had completed 2 years of study treatment.

The SWiTCH study is enrolling children with severe disease into a randomized trial of transfusions and chelation versus hydroxyurea and phlebotomy. The primary outcomes are secondary stroke and iron overload. Study recruitment began in October, 2006 at 21 sites across the United States. As of October 4, 2007, a total of 114 patients had been screened, 80 had consented to enrollment, and 52 had been randomized to treatment. The study target is 130 randomized patients.

A small observational study in Israel will assess long-term outcomes in patients with Hb SS or SB thalassemia who have been treated with hydroxyurea for 5 to 12 years. The other observational study is expecting to enroll 285 patients and follow them prospectively for long-term outcomes. Details of this study from St. Jude Children's Research Hospital are sparse, but the long-term outcomes will include cellular and molecular outcomes. Of the interventional studies, three are funded by the National Heart, Lung, and Blood Institute, and two are funded by the FDA. One of the studies is a phase I study designed to look at the effect of hydroxyurea on morbidity and aerobic capacity in patients with chronic kidney disease and pulmonary hypertension. In this trial, erythropoetin will be administered as well. Another phase I/II study will use tricuspid regurgitant jet velocity as an endpoint to assess improvement in patients with pulmonary hypertension. Two trials were described as evaluating the use of clotrimazole with hydroxyurea, but these trials were listed as starting in 1997 and 1999, so we are uncertain if these trials are in progress or were never initiated.

In addition, analyses based on the MSH trial and the subsequent followup studies are continuing. From an e-mail communication with Bruce Barton, PhD, of the Maryland Medical Research Institute, we are aware of 17 analyses at various stages of development that will be extremely useful contributions to this body of knowledge. These are listed in Appendix C, Evidence Table 30, and include analyses of reproductive outcomes associated with the use of hydroxyurea, analgesia usage, pulmonary hypertension progression in patients on hydroxyurea, and others.

[*] Appendixes cited in this report are provided electronically at: http://www.ahrq.gov/clinic/tp/hydscdtp.htm

Future Research Needs

The studies described above should answer some of the important questions that remain, particularly regarding the use of hydroxyurea in infants and the role of this drug in reducing the risk of secondary stroke. However, there are still substantial research needs that relate to the use of hydroxyurea in patients with sickle cell disease.

The paucity of randomized trials suggests that additional RCTs with other clinical outcomes may be appropriate, including randomized trials that are aimed at preventing other complications of sickle cell disease, such as kidney disease, pulmonary hypertension, neurological events in adults, and psychiatric complications. Also, effectiveness trials are needed to assess the use of hydroxyurea in a regular care setting. These could be clustered randomized trials in which some providers are randomized to use hydroxyurea in all patients and other are randomized to usual care, including the use of hydroxyurea when clinically indicated, or effectiveness studies in which one group of providers is actively encouraged to consider hydroxyurea when appropriate and another clinic is not targeted for education.

Longer studies are needed to assess the toxicities of this drug. Studies are needed in which patients are treated for a longer time, as are studies in which patients are followed for a longer time, even if the treatment is discontinued. This design is most relevant to assessing outcomes with a long latency period, such as leukemia and secondary malignancies, including skin cancers. Certainly, it may not be feasible to run randomized trials for many years, so a well-designed prospective study may be the optimal design. A registry of users of hydroxyurea could also be considered if the data collection and followup can be sufficiently rigorous. Other toxicities requiring further study are the developmental toxicities and risk to subsequent generations that are described in detail in the CERHR report.

Many subgroups require further study, particularly patients with genotypes other than Hb SS. While there have been observational studies of patients with other genotypes, the randomized trials enrolled only patients with Hb SS. Patients with Hb SC were particularly understudied. Additional studies of hydroxyurea at doses other than the MTD are appropriate, particularly since the use of the MTD in resource-poor populations may be less practical. Effectiveness studies of the drug in resource-poor populations would be particularly beneficial. Other subgroups of interest are patients with comorbid illnesses, specifically HIV/AIDS and/or hepatitis C. The interactions between hydroxyurea and these underlying diseases, and between hydroxyurea and therapies for these diseases, need to be understood. Further research on the place of hydroxyurea in therapy is indicated, since the existing studies have not defined the optimal time for initiation of the drug or identified the indicators that a patient has “failed” therapy with hydroxyurea. Other questions remain to be answered: Is there a role for rechallenge with the drug if there was no previous efficacy? Is there a role for hydroxyurea as an adjunctive therapy with other drugs? What are the best intermediate outcomes that will predict clinical response to the drug?

Given that we have concluded that there is evidence to support the efficacy of hydroxyurea, there is clearly a need for further research on the barriers to the use of this drug. We identified no studies that specifically addressed this question. These studies should specifically aim to identify barriers at the level of the patient, at the level of the provider, and at a societal level, perhaps with special attention to adult patients. After these barriers are better characterized, interventions to overcome these barriers should be tested, including replication of the one promising study that

demonstrated improved receipt of routine care in patients with sickle cell disease. The barriers and intervention that we identified as influencing the use of other treatments in sickle cell disease may provide an appropriate starting point for further study, and comparative effectiveness studies may be appropriate as well, in particular for testing established interventions for improving pain control.

Implications

This systematic review has important implications for clinicians, policymakers, and researchers. Clinicians should be encouraged by the established efficacy of hydroxyurea in sickle cell anemia. This drug has been demonstrated to have favorable hematological effects that, importantly, have been shown to clearly translate into clinical benefits. These findings affect the care of both children and adults with sickle cell disease. However, clinicians must also be aware of the paucity of long-term safety data, although the scanty evidence that exists is somewhat reassuring. In addition, clinicians must appreciate that there is very little information available regarding many important clinical issues, including the optimal dose for producing the best clinical outcomes, as well as clear indicators for initiating therapy or for discontinuing therapy because of a poor response. The major gaps in our knowledge about hydroxyurea, described in this report, should motivate researchers to search for answers. Also, if this drug is shown to have long-term safety, research needs to be directed at testing interventions to overcome barriers to the use of this drug so that patients have the opportunity to enjoy its benefits.

One should consider in interpreting this report that this is the only FDA-approved medication for the treatment of sickle cell disease. This medication is not being evaluated for comparative effectiveness or comparative safety with reference to established therapies. It is the only available drug that alters the disease process, and therefore its toxicities or potential toxicities should be interpreted in this light, particularly since it is being used to treat a disease that has tremendous morbidity and predictably shortens patients' lifespan.

Although it was beyond the scope of this report to describe the funding challenges in sickle cell disease research, we note a recent article that describes the state of funding for such research.[186] In their paper, Smith et al. describe both federal and foundation funding for both sickle cell disease and cystic fibrosis. The report noted that even though cystic fibrosis affects fewer than half the number of Americans affected by sickle cell disease, there is a dramatic discrepancy in their funding. The total amount of funding from both private philanthropic support and NIH research support per person affected with sickle cell disease was found to be $1,130, as compared to $9,340 for each person affected by cystic fibrosis. The implication is that patients from racial minorities, and often a low-socioeconomic stratum, may not have the organizational strength and resources to command research dollars.

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List of Acronyms

Acronym	Definition
3TC	lamivodine
ABC/EFV/ddI	abacavir/efavirenz/didanosine
ACEI	angiotensin-converting enzyme inhibitors
ACS	acute chest syndrome
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine transferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ARV	antiretroviral
ASA	acetylsalicylic acid
AST	aspartate transaminase
AUC	area under the curve
BM	bone marrow
BMT	bone marrow transplant
BS/B-thal	hemoglobin S beta-thalassemia
Bu	busulfan
BUN	blood urea nitrogen
CA	cancer
CAR	Central African Republic Haplotype
CBT	cognitive behavioral therapy
CCNU	lomustine
CCT	clinically controlled trial
CERHR	Center for the Evaluation of Risks to Human Reproduction
CI	confidence interval
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CSSCD	Cooperative Study of Sickle Cell Disease
d4t	didehydrodeoxythymidine
ddI	didanosine
DH	day hospital
DNA	deoxyribonucleic acid
dz	disease
ED	emergency department
EFV	efavirenz
EFW	estimated fetal weight
eGFR	estimated globular filtration rate
EPC	Evidence-based Practice Center
ER	emergency room
ET	essential thrombocythemia
FDA	Food and Drug Administration
f/u	follow-up
GI	gastrointestinal
GMP	Granual membrane protien
Hb	hemoglobin
Hb F	fetal hemoglobin
HIV	human immunodeficiency virus
HPRT	hypoxanthine phosphoribosyl transferase
HR	hazard ratio
HTN	hypertension
HU	hydroxyurea
HUG KIDS	pediatric hydroxyurea safety trial
HUSOFT	The Hydroxyurea Safety and Organ Toxicity trial
IBW	isobutyramide
IDV	indinavir
IFN	Interferon

IMF	idiopathic myelofibrosis
IR	index of rigidity
IV	intravenous
JHU	Johns Hopkins University
LACA	left anterior cerebral artery
LMCA	left main coronary artery
LOS	length of stay
LPCA	left posterior cerebral artery
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MeSH	medical subject heading
MF	myelofibrosis
MPD	myeloproliferative disorders
MRIs	magnetic resonance imaging
MSH	Multicenter Study of Hydroxyurea for Sickle Cell Anemia
MTD	maximum tolerated dose
NA	not applicable
NEJM	New England Journal of Medicine
NHLBI	National Heart, Lung, and Blood Institute
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NR	not reported
NA	not applicable
NS	not specified
NTP	National Toxicology Program
OCP	oral contraceptive pill
OMAR	Office of Medical Applications of Research
OR	odds ratio
PBMC	peripheral blood mononuclear cells
PDF	portable document format
PHTN	pulmonary hypertension
PI	pipobraman
plt	platelet
PP	pre/post
preg	pregnancy
PV	polycythemia vera
PVSG	Polycythemia Vera Study Group
QOD	4 times per day
RACA	right anterior cerebral artery
RBC	red blood cells
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RMCA	right main cerebral artery
RPCA	right posterior cerebral artery
RR	relative risk
S ß+ thal	sickle ß+ thalassemia
S ßº thal	sickle ßº thalassemia
S α+ thal	sickle α+ thalassemia
S/O	hemoglobin SO Arab
SA	substance abuse
SC	sickle-hemoglobin C disease
SCA	sickle cell anemia
SCD	sickle cell disease
SD	standard deviation
SEM	standard error of the mean
SS	sickle Hemoglobin SS Disease
SWiTCH	Stroke With Transfusions Changing to Hydroxyurea
TCD	transcranial Doppler
TIA	transient ischemic attack
trans	Transfusion
UGTIA	uridine diphosphoglucuronate glycuronosyltransferase 1A
ULN	upper limit of normal

ULT	upper limit
VOC	vaso-occlusive crisis
WBC	white blood cells
WHO	World Health Organization
ZDV	Zidovudine

Appendix A: Detailed Search Strategies

MEDLINE

Search String	Returns
(“Anemia, Sickle Cell”[MeSH] OR “sickle cell”[tiab]) AND (“Hydroxyurea”[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	5708
(“Hydroxyurea”[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab]) AND ("Drug Toxicity"[MeSH] OR "drug toxicity"[tiab] OR toxicity[tiab] OR harm[tiab] OR "adverse event"[tiab] OR neoplasms[mh] OR neoplasm*[tiab] OR malignancy[tiab] OR cancer[tiab] OR "Leg Ulcer"[MeSH] OR "leg ulcer"[tiab] OR "Nausea"[MeSH] OR nausea[tiab] OR vomit*[tiab] OR "Alopecia"[MeSH] OR "hair loss"[tiab] OR myelosuppression[tiab] OR (delay[tiab] AND (development*[tiab] OR growth[tiab])) OR teratogen*[tiab] OR "Safety"[MeSH] OR safety[tiab] OR "Leukemia"[MeSH] OR leukemia[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	
("Anemia, Sickle Cell"[MeSH] OR "sickle cell"[tiab]) AND ("Hydroxyurea"[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab] OR "Phenylbutyrates"[MeSH] OR "sodium phenylbutyrate"[tiab] OR arginine[mh] OR butyrate[mh] OR "arginine butyrate"[tiab] OR "decitabine"[Substance Name] OR decitabine[tiab] OR "Azacitidine"[MeSH] OR azacitidine[tiab] OR azacytidine[tiab] OR "5-azacitidine"[tiab] OR "5-azacytidine"[tiab] OR "Penicillins"[MeSH] OR penicillin[tiab] OR "Folic Acid"[MeSH] OR "folic acid"[tiab] OR folate[tiab] OR "Vaccines"[MeSH] OR "Vaccination"[MeSH] OR vaccine*[tiab] OR "iron chelation"[tiab] OR (("Iron"[MeSH] OR iron[tiab] or Fe[tiab]) AND ("Chelation Therapy"[MeSH] OR "Therapeutics"[MeSH] OR "chelation therapy"[tiab])) OR "Nutrition Therapy"[MeSH] OR "nutrition therapy"[tiab] OR "nutrition counseling"[tiab] OR ("Pain"[MeSH] AND management[tiab]) OR "pain management"[tiab] OR "Dental Care for Chronically Ill"[MeSH] OR "chronic transfusion"[tiab] OR (chronic[tiab] AND transfusion[tiab]) OR "Bone Marrow Transplantation"[MeSH] OR "bone marrow transplant*"[tiab] OR treatment[tiab] OR "Patient Care Management"[MeSH] OR "case management"[tiab]) AND ("Health Policy"[MeSH] OR "Ethics"[MeSH] OR ethic*[tiab] OR "Delivery of Health Care"[MeSH] OR "delivery of health care"[tiab] OR "health care delivery"[tiab] OR "Social Support"[MeSH] OR "Psychology"[MeSH] OR psychology[tiab] OR bias[tiab] OR "Psychology"[MeSH] OR "Costs and Cost Analysis"[MeSH] OR cost[tiab] OR "Health behavior"[MeSH] OR communication[tiab] OR Barrier*[tiab] OR "patient satisfaction"[tiab] OR "Comorbidity"[MeSH] OR comorbidity[tiab] OR "Depression"[MeSH] OR depression[tiab] OR "socioeconomic status"[tiab] OR "Social Support"[MeSH Major Topic] OR "family support"[tiab] OR "Education"[MeSH] OR education[tiab] OR "Insurance, Health, Reimbursement"[MeSH] OR "Quality of Health Care"[MeSH] OR "quality of care"[tiab] OR "practice pattern"[tiab] OR "disease severity"[tiab] OR burden[tiab] OR "cognitive ability"[tiab] OR respect[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	
(“Anemia, Sickle Cell”[MeSH] OR “sickle cell”[tiab] OR "Thrombocythemia, Hemorrhagic"[MeSH] OR “essential thrombocythemia”[tiab]) AND (“Hydroxyurea”[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	
("Anemia, Sickle Cell"[MeSH] OR "sickle cell"[tiab]) AND ("Health Policy"[MeSH] OR "Ethics"[MeSH] OR ethic*[tiab] OR "Delivery of Health Care"[MeSH] OR "delivery of health care"[tiab] OR "health care delivery"[tiab] OR "Social Support"[MeSH] OR "Psychology"[MeSH] OR psychology[tiab] OR bias[tiab] OR "Psychology"[MeSH] OR "Costs and Cost Analysis"[MeSH] OR cost[tiab] OR "Health behavior"[MeSH] OR communication[tiab] OR Barrier*[tiab] OR "patient satisfaction"[tiab] OR "Depression"[MeSH] OR depression[tiab] OR "socioeconomic status"[tiab] OR "Social Support"[MeSH Major Topic] OR "family support"[tiab] OR "Education"[MeSH] OR education[tiab] OR "Insurance, Health, Reimbursement"[MeSH] OR "Quality of Health Care"[MeSH] OR "quality of care"[tiab] OR "practice pattern"[tiab] OR burden[tiab] OR respect[tiab] OR religion[MeSH] OR spirituality[tiab] OR religion[tiab] OR “internal-external control”[MeSH]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	

EMBASE

Search String	Returns
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(“Hydroxyurea”[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab]) AND ("Drug Toxicity"[MeSH] OR "drug toxicity"[tiab] OR toxicity[tiab] OR harm[tiab] OR "adverse event"[tiab] OR neoplasms[mh] OR neoplasm*[tiab] OR malignancy[tiab] OR cancer[tiab] OR "Leg Ulcer"[MeSH] OR "leg ulcer"[tiab] OR "Nausea"[MeSH] OR nausea[tiab] OR vomit*[tiab] OR "Alopecia"[MeSH] OR "hair loss"[tiab] OR myelosuppression[tiab] OR (delay[tiab] AND (development*[tiab] OR growth[tiab])) OR teratogen*[tiab] OR "Safety"[MeSH] OR safety[tiab] OR "Leukemia"[MeSH] OR leukemia[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	
("Anemia, Sickle Cell"[MeSH] OR "sickle cell"[tiab]) AND ("Hydroxyurea"[MeSH] OR hydroxyurea[tiab] OR hydrea[tiab] OR hydroxycarbamide[tiab] OR "Phenylbutyrates"[MeSH] OR "sodium phenylbutyrate"[tiab] OR arginine[mh] OR butyrate[mh] OR "arginine butyrate"[tiab] OR "decitabine"[Substance Name] OR decitabine[tiab] OR "Azacitidine"[MeSH] OR azacitidine[tiab] OR azacytidine[tiab] OR "5-azacitidine"[tiab] OR "5-azacytidine"[tiab] OR "Penicillins"[MeSH] OR penicillin[tiab] OR "Folic Acid"[MeSH] OR "folic acid"[tiab] OR folate[tiab] OR "Vaccines"[MeSH] OR "Vaccination"[MeSH] OR vaccine*[tiab] OR "iron chelation"[tiab] OR (("Iron"[MeSH] OR iron[tiab] or Fe[tiab]) AND ("Chelation Therapy"[MeSH] OR "Therapeutics"[MeSH] OR "chelation therapy"[tiab])) OR "Nutrition Therapy"[MeSH] OR "nutrition therapy"[tiab] OR "nutrition counseling"[tiab] OR ("Pain"[MeSH] AND management[tiab]) OR "pain management"[tiab] OR "Dental Care for Chronically Ill"[MeSH] OR "chronic transfusion"[tiab] OR (chronic[tiab] AND transfusion[tiab]) OR "Bone Marrow Transplantation"[MeSH] OR "bone marrow transplant*"[tiab] OR treatment[tiab] OR "Patient Care Management"[MeSH] OR "case management"[tiab]) AND ("Health Policy"[MeSH] OR "Ethics"[MeSH] OR ethic*[tiab] OR "Delivery of Health Care"[MeSH] OR "delivery of health care"[tiab] OR "health care delivery"[tiab] OR "Social Support"[MeSH] OR "Psychology"[MeSH] OR psychology[tiab] OR bias[tiab] OR "Psychology"[MeSH] OR "Costs and Cost Analysis"[MeSH] OR cost[tiab] OR "Health behavior"[MeSH] OR communication[tiab] OR Barrier*[tiab] OR "patient satisfaction"[tiab] OR "Comorbidity"[MeSH] OR comorbidity[tiab] OR "Depression"[MeSH] OR depression[tiab] OR "socioeconomic status"[tiab] OR "Social Support"[MeSH Major Topic] OR "family support"[tiab] OR "Education"[MeSH] OR education[tiab] OR "Insurance, Health, Reimbursement"[MeSH] OR "Quality of Health Care"[MeSH] OR "quality of care"[tiab] OR "practice pattern"[tiab] OR "disease severity"[tiab] OR burden[tiab] OR "cognitive ability"[tiab] OR respect[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT “meta-analysis”[pt]	
((((('sickle cell anemia'/exp) OR ('sickle cell':ti,ab) OR ('thrombocythemia'/exp) OR ('essential thrombocythemia':ti,ab)) AND (('hydroxyurea'/exp) OR (hydroxyurea:ti,ab) OR (hydrea:ti,ab) OR (hydroxycarbamide:ti,ab))) AND english:la) NOT ((review:it) OR ('meta analysis':it)) AND [humans]/lim	
((((('sickle cell anemia'/exp) OR ('sickle cell':ti,ab)) AND (('health policy'/exp) OR ('ethics'/exp) OR ('delivery of healthcare':ti,ab) OR ('health care delivery':ti,ab) OR ('social support'/exp) OR ('social support':ti,ab) OR ('psychology'/exp) OR (psychology:ti,ab) OR ('health care cost'/exp) OR (cost:ti,ab) OR ('health behavior'/exp) OR ('communication':ti,ab) OR (barrier:ti,ab) OR ('patient satisfaction'/exp) OR ('depression'/exp) OR (depression:ti,ab) OR ('social class'/exp) OR ('socioeconomic status':ti,ab) OR ('education'/exp) OR (education:ti,ab) OR ('health insurance'/exp) OR ('health insurance':ti,ab) OR ('health care quality'/exp) OR (burden:ti,ab) OR (respect:ti,ab) OR ('religion'/exp) OR (religion:ti,ab) OR ('control'/exp))) AND english:la) NOT ((review:it) OR ('meta analysis':it)) AND [humans]/lim	

TOXLine

Search String	Returns
((hydroxyurea OR hydrea OR hydroxycarbamide OR 127-07-1 [rn]) NOT ("in vitro" OR (animals) OR pregnant OR (pregnancy) OR reproductive OR (child) OR pediatric OR (adolescent))) AND (eng [la]) AND (BIOSIS [org] OR CIS [org] OR CRISP [org] OR EPIDEM [org] OR FEDRIP [org] OR IPA [org] OR MTGABS [org] OR PubMed [org] OR RISKLINE [org] OR TSCATS [org])	1602

CINAHL

Search String	Returns
(MM hydroxyurea or TX hydroxyurea or TX hydrea or TX hydroxycarbamide) and (MM ("drug toxicity" or "adverse drug event" or neoplasms or "leg ulcer" or nausea or alopecia) or TX ("drug toxicity" or "adverse drug event" or neoplasms or "leg ulcer" or nausea or alopecia or malignancy or cancer or vomiting or "hair loss" or myelosuppression))	231
(MM "anemia, sickle cell" or TX "sickle cell" or TX thrombocythemia) and (MM (Hydroxyurea or arginine or vaccines or “dental care for chronically ill” or “case management”) or TX (folate or “iron chelation” or “chronic transfusion”))	
((MM "anemia, sickle cell" or TX "sickle cell" or TX thrombocythemia)) and (MM (“practice pattern” or “insurance, health, reimbursement” or education or “support, psychosocial” or depression or communication or “health behavior” or “cost and cost analysis” or “health care costs” or “health care delivery” or ethics or “health policy” thrombocythemia) or TX (“social support” or bias or barriers or “socioeconomic status” or support or “disease severity”))	

Handsearching = 5 returns

Appendix B

Previewing Only: You cannot submit data from this form

Previewing at Level 3

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

ARTICLE Review Form

Does this article POTENTIALLY apply to any of the Key Questions?

1. **NO, this article DOES NOT apply to any of the Key Questions** (check all of the following reasons that apply):

- [ ] no original data (include ineligible reviews in this category)
- [ ] in vitro only
- [ ] too small-case report or case series of < 20 unless it is PRIMARILY reporting toxicities
- [x] not relevant to key questions
- [ ] other: specify

2. **ARTICLE OF INTEREST (does not apply to key questions)**

- ( ) Pull article for hand searching or reference
- ( ) Not relevant to project but please tag

Clear Selection

This article MAY apply to one or more of the Key Questions, choose all that apply. (identify which key question an article applies to AND the subquestion it applies to)

Key Question 1

What is the evidence regarding efficacy of hydroxyurea treatment for patients with SCD?

Key Question 1	This is a study of patients with **sickle cell anemia**, taking **HU alone or in combination** and is a:
( ) Applies to KQ1 Clear Selection	[ ] Controlled trial or randomized trial of any size [ ] Case series/cohort involving > or = 20 patients [ ] Small Case series involving < 20 patients with sickle cell but leukemia or malignancy is mentioned as an outcome despite this being an effectiveness study [ ] Study of biomarkers in > or = 20 patients on HU

Key Question 2

What is the evidence regarding effectiveness of hydroxyurea treatment for patients with SCD?

Key Question 2	This is a study of patients with **sickle cell anemia**, taking **HU alone or in combination** and is a:
( ) Article applies to KQ2 Clear Selection	[ ] Controlled trial or randomized trial of any size in a community or primary care setting [ ] Case series/cohort involving > or = 20 patients [ ] Small Case series involving < 20 patients with sickle cell but leukemia or malignancy is mentioned as an outcome despite this being an effectiveness study

	☐ Study of biomarkers in > or = 20 patients on HU

Key Question 3

What is the evidence regarding the short- and long-term harms of hydroxyurea treatment?

Key Question 3	This study is:
○ Applies to KQ3 Clear Selection	☐ Any study design, any size, describing toxicities of HU *alone or in combination* in sickle cell anemia ☐ Observational studies (> or = 20) of HU *alone* in CML/ET/PV/HIV/psoriasis/etc. including desription of toxicities ☐ Case report or small case series (<20) ***primarily*** describing toxicities of HU *alone* in these other diseases (CML/ET/PV/HIV/psoriasis/etc) ☐ Controlled trials or randomized trials (two or more arms): in CML/ET/PV/psoriasis where the comparison is HU vs. anything including placebo (must have at least 20 patients in the HU alone arm) ☐ Controlled trials or randomized trials (two or more arms): in HIV where the comparison is: HU vs. HIV drugs; HU vs. HU/HIV drugs; HU vs. no drug (must have at least 20 patients in the HU alone arm)

Key Question 4

What barriers to the use of therapies for treatment of SCD have been investigated and what is the evidence that these purported barriers influence use of these treatments?

Key Question 4	This study is:
○ Applies to KQ4 Clear Selection	☐ Any study design with primary data about the *test of an intervention to overcome barriers to care* that interfere with 1) receipt of medication, 2) receipt of scheduled care, 3) adherence to mediciation ☐ Any study design in which *barriers to care* were investigated as affecting 1) receipt of medication, 2) receipt of scheduled care, 3) adherence to mediciation ☐ Any study design in which patients/providers/family report what they perceive to be barriers to 1) receipt of medication, 2) receipt of scheduled care, 3) adherence to mediciation ☐ Any study design with primary data about the existence of the barriers in our causal diagram*

*we are not collecting studies about the existence of a) cognitive difficulties, b) genotype differences, c) disease severity, d) comorbidities unless these are described specifically as barriers to care

11. **Reviewer Comments**

Enlarge Shrink

Submit Data

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Previewing at Level 9

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

Key Question 4

What barriers to the use of therapies for treatment of SCD have been investigated and what is the evidence that these purported barriers influence use of these treatments?

This form is to be filled out for ALL studies applying to KQ4

1. Does study provide evidence: (check all that apply)

- ☐ for the existence of putative barrier **(D)**
- ☐ for patients/providers reports of barriers **(C)**
- ☐ that a (putative or other) barrier is a barrier **(B)**
- ☐ for the effectiveness of an intervention to overcome a barrier? **(A)**

2. Study Design

- ○ RCT
- ○ CCT
- ○ Pre-post intervention evaluation
- ○ Descriptive--quantitative
- ○ Descriptive--qualitative
- ○ Descriptive--Mixed

Clear Selection

3. Nurses	4. Physicians	5. Other Health Professionals	6. Patients	7. Family/caregivers
☐ mixed or unspecified	☐ unspecified or mixed	☐ PA	○ check here if this population is providing data	○ specify
☐ inpatient	☐ hematologists	☐ social worker	Clear Selection	Clear Selection
☐ outpatient	☐ ED doctors	☐ other		
☐ ED	☐ internists			
☐ other	☐ pediatricians			
	☐ physiciens-in-training			
	☐ other			

Population characteristics of each category identified above

Population characteristics of PATIENTS only

8. N	9. Age	10. Gender	11. Race	12. Genotype	13. Substance use	14. Socioeconomic status
Enlarge Shrink	Mean	Male, n (%)	White (non-hispanic), n (%)	SS, n (%)	Alcohol user, n (%)	Low, define
	Median	Female, n (%)	Black (non-hispanic), n (%)	SC, n (%)	Smoker, n (%)	n (%)
	Range		White hispanic, n (%)	S ß+ thalassemia, n (%)	Illegal dug user, n (%)	Middle, define
			Black hispanic, n (%)	S ß^0 thalassemia, n (%)		n (%)
			Latino/Hispanic, n (%)	other, define, n (%)		High, define
			Asian/Pacific Islander, n (%)			n (%)
			Other (specify), n (%)			

Population characteristics of NON-PATIENTS only

	describe	n	sex	race
15. Category 1				
16. Category 2				
17. Category 3				
18. Category 4				

Type of Barrier (check all that apply)

System	Patient	Provider	Other
☐ health system organization	☐ age	☐ provider race/ethnicity	specify
			specify

insurance	health beliefs	speciality	
costs	risk tolerance	respect for patients	specify
continuity of care	depression	outcome expectancy	specify
access to providers	distrust	familiarity	
patient-provider communication	self-efficacy	practice Patterns	
quality of pain management	substance abuse	risk tolerance	
	preferences	attitudes	
	genotype	time constraints	
	knowledge	knowledge	
	SES	resources	
	burden	monitoring burden	
	family/social support	training	
	cognitive abilities	self-efficacy	
	disease severity	inertia	
	comorbid conditions		
	pseudoaddiction		

For A, B, and C ONLY

23. Type of outcome measure (check all that apply)

- Attendence at scheduled provider visits
- Receipt of medications
- Adherence to medications

24. If outcome measure is about use of a medication/therapy: (check all that apply)

- hydroxyurea
- folate
- penicillin
- iron chelators
- transplant
- transfusion
- vaccines
- other drugs (arginine,azacitine, sodium butyrate, decitabine)
- dental care
- pain management regimen
- other, specify
- not specified

For A and B ONLY

25. How was the Outcome Measured? (check all that apply)

- Patient report
- Provider report
- Family report
- Administrative data
- Biologic outcome, specify (e.g tooth decay, HgF, etc.)
- Other, specify

For A Only

26. Objective of intervention (concisely write in)

Enlarge Shrink

27. Description of the intervention including a brief description of any control population (concisely write in)

Enlarge Shrink

28. Reviewer interpretation of data from intervention studies:

- [ ] Improvement as a results of the intervention
- [ ] Partial improvement as a results of the intervention
- [ ] No improvement as a results of the intervention
- [ ] Worsening as a results of the intervention

For ALL KQ 4 Studies

29. Main Results (concisely write in)

Enlarge Shrink

30.

Comments

Enlarge Shrink

Submit Data

Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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Previewing at Level 11

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

QUALITY FORM
JADAD (quality for controlled trials)

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? *In other words, was the allocation concealed?*

Hint: appropriate methods of randomization are computer-generated random numbers, random number tables (if unspecified, don't give them a +1 or a -1)

- Yes
- No

Clear Selection

2. If the answer to question #1 is "yes," then answer the following:

- Was the method used to generate the sequence of randomization described and it was appropriate? (+1)
- Was the method of randomization was described but it was inappropriate? (-1)
- Neither a nor b

Clear Selection

3. Was the study described as double blind? *In other words, were the outcome assessors blind in addition to the patients?*

- Yes
- No

Clear Selection

4. If the answer to question #3 is "yes," then answer the following:

- the method of double blinding was described and it was appropriate (+1)
- the study was described as being blind but the method of blinding was inappropriate (-1)

Clear Selection

5. Was there a description of withdrawals and dropouts?

- Yes
- No

Clear Selection

Did the study report the number lost to follow-up?

	Yes (enter "n")	No
6. Arm 1		Clear
7. Arm 2		Clear
8. Arm 3		Clear

9. Arm 4 Clear

Submit Data

Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
10. QUALITY--observational studies
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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Form Last Modified: Not available

Previewing Only: You cannot submit data from this form

Previewing at Level 12

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

QUALITY FORM
Qualitative Research

1. How were the data generated? (Check all that apply)

- [ ] Field observation/participant observation
- [ ] In-depth interviews
- [ ] Focus groups
- [ ] Document analysis
- [ ] Other _____

2. Is there a description of the theoretical basis for the study?

- ( ) No
- ( ) To some extent
- ( ) Yes, with description of a named theory or presentation of a causal diagram

Clear Selection

3. Is there description of why these participants were selected?

- ( ) No
- ( ) To some extent
- ( ) Yes, with detailed description: *how these specific people are expected to contribute, conditions which make them eligible for study*

Clear Selection

4. Did the researchers compose the focus groups or interview setting to maximize data gathering (ensuring patient comfort, confidentiality, choice of appropriate interviewer or techniques for data gathering)?

- ( ) No or can't tell
- ( ) To some extent
- ( ) Yes, with detailed description

Clear Selection

5. Do the authors report theme exhaustion (continuing the discussion until no new themes emerge)?

- ( ) NA
- ( ) No
- ( ) To some extent
- ( ) Yes, with detailed description

Clear Selection

6. Has the author rendered transparent the processes by which data have been collected, analyzed and presented? (can be audited, verified)

- ( ) No

- To some extent
- Yes: *detailed description of theoretical, methodological and analytic decisions*

Clear Selection

7. Do the authors describe their own biases? (also called reflexivity)

- No
- To some extent
- Yes, with detailed description

Clear Selection

8. Is there any use of triangulation, i.e. gathering of additional data to provide a more complete picture of the participants' world and experiences? An additional piece of the puzzle?

- No mention
- To some extent
- Yes, with detailed description of the source of additional data and how it corroborates observed results

Clear Selection

9. Do the authors synthesize, interpret, or develop a concept, model, or theory based on the subjective data collected?

- No (just present raw material)
- To some extent (just synthesis of data)
- Yes, well-developed interpretation of how reports support model

Clear Selection

Submit Data

Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
13. QUALITY--surveys
19. Renee data abstraction

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Previewing at Level 13

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

QUALITY FORM
Surveys

1.
What data collection methods were used in the study? (Check all that apply)

- [ ] Self-administered questionnaire
- [ ] Mailed questionnaire
- [ ] Group-administered setting
- [ ] Face-to-face interviews
- [ ] Telephone interviews
- [ ] Computer or computer assisted device (CAD)
- [ ] Other/unclear

2. Did the study describe the setting or population from which the study sample was drawn?

- ( ) No
- ( ) To some extent
- ( ) Yes, with detailed description: *setting (e.g., clinic), location, and dates*

Clear Selection

3. Were the inclusion or exclusion criteria described? (just saying “sickle cell disease” is insufficient)

- ( ) No
- ( ) To some extent
- ( ) Yes, with detailed description: *methods for selection of participants, or inclusion/exclusion criteria, or diagnostic criteria for enrollment*

Clear Selection

4. Does the study describe key characteristics of study participants at enrollment/baseline?

- ( ) No
- ( ) To some extent
- ( ) Yes, with detailed description: *ages, sex, genotype, relevant comorbidities which would influence outcomes*

Clear Selection

5. What is the survey completion rate?

- ( ) Can’t calculate
- ( ) n/N
- ( ) %

Clear Selection

6. Is there a statement that the authors used a previously validated instument?

- ( ) No

- To some extent (provides a reference)
- Yes, providees a reference and states that it was validated in the sickle cell population

Clear Selection

7.

Is there any discussion of the **validity** of the survey instrument (any one is sufficient)

- NA--this is NOT an option do not select this answer!
- No
- Yes. Only poor discussion of validity or good discussion with poor validity
- Yes, good definition and high validity

Clear Selection

Face / content validity	Degree to which an instrument accurately represents the skill or characteristic it is designed to measure, based on people's experience and available knowledge
Concurrent criterion validity	Degree to which an instrument produces the same results as another accepted or proven instrument that measures the same variable
Predictive criterion validity	Degree to which a measure accurately predicts expected outcomes
Construct validity	Degree to which a test measures the theoretical construct it intends to measure

8. Is there any discussion of the **reliability** of the survey insturment? (any one is sufficient)

- No
- Yes. Only poor discussion of reliability or good discussion with poor reliability
- Yes, good discussion and high reliability

Clear Selection

Intra-rater reliability	Degree to which measurements are the same when repeated by the same person
Inter-rater reliability	Degree to which measurements are the same when obtained by the different persons
Test-retest reliability	Degree to which the same test produces the same results when repeated under the same conditions
Equivalence reliability	Degree to which alternate forms of the same measurement instrument produce the same results
Internal consistency (inter-item) reliability	How well items reflecting the same construct yield similar results

Submit Data

Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
19. Renee data abstraction

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Previewing at Level 1

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

1. Does this article POTENTIALLY apply to ANY of the Key Questions

- YES--this article POTENTIALLY applies
- NO--this article DOES NOT apply

Clear Selection

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Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Submit Data

Key Question 3
Causality Form for Toxicity Case Reports

Case 1

1. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

2. Age

years:

3. Sex:

- ( ) Male
- ( ) Female

Clear Selection

4. Is the treated patient a child (under 18) or an adult?

- ( ) Child
- ( ) Adult

Clear Selection

5. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
6. Is the time relationship from drug administration to the event *plausible* for causality to be established?	( )	( )	Clear
7. Is there an absence of concurrent diseases or other drugs that may have caused the event?	( )	( )	Clear
8. Is there a reasonable response to drug withdrawal?	( )	( )	Clear
9. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	( )	( )	Clear

10. Duration of Treatment

Enlarge Shrink

11. Time to occurene of toxicity

Enlarge Shrink

Case 2
DO NOT fill in this portion of the form if only 1 case is reported

12. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

13. Age

years:

14. Sex:

- ◯ Male
- ◯ Female

Clear Selection

15. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

16. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
17. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
18. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
19. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
20. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

21. Duration of Treatment

Enlarge Shrink

22. Time to occurene of toxicity

Enlarge Shrink

Case 3
DO NOT fill in this portion of the form if only 1 case is reported

23. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

24. Age

years:

25. Sex:

- ( ) Male
- ( ) Female

Clear Selection

26. Is the treated patient a child (under 18) or an adult?

- ( ) Child
- ( ) Adult

Clear Selection

27. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
28. Is the time relationship from drug administration to the event *plausible* for causality to be established?	( )	( )	Clear
29. Is there an absence of concurrent diseases or other drugs that may have caused the event?	( )	( )	Clear
30. Is there a reasonable response to drug withdrawal?	( )	( )	Clear
31. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	( )	( )	Clear

32. Duration of Treatment

Enlarge Shrink

33. Time to occurene of toxicity

Enlarge Shrink

Case 4
DO NOT fill in this portion of the form if only 1 case is reported

34. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

35. Age

years:

36. Sex:

- ◯ Male
- ◯ Female

Clear Selection

37. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

38. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
39. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
40. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
41. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
42. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

43. Duration of Treatment

Enlarge Shrink

44. Time to occurene of toxicity

Enlarge Shrink

Case 5

DO NOT fill in this portion of the form if only 1 case is reported

45. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

46. Age

years:

47. Sex:

- ◯ Male
- ◯ Female

Clear Selection

48. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

49. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
50. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
51. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
52. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
53. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

54. Duration of Treatment

Enlarge Shrink

55. Time to occurene of toxicity

Enlarge Shrink

Case 6

DO NOT fill in this portion of the form if only 1 case is reported

56. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

57. Age

years:

58. Sex:

- ◯ Male
- ◯ Female

Clear Selection

59. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

60. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
61. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
62. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
63. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
64. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

65. Duration of Treatment

Enlarge Shrink

66. Time to occurene of toxicity

Enlarge Shrink

Case 7

DO NOT fill in this portion of the form if only 1 case is reported

67. What is the underlying disease?

- [ ] Sickle cell anemia

- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

68. Age

years:

69. Sex:

- ( ) Male
- ( ) Female

Clear Selection

70. Is the treated patient a child (under 18) or an adult?

- ( ) Child
- ( ) Adult

Clear Selection

71. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
72. Is the time relationship from drug administration to the event *plausible* for causality to be established?	( )	( )	Clear
73. Is there an absence of concurrent diseases or other drugs that may have caused the event?	( )	( )	Clear
74. Is there a reasonable response to drug withdrawal?	( )	( )	Clear
75. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	( )	( )	Clear

76. Duration of Treatment

Enlarge Shrink

77. Time to occurene of toxicity

Enlarge Shrink

Case 8

DO NOT fill in this portion of the form if only 1 case is reported

78. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML

- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

79. Age

years:

80. Sex:

- ◯ Male
- ◯ Female

Clear Selection

81. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

82. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
83. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
84. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
85. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
86. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

87. Duration of Treatment

Enlarge Shrink

88. Time to occurene of toxicity

Enlarge Shrink

Case 9

DO NOT fill in this portion of the form if only 1 case is reported

89. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia

- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

90. Age

years:

91. Sex:

- ◯ Male
- ◯ Female

Clear Selection

92. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

93. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
94. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
95. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
96. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
97. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

98. Duration of Treatment

Enlarge Shrink

99. Time to occurene of toxicity

Enlarge Shrink

Case 10

DO NOT fill in this portion of the form if only 1 case is reported

100. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis

- [ ] Other cancer
- [ ] HIV
- [ ] Other

101. Age

years:

102. Sex:

- ( ) Male
- ( ) Female

Clear Selection

103. Is the treated patient a child (under 18) or an adult?

- ( ) Child
- ( ) Adult

Clear Selection

104. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
105. Is the time relationship from drug administration to the event *plausible* for causality to be established?	( )	( )	Clear
106. Is there an absence of concurrent diseases or other drugs that may have caused the event?	( )	( )	Clear
107. Is there a reasonable response to drug withdrawal?	( )	( )	Clear
108. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	( )	( )	Clear

109. Duration of Treatment

Enlarge Shrink

110. Time to occurene of toxicity

Enlarge Shrink

Case 11

DO NOT fill in this portion of the form if only 1 case is reported

111. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV

Other

112. Age

years:

113. Sex:

Male

Female

Clear Selection

114. Is the treated patient a child (under 18) or an adult?

Child

Adult

Clear Selection

115. What is the reported event?

Leg ulcer

Nail change

Rash

Cytopenia

Leukemia

Cytogenetic change

Other cancer

Birth defect

Other

Causality assessment

	Yes	No	
116. Is the time relationship from drug administration to the event *plausible* for causality to be established?			Clear
117. Is there an absence of concurrent diseases or other drugs that may have caused the event?			Clear
118. Is there a reasonable response to drug withdrawal?			Clear
119. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?			Clear

120. Duration of Treatment

Enlarge Shrink

121. Time to occurene of toxicity

Enlarge Shrink

Case 12

DO NOT fill in this portion of the form if only 1 case is reported

122. What is the underlying disease?

Sickle cell anemia

Thalessemia

CML

Polycythemia vera

Essential thrombocythemia

Leukemia

Psoriasis

Other cancer

HIV

Other

123. Age

years:

124. Sex:

- Male
- Female

Clear Selection

125. Is the treated patient a child (under 18) or an adult?

- Child
- Adult

Clear Selection

126. What is the reported event?

- Leg ulcer
- Nail change
- Rash
- Cytopenia
- Leukemia
- Cytogenetic change
- Other cancer
- Birth defect
- Other

Causality assessment

	Yes	No	
127. Is the time relationship from drug administration to the event *plausible* for causality to be established?	○	○	Clear
128. Is there an absence of concurrent diseases or other drugs that may have caused the event?	○	○	Clear
129. Is there a reasonable response to drug withdrawal?	○	○	Clear
130. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	○	○	Clear

131. Duration of Treatment

Enlarge Shrink

132. Time to occurene of toxicity

Enlarge Shrink

Case 13

DO NOT fill in this portion of the form if only 1 case is reported

133. What is the underlying disease?

- Sickle cell anemia
- Thalessemia
- CML
- Polycythemia vera
- Essential thrombocythemia
- Leukemia
- Psoriasis
- Other cancer
- HIV
- Other

134. Age

years:

135. Sex:

Male

Female

Clear Selection

136. Is the treated patient a child (under 18) or an adult?

Child

Adult

Clear Selection

137. What is the reported event?

Leg ulcer

Nail change

Rash

Cytopenia

Leukemia

Cytogenetic change

Other cancer

Birth defect

Other

Causality assessment

	Yes	No	
138. Is the time relationship from drug administration to the event *plausible* for causality to be established?			Clear
139. Is there an absence of concurrent diseases or other drugs that may have caused the event?			Clear
140. Is there a reasonable response to drug withdrawal?			Clear
141. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?			Clear

142. Duration of Treatment

Enlarge Shrink

143. Time to occurene of toxicity

Enlarge Shrink

Case 14

DO NOT fill in this portion of the form if only 1 case is reported

144. What is the underlying disease?

Sickle cell anemia

Thalessemia

CML

Polycythemia vera

Essential thrombocythemia

Leukemia

Psoriasis

Other cancer

HIV

Other

145. Age

years:

146. Sex:

Male

Female

Clear Selection
147. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection
148. What is the reported event?

- ☐ Leg ulcer
- ☐ Nail change
- ☐ Rash
- ☐ Cytopenia
- ☐ Leukemia
- ☐ Cytogenetic change
- ☐ Other cancer
- ☐ Birth defect
- ☐ Other

Causality assessment

	Yes	No	
149. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
150. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
151. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
152. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

153. Duration of Treatment

Enlarge Shrink
154. Time to occurene of toxicity

Enlarge Shrink

Case 15
DO NOT fill in this portion of the form if only 1 case is reported

155. What is the underlying disease?

- ☐ Sickle cell anemia
- ☐ Thalessemia
- ☐ CML
- ☐ Polycythemia vera
- ☐ Essential thrombocythemia
- ☐ Leukemia
- ☐ Psoriasis
- ☐ Other cancer
- ☐ HIV
- ☐ Other

156. Age

years:

157. Sex:

- ◯ Male
- ◯ Female

Clear Selection
158. Is the treated patient a child (under 18) or an adult?

- ◯ Child

Adult

Clear Selection

159. What is the reported event?

- Leg ulcer
- Nail change
- Rash
- Cytopenia
- Leukemia
- Cytogenetic change
- Other cancer
- Birth defect
- Other

Causality assessment

	Yes	No	
160. Is the time relationship from drug administration to the event *plausible* for causality to be established?			Clear
161. Is there an absence of concurrent diseases or other drugs that may have caused the event?			Clear
162. Is there a reasonable response to drug withdrawal?			Clear
163. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?			Clear

164. Duration of Treatment

Enlarge Shrink

165. Time to occurene of toxicity

Enlarge Shrink

Case 16

DO NOT fill in this portion of the form if only 1 case is reported

166. What is the underlying disease?

- Sickle cell anemia
- Thalessemia
- CML
- Polycythemia vera
- Essential thrombocythemia
- Leukemia
- Psoriasis
- Other cancer
- HIV
- Other

167. Age

years:

168. Sex:

- Male
- Female

Clear Selection

169. Is the treated patient a child (under 18) or an adult?

- Child
- Adult

Clear Selection

170. What is the reported event?

- [ ] Leg ulcer
- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
171. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
172. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
173. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
174. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

175. Duration of Treatment

Enlarge Shrink

176. Time to occurene of toxicity

Enlarge Shrink

Case 17

DO NOT fill in this portion of the form if only 1 case is reported

177. What is the underlying disease?

- [ ] Sickle cell anemia
- [ ] Thalessemia
- [ ] CML
- [ ] Polycythemia vera
- [ ] Essential thrombocythemia
- [ ] Leukemia
- [ ] Psoriasis
- [ ] Other cancer
- [ ] HIV
- [ ] Other

178. Age

years:

179. Sex:

- ◯ Male
- ◯ Female

Clear Selection

180. Is the treated patient a child (under 18) or an adult?

- ◯ Child
- ◯ Adult

Clear Selection

181. What is the reported event?

- [ ] Leg ulcer

- [ ] Nail change
- [ ] Rash
- [ ] Cytopenia
- [ ] Leukemia
- [ ] Cytogenetic change
- [ ] Other cancer
- [ ] Birth defect
- [ ] Other

Causality assessment

	Yes	No	
182. Is the time relationship from drug administration to the event *plausible* for causality to be established?	◯	◯	Clear
183. Is there an absence of concurrent diseases or other drugs that may have caused the event?	◯	◯	Clear
184. Is there a reasonable response to drug withdrawal?	◯	◯	Clear
185. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation?	◯	◯	Clear

186. Duration of Treatment

Enlarge Shrink

187. Time to occurene of toxicity

Enlarge Shrink

Submit Data

Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

Form took 1.0625 seconds to render
Form Creation Date: Not available
Form Last Modified: Not available

Previewing Only: You cannot submit data from this form

Previewing at Level 2

Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

Keywords:
No keywords available

Increase Font Size
Decrease Font Size

Abstract:
Hydroxyurea is a drug recently approved to treat sickle cell diseases. Hydroxyurea benefits the patients by increasing the level of fetal hemoglobin via a nitroxide radical pathway. Here, we report an unpaired-electron-delocalization approach to tune the stability of nitroxide radicals. In this approach, the substitution by an unsaturated alkyl group containing conjugated C=C double bonds for the hydrogen on the nitrogen atom attached to the hydroxyl of hydroxyurea can significantly increase its ability to generate nitroxide radical. Furthermore, the increase can be remarkably enhanced by increasing the number of conjugated C=C double bonds. For a hydroxyurea derivative that contains two conjugated C=C double bonds, the reaction rate to generate its radical is 118 times faster than that of hydroxyurea, and for a hydroxyurea derivative containing 20 conjugated C=C double bonds, the reaction rate to form its radical is 238 times faster than that of hydroxyurea. For this reason, hydroxyurea derivatives with conjugated C=C double bonds may constitute new potential drugs for the treatment of sickle-cell diseases.

Increase Font Size
Decrease Font Size

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ABSTRACT Review Form

Does this article POTENTIALLY apply to any of the Key Questions?

1. **NO, this article DOES NOT apply to any of the Key Questions** (check all of the following reasons that apply):

- [ ] not English
- [ ] no original data (include ineligible reviews in this category)
- [ ] animals only
- [ ] in vitro only
- [ ] case report or case series of less than 10 unless it is PRIMARILY reporting toxicities **{see below for details}**
- [x] not relevant to key questions
- [ ] other: specify

2. **ARTICLE OF INTEREST (does not apply to key questions)**

- ( ) Pull article for hand searching
- ( ) Not relevant to project but please tag

Clear Selection

3. **UNCLEAR**

- ( ) can not determine from abstract alone OR no abstract available

Clear Selection

4. **This article MAY apply to one or more of the Key Questions** (choose all that apply, ONLY if you have not marked any of the options above)

- [ ] Key Question 1: What is the evidence regarding efficacy of hydroxyurea treatment for patients with SCD?
- [ ] Key Question 2: What is the evidence regarding effectiveness of hydroxyurea treatment for patients with SCD?
- [ ] Key Question 3: What is the evidence regarding the short- and

long-term harms of hydroxyurea treatment?

☐ Key Question 4: What barriers to the use of therapies for treatment of SCD have been investigated and what is the evidence that these purported barriers influence use of these treatments? Specifically, what are barriers to use of treatments to increase hemoglobin F (hydroxyurea, sodium phenylbutyrate, arginine butyrate, decitibine, and 5-azacytidine); barriers to established therapies for disease-management (penicillin, folate, vaccinations, iron chelation, nutrition counseling, pain management, dental care, and chronic transfusions); and barriers to bone marrow transplantation?

Notes on Key Question 4

We think that we will have evidence in the following three evidence subgroups. These are ordered by what we consider to be the strength of this evidence for answering the question.

1. Evidence to support interventions for overcoming barriers to treatments.
2. Evidence about how named barriers are associated with 1) use of therapies, 2) biological outcomes, or 3) access to therapies
3. Evidence which describes the existence of the purported barriers. This will include:
    a. Description of the existence of elements from our causal diagram (whether described in the article as a "barrier" or not)
    b. Description of barriers where the respondent states that something is a barrier in that it interferes with receipt of care or interferes with optimal health

CASE SERIES RULES
1. Include biomarker studies ONLY IF IN 10 OR MORE.
2. Include effiicay studies ONLY IF IN 10 OR MORE
3. Efficacy study exception: can include if there are LESS THAN 10 if the abstract specifically states they observed LEUKEMIA OR OTHER MALIGNANCY
4. Include studies of less than 10 if they are PRIMARILY describing toxicities (skin rashes, leg ulcers, leukemia)

5. **Comments:**

Enlarge Shrink

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Refid: 10, Hu, Y. H. and Ruckenstein, E., Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements, *J Phys Chem B*, 2007

State: Excluded, Level: 2

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HYDROXYUREA TREATMENT FOR SICKLE CELL DISEASE

GENERAL FORM
Complete this form for all key questions.

1. This study is best described as (check all that apply):

- ☐ efficacy study: is in a controlled setting
- ☐ effectiveness study: is in a primary care setting, has less stringent eligibility criteria, reports on health outcomes rather than surrogate measures, describes how the drug is used in practice
- ☐ toxicity study

Study Characteristics

2. Study design

- ○ RCT
- ○ Cohort with a comparison arm
- ○ Case series
- ○ Case-control
- ○ Case report--individually describes patients **do not continue filling out this form**
- ○ Other

Clear Selection

3. Study location

- ☐ United States/Canada
- ☐ Europe
- ☐ Central/South America/Mexico
- ☐ Carribean
- ☐ Middle East
- ☐ Southeast Asia
- ☐ Africa
- ☐ Other (specify)

4. Disease (check all that apply)

- ☐ Sickle cell anemia
- ☐ CML
- ☐ AML
- ☐ Polycythemis vera
- ☐ Essential thronbocytosis
- ☐ Psoriasis
- ☐ Solid tumors
- ☐ Thalasssemia
- ☐ HIV
- ☐ Other

5. Study Duration

- ☐ NA

Planned duration of treatment (include units)

6. Recruitment Period

Start date (mm/dd/yyyy)

End date (mm/dd/yyyy)

Duration (include units)

STUDY inclusion/exclusion criteria

	Inclusion	Exclusion	Specify
7. Age (specify)	☐	☐	
8. Race (specify)	☐	☐	
9. Sickle Cell Anemia	☐	☐	
10. Sickle ß+ thalassemia	☐	☐	
11. Sickle ß° thalassemia	☐	☐	
12. Sickle α+ thalassemia	☐	☐	
13. SC genotype	☐	☐	
14. Splenomegaly	☐	☐	
15. Neutropenia	☐	☐	
16. Leukopenia	☐	☐	
17. Transfusion dependant	☐	☐	
18. Pregnancy	☐	☐	
19. Opiod Use	☐	☐	

20. Substance abuse
21. Concurrent treatment with an antisickling agent
22. Pain episodes (include number and time period)
23. Cardiovascular event including stroke (define)
24. Renal failure
25. Liver failure
26. Sepsis
27. Acute chest syndrome (include n if available)
28. HIV+
29. Current medication use that can increase the toxicity of HU
30. Prior hydroxyurea treatment
31. Other (specify)
32. Other (specify)
33. Other (specify)
34. Other (specify)
35. Other (specify)
36. Other (specify)
37. Other (specify)
38. Other (specify)

39. Does this study contain more than 1 arm?

- Yes define arms (including control) below
- No proceed to patient characteristics--ONLY fill in ARM 1 information

Clear Selection

	Define (i.e., low dose HU, high dose HU, etc.)	Total N	Drug	Starting dose	Titration regimen
40. ARM 1 (HU or single arm)					
41. ARM 2					
42. ARM 3					
43. ARM 4					

Description of administered therapies:

ARM 1
ALWAYS use for HU
Use when only one set of data is available for study population

44. drugs(s)	45. # on MTD	46. Duration of therapy	47. concomittant therapy recieved	48. duration of observation	49. Indicator of adherence	50. denominator for outcomes (ITT if available)	51. frequency of monitoring labs (write in)
Enlarge Shrink	Enlarge Shrink	Months / mean / median	Enlarge Shrink	Months / mean / median	Please Select	Enlarge Shrink	Enlarge Shrink

ARM 2

52. drugs(s)	53. # on MTD	54. Duration of therapy	55. concomittant therapy recieved	56. duration of observation	57. Indicator of adherence	58. denominator for outcomes (ITT if available)	59. frequency of monitoring labs (write in)
Enlarge Shrink	Enlarge Shrink	Months / mean / median	Enlarge Shrink	Months / mean / median	Please Select	Enlarge Shrink	Enlarge Shrink

ARM 3

60. drugs(s)	61. # on MTD	62. Duration of therapy	63. concomittant therapy recieved	64. duration of observation	65. Indicator of adherence	66. denominator for outcomes (ITT if available)	67. frequency of monitoring labs (write in)
Enlarge Shrink	Enlarge Shrink	Months / mean / median	Enlarge Shrink	Months / mean / median	Please Select	Enlarge Shrink	Enlarge Shrink

ARM 4

68. drugs(s)	69. # on MTD	70. Duration of therapy	71. concomittant therapy recieved	72. duration of observation	73. Indicator of adherence	74. denominator for outcomes (ITT if available)	75. frequency of monitoring labs (write in)
Enlarge Shrink	Enlarge Shrink	Months / mean / median	Enlarge Shrink	Months / mean / median	Please Select	Enlarge Shrink	Enlarge Shrink

Patient Population Characteristics
Fill out PATIENT characteristics for each arm. If the study is a TRIAL, ALWAYS use arm 1 for data on the HU group. If the study is not a trial use arm 1 ONLY for data abstraction

ARM 1
ALWAYS use for HU group
Use when only one set of data is available for study population

DATA ENTRY INSTRUCTIONS: for ALL ARMS, report percentages in ( ), do not use the % within the ( ); report ranges in (-).

76. Age	77. Gender	78. Race	79. Genotype	80. Haplotype	81. Substance use	82. Socioeconomic status	83. Blood	84. Crises
Mean	Male, n (%)	White (non-hispanic), n (%)	SS, n (%)	Benin, n (%)	Alcohol user, n (%)	Low, define	Total Hg (g/dl), mean or median	Pain crises
Median	Female, n (%)	Black (non-hispanic), n (%)	SC, n (%)	Indian/Arab, n (%)	Smoker, n (%)	n (%)	% Hemoglobin F, mean or median	mean or median
Range		White hispanic, n (%)	S &+ thalassemia, n (%)	Senegal, n (%)	Illegal dug user, n (%)	Middle, define	White count (cells/µl), mean or median	Stroke
		Black hispanic, n (%)	S &º thalassemia, n (%)	CAR, n (%)		n (%)	Platelet count (k/mm^3), mean or median	mean or median
		Asian/Pacific Islander, n (%)	other, define, n (%)			High, define	Absolute neutrophil count (cells/µl), mean or median	Transfusions (per year or total)--specify
		Other (specify), n (%)				n (%)		mean or median
								Chest syndrome
								mean or median
								Ulcer
								mean or median

ARM 2

DATA ENTRY INSTRUCTIONS: for ALL ARMS, report percentages in ( ), do not use the % within the ( ); report ranges in (-).

88. Age	89. Gender	90. Race	91. Genotype	92. Haplotype	93. Substance use	94. Socioeconomic status	95. Blood	96. Crises
Mean	Male, n (%)	White (non-hispanic), n (%)	SS, n (%)	Benin, n (%)	Alcohol user, n (%)	Low, define	Total Hg (g/dl), mean or median	Pain crises
Median	Female, n (%)	Black (non-hispanic), n (%)	SC, n (%)	Indian/Arab, n (%)	Smoker, n (%)	n (%)	% Hemoglobin F, mean or median	mean or median
Range		White hispanic, n (%)	S &+ thalassemia, n (%)	Senegal, n (%)	Illegal dug user, n (%)	Middle, define	White count (cells/µl), mean or median	Stroke
		Black hispanic, n (%)	S &º thalassemia, n (%)	CAR, n (%)		n (%)	Platelet count (k/mm^3), mean or median	mean or median
		Asian/Pacific Islander, n (%)	other, define, n (%)			High, define	Absolute neutrophil count (cells/µl), mean or median	Transfusions (per year or total)--specify
		Other (specify), n (%)				n (%)		mean or median
								Chest syndrome
								mean or median
								Ulcer
								mean or median

ARM 3

DATA ENTRY INSTRUCTIONS: for ALL ARMS, report percentages in ( ), do not use the % within the ( ); report ranges in (-).

100. Age	101. Gender	102. Race	103. Genotype	104. Haplotype	105. Substance use	106. Socioeconomic status	107. Blood	108. Crises
Mean	Male, n (%)	White (non-hispanic), n (%)	SS, n (%)	Benin, n (%)	Alcohol user, n (%)	Low, define	Total Hg (g/dl), mean or median	Pain crises
Median	Female, n (%)	Black (non-hispanic), n (%)	SC, n (%)	Indian/Arab, n (%)	Smoker, n (%)	n (%)	% Hemoglobin F, mean or median	mean or median
Range		White hispanic, n (%)	S &+ thalassemia, n (%)	Senegal, n (%)	Illegal dug user, n (%)	Middle, define	White count (cells/µl), mean or median	Stroke
		Black hispanic, n (%)	S &º thalassemia, n (%)	CAR, n (%)		n (%)	Platelet count (k/mm^3), mean or median	mean or median
		Asian/Pacific Islander, n (%)	other, define, n (%)			High, define	Absolute neutrophil count (cells/µl), mean or median	Transfusions (per year or total)--specify
		Other (specify), n (%)				n (%)		mean or median
								Chest syndrome
								mean or median
								Ulcer
								mean or median

ARM 4

DATA ENTRY INSTRUCTIONS: for ALL ARMS, report percentages in ( ), do not use the % within the ( ); report ranges in (-).

112. Age	113. Gender	114. Race	115. Genotype	116. Haplotype	117. Substance use	118. Socioeconomic status	119. Blood	120. Crises
Mean	Male, n (%)	White (non-hispanic), n (%)	SS, n (%)	Benin, n (%)	Alcohol user, n (%)	Low, define	Total Hg (g/dl), mean or median	Pain crises
Median	Female, n (%)	Black (non-hispanic), n (%)	SC, n (%)	Indian/Arab, n (%)	Smoker, n (%)	n (%)	% Hemoglobin F, mean or median	mean or median
Range		White hispanic, n (%)	S &+ thalassemia, n (%)	Senegal, n (%)	Illegal dug user, n (%)	Middle, define	White count (cells/µl), mean or median	Stroke
		Black hispanic, n (%)	S &º thalassemia, n (%)	CAR, n (%)		n (%)	Platelet count	mean or median
		Asian/Pacific	other, define, n (%)			High, define		Transfusions (per year or total)--specify
						n (%)		mean or

		Islander, n (%) Other (specify), n (%)					(k/mm^3), mean or median Absolute neutrophil count (cells/ul), mean or median	median Chest syndrome mean or median Ulcer mean or median

124. Comments

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Click a link below to review this article at these other levels.

4. TRIAGE
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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State: Excluded, Level: 2

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Efficacy/Effectiveness AND Toxicity

Complete this form for Key Questions 1, 2 and 3 where applicable.

Categorical Outcomes

Efficacy/effectiveness outcomes:	**Toxicities**
1 any acute chest	**11** neutropenia
2 any acute painful event	**12** thrombocytopenia
3 death	**13** reticulocytopenia
4 symptomatic stroke	**14** anemia
5 definitive new changes on MRI	**15** leukemia
6 transfusion	**16** other neoplasm
7 crisis requiring hosp	**17** leg ulcer
	18 skin rash/nail alterations
	19 hair loss
	20 gastrointestinal upset
	21 cytogenetic or oncogenic abnormalities
	22 fetal abnormalities
	23 spontaneous abortion
8 other	**24** other
9 other	**25** other
10 other	**26** other

3.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
4. ARM 1 arm identification should be identical to that in the GENERAL form							
5. ARM 2							
6. ARM 3							
7. ARM 4							

8.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
9. ARM 1 arm identification should be identical to that in the GENERAL form							
10. ARM 2							
11. ARM 3							
12. ARM 4							

13.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
14. ARM 1 arm identification should be identical to that in the GENERAL form							
15. ARM 2							
16. ARM 3							
17. ARM 4							

18.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
19. ARM 1 arm identification should be identical to that in the GENERAL form							

20. ARM 2							
21. ARM 3							
22. ARM 4							

23.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
24. ARM 1 arm identification should be identical to that in the GENERAL form							
25. ARM 2							
26. ARM 3							
27. ARM 4							

28.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
29. ARM 1 arm identification should be identical to that in the GENERAL form							
30. ARM 2							
31. ARM 3							
32. ARM 4							

33.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
34. ARM 1 arm identification should be identical to that in the GENERAL form							
35. ARM 2							
36. ARM 3							
37. ARM 4							

38.
Outcome (select number from list above)
Please Select

	n (with outcome)	%	effect estimate relative to	CI	n per year (if applicable)	p-vaule	denominator for this outcome (if different)
39. ARM 1 arm identification should be identical to that in the GENERAL form							
40. ARM 2							
41. ARM 3							
42. ARM 4							

43.
Continuous Outcomes at last observation

time point of last ovbservation

Efficacy/effectiveness	**Toxicities**
27 Hb F % **28** % F cells **29** hemoglobin **30** MCV **31** reticulocyte count **32** white blood cell count **33** transcranial doppler velocity **34** height **35** weight **36** head circumference **37** Total days in hosp **38** Time to first crisis **39** Time to first acute chest **40** Time to neoplasm **41** Daily pain severity **42** Number of transfusions	**47** platelet count **48** neutrophil count(ANC) **49** sperm count **50** sperm motility

43 Units (RBC) transfused	
44.	45.
44 other	**51** other
45 other	**52** other
46 other	**53** other

46.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
47. ARM 1 arm identification should be identical to that in the GENERAL form							
48. ARM 2							
49. ARM 3							
50. ARM 4							

51.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
52. ARM 1 arm identification should be identical to that in the GENERAL form							
53. ARM 2							
54. ARM 3							
55. ARM 4							

56.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
57. ARM 1 arm identification should be identical to that in the GENERAL form							
58. ARM 2							
59. ARM 3							
60. ARM 4							

61.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
62. ARM 1 arm identification should be identical to that in the GENERAL form							
63. ARM 2							
64. ARM 3							
65. ARM 4							

66.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
67. ARM 1 arm identification should be identical to that in the GENERAL form							
68. ARM 2							
69. ARM 3							
70. ARM 4							

71.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
72. ARM 1 arm identification should be identical to that in the GENERAL form							
73. ARM 2							
74. ARM 3							
75. ARM 4							

76.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
77. ARM 1 arm identification should be identical to that in the GENERAL form							
78. ARM 2							
79. ARM 3							
80. ARM 4							

81.
Outcome (select number from list above)
Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Signficance
82. ARM 1 arm identification should be identical to that in the GENERAL form							
83. ARM 2							
84. ARM 3							
85. ARM 4							

86.
What characteristics predict benefit?

Enlarge Shrink
87.
What characteristics predict toxicity?

Enlarge Shrink
88.

The article reports the outcomes by the following groups.

- age
- genotype
- ethnicity/race
- disease
- resource-poor

89.

Comments:

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Click a link below to review this article at these other levels.
4. TRIAGE
5. GENERAL
7. Additional Arms
8. KQ3 TOX Case Reports

9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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State: Excluded, Level: 2

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QUALITY FORM
Observational Studies

1. Did the study describe the setting or population from which the study sample was drawn?

- No
- To some extent
- Yes, with detailed description: *setting (e.g., clinic), location, and dates*

Clear Selection

2. Were the inclusion or exclusion criteria described? (just saying “sickle cell disease” is insufficient)

- No
- To some extent
- Yes, with detailed description: *methods for selection of participants, or inclusion/exclusion criteria, or diagnostic criteria for enrollment*

Clear Selection

3. Does the study describe the key characteristics of study participants at enrollment/baseline?

- No
- To some extent
- Yes, with detailed description: *age, sex, genotype, relevant comorbidities which can influence outcomes*

Clear Selection

4. Was the intervention described? (intervention may be a drug or an intervention to overcome a barrier)

- NA
- No
- To some extent
- Yes, with detailed description:*how intervention was administered (does, titration schedule), who does intervention, instructions for patients*

Clear Selection

5. Was there a description of adherence to the drug or the completeness of the intervention?

- No
- To some extent
- Yes, with description of method of assessment, *number completing intervention, and how adherence was measured*
- NA

Clear Selection

6. Do the authors report an adjusted or stratified estimate of the treatment effect *if* this study compared two or more groups

- NA
- No

- To some extenrt
- Yes:*multivariate analyses accounting for all potential confounders*

Clear Selection

7. Do the authors report at least one objective outcome from the intervention?

- No
- To some extent
- Yes: *method of assessment is objective, replicable, relevant to the intervention*
- NA

Clear Selection

8. Did the study report the number of participants lost to follow-up?

- No
- To some extent (number only)
- Yes, with description of reasons for loss: *number lost and reason for loss*
- NA

Clear Selection

9. What was the percentage of participants who were lost to follow-up?

- Not reported
- n/N
- %
- NA

Clear Selection

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Click a link below to review this article at these other levels.

4. TRIAGE
5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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Previewing at Level 4

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State: Excluded, Level: 2

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TRIAGE FORM

Use this form ONLY:

1. If you have reviewed an article for data abstraction and have found that the article SHOULD NOT be reviewed {choose the appropriate reason below}, or

2. If article requires group discussion before data abstraction.

1. This article should NOT be reviewed at this time ofr the following reason(s):

- ○ insufficient data to address question, or very minimal description of study population (e.g. provides no relevant outcome data or no details about the included patients or no description about the intervention except that it was hydroxyurea)
- ○ study is a case series <100 patients
- ○ study is a case report but there is no description of duration of use of hydroxyruea OR no description of dose
- ○ study addresses pregnancy
- ○ triage for group discussion about relevance

Clear Selection

2.

Comment: please write a sentence about the article if it may be a useful article for the discussion

Enlarge Shrink

Submit Data

Click a link below to review this article at these other levels.

5. GENERAL
6. KQs 1, 2, or 3
7. Additional Arms
8. KQ3 TOX Case Reports
9. KQ4 Barriers
10. QUALITY--observational studies
11. QUALITY--controlled trials
12. QUALITY--qualitative studies
13. QUALITY--surveys
19. Renee data abstraction

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Appendix C

Evidence Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease

Author, year	Location	Design	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention	Starting dose: titration dose	Planned duration of treatment	Jadad [29] score
Adults-MSH								
Charache, 1995[21]	North America	RCT	Jan 1992 - Apr 1993	**Inclusion**: Age >18; SCA; Hb Sα$^+$ thal, Pain >3/yr **Exclusion**: Hb Sß$^+$ thal; ß^0 thal; SC; xfuse dependant; Preg; Op; SA; CTA; stroke in last 6 years; HIV; HU; not willing to use contraception; blood counts that could not be distinguished from marrow suppression; >15% HbA if recent transfusion; breastfeeding			2 years	5
Charache, 1996[39]							2 years	4
Hackney, 1997[41]							18 months	3
Steinberg, 1997[40]							2 years	4
Moore, 2000 [22]							2 years	4*
Steinberg, 2003 [43]		Cohort (f/u of MSH)						†
Ballas, 2006 [42]		RCT			HU	15 mg/kg/day: increased 5 mg/kg every 12 weeks if ANC ≥2000, retic and platelets ≥80,000/ul, and Hb ≥4.5 g/dl	2 years	4
					Placebo	Escalation per Data Coordinating Center (random)		
Pediatric-Belgian Trial								
Ferster, 1998[44]	Europe	Cross-over	June 1992 - Dec 1993	**Inclusion**: SCA, Hb Sα$^+$ thal; 3/yr pain episodes, stroke; acute chest; splenic sequestration **Exclusion**: Hb Sß$^+$ thal; Hb S ß^0 thal	HU	20mg/kg/day: increased by 5mg/kg/day after 2 months, if no response increased to 25 mg/kg	6 months	3
					Placebo	Not described	6 months	

Evidence Table 1. Description of Randomized Controlled Trials Investigating the Efficacy of Hydroxyurea Treatment for Sickle Cell Disease (continued)

* Quality Deficiency: No description of withdrawals or dropouts.
† Observational Study

ANC = absolute neutrophil count; CTA = concurrent treatment with an anti-sickling agent; f/u = follow up; Hb Sß$^{+}$ thal = sickle ß$^{+}$ thalassemia; Hb S ß^{0} thal = Sickle ß^{0} thalassemia; Hb Sα^{+} thal = Sickle α^{+} thalassemia; HbA = hemoglobin A; HIV = Human Immunodeficiency Virus; HU = hydroxyurea; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; Op = opioid use; Pain = pain episode; Preg = pregnancy; RCT = Randomized controlled trial; retic = reticulocytes; SA = substance abuse; SC = SC genotype; SCA = sickle cell anemia; xfuse = transfusion dependant.

Evidence Table 2. Adequacy of Reporting in Sickle Cell Disease Controlled Trials*

Author, year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Q Score
Ballas, 2006 [42]	1	1	1		1	4
Moore, 2000 [22]	1	1	1	1	0	4
Hackney, 1997 [41]	1	1	1		0	3
Steinberg, 1997 [40]	1	1	1		1	4
Charache, 1996 [39]	1	1	1		1	4
Charache, 1995 [21]	1	1	1	1	1	5
Ferster, 1998 [44]	1	1	0		1	3

* Blank cells represent categories that were not applicable to the question.

Q = quality

Evidence Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease

Author, year	Patient groups / Intervention	N	Recruitment start date - end date	Mean Age	% Male	Race, n	Genotype/ haplotype, n (%)	Last observation
MSH								
Charache, 1995 [21]	HU	152	Jan 1992-April 1993	30	49	Black Non-Hispanic, 149 Black Hispanic, 1 Other, 2	SS, 151; Hb Sß^{o} thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3), Other (23)	28 months
	Placebo	147		31	48	Black Non-Hispanic, 142; White Hispanic, 2 Other, 3	SS, 145; Hb Sß^{o} thalassemia, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3), Other (17)	
Charache, 1996 [39]	HU	152	Jan 1992-April 1993	30	49	Black Non-Hispanic, 149 Black Hispanic, 1 Other, 2	SS, 151; Hb Sß^{o} thal, 1 Benin/Benin, (36); Benin/CAR, (21); Benin/Senegal, (3); Senegal/CAR, (3), Other (23)	Mean 28±6 months
	Placebo	147		31	48	Black Non-Hispanic,142 White Hispanic, 2 Other, 3	SS, 145; Hb Sß^{o} thal, 2, Benin/Benin, (43); Benin/CAR, (20); Benin/Senegal, (3); Senegal/CAR, (3), Other (17)	Mean 28±7 months
Hackney, 1997 [41]	HU	10	Jan 1992-April 1993	30.5	60		SS (100)	18 Months
	Placebo	14		29.8	57			
Steinberg, 1997 [40]	HU	152	Jan 1992-April 1993	30				Mean 28 months (range = 21-38)
	Placebo	147		31				
Moore, 2000 [22]	HU	152	Jan 1992-April 1993	30	49			NR
	Placebo	147		31	48			
Steinberg, 2003 [43]	HU	152	Jan 1992-April 1993					7.7 years
	Placebo	147						7.4 years
Ballas, 2006 [42]	HU	141	Jan 1992-April 1993				SS (100)	24 months
	Placebo	136						
Other trial								
Ferster, 1998[44]	HU	25	June 1993-Dec 1993	Median, 9; Range, 2-22	48	Black Non-Hispanic, 25	SS, 25	12 months

Evidence Table 3. Description of Patient Populations in Randomized Controlled Trials Concerning the Efficacy of Hydroxyurea in Sickle Cell Disease (continued).

CAR = Central African Republic; Hb = hemoglobin; Hb Sßº thal = Sickle ßº thalassemia; HU = hydroxyurea; NR = not reported; SS = Sickle Hemoglobin SS Disease.

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Location	Patient type/ design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
HUG-KID CLUSTER									
Kinney, 1999 [68]	North America	Children-prospective	Toxicity	To determine the safety and efficacy of HU in pediatric patients with SCA. This is the phase I/II HUG KIDS study- goal was to establish MTD	Dec 1994-Mar 1996	**Inclusion**: 5-15 years, SCA, pain ≥ 3/yr or ACS episodes in last year, 6 documented heights and weights for at 2 years preceding enrollment **Exclusion**: Trans, preg, renal failure, liver failure, sepsis, ALT > 2, HIV+, theophyline containing drugs, estrogen, Ca-blockers	15mg/kg/d: Up 5mg/kg for 8 wks up to 30mg/kg	Up to 24	86
Ware, 2002 [73]	North America	Children-prospective	Efficacy*	To identify predictors of Hb response in school-aged children with SCA receiving HU at MTD	Dec 1994-Mar 1996	**Inclusion**: Age = children, Pain ≥ 3 in past year or ≥ 3 pain and ACS episodes within 1 year of enrollment, ACS ≥3 in past 2 years **Exclusion**: renal failure, "dysfunction", liver failure	15 mg/kg/d: Increase every 8 weeks to MTD or 30mg/kg	11.7	86
Zimmerman, 2004 [81]	North America	Children-prospective	Effective-ness	To investigate the long-term efficacy of HU (in improving hematologic parameters) in children with SCD receiving the MTD†	1995-2002	**Inclusion**: on HU for at least 6 mo, SCD	15 or 20mg/kg: Up to 30mg/kg if tolerated	45 (24) [6-10]	88

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient Type/ Design	Goal of Study	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q Score
HUSOFT Cluster									
Wang, 2001 [60]	North America	Children-prospective	Efficacy	To conduct a collaborative pilot trial of HU in infants with SCA to assess (1) feasibility of administration, (2) toxicity, (3) hematologic effects, and (4) effect on spleen function‡	Nov 1996 – Jun 1997	**Inclusion**: Age, infants-not specified by age, SCA, Hb Sß^0 thal **Exclusion**: Splenomegaly, Preg, renal failure, CRCL<120ml/min/1.73 m2, liver failure, ALT>5n, HIV+, iron deficiency, HbA>10% from transfusion, sig. non-sickle-related medical problem	20mg/kg: No titration	24	67
Hankins, 2005 [72]	North America	Children-prospective	Efficacy	To study the long-term efficacy and toxicity of HU on infants, and to define the role of HU in preventing organ dysfunction	as in HUSOFT	**Inclusion**: enrolled in HUSOFT§	20mg/kg: 5mg/kg every 6 months to max 30mg/kg	58.8 [25-72]	67

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient Type/ Design	Goal of Study	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q Score
French Cluster									
de Montal-embert, 1997 [76]	Europe	Children-prospective	Efficacy	To observe the safety and efficacy of HU in previously severely ill children with SCD	NR	**Inclusion**: Age, 4 to20 years, SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, S α^{+} thal, SC, Pain ≥ 3 hospitalizations in last year **Exclusion**: HIV+, renal insufficiency CrCL <120ml/1.73 m^2/min, iron deficiency or current iron supplementation, history of frequent and severe infections, monthly f/u would be difficult, hypersplenism, hepatic insufficiency (ALT>5xULN, or chronic hepatic disease)	20 mg/kg/day 4 days/week: Increase 5 mg/kg/day every 4 weeks to a max dose of 40 mg/kg/day	32 [12 to 59]	85
Maier-Redel-sperger, 1998 [75]	Europe	Children-prospective	Efficacy	To study the cellular and molecular responses to long-term HU treatment in 29 severely affected young patients with SCD	NR	**Inclusion**: Pain **Exclusion**: Preg, renal failure, renal function within normal limits, liver failure, ALT >1.5 ULN, HIV+, hx of severe infections, iron deficiency	20mg/kg/d 4 d/wk: Increase 5mg/kg/d monthly to max 40‖	22 [12 to 36]	77

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
French Cluster (continued)									
de Montalembert, 1999 [55]	Europe	Children-prospective	Toxicity	To evaluate the tolerance of HU in children affected with SCD	NR – Sep 1998	**Inclusion**: 2-20 years when starting HU	NR	22 [0.5-93]	18
de Montalembert, 2006 [48]	Europe	Children-prospective	Toxicity	To asses the tolerability of HU treatment in 225 children with SCD	Jan 1992 – Dec 2003	**Inclusion**: Pain ≥ 3 admissions, stroke and unable or refused transfusion, ACS, recurrent severe chronic anemia Hb < 6-7, high TCD velocity, cardiac ischemia	20 mg/kg/d 4 d/wk, then 4 to 7 d/wk from 1997-2003: Up to 40 mg/kg/d, increased up to 40 mg/kg/d if no response after 6 months	46 [0-152]	71
Belgian Cluster									
Ferster, 2001 [58]	Europe	Children-prospective	Effective-ness	To evaluate the long-term efficacy and toxicity of HU in the Belgian registry of HU-treated SCD patients	1993 - NR	**Inclusion**: Age, children and young adults, Pain ≥ 2 admissions/year, or stroke, or TIA, or ACS, or priapism, ischemic bone	20mg/kg: 5mg/kg at will of doctor[¶]	42	63
Gulbis, 2005 [82]	Europe	Children-prospective	Effective-ness	To assess the efficacy and safety of HU	1993-2002	**Inclusion**: Age, children and young adults, Pain ≥ 2 admissions/year, or stroke, or TIA, or ACS, or priapism, or ischemic bone	20mg/kg: 5mg/kg at will of doctor	47[#]	54

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others									
el-Hazmi, 1992 [45]	Middle East	Adults-prospective	Efficacy	To assess the effectiveness of HU in managing severe forms of SCD		NR	20mg/kg/day: no titration	3	57
Charache. 1992 [46]	North America	Adults-prospective	Efficacy	To assess pharmacokinetics, toxicity, and increase in fetal Hb production in response to daily doses of HU in patients with SCA	Feb 1988-NR	**Inclusion**: Age >18 years, SCA, S α^{+} thal, pain admissions >1 in last year (including ED visits) **Exclusion**: Hb Sβ^{+} thal, Hb Sβ^{0} thal, Trans, preg, renal failure, abnormal renal function tests, liver failure, abnormal hepatic function tests, HIV+, AST >100 U/L, albumin <3 g/dl, theophylline containing drugs, androgens, estrogens, or progesterones (other than birth control)	10 - 20 mg/kg/d depending on AUC at 6 hours: Increase 5 mg/kg/d Every 8 weeks	9 [0-25]	89
Voskaridou, 1995 [78]	Europe	Adults-prospective	Efficacy	To report on the response of Caucasian patients with SCD with complications of the disease (pain crises) to high "sub-toxic" doses of HU	NR	**Inclusion**:, Hb Sβ^{+} thal, Hb Sβ^{0} thal, pain frequent	15 mg/kg/d, rounded up to the next 500mg 4days/wk: Increase by 5mg/kg increments, rounded up to the next 500mg q 4wks, maximal total dose of 2.5g/d**	[5-8.7]	54

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Scott, 1996 [77]	North America	Children-prospective	Efficacy	To assess the safety and efficacy of HU for the treatment of severe SCD in children	Feb 1992 – Jun 1995	**Inclusion**: Age 10 to 17 years, SCA, Hb Sß^0 thal, S α$^+$ thal, pain admissions ≥ 3/year , ACS, or priapism, contraceptive measures to prevent pregnancy **Exclusion**: abnormal renal or hepatic function, noncompliance	10-20 mg/kg/day: 5 mg/kg/day Every 12 weeks	43.6 [24-63]	93
Loukopoulos, 1998 [69]	Europe	Adults-retro-spective	Efficacy	To report on the effectiveness of HU in patients with thalassemia--a report of a physician's experiences	NR	**Inclusion**: Age, adults, Hb Sß$^+$ thal, Hb Sß^0 thal	15-35 mg/kg/day on 4-7 days/week: no titration	NR	23
Olivieri, 1998 [64]	North America	Children-prospective	Toxicity	To monitor compliance with treatment of HU and evaluate the impact of HU on splenic function in children with SCD	NR	**Inclusion**: SCA, Pain ≥ 3 in the previous yr, ACS, any episode in the previous yr **Exclusion**: Neutropenia, Trans, Preg, SA or severe psychologic disease interfering with accurate reporting of pain, renal failure, liver failure, ALT >x2UNL, untreated folate or iron deficiency, thrombocytopenic conditions	12.9 ± 2.7 mg/kg/d, reduced to 10mg/kg/d later: Dose increased by 5 mg/kg q 8-12 wks until ANC<2,000/ ml, retic < 80,000/ml, plt<100k/mcL, or Hb more than 2g/dL below steady state	18	88

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Hanft, 2000 [57]	North America	Adults and Children-retro-spective	Toxicity	To investigate the mutagenic and carcinogenic potential of long-term HU use in patients with SCD or MPDs	NR	**Inclusion**: SCA, MPD, abnormal TCD, cardiac ischemia	NR	up to 180	31
Loukopoulos, 2000 [74]	Europe	Adults-prospective	Efficacy	To report on a clinical trial of HU in 55 Greek-origin patients with sickle cell/B thalassemia and patients with homozygous HbS disease who had been treated with HU for several years	NR–Jun 1999	**Inclusion**: Age ≥ 17 years, SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, pain ≥ 3/yr, severe disease (e.g. stroke, hyperbiliuremia) **Exclusion**: pregnancy or intention to conceive	15mg/kg/day for 4 days week then 25 mg/kg/day: Titrate up to 25mg/kg/d stable for 6mos and taper to 1.0g daily	[6-48]	63
Rigano, 2001 [71]	Europe	Adults-prospective	Efficacy	To evaluate the efficacy of HU in a group of 22 Sicilian patients with BS/B-thal by studying the incidence of crises, frequency of hospitalization, complications and mortality	NR	**Inclusion**: Sicilians, ≥ 3 sickle crises (any type) in previous year **Exclusion**: HIV^{+}, bone marrow hypoplasia	15 mg/kg/day: Increased after 3 months if no response	>24	70
Chaine, 2001 [66]	Europe	Adult-retro-spective	Toxicity	To evaluate the risk of cutaneous adverse reactions in SCD patients treated with HU	NR	**Inclusion**: adult, SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, S α^{+} thal, SC, on HU††	NR	12 (MTD plus time to escalate)	52

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Al-Jam'a, 2002 [70]	Middle East	Adults-Children-prospective	Efficacy	To assess the efficiency and safety of HU in patients with SCD from the Eastern Province, Kingdom of Saudi Arabia	Jun 1994 – Jun 1998	**Inclusion**: Age, >5 years, SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, S α^{+} thal, pain ≥ 4 admissions for VOC in past year **Exclusion**: Trans, Preg, renal failure, abnormal renal tests, liver failure, abnormal hepatic function tests, HIV+, progesterones other than in OCPs, theophyllines, androgens, estrogens	500 mg/day, 500 mg QOD if wt <50 kg: 500 mg each month until MTD or 35 mg/kg reached	18.5 [12 to 49]	89
Ferguson, 2002 [52]	North America	Adults-retro-spective‡‡	Effective-ness	To assess the efficacy of HU in settings outside a clinical trial with longer follow-up	Sep 1997 – Sep 1999	**Inclusion**: Age, adults, SCA, treated at two hospitals **Exclusion**: Hb Sß$^{+}$ thal, Hb Sß^{0} thal, Sα^{+} thal, SC, Trans, Preg, SA, stroke in past 6 years	Every 8 weeks	21.6 [3-60]§§	57
Schultz, 2003 [53]	North America	Adult-retro-spective	Toxicity	To report on cases of malignancy in patients with SCD			NR	22	14

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Cummins, 2003 [61]	Europe	Adults-prospective ‖ ‖	Efficacy	To compare patients with SCD treated with cognitive behavioral therapy with patients treated with HU in terms of quality of life, pain experience, health service utilization, and pain coping strategies	Jan 2000-Dec 2002	**Inclusion**: Age, adult, SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, S α^{+} thal, SC	Weight-based	23 [12-39]	37
Ware, 2004 [67]	North America	Children-prospective	Effective-ness	To describe the clinical outcome and long-term follow-up for a cohort of pediatric patients with SCD receiving HU for prevention of secondary stroke	NR	**Inclusion**: Age = pediatric, SCA, Trans, stroke **Exclusion**: Hb Sß$^{+}$ thal, S α^{+} thal, S α^{+} thal, SC	15-20 mg/kg per day	29 [12-49]	88
Bakanay, 2005 [51]	North America	Children-Retro-spective	Effective-ness	To report on the demographic, clinical and laboratory characteristics of a group of patients who died of complications while on HU therapy compared with HU-treated surviving patients	NR	NR	15 mg/kg/day: 5mg/kg as tolerated	36 [5-78]	50

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Vicari, 2005i [80]	Central or South America or Mexico	Adults-prospective	Effective-ness	To see if genetic determinants influence response and toxicity with HU	NR	**Inclusion**: Age, >18 years, SCA, Pain ≥3/yr, ACS **Exclusion**: HIV+, bone marrow depression	NR	30.45 [12-60]	25
Khayat, 2006 [47]	Central or South America or Mexico	Adults and children-retro-spective	Toxicity	To determine the frequency of chromosome aberrations and the mitotic index as a criteria for evaluation of the genotoxicity and cytotoxicity of HU in SCD patients	NR	NR	25mg/kg/d	12	27
Kratovil, 2006 [62]	North America	Children-prospective	Efficacy	To determine if HU therapy affected transcranial Doppler velocities and whether changes in velocities could be associated with changes in hematologic parameters	1998-2004	**Inclusion**: SCA, Pain >5/year, stroke and not transfused, 2nd alloantibodies, or poor chelation, severe ACS, TCD exam before and during HU **Exclusion**: Trans, none in 6 months, SA, drugs	15 mg/kg/day: 5 mg/kg/day every 8 weeks to max of 30-25 mg/kg/day or 2000 mg/day or MTD	[6-48]	73

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Ataga, 2006 [79]	North America	Adults-prospective	Effective-ness	To evaluate the trends of development of pulmonary hypertension, the association of pulmonary hypertension with clinical and laboratory measures and the effect of pulmonary hypertension on mortality in SCD patients	NR	**Inclusion**: SCA, Hb Sß$^{+}$ thal, Hb Sß^{0} thal, S α^{+} thal, SC **Exclusion**: ACS in last 4 weeks, current crisis or acute illness	NR	NR	40
Svarch, 2006 [50]	Central or South America or Mexico	Children-retro-spective	Efficacy	To demonstrate that good results can be achieved and toxicity avoided by maintaining dose of HU at 15 mg/kg/day in patients with SCD	NR	**Inclusion**: Age, 4-18 years, SCA, Pain ≥ 3 in past year or, sepsis ≥ 1 in past 2 years **Exclusion**: ACS	15mg/kg/d: No titration	Median = 24	35
Zimmerman, 2007 [63]	North America	Children - prospective	Efficacy	To describe a prospective, single-institution Phase II trial of HU for children with SCD and increased transcranial doppler flow velocities	2000-2004	**Inclusion**: Age all pediatric, SCA, S/O Arab **Exclusion**: sickle ß$^{+}$ thal, sickle ß^{o} thal, sickle α^{+} thal, SC	"as in routine practice": To MTD	10 (5) Median = 8	73

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
McKie, 2007 [49]	North America	Children-retro spective	Effective-ness	To define the age of onset of microalbuminuria and proteinuria in children with SCD and evaluate their association with age, sex, and hemoglobin levels, Also to explore the safety and utility of HU and ACEI in prevention and treatment of sickle cell nephropathy	Sep 1996–Dec 2002	**Inclusion**: Age, >2 and < 21 years, SCA	15 mg/kg/day: Based on clinical responses, MCV, HbF	21.8	50
Harrod, 2007 [56]	North America	Children-prospective	Toxicity	To quantitate Howell-Jolly Bodies in a large cohort of children with SCD and analyze according to sicklegenotype, age, splenectomy status, and HU exposure	NR	**Inclusion**: < 20 years **Exclusion**: Hb Sß$^{+}$ thal, Hb Sß^{0} thal	NR	NR	39
Hankins, 2007 [65]	North America	Children-prospective	Effective-ness	To investigate the effects of HU on spleen and brain through retrospective data review of children with SCD treated with HU	Jul 1995 – Oct 2004	**Inclusion**: children, SCA, Hb Sß^{0} thal	15-20 mg/kg/day: Every 8weeks to 30-35mg/kg¶¶	29 [2-103]	43

Evidence Table 4. Design of Observational or Single-Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Location	Patient type/ Design	Study Goal	Objective	Recruitment start date - end date	Inclusion and exclusion criteria	HU Starting Dose: Titration schedule	Mean Observation Duration in months, (SD) [range]	Q score
Others (continued)									
Santos, 2002 [59]	Central, South America	Children-prospective	Effectiv-eness	To evaluate the effects of long-term therapy with hydroxyurea on recovery of splenic function	NR	**Inclusion**: Age 3 to 22, SCA, Sß0 thal, ≥ 2 episodes of priapism or ACS, ≥ 6 painful crisis	15 mg/kg/day: every 8 weeks increase by 5 mg/kg/day to max of 30 mg/kg/day or toxicity	12 months	47

*Used data from the phase I/II HUG KIDS study but analyses only included children who reached MTD; 5.6% of pills were returned.
†Included patients who were in HUG-KIDS (n=15), in HUSOFT (n=7), and 33 patients in a secondary prevention of stroke study.
‡Investigators matched 3 patients from CSSCD to enrolled patients by diagnosis, gender, age.
§This was the extension study of HUSOFT. Of the 21 who completed the 2 years in HUSOFT, 17 (of the 21) completed 4 years, and 11 (of the 21) completed 6 years from start. ‖ Mean dosage 34.2mg/kg administered 4 days a week.
¶ At the end of year one of the study, 55% were on 20-25mg/kh, 41% were under 20mg/kg, 4% were on 25-30mg/kg, and 1 was on more than 30mg/kg.
#109 patients for a total of 426 patient-yrs. The initial 109 children were followed for up to 8 years (14 children with this duration).
**The maintenance phase (after first 24 weeks) was 100mg/d for 4d/week and then patients were put into one of three arms that differed slightly in administration.
††Recruited all adult patients who came to their institution for skin exam who had SCD and were on HU.
‡‡Patients were stratified by duration of therapy (or completeness of therapy). Fourteen patients had previously participated in MSH study.
§§Mean observation duration was 9.7 months in the group on HU for <24 months.
‖‖The cross-sectional design was based on questionnaires (in 2002 for HU patients, 2000 for CBT patients) and review of records: there is a strong likelihood of selection bias.
¶¶ The median MTD was 30mg/kg/day (range 15-35 mg/kg/day).

ACEI =ACE Inhibitors; ACS = acute chest syndrome; ALT = Alanine Aminotransferase; ANC = absolute neutrophil count; AUC = area under the curve; BS/B-thal = hemoglobin S beta-thalassemia; Ca = calcium; CBT = cognitive behavioral therapy; CrCL = creatinine clearance; CSSCD = Cooperative Study of Sickle Cell Disease; ED = Emergency Department; f/u = follow up; Hb = hemoglobin; Hb Sß$^+$ thal = Sickle ß$^+$ thalassemia; Hb S ß° thal = Sickle ß° thalassemia; HbA = hemoglobin A; HbF = fetal hemoglobin; HbS = sickle hemoglobin; HU = hydroxyurea; HUG KIDS = pediatric hydroxyurea safety trial; HUSOFT = The Hydroxyurea Safety and Organ Toxicity trial; hx = history; MCV = mean corpuscular volume; MPD = myeloproliferative disorder; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; MTD = maximum tolerated dose; NR = not reported; OCP = oral contraceptive pill; plt = platelets; Preg = pregnancy; Q = quality; QOD = 4 times a day; retic = reticulocytes; S α^+ thal = sickle α^+-thalassemia; S/O = hemoglobin SO Arab; SA = substance abuse; SC = Sickle-Hemoglobin C Disease; SCA = sickle cell anemia; SCD = Sickle Cell Disease; SD = standard deviation; TCD = transcranial Doppler; TIA = transient ischemic attack; Trans = transfusion; ULN = upper limit of normal; VOC = vaso-occlusive crisis.

Evidence Table 5. Adequacy of Reporting in Observational Studies and Surveys on Hydroxyurea Use in Sickle Cell Disease*

Observational Studies									
Author, year	**Study description**	**Inclusion or exclusion criteria described**	**Key characteristics of participants described**	**Intervention described**	**Adherence to the drug described**	**Adjusted or stratified estimate of the treatment effect provided**	**Reported ≥ 1 objective outcome**	**Reported # participants lost to follow-up**	**Q score**
Kinney, 1999 [68]	1	2	1	2	2		2	2	86
	1	2	1	2	2		2	2	
Ware, 2002 [73]	1	2	1	2	2		2	2	86
	1	2	2	2	2		2	1	
Zimmerman, 2004 [81]	2	1	2	2	1				86
	1	2	2	2	2		2	2	
Wang, 2001 [60]	1	1	2	2	0		2	2	67
	1	2	1	2	0	0	2	2	
Hankins, 2005 [72]	1	2	2	2	0		2	2	67
	1	1	1	2	0	0	2	2	
de Montalembert, 1997 [76]	0	2	2	2	1		2	2	85
	2	2	2	2	1		2		
Maier-Redelsperger, 1998 [75]	2	2	2	2	0	1	2	2	77
	1	2	1	2	0		2	2	
de Montalembert, 2006 [48]	2	1	1	2	1		2	1	71
	2	1	1	1	2		2	1	
Ferster, 2001 [58]	2	2	1	2	0	1	2	0	63
	0	2	2	1	0		2	2	
Gulbis, 2005 [82]	1	2	2	1	0		2	1	54
	1	2	1	1	1	0	1	1	
el-Hazmi, 1992 [45]	1	1	1	2	2	0	2		57
	1	1	1	1	1		2	0	
Charache. 1992 [46]	0	2	2	2	1		2	2	89
	2	2	2	2	2		2	2	
Voskaridou, 1995 [78]	0	1	2	2	0		2	0	54
	1	0	2	2	1		2	0	
Scott, 1996 [77]	2	2	2	2	1		2	2	93
	1	2	2	2	2		2	2	
Loukopoulos, 1998 [69]	0	0	0	1	0	0	1	0	23
	0	1	1	1	0		2	0	
Olivieri, 1998 [64]	2	2	2	2	2		2		88
	1	1	1	2	2		2		
Hanft, 2000 [57]	1	0	1	1	0	1	2		31
	0	0	1	0	0	0	2	0	

Evidence Table 5. Adequacy of Reporting in Observational Studies and Surveys on Hydroxyurea Use in Sickle Cell Disease (continued)

Observational Studies (continued)									
Author, year	**Study description**	**Inclusion or exclusion criteria described**	**Key characteristics of participants described**	**Intervention described**	**Adherence to the drug described**	**Adjusted or stratified estimate of the treatment effect provided**	**Reported ≥ 1 objective outcome**	**Reported # participants lost to follow-up**	**Q score**
Loukopoulos, 2000 [74]	1	1	1	2	0	0	2	2	63
	1	2	2	1	0		2	2	
Rigano, 2001 [71]	1	2	1	1	0	0	2	2	70
	0	2	2	2	2		2	2	
Chaine, 2001 [66]	2	1	2	1	0		2		52
	0	0	1	1	0	1	2		
Al-Jam'a, 2002 [70]	2	2	1	1	1		2	2	89
	2	2	2	2	2		2	2	
Ferguson, 2002 [52]	2	1	1	1	0	1	2		57
	2	2	1	1	1	0	2	0	
Cummins, 2003 [61]	1	1	1	1	0	0	2		37
	1	0	1	1	0	0	2	0	
Ware, 2004 [67]	2	2	2	2	2		2		88
	1	1	1	2	2		2		
Bakanay, 2005 [51]	2	1	2	2	0	2	2	0	50
	1	0	1	1	0	1	1	0	
Vicari, 2005i [80]	0	1	1	0	0		1	0	25
	0	1	1	0	0		2	0	
Khayat, 2006 [47]	0	0	0	1	0		2		27
	0	1	0	1	0		2	0	
Kratovil, 2006 [62]	2	2	2	2	0	2	2		73
	2	1	1	1	0	2	2	1	
Ataga, 2006 [79]	2	2	1	0	0	0	2		40
	2	1	2	0	0	0	0	0	
Svarch, 2006 [50]	0	2	0	1	0		2		35
	1	1	0	1	0		1	0	
Zimmerman, 2007 [63]	2	2	2	2	0	0	2	0	73
	2	2	2	1	1		2	2	
McKie, 2007 [49]	2	1	1	1	0	0	2	1	50
	2	1	1	1	0		2	0	
Harrod, 2007 [56]	1	1	1	0	0	1	2		39
	1	1	1	0	0	0	2		
Hankins, 2007 [65]	0	1	1	1	0		2	0	43
	2	0	1	2	0		2	0	
Santos, 2002 [59]	1	2	2	1	0	0	1		47
	0	2	2	2	0	0	2		

Evidence Table 5. Adequacy of Reporting in Observational Studies in Sickle Cell Disease (continued)

Surveys								
Author, year	**Study description**	**Inclusion or exclusion criteria described**	**Key characteristics of participants described**	**Completion Rate**	**Instrument Validated**	**Validity Discussed**	**Reliability Discussed**	**Q Score**
de Montalembert, 1999 [55]	2	0	1		0	0	0	18
	1	0	1		0	0	0	
Schultz, 2003 [53]	2	1	0		0	0	0	14
	1	0	0		0	0	0	

* blank cells indicate “not applicable” response by one reviewer

Q = quality

Evidence Table 6. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease

Author, year	Comparison group	N	Genotype, %	Haplotype, %	Mean age in years (SD) [range]*	Male, %	Race (%)	Clinical disease activity (SD) [range]
HUG-KIDS Cluster								
Kinney, 1999 [68]	NR/NA	84	SS 100	NR	9.8; 9.1* [5-15]	NR	Black (100)	
Ware, 2002 [73]	NR/NA	68	NR	NR	9.5		NR	
Zimmerman, 2004 [81]	NR/NA	122	SS 86; SC 5.7 Sß^0 thal 5.7; S/O-Arab 1.6	NR	11.1* [0.5 - 19.7]	58	NR	
HUSOFT Cluster								
Wang, 2001 [60]	NR/NA	28	SS 96; Sß^0 thal 4	NR	1.3* [0.5-2.3]	57	NR	
Hankins, 2005 [72]	NR/NA	21	SS 95; Sß^0 thal 5	NR	3.4* [2.6-4.4]	43	Black (100)	
French Cluster								
de Montalembert, 1997 [76]	NR/NA	35	SS 94; Sß^0 thal 3; Sß$^+$thal 3	NR	11* [3-20]	74	NR	Hospital days 29 [0-117]
Maier-Redelsperger, 1998 [75]	NR/NA	29	NR	Benin 9; Senegal 3; CAR 8	10.9 [4-19]	72	NR	
de Montalembert, 1999 [55]	NR/NA	101	SS 98; Sß$^+$ thal 1; Sß^0 thal 1	NR	9.8 [2-20]	55	NR	One HIV$^+$
de Montalembert, 2006 [48]	NR/NA	225	SS 94; SC 1.3; Ssthal 3.5; Hb-Punjab 0.8	NR	9.2 [1.42-19]	61	NR	
Belgian Cluster								
Ferster, 2001 [58]	NR/NA	93	SS 99; HB-Punjab 1	NR	7* [0.7 to 45]	52	Black (94)	67 had ≥2 pain crises; 9 had stroke; 19 had prior ACS
Gulbis, 2005 [82]	NR/NA	109	SS 93; SC 3; Sß^o thal 3	NR	6 [.75 - 19]	NR	NR	99 had ≥ 2 pain crises, 21 had prior ACS, 7 had prior stroke, 1 with prior TIA

Evidence Table 6. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group	N	Genotype %	Haplotype %	Mean age in years (SD) [range]*	% Male	Race (%)	Clinical disease activity (SD) [range]
Others								
el-Hazmi, 1992 [45]	NR/NA	21	SS 71; Sß^0 thal 28	NR	[17-32]	NR	NR	
Charache. 1992 [46]	NR/NA	49	SS 100	Benin 61; Senegal, 9.3; CAR 25	27.6	55	Black (100)	
Voskaridou, 1995 [78]	NR/NA	14	Sß$^+$ thal 42; Sß^0 thal 58	NR	28.6 [19-48]	64	NR	
Scott, 1996 [77]	NR/NA	15	SS 73; Sß^0 thal 13; Sα$^+$ thal 13	NR	14 [(10-17)	40	NR	
Loukopoulos, 1998 [69]	NR/NA	44	Sß$^+$ thal 34; Sß^0 thal 65	NR	NR	NR	NR	
Olivieri, 1998 [64]	NR/NA	17	NR	NR	12.4 [5 - 18]	NR	NR	Transfusions, 1.8; (0.5)/yr; Chest syndrome, 1.3; (0.5) /yr; Hospitalized days 29.1; (4.8)/yr
Hanft, 2000 [57]	Adults with MPD and HU exposure	12	NR	NR	62	NR	NR	
	Adults with SCD and short HU exposure	15			29			
	Children with SCD and no HU	21			11			
	Children with SCD and low HU exposure	17			11			
Loukopoulos, 2000 [74]	NR/NA	69	SS 20; Sß^0 thal 79	All HbS was Benin	[17-50]	58	White (100)	
Rigano, 2001 [71]	NR/NA	22	Sß^0 thal 76; Sß$^+$thal 27	Benin 100%	[29-53]	68	White (100)	Pain crises 7/yr (mean)
Chaine, 2001 [66]	NR/NA	17	SS 94; Sß^o thal 6	Benin 12.5; Senegal 2; CAR 3	27.1 [19-51]	53	Black (100)	2 with leg ulcers
Al-Jam'a, 2002 [70]	NR/NA	27	NR	NR	21.3 [10-36]	67	NR	Yearly pain crises 6.5 (2.8); Days in hospital 34 (26)
Ferguson, 2002 [52]	HU at least 24 months	30	SS 100	NR	[20-58]	43	NR	Transfusions 5/yr; Hospitalizations 3.3/year
	HU less than 24 months	30	NR	NR	[19-54]	30		Transfusions 5.8/yr; Hospitalizations, 5.7/yr

Evidence Table 6. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group	N	Genotype %	Haplotype %	Mean age in years (SD) [range]*	% Male	Race (%)	Clinical disease activity (SD) [range]
Others (continued)								
Schultz, 2003 [53]	Patients with cancer	49	SS 63; SC 22; Sß thal 14	NR	34* [1.2-62]	NR	NR	
	Patients on HU who developed cancer	3	NR	NR				
Cummins, 2003 [61]	HU	15	SS 93	NR	33	67	NR	
	CBT	21	SS 57; SC 29	NR	30.9	33		
Ware, 2004 [67]	NR/NA	35	SS 94; Sß^0 thal 3; S/O Arab 3	NR	11.9 [3 - 19.9]	66	NR	Stroke incidence, 5.7 per 100 patient years
Bakanay, 2005 [51]	NR/NA	226	NR	NR	NR	51	NR	
Vicari, 2005i [80]	NR/NA	22	SS 100	homo Bantu 41; homo Benin 18; hetero Bantu-Benin 31	25.6 [18-46]	32	NR	
Khayat, 2006 [47]	NR/NA	8	NR	NR	[7-20]	NR	NR	
Kratovil, 2006 [62]	HU	24	SS 100	NR	9.9 [1.7-16]	58	NR	Average of Max TCD velocity 125 (32.3) cm/sec2
	No HU	24	NR	NR	9.4 [2.1-16]	67		Average of Max TCD velocity, 128.9 cm/sec2 range 79-220
Ataga, 2006 [79]	HU (with PHTN)	9	SS 74: SC 12; Sß^0 thal 5; Sß$^+$thal 9 (PHTN & no PHTN groups combined)	NR	42.3 (11)	42	NR	History of acute chest syndrome, 88%; Crises in past year, 3.0 (3.6); History of stroke, 15%
	HU (No PHTN)	32			38.4 (12)	38		History of acute chest syndrome, 82%; Crises in past year: 3.8 (4.3); History of stroke, 8%
Svarch, 2006 [50]	NR/NA	51	SS 100	NR	[4-18]	NR	NR	Pain crises 3 [0-4]; Transfusions 3.9 [0-8] Chest syndrome [0-3]; Hospitalizations admissions 4 [0-6]
Zimmerman, 2007 [63]	Increased TCD velocities	37	NR	NR	6.8; 5.6*	NR	NR	Median RMCA, 162 cm/sec2; Median LMCA, 166 cm/sec2

Evidence Table 6. Patient Characteristics in Observational Studies of Hydroxyurea for Sickle Cell Disease (continued)

Author, year	Comparison group	N	Genotype %	Haplotype %	Mean age in years (SD) [range]*	% Male	Race (%)	Clinical disease activity (SD) [range]
Others (continued)								
McKie, 2007 [49]	HU no microalbuminuria	19	SS 100	NR	NR	NR	NR	
	HU and microalbuminuria	9	NR	NR				
	ACE-Inhibitor for microalbuminuria	9	NR	NR				
	Usual care	154	NR	NR	NR	NR	NR	
Harrod, 2007 [56]	HU, no splenectomy	46	SS 100	NR	12.1	NR	NR	
	No HU, no splenectomy	58	NR	NR	4.6			
	HU with splenectomy	11	NR	NR	10.7			
	No HU with splenectomy	10	NR	NR	8.7			
Hankins, 2007 [65]	NR/NA	52	SS 99; Sß^0 thal 1	NR	9.9* [3-17.6]	65	Black (98)	
Santos, 2002 [59]	HU	21	SS 14; Sß^0 thalassemia 7	NR	Mean, 11.7 [3-22]	14	NR	

* Median age reported instead of mean

ACE = Angiotensin-Converting Enzyme; ACS = Acute chest syndrome; CAR = Central African Republic; CBT = cognitive behavioral therapy; Hb = hemoglobin; hetero = heterozygous; homo = homozygous; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; HUSOFT = Hydroxyurea Safety and Organ Toxicity; LMCA = left main coronary artery; MPD = myeloproliferative disorders; NA = not applicable; NR = not reported; PHTN = pulmonary hypertension; RMCA = right middle cerebral artery; Sß$^+$ thal = Sickle ß$^+$ thalassemia; Sß° thal = Sickle ß° thalassemia; S/O-Arab= hemoglobin SO-Arab; Sα$^+$ thal = Sickle α$^+$ thalassemia; SC= Sickle-Hemoglobin C Disease; SCD = Sickle Cell Disease; SD = standard deviation; SS = Sickle Hemoglobin SS Disease; TCD = transcranial Doppler; TIA = transient ischemic attack

Evidence Table 7. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease

Author, year	Interven-tion	N	Mean durations of drug Mean duration of followup	Deaths, n (%)	Hb F, % ± SD	F cells, % ± SD	Hemo-globin, g/dl	MCV, fl ± sd	Retic-ulocyte count, k/ul	Weight change, kg (%)	Change in peak power, watts ± sem	Pain crises & admis-sions	Trans-fusion
MSH													
Ballas, 2006 [42]	HU	141	24 months										
	Placebo	136											
Steinberg, 2003 [43]	HU	152	7.7 years	36 (23.7)								Stroke, 8*	
	Placebo	147	7.4 years	39 (26.5)								Stroke, 6*	
Moore, 2000 [22]	HU	152	24 months										
	Placebo	147	NR										
Hackney, 1997 [41]	HU	10	24 months							3.2 ± 0.8†	104.9 ± 31		
	Placebo	14	18 months							1.8 ± 0.8‡	57.7 ± 20		
Steinberg, 1997 [40]	HU	152	24 months		3.6 ± 5.4§	15.2 ± 17.3§		9.7 ± 11.2§	97 ± 107§				
	Placebo	147	28 months (range, 21-38)		-0.4 ± 2§	2.3 ± 7.1§		-0.4, ± 4.8§	21 ± 72§				
Charache, 1996 [39]	HU	152	24 months	2									55‖
	Placebo	147	28 months ± 6	5 or 6									79¶
Charache, 1995 [21]	HU	152	24 months		8.6 ± 6.8		9.1 ± 1.5		231 ± 100	(3)		ACS, 25#	48**
	Placebo	147	28 months		4.7 ± 2.2		8.5 ± 1.3		300 ± 99	(6)		ACS, 51††	73‡‡††

Evidence Table 7. Efficacy Results of Randomized Controlled Trials in Sickle Cell Disease (continued)

Author, year	Interven-tion	N	Mean durations of drug Mean duration of followup	Deaths, n (%)	Hb F, % ± SD	F cells, % ± SD	Hemo-globin, g/dl	MCV, fl ± sd	Retic-ulocyte count, k/ul	Weight change, kg (%)	Change in peak power, watts ± sem	Pain crises & admis-sions	Trans-fusion
Other controlled trial													
Ferster, 1998 [44]	HU	22	6 months		10.8§ §§		0.4§ ‖‖	10.41 § §§	-46§ §§			1.1¶¶	
	Placebo	22	22 months									2.8##	

* Stroke
† Mean ± SEM, p = <0.005
‡ (Mean ± SEM)
§ Change from baseline, mean ± SD where applicable.
‖ Patients, P = 0.002, RBC units transfused, 423 P=0.002
¶ Patients, RBC units transfused, 670.
# p <0.001, Median time to first crisis, 3 months, p < 0.01, Pain crises per year, 2.5 (OR 0.6-7).
** p <0.001, RBC units transfused, 336.
†† Median time to first crisis, 1.5 months. Pain crises per year, 4.5 (IQR 2-10.2)
‡‡ RBC units transfused, 586
§§ p < 0.001
‖‖ p = NS
¶¶ p = 0.016, Days hospitalized, 3.6, p = 0.0027, hospitalizations per year
Days hospitalized, 11.7, hospitalizations per year

ACS=acute chest syndrome; HbF = Fetal hemoglobin; HU=hydroxyurea; IQR = interquartile range; MCV = mean corpuscular volume; MSH = Multicenter Study of Hydroxyurea for Sickle Cell Anemia; NR = not reported; OR = odds ratio; RBC = red blood cells; SD = standard deviation; SEM = standard error of the mean.

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
HUG-KIDS											
Kinney, 1999 [68]	Children-prospective	HU	84	17.8 (7.2)†	66.5 (19.6) †	9 (1.4) †	101.3 (10.2) †	9,200 (3200) †			Hematological effects were attained by 6 months (even before MTD). There was little difference between 6 and 12 month data. Continued weight gain and linear growth.
		Baseline (pre-HU)		7.3	34.6 (17.8)	7.8	85.9 (6.6)	13,600			
Ware, 2002 [73]	Children-prospective	HU	68 (53 with suff-icient data)	Median = 17.6, [2.9-32.4]							HbF% was predicted by HbF% at baseline (p=.001) and Hb at baseline (p=0.01); HbF% was negatively associated with # of pills returned (p=0.02), postively with change in Hb (p<0.0001), MCV (p=0.01) and decline in reticulocytes (p=0.01), and decline in white blood count (p=0.006).
		Baseline (pre-HU)		6.7		7.7	85.7	14,000			
Zimmer-man, 2004 [81]	Children-prospective	HU	122	19.7(8.5)‡		9.7(1.3) ‡	105.8 (13.8) ‡	7.0			Efficacy (in Hb, MCV, % Hb F, WBC count, ANC, reticulocyte, bilirubin) maintained over 7 years of follow-up.
		Baseline (pre-HU)		7.6		8.2	84.4 (8.5)	12,400			

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ Design	Study Arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
HUSOFT											
Wang, 2001[60]	Children-prospective	HU	28	20.3 (4.9)	76.2 (12.4)	8.8 (1.2)	90 (9.6)	10,100 (3,200)			Outcomes are for 21 patients who completed 2 years of treatment (not necessarily on MTD).
		Baseline (pre-HU)		21.8 (7.8)	80.6 (14.1)	8.5 (1.2)	81.7 (8.0)	12600 (4,400)			
		CSSCD		10.9 (7.9)	65.4 (11.2)	7.7 (1.0)	84.1 (10.1)	14,300 (2,400)			
Hankins, 2005 [72]	Children-prospective	HU	21	23.7 (7.4) ‡	82.6 (7.9) ‡	9.1 (1.4) ‡	95.1 (10.4) ‡	10,100 (5,000) ‡	33.8/ 100 pt-yr comp-ared to 32.4/ 100 pt-yr in CSSCD §		Outcomes are for 17 children after 4 years of therapy.
		Baseline (pre-HU)		21.8 (7.8)	80.6 (14.1)	8.5 (1.2)	81.7 (8.0)	12,600 (4,400)			
French Cluster											
de Montalem-bert, 1997 [76]	Children-prospective	HU	35	13.7 [3.2-27.0] †		9 (1.4) p= 0.03					All but two patients had decreased frequency or termination of crises. No clear difference in weight or height velocity.
		Baseline (pre-HU)		4 [0.85-13.9]		8.4 (1.2)					
Maier-Redel-sperger, 1998 [75]	Children-prospective	HU	29	13 (9.4)	54.2 (22.1)	9.1 (0.9)	101.8 (15.9)				
		Baseline (pre-HU)		4 [0.85-13.9]	24.4	8.4 (1.2)	84.5				

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Belgian Cluster											
Ferster, 2001 [58]	Children-prospective	HU	93	16.7(10.6) ‖		8.8 (1.2) ‖	94 (11) ‖			1.06 / pt-yr	Acute chest were 3.5/100 pt-yr, with no strokes during study.
		Baseline (pre-HU)		7.3		8.2	91 [70-118]			2.76 (2.3) / pt-yr	
Gulbis, 2005 [82]	Children-prospective	HU	70	1.4 g/dl (HbF)		8.7 [6.8-13] at 3 years	91[70-118]		2.2 / pt-yr that required hospitalization	1.38 / pt-yr	There were 426 total patient years of follow-up. Hematological outcomes at 3 years (n=70) were 1 stroke and 5 transient ischemic attacks (1.3/100 pt-yrs).
		Baseline (pre-HU)	109	0.3 g/dl (HbF)		8.2 [6.7-10]	83 [68-113]			3.2 (2.7) / pt-yr	
Others											
el-Hazmi, 1992 [45]	Adults-prospective	HU	21	19.8 (4) †		NR †	NR †	6,629 (2603) †			P-value relative to baseline
		Baseline (pre-HU)		11.8 (3.5)				14,0667 (6,716)			
Charache. 1992 [46]	Adults-prospective	HU (at MTD)	32 completed	15 (6) †	73 (17) †	9.7 (1.8) †	117 (15) †	8400 (1400) †	1.3 (2) / 6-months [0 -9] ‖		Mean 4.3 kg weight gain†
		Baseline (pre-HU)	49	4 (2)	28 (14)	8.4 (1.4)	94 (8)	13,400 (3200)	4 [0-20]/6 months		
Voskaridou, 1995 [78]	Adults-prospective	HU	14	22.9 (7.7)		9 (1.3)	95 (14.1)				
		Baseline (pre-HU)		3.6 (2.1)		9.0 (1.2)	71.9 (5.7)				

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Others (continued)											
Scott, 1996 [77]	Children-prospective	HU	15	15.2 (9.8,) [4.1-31] ¶		9.5 (1.5) [7.7-13.1]	100 (15) [80-127) †			3/yr (4)	
		Baseline (pre-HU)		6.9 (6.2)		8.2 (1.0)	85 (11)			7/yr(2.4)	
Loukopoulos, 1998 [69]	Adults-retro-spective	HU	44	23.1 (9.2)		9.3	98.1 (15)				
		Baseline (pre-HU)		6.7(4.7)		8.9	75.7 (11)				
Olivieri, 1998 [64]	Children-prospective	HU	17	16.7 (1.8)		10.2 (3.6)	104 (3)		1.2/yr(0.4)	1.7/yr (2.0)	Acute chest syndrome rate declined from 1.3/yr to 0.2/yr. No difference in number of pitted red blood cells (n=12 children) was observed.
		Baseline (pre-HU)		7.6 (1.6)		8.9 (4.3)	87 (7)		3.1/yr(0.5)	6.7/yr (2.8)	
Loukopoulos, 2000 [74]	Adults-prospective	HU	69	Hematological results were reported stratified by sex and by genotype at baseline, also at maximum HbF during first 6 months and maximum HbF during whole study.							Mean clinical severity score of 81.7 over 12,018 pt-weeks was down from baseline score of 1182 (arbitrary scale).
Rigano, 2001[71]	Adults-prospective	HU	22	25.2 (5.2)‡		10 (1.5)	96.4 (7.2) ‡	10,200 (3,900)	1.1 (1.8)/yr median = 0.5‡	0.5 (1.6)†; hospital days 1.2 (2.3) †	
		Baseline (pre-HU)		7.5 (5.3)		6 (1.3)	73.9	11,400 (3900)	7 /yr median = 9 (all crises including pain)	hospital days 22.4	

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Others (continued)											
Al-Jam'a, 2002 [70]	Adults-Children-prospective	HU	27	25.7 (7.3) median= 25[#]		10.7 (1.4) median= 10.8[#]		6,260 (2,580) median 5,600[#]		0.93 (2.2) median = 0[†]; hospital days 5.1 (13.5) median 0[#]	
		Baseline (pre-HU)		12.6 (5.4)		9.71 (1.2)		8,990 (3,480)	6.5 /yr(2.8)	hospital days 33.9 (26.1)	
Ferguson, 2002 [52]	Adults-retrospective/ effectiveness	HU at least 24 months	30							2.1 /yr p=.04 relative to baseline	14 patients were treated for 48 months. Between baseline and year 4: admissions decreased from 3.56 to 1.64 /yr, transfusions 8.64 to 3.00/yr.
		Baseline (pre-HU)								3.1/yr	
		HU less than 24 months	30							4.8/yr p=0.49 relative to baseline	
		Baseline (pre-HU)								5.7 /yr	
Cummins, 2003 [61]	Adults-prospective with comparison group	HU	15						1.4 /yr (2.1)[#]	1.1/yr (2.4)	Significant improvement in General Health perception (SF36) over CBT group
		CBT	21						4.3/yr (4.3)	0.9/yr (1.2)	

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Others (continued)											
Ware, 2004 [67]	Children-prospective	HU	35	18.6 (6.6)		9.2(1.4)	112(9)	7300 (2500)			Data collected on two groups; patients initiating HU after an abrupt halt to transfusion therapy, and patients initiating HU before transfusion therapy was completely halted. Pooled data was presented here. Stroke recurrence rate 5/7/100 pt-yrs (7 children, 4 of whom were noncompliant with HU).
Bakanay, 2005 [51]	Children-retrospective	HU	226								Very little description of study population and treatment, also had concern about confounding by indication.
Vicari, 2005i [80]	Adults-prospective	HU	22	10.2 (5)**		8.6(1.1)‡					Outcomes reported by haplotype.
		Baseline (pre-HU)		5 (3)		7.9 (0.9)					
Kratovil, 2006 [62]	Children-prospective with a comparison group	HU	24	11.79, [3.8 - 25.4]†† relative to untreated		8.2 [5.2 - 10.6] ‡‡ relative to untreated					Mean of maximum TCD =111.2 cm/sec
		No HU									Mean of maximum TCD =124 cm/sec
Ataga, 2006[79]	Adults-prospective	HU (with PHTN)	9								In patients with PHTN, 9/26 (35%) were on HU. In patients without PHTN, 32/50 (65%) were on HU.
		HU (No PHTN)	32								

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Others (continued)											
Svarch, 2006 [50]	Children - retrospective	HU	51	12.4 (7.9) †		8.5 (1) p=.0001		9,800 (2,100) p=0.12	Median 0.8/yr [0-2]	0.5 [0-4]	Resource-poor environment
		Baseline (pre-HU)		6.4		7.8		10,900	Median 3/yr	4 [0-6]	
Zimmerman, 2007 [63]	Children - prospective	Patients with increased TCD velocities	37	22.7 (7.9) median= 23.3 †		9.4 (1.1) median= 9.4 †	104 (9) median †				Significant decline in TCD of RMCA, LMCA, RACA, LACA, and LPCA, but not RPCA. Stroke rate on treatment 0.52/100 pt-years, RMCA on treatment 134 cm/sec, p<.0001.
				10.3		7.8	86 (8)				RMCA 162 cm/sec
McKie, 2007 [49]	Children-retrospective	HU with no micro-albuminuria	19								16/17 remained free from microalbuminuria during treatment
		HU + micro-albuminuria	9	19.8 (21.5) n=7		8.6 (1.0)	104.7 (7.1)				4 of 9 normalized microalbuminuria during treatment
		HU + micro-albuminurea at baseline	9	8.6 (1.0)		8.0 (1.4)	92.1 (7.0)				
		Baseline (pre-HU)	154								

Evidence Table 8. Efficacy and Effectiveness Results of Observational or Single Arm Studies of Hydroxyurea in Sickle Cell Disease (continued)

Author	Patients/ design	Study arm	N	Hb F%*	%F cells*	Hemo-globin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admiss-ions*	Comments
Others (continued)											
Harrod, 2007 [56]	Children-cross sectional	HU, no splenectomy	46								Mature reticulocytes with Howell-Jolly bodies: 3533 ± 2665
		No HU, no splenectomy	58								1263 ± 1193
		HU with splenectomy	11								4984 ± 2037
		No HU with splenectomy	10								2101 ± 945
Hankins, 2007 [65]	Children-prospective	HU	52								6 patients had recovery of splenic function; 24/25 had stable brain MRIs
Santos, 2002 [59]	Children-prospective	HU	21	15.1[§§]							10 patients had improvement in splenic function

* Mean, (SD) [range] unless otherwise noted
† $p \leq 0.0001$
‡ $p \leq 0.001$
§ $p \leq$ not significant
‖ $p \leq 0.01$
¶ $p \leq 0.002$
# $p \leq 0.005$
** $p = 0.0002$
†† $p \leq 0.00001$
‡‡ $p = 0.057$
§§ Change from baseline

ANC = absolute neutrophil count; CBT=cognitive based therapy; CSSCD= Cooperative Study of Sickle Cell Disease; Hb = hemoglobin; HbF = fetal hemoglobin; HTN=hypertension; HU = hydroxyurea; HUG-KIDS = Safety of Hydroxyurea in Children With Sickle Cell Anemia; LACA=left anterior cerebral artery; LMCA = left main coronary artery; LPCA= left posterior cerebral artery; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NR = not reported; PHTN = pulmonary hypertension; pt-yr = patient-year; RACA=right anterior cerebral artery; RMCA = right middle cerebral artery; RPCA = right posterior cerebral artery; SCD = sickle cell disease; SD = standard deviation; TCD = transcranial Doppler; WBC = white blood cell.

Evidence Table 9. Description and Results of Studies (Cohort with Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose: Titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Athanassiou, 2006 [85]	Europe	**Inclusion**: Sß° thal, S α+ thal	HU		60 months	Index of rigidity (IR)	31.9± 12.2*	Mean elastic shear modulus (u x 10^-3 dyn/cm)	15± 1.3†		
			SCD no HU				46.1± 13.08		21.1± 2.1		
			NO SCD or HU				13.15± 0.5				
Iyamu, 2005 [86]	North America	**Inclusion**: Age 8-21; SCA; in steady state **Exclusion**: Transfusion in last 6 months; smoking; SA	HU steady-state	15-30 mg/kg/d	Cross-sectional	Hb F %	13.8	Nitric oxide synthase (nmol/ml/min)	0.50	Arginase (U/nmol/10^8 cells ± SEM)	1.36± 0.20‡
			No HU steady-state	No HU			6.8		0.27		3.31± 0.29
			African American Hb AA	No HU					0.32		0.23
Nahavandi, 2002 [87]	North America	**Inclusion**: SCA **Exclusion**: Transfusion within 3 months; significant renal insufficiency; infection; PHT	HU	1200 mg/d	35	Hb F% (range)	17 (6.7-28)	Cyclic GMP (pmol/ml ± SEM)	2.45± 0.32	Nitric oxide metabolites (microM ± SEM)	29± 2.5
			Non-HU steady state	No HU			3.6, (1.7-6)§		1.75± 0.42		19± 1.8§
			HU during VOC	1200 mg/d			19 (7-31)		2.56± 0.3		32± 5
			Non-HU during VOC	No HU			4.2 (1.5-6.7)§		1.56± 0.1§		17± 1.7§
Lapoumeroulie, 2005 [88]	Europe	**Inclusion**: Children, SCA in steady-state	Clinical events (8 on HU, 10 untreated)		> 12 months	Endothelin-1 (pg/ml ± SEM)	1.32± 0.17				
			steady state, No HU				0.65± 0.11				
			steady state, HU				0.37± 0.05†				
			Healthy AA				0.65± 0.07				

Evidence Table 9. Description and Results of Studies (Cohort with Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose: Titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Tavakkoli, 2004 [89]	North America	**Inclusion**: SCA **Exclusion:** Transfusion in last 3 months	HU	1000-1500mg: N/A		TNF-α (pm/ml)	4.89				
			Steady state condition, not on HU				3.78				
			VOC, on HU	1000-1500mg: N/A			6.45				
			VOC, not on HU				5.86				
Teixeira, 2003 [92]	South America/ Mexico	**Inclusion**: SCA, S ß+ thal; S ßo thal; S α+ thal; SC; Age >12	HU		2 to 60 months	Hb F (%)	14.2± 8.3[§]	Hb (g/dl)	9.6± 2.2[§]		
			No HU				8.8± 4.1		8.1± 0.9		
Heeney, 2003 [90]	North America	**Inclusion**: Children; SCA; S ß+ thal; S ßo thal **Exclusion**: HU before age 5 years; No labs before HU; <12 months of HU; Unknown or rare UGT1A genotype	UGT1A 6/6	15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/ day	at least 12 months	Hb F (%)[‡]	16.4	Hb (g/dl)[‡]	1.7	Total bilirubin (mg/dl)[‡]	-1.4
			UGT1A 6/7	15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/ day			12.1		1.5		-1.3
			UGT1A 7/7	15-20 mg/kg/day: every 8 weeks to max of 30-35 mg/kg/ day			13.5		1.9		-2.8

Evidence Table 9. Description and Results of Studies (Cohort with Comparison Arm) Focusing on Biomarkers in Hydroxyurea Treatment of Sickle Cell Disease (continued)

Author, year	Location	Inclusion & exclusion criteria	Intervention	Starting dose: Titration	Planned treatment duration	Outcome	Result	Outcome	Result	Outcome	Result
Nahavandi, 2003 [91]	North America	**Inclusion**: Age 18-48; SCA **Exclusion**: ACS; transfused in last three months; renal insufficiency; infection; hypoxemia	HU, no VOC	1000-1500 mg/day		Venous oxyhemo-globin (%)	65	Venous reduced Hb (%)	28	Nitric Oxide Metabo-lites (µM)	17 ± 9[§]
			No HU no VOC				60		36		
			HU and VOC	1000-1500 mg/day			81		13		
			No HU, VOC				73		22		

* p = 0.02
† p = 0.03
‡ p < 0.001
§ p < 0.05

AA = African American; ACS = acute chest syndrome; GMP = granual membrane protein; Hb = hemoglobin; HU = hydroxyurea; IR = index of rigidity; N/A = not applicable; PHT = pulmonary hyptertension; S ß+ thal = S ß+ thalassemia; S ßº thal = S ßº thalassemia; S α+ thal = S α+ thalassemia; SA = Substance abuse; SC = Sickle-Hemoglobin C Disease; SCA = sickle cell anemia; SCD = Sickle cell disease; SEM = standard error of the mean; TNF-α = tumor necrosis factor alpha; VOC = vaso-occlusive crisis.

Evidence Table 10. Patient Characteristics in Studies of Biomarker Studies on Treatment with Hydroxyurea in Sickle Cell Disease†

Author, year	Intervention	N	Age, mean (SD) [range]*	Male, n (%)	Genotype/ haplotype (%)	Last observation
Athanassiou, 2006 [85]	HU	22	Median, 30; [20-46]	(14)	NR	NR
	SCD no HU	14	Median, 32; [25-42]	(5)		
	NO SCD or HU	5	Mean, similar age	(40)		
Iyamu, 2005[86]	HU, steady state	23	13.5 [9-21]	NR	SS, (100)	Cross-sectional--once
	No HU, steady state	12	12.5 [(8-19]		SS, (100)	
	African-American Hb AA	10	15.6 [11-21]		Hb AA (100)	
Nahavandi, 2002 [87]	HU	12	32 [18-47]	9	SS, (100)	NR
	Non-HU steady state	26	34 [18-53]	8		
	HU during VOC	14	34 [18-48]	8		
	Non-HU during VOC	12	31 [18-45]	NR		
Lapoumeroulie, 2005 [88]	Clinical events; Hb SS 8 HU, 10 none	18	[2.9-13.2]	NR	SS, (100)	NR
	Hb SS, no HU	17	[3.0-14.9]			
	Hb SS, HU	16	[3.5-15.1]			
	Nl AA, controls none	26	[2.6-15.8]			
Tavakkoli, 2004 [89]	HU	10	32 [18-47]	NR	SS, (100)	NR
	Steady state condition, not on HU	10	34 [15-53]			
	VOC, on HU	10	34 [18-48]			
	VOC, not on HU	10	31 [18-45]			
	No HU	30				
Teixeira, 2003 [92]	HU	31	NR	NR	NR	NR
	No HU	30				
Heeney, 2003 [90]	HU UGT1A 6/6	17	Mean, 11.4	13	NR	At least 12 months
	HU UGT1A 6/7	24	Mean, 11.3	15		
	HU UGT1A 7/7	18	Mean, 12.6	11		
Nahavandi, 2003 [91]	HU	12	32 [18-47]	9	SS, (100)	NR
	HU untreated, with VOC	12	31 [18-45]	8		
	HU treated, with VOC	14	34 [18-48]	8		
	HU untreated control, no VOC	31	34 [18-53]	NR		

* Unless otherwise specified. † Recruitment start and end dates as well as race of patients were unreported for all studies in this table.

AA = African American; Hb = hemoglobin; HU = hydroxyurea; NR = not reported; SCD = sickle cell disease; SD = standard deviation; SS = Sickle Hemoglobin SS Disease; VOC = vaso-occlusive crisis

Evidence Table 11. Adequacy of Reporting in Biomarker Studies in Sickle Cell Disease*

Author, year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Adjustment when reporting outcome comparisons	Objective outcome	Losses to follow-up	Q Score
Athanassiou, 2006 [85]	0.5	0.5	1	0	0	0	2		29
Iyamu, 2005 [86]	0	0.5	1	1	0	0	2		32
Nahavandi, 2002 [87]	0.5	1	1	1	0	0	2		39
Lapoumeroulie, 2005 [88]	1	0	1	0	0		2		29
Tavakkoli, 2004 [89]	1	1	1.5	1.5		0	2		58
Teixeira, 2003 [92]	1	0	0.5	0.5	0	0	1.5		23
Heeney, 2003 [90]	1	2	1.5	2	0	0	2		57
Nahavandi, 2003 [91]	1.5	1.5	2	1	0	0	2	0	50

* Blank cells represent categories that were not applicable to the question

Q = quality

Evidence Table 12. Toxicity Results in Randomized Controlled Trials of Hydroxyurea Treatment in Sickle Cell Disease

Author, year	Intervention	N	Mean drug duration / Mean follow-up duration	Death, n (%)	Thrombo-cytopenia	Netropenia, %	Absolute neutrophil count, ul +/- SD	% GI disturbance,	% Rash or Nail changes	Lower extremity ulcers	Other
MSH											
Steinberg, 2003 [43]	HU	152	NR / 7.7 years	36 (23.7)							Malignancy, 1 Sepsis/Infection, 18 Hepatic Failure, 3 Renal Failure, 14
	Placebo	147	NR / 7.4 years	39 (26.5)							Malignancy, 1 Sepsis/Infection, 20 Hepatic Failure, 10 Renal Failure, 14
Steinberg, 1997 [40]	HU	152	24 months				1,900* ± 2,400				
	Placebo	147	28 months (range,21-38)				400 ± 2,200				
Charache, 1996 [39]	HU	152	24 months	(2)		66		59	25	15	Hair Loss, 18 Fever, 91 Aplastic crisis, 1 Aseptic Necrosis, 9 Lymphadenopathy, 45 Bleeding Tendency, 7
	Placebo	147	28 months ± 6	(6)				58	25	17	Hair Loss, 28 Fever, 96 Aplastic crisis, 5 Aseptic Necrosis, 9 Lymphadenopathy, 56 Bleeding Tendency, 3
Charache, 1995 [21]	HU	152	24 months	(2)	4		4,900± 2,000			15	Hemoglobin > 12.8 g/dl , 11 Platelets >800,000/ul, 4
	Placebo	147	28 months	(5)	5		6,400± 2,000			17	Hemoglobin > 12.8 g/dl , 1 Total Bilirubin > 10 mg/dl, 4
Belgian Study											
Ferster, 1998 [44]	HU	25	6 months		2						No clinically significant toxicity
			22 months		0						

Evidence Table 12. Toxicity Results in Randomized Controlled Trials on Sickle Cell Disease (continued)

*Change from baseline, mean ± SD

GI = gastrointestinal; HU = hydroxyurea; NR = not reported; SD = standard deviation

Evidence Table 13. Toxicities of Hydroxyurea Reported in Single Arm Studies in Sickle Cell Disease

Author	Group	N	Primarily toxicity study	Deaths, n (per pt/yr)	Neutro-penia	Thrombo-cytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
HUG-KID										
Kinney, 1999 {#2977}	HU	84	Yes		56 with ANC< 2000/µl	7			5	
Zimmerman, 2004 {#2960}	HU	122		(2/ 455)			0			No increase in the acquired illegitimate VDJ rearrangements.
HUSOFT										
Wang, 2001 {#2964}	HU	28		1	17 with ANC< 1500/µl 6 with ANC< 500/µl	1 with <80,000/µl				
Hankins, 2005 {#2954}	HU	21		1	21 episodes in 10 patients in year 3, 21 episodes in 9 patients in year 4	2 in year 5 1 in year 6				Severe anemia 3 times in 3 patients in year 3; 4 times in 1 patient in year 4.
French Cluster										
de Montalembert, 1997 {#2980}	HU	35							5	
de Montalembert, 1999 {#2976}	HU	101	Yes		2 with ANC 500-1000/µl 3 with ANC 1000-1500/µl	4 with 90-100,000/µl	1	1	8	
de Montalembert, 2006 {#2962}	HU	225	Yes	1	8	8	1 (same patient as in earlier study {#2980})			81 patients discontinued therapy, mostly for lack of efficacy

Evidence Table 13. Toxicities of Hydroxyurea Reported in Single Arm Studies in Sickle Cell Disease (continued)

Author	Group	N	Primarily toxicity study	Deaths, n (per pt/yr)	Neutro-penia	Thrombo-cytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Belgian Cluster-										
Gulbis, 2005 {#2877}	HU	109		1 (0.23/ 100)						Transient hematological toxicity in 1.4/100 pt-yrs
Others										
el-Hazmi, 1992 {#154}	HU	21								6 with leukopenia (WBC<4500/µl)
Charache. 1992 {#2991}	HU	49			17	1				No unusual infections; karotypic analysis showed no difference in % abnormal chromosomes pre and post treatment
Voskaridou, 1995 {#2988}	HU	14								Leukopenia or thrombocytopenia in 6; rapidly reversed by holding therapy
Scott, 1996 {#2984}	HU	15		1					1	Anemia in 3 of 13 completing study
Olivieri, 1998 {#2979}	HU	17	Yes		9	3			1	
Hanft, 2000 {#197}	HU and no HU (SCD and MPD)	95	Yes							HPRT cloning efficiency and VDJ recombination events described in text.
Loukopoulos, 2000 {#2971}	HU	69						3	0	2 with severe anemia; 0/40 with oncogenes; 0/10 with cytogenetic abnormalities
Chaine, 2001 {#2970}	HU	17	Yes					5	13	Prior leg ulcer associated with ulcer on treatment (p<.005); patients with ulcer were older than those without (p<.001); 3 of 5 resolved with holding HU

Evidence Table 13. Toxicities of Hydroxyurea Reported in Single Arm Studies in Sickle Cell Disease (continued)

Author	Group	N	Primarily toxicity study	Deaths, n (per pt/yr)	Neutro-penia	Thrombo-cytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
Others (continued)										
Ferguson, 2002 {#2908}	HU ≥ 24 months	30								Stated no adverse events
	HU < 24 months	30								
Schultz, 2003 {#2959}	Patients with SCD and cancer	49	Yes				7 of 16,613; not all on HU			49 cancers in patients with SCD described, in survey of providers
	Patients on HU with cancer	3					1			Unknown # taking HU, but among 49 patients, 3 were on HU, including 1 with leukemia
Vicari, 2005i {#2957}	HU	22			3					
Khayat, 2006 {#28}	HU	8	Yes							There was no significant difference in mitotic index (p>0.05). There was no significant difference in chromosomal aberrations (p>0.05) pre-and post-treatment

ANC = absolute neutrophil count; HPRT = hypoxanthine phosphoribosyl transferase; HU = hydroxyurea; HUG-KID = pediatric hydroxyurea safety trial; HUSOFT = The Hydroxyurea Safety and Organ Toxicity trial; MPD = myeloproliferative disorders; SCD = Sickle Cell Disease; WBC = white blood cells.

Evidence Table 14. Rarely Reported Adverse Events of Hydroxyurea Treatment for Sickle Cell Disease in Observational Studies

Adverse event	Author, year	# events/# exposed patients
Labyrinthitis	Vicari, 2005i [80]	1/22
Myelotoxicity	Vicari, 2005i [80]	2/22
Dyspepsia	Rigano, 2001 [71]	2/22
	Olivieri, 1998 [64]	1/17
	Yan, 2005 [188]	2/17
Headache	Rigano, 2001 [71]	2/22
	Kinney, 1999 [68]	3/101
	de Montalembert, 1999 [55]	12/84
	Scott, 1996 [77]	2/15
Pancreatitis	Loukopoulos, 2000 [74]	2/69
Need for splenectomy	Loukopoulos, 2000 [74]	2/69
Renal failure	de Montalembert, 1997 [76]	1/35
	Yan, 2005 [188]	1/17 (thought to be unrelated to drug)
Increase in creatinine	Olivieri, 1998 [64]	11/17
Amenorrhea	de Montalembert, 1997 [76]	1/35
ALT elevation	Kinney, 1999 [68]	11/84
Pancytopenia	de Montalembert, 2006 [48]	1/225
Hypersplenism	de Montalembert, 2006 [48]	6/225
Ulcer	Chaine, 2001 [66]	5/17
Conjunctivitis	Olivieri, 1998 [64]	1/17
Hyperbilirubinemia	Zimmerman, 2004 [81]	2/122
Intracranial hemorrhage	Scott, 1996 [77]	1/15

Evidence Table 15. Toxicity Results from Case Reports in Hydroxyurea Treatment of Sickle Cell Disease Only

Outcome	Number of case reports	Females/ Males	Mean age at toxicity	Median # of weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	Level of evidence for this outcome (1, 2, 3)*
Leg ulcer	1	1/0	45	104	0	0	1	3
Leukemia	3	3/0	32	288	0	0	3	3
Cytopenia	1	1/0	26	153	0	1	0	2
Avascular necrosis	2	2/0	17	NR	0	0	2	3
Splenomegaly	1	1/0	32	NR	0	0	1	3
Cryptosporidial infection	1	1/0	36	80	0	0	1	3
Intracerebral hemorrhage	1	0/1	22	52	0	0	1	3
Hodgkin's lymphoma	1	0/1	8	24	0	0	1	3
Low sperm count/ Motility decrease	4	0/4	31	128	0	0	4	3
Acute myocardial infarction	1	0/1	28	NR	0	0	1	3
Hyperpigmentation of skin	2	1/1	16	75	0	0	2	3

*WHO causality assessment

HU = hydroxyurea; NR = not reported.

Evidence Table 16. Description of Hydroxyurea Toxicity in Randomized Controlled Trials in Diseases Other than Sickle Cell Disease

Author, year	Location	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention	Starting dose*	Jadad[29] score
HIV						
Frank, 2004[†] [104]	North America	Oct 1996 – Jan 1998	**Inclusion:** Age >18; HIV+; ANC >1000/cmm, platelet >75,000/cmm; Hb >9.2g/dL for men, >8.8g/dL for women, CD4 200-700 **Exclusion:** Preg; renal failure; liver failure; prior HU; pancreatitis; peripheral neuropathy	ddI		4
				HU (low dose) with/without ddI	HU 1000 mg/d	
				HU (high dose) with/without ddI	HU 1500 mg/d	
Havlir, 2001 [189]	North America	Nov 1998 – Jul 1999	**Inclusion:** Age >12 years; HIV+; at least 6 months on IDV, ZDV (or d4T), and 3TC); HIV RNA <200/ml; CD4 >200/ul, >100/ul prior to starting IDV **Exclusion:** ANC <1000/ul; liver failure AST, ALT >3 ULT, documented or suspected hepatitis; prior treatment with HIV protease inhibitor other than IDV or both ddI and d4T; thrombocytopenia <75000/ul; anemia, <8.9 for female and 9.1 g/dl for men; history of grade 2 or greater peripheral neuropathy	HU IDV ddI d4T	HU 600 BID	2
				IDV ddI d4T + placebo		
				IDV ZDV (or d4T) 3TC		
Swindells, 2005 [111]	North America	Sep 1999 – Apr 2007	**Inclusion:** Age >12; neutrophil count >1000; HIV-1 RNA between 400-100,000 and CD4 >100; failure of initial anti-retroviral treatment; had not received non-nucleoside reverse transcriptase inhibitors, ABC or ddI; Hb >9 for women >10 for men; plts > 75,000; estimated creatinine clearance >50mL/min, serum lipase <ULN, serum amylase <1.5x ULN, ALT<5x ULN **Exclusion:** Preg or breast feeding; acute hepatitis within 6 months; immunotherapeutic vaccine or cytotoxic agents within 8 wks before start of study; hx of pancreatitis or peripheral neuropathy within 2 mo before study start	ABC/EFV/ ddI and HU	HU 500 mg BID	2
				ABC/EFV/ ddI		
Beeson, 1999 [190]	Europe	Jun 2005 – Jun 2005	**Inclusion:** Hb >10g/dL; normal amylase; neutrophil >1500/mcl; included if leucopenia; included if plt >150k/mcl; absence of current HIV-associated disease or prior hx of any AIDS-defining illness	ddI + HU	HU 500 mg BID	3
				ddI		
Bloch, 2006 [191]	Australia	Jan 2000 – Feb 2002	**Inclusion:** acute primary HIV infection	IDV/RTV/ddI + either stavudine or lamiduvine + HU	HU 500 mg BID	2
				IDV/RTV/ddI + either stavudine or lamiduvine		

Evidence Table 16. Description of Hydroxyurea Toxicity in Randomized Controlled Trials in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention	Starting dose*	Jadad[29] score
Rutschmann Cluster/ HIV						
Rutschmann, 1998 [192]	Europe		**Inclusion:** Age ≥ 20 years; HIV+; CD4 from >200 to <500 (twice); two HIV RNA >1000/ml **Exclusion:** prior HU; pancreatitis; alcohol; peripheral neuropathy; use of d4T	ddI/d4T/HU‡	HU 500 mg bid	3
				ddI/stavudine + placebo		
Rutschmann, 1998 [193]	Europe		**Inclusion:** HIV+; CD4 200-500/ul; HIV RNA >1000/ml; staveudine and HU naïve **Exclusion:** > 6 months of ddI	ddI/stavudine/HU§	HU 500 mg BID	1
				ddI/stavudine		
Rutschmann, 2000‖ [194]	Europe		**Inclusion:** CD4 between 2---500; HIV RNA >1000 x2 **Exclusion:** prior HU; prior stavudine; ddI >6 months	ddI/stavudine/HU	HU 500 mg BID	2
				Placebo, ddI stavudine		
CML						
Hehlmann, 2003 [113]	Europe	Feb 1991 - Dec 1994	**Inclusion:** newly diagnosed CML in chronic phase **Exclusion:** prior therapy	HU	40mg/kg/d	2
				IFN-alpha 2a + HU	IFN $5*10^6$IU/m2/d + HU added as required	
no author, 1998 [115]	Europe	Dec 1987 - Dec 1992	**Inclusion:** Age ≥ 18; previously untreated, newly diagnosed Ph+ CML in chronic phase; BCR-ABL (+); WHO performance status 0,1, or 2; adequate renal/hepatic fxn (bilirubin and creatinine <2x ULN) **Exclusion:** cytogenetic abnl other than -y, +8 or second 22q-	HU	NR	2
				IFN and HU if needed	3 million units 5x/wk	
Hehlmann, 1994 [114]	Europe	Jul 1983 - Jan 1991	**Inclusion:** newly diagnosed, not pretreated CML in chronic phase; fatigue or weight loss or fever or organomegaly-related symptoms or WBC >50,000 or Thrombocytosis >1 million exclusion, Ph(-) or unknown Ph status	HU	40mg/kg/d	3
				IFN	4 million units/m^2	
				Busulfan	0.1mg/kg/d	
Broustet, 1991 [116]	Europe	May 1987 - Jul 1990	**Inclusion;** Age >18; Ph+ CML **Exclusion:** prior chemo; trisomy 8, isochromosome 17, double Ph+	HU		3
				IFN	4 million units/m^2	
Hehlmann, 1993 [195]	Europe	Jul 1983 - Jan 1991	**Inclusion:** newly diagnosed CML in chronic phase **Exclusion:** not in chronic phase; no treatment required; prior treatment with IFN or irradiation or cytostatics; lack of consent; second neoplasia; any other reason that made treatment with protocol unlikely	HU	40 mg/kg/d	2
				Busulfan	0.1 mg/kg/d	

Evidence Table 16. Description of Hydroxyurea Toxicity in Randomized Controlled Trials in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Recruitment start date - end date	Inclusion and exclusion criteria	Intervention	Starting dose*	Jadad[29] score
Solid Tumor						
Stephens, 1984 [121]	North America		**Inclusion:** advanced prostate cancer (stage D disease) **Exclusion:** unstable ischemic or rheumatic heart disease; heart failure	HU	3600mg/m^2, 2days/week	2
				Adriamycin + cyclophosphamide	Adriamycin at 40 mg/m^2 and cyclophosphamide at 200 mg/m^2; reduced to AC 20+cyclophosphamide 100 if in poor-risk group	
Loening, 1981 [122]	North America	May 1977 – Apr 1979	**Inclusion:** histologically proven prostate CA with distant mets and progression	HU	3g/m^2	2
				Cyclophosphamide	1g/m^2	
				Methyl-CCNU	175mg/m^2	
Najean Cluster/ PV						
Najean, 1997 [123]	Europe	May 1997 – Jun 2005	**Exclusion:** age > 65 excluded; previous treatment with radiotherapy; previous treatment with chemotherapy	HU	25 mg/kg/d	2
				Pipobroman	1.25 mg/kg/d	
Kiladjian, 2006¶ [103]				HU		1
				Pipobroman		
ET						
Harrison, 2005 [131]	Europe	Aug 1997 – Aug 2002	**Inclusion:** Age at least 18 yr with ET	HU + aspirin 75mg/d	HU: 0.5-1g/d	2
				Anagrelide + aspirin 75mg/d	anagrelide 0.5mg BID	
Finazzi Cluster/ET						
Finazzi, 2000 [130]	Europe	1990-1993	**Inclusion:** ET; high risk of thrombosis (>60 yrs or prior thrombosis)	HU	15mg/kg	2
				No myelosuppressive agent at randomization¶		
Cortelazzo, 1995 [129]	Europe	Apr 1990 – Aug 1993	**Inclusion:** Age >60; previous thrombosis; plt count <1.5 million	HU	15 mg/kg	2
				None		

Evidence Table 16. Description of Hydroxyurea Toxicity in Randomized Controlled Trials in Diseases Other than Sickle Cell Disease (continued)

***** In HIV only HU doses are given
† This was a five-arm study but adverse event data is given for three arms due to pooling of some arms. Treatments naive as well as treatment experienced patients are included. Baseline data is reported for all groups combined (listed in Arm 1) and stated to be similar between arms.
‡ Randomized for 12 weeks then switched to open-label according to patient response in the first 12 weeks.
§ Many patients crossed over after the 12 week-blinding was removed. If they had a poor response (viral load>200/ml) patients were permitted to start HU or dropped if already in HU arm. The HU arm had 34 responders, 24 crossovers after 3 months and 19 remained in the "placebo" arm.
‖ See Rutschmann, 1998[102] for other details of inclusion criteria, this is the same report after 24 months (instead of 12 months)
¶ This is a follow-up of the previous Najean trial[123]. Very limited data is given on patients.
# Many patients from the placebo group crossed over to HU. 79 received HU alone, 15 received HU and busulfan, and 20 received no chemotherapy.

3TC = Lamivudine; ABC = abacavir; Abnl = abnormal; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate transaminase; BID = twice a day; CA = cancer; CCNU = Lomustine; CML = chronic myelogenous leukemia; d4T = Didehydrodeoxythymidine; ddI = didanosine; EFV = efavirenz; ET = essential thrombocytopenia; Fxn = function; HIV = human immunodeficiency virus; HU = hydroxyurea; hx = history; IDV = indinavir; IFN = interferon; mets = metastases; NR = not reported; Ph = Philadelphia; plt = platelet; preg = pregnancy; PV = polycythemia vera; RNA = ribonucleic acid; RTV=ritonavir; ULN = upper limit of normal; ULT = upper limit; WBC = white blood cells; WHO = World Health Organization; ZDV = zidovudine.

Evidence Table 17. Description of Patient Populations in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease

Author, year	Intervention groups	N	Age*	Male, n (%)	Race (%)	Last observation
HIV						
Frank, 2004[† 104]	ddI	28	NR	(79)	White (38); Black (50); White Hispanic (10)	6 months
	HU (low dose) with/without ddI	53				
	HU (high dose) with/without ddI	50				
Havlir, 2001 [189]	IDV, ddI, d4T + HU	68	NR	(82)	White (69); Black (16); White Hispanic (13)	
	IDV, ddI, d4T + placebo	68		(84)	White (62); Black (22); White Hispanic(12)	
	IDV, ZDV(or d4T), 3TC	66		(89)	White (71); Black (23); White Hispanic(5)	
Swindells, 2005 [111]	ABC, EFV, ddI + HU	30	38.1; Median, 37; [26-59]	26 (87)	White 16, (53); Black 4, (13); White Hispanic 7, (23); Other 3, (10)	48 wks
	ABC, EFV, ddI	24	39.5; Median, 37; [29-62]	21 (88)	White 13, (54); Black 8, (33); White Hispanic 2, (8); Other 1,(4)	
Beeson, 1999 [108]	ddI +HU	40	33.8; [26- 47]	26 (65)	NR	40 weeks
	ddI	21	31; [21- 48]	13 (62)		
Bloch, 2006 [191]	Indinavir, ritonavir, ddI and either stavudine or lamiduvine + HU	35	Median, 36; [31-39]	NR	NR	
	Indinavir, ritonavir, ddI and either stavudine or lamiduvine	33	Median, 34; [29-40]			
Rutschmann Cluster/ HIV						
Rutschmann, 1998 [109]	ddI, stavudine + HU	72	NR	NR	NR	24 wks
	ddI, stavudine + placebo	72				
Rutschmann, 1998 [102]	ddI, stavudine + HU	72				48 weeks
	ddI, stavudine + placebo	72				
Rutschmann, 2000[‡ 110]	ddI + stavudine + HU	72				24 months
	ddI, stavudine + placebo	72				

Evidence Table 17. Description of Patient Populations in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention groups	N	Age*	Male, n (%)	Race (%)	Last observation
CML						
Hehlmann, 2003 [114]	HU	308	Median, 47; [11-83]	(54)	NR	
	IFN-alpha 2a + HU	226	Median, 49; [10 – 78]	(60)		
no author, 1998 [115]	HU	95	Median, 56.4; [27-84]	53		
	IFN and HU if needed	100	Median, 55.7; [20-83]	58		
Hehlmann, 1994 [113]	HU	194	46.9; Median, 47; [15-84]	(51)		
	IFN	133	47.4; Median, 47; [18-85]	(66)		
	Busulfan	186	48.5; Median, 49; [17-84]	(61)		
Broustet, 1991 [116]	HU	26	58.6	16 (61.5)		
	IFN	24	55.6	15 (62.5)		
Hehlmann, 1993 [112]	HU	216	49.2 (unclear if mean or median reported)	(52)		
	Busulfan	225	50.2 (unclear if mean or median reported)	(61)		
Solid Tumor						
Stephens,19 84 [121]	HU	69	Median, 64	(100)	White 55, (77); Black 15, (22); Other 2, (3)	
	Adriamycin + cyclophosphamide	68	Median, 65	(100)	White 55, (84); Black 11, (16); Other 2 (3)	
Loening, 1981 [122]	HU	40	67.3	(100)	NR	23 months
	Cyclophosphamide	43	68.8	(100)		
	Methyl-CCNU	38	68.5	(100)		
Najean Cluster/ PV						
Najean, 1997 [123]	HU	150	53.2, men; 53.6, women	m/f ratio = 0.89	NR	NR
	Pipobroman	142	55.1, men; 53.3, women	m/f ratio = 1.20		
Kiladjian, 2006 [103]	HU	123	NR	NR	NR	
	Pipobroman	134				
ET						
Harrison, 2005 [103]	aspirin 75mg/d + HU	404	Median, 62; [21-88]	180 (45)	NR	
	aspirin 75mg/d + Anagrelide	405	Median, 61; [23-88]	162 (40)		

Evidence Table 17. Description of Patient Populations in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention groups	N	Age*	Male, n (%)	Race (%)	Last observation
Finazzi Cluster/ET						
Finazzi, 2000 [130]	HU	56	Median, 67; [40-82]	23.00	NR	
	No myelosuppressive agent at randomization	58	Median, 69; [50-85]	14		
Cortelazzo, 1995 [129]	HU	56	Median, 67	23.00	NR	
	None	58	Median, 69	14		

***** Mean (SD) [range] unless otherwise specified.
† The characteristics represent the whole population (all three arms).
‡ This study included 30 patients that crossed over to the HU arm (regrouped the arms as received HU at some point vs. no HU), but did not report the numbers of the placebo arm. Denominators for the outcomes range from 64 to 80, because the numbers of patients at the time of the outcome event were used as denominators.

3TC = lamivudine; ABC = abacavir; CCNU = lomustine; CML = chronic myelogenous leukemia; d4T = didehydrodeoxythymidine; ddI = didanosine; EFV = efavirenz; HU = hydroxyurea; IDV = indinavir; IFN = interferon; m/f = male/female; NR = not reported; ZDV = zidovudine.

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
HIV												
Frank, 2004 [104]	ddI mono	28	D: 6 months		3 (11)	0	0					Grade 3 chemistry or more, 3 (11)
	HU (low dose) with/without ddI	53			10 (19)	1 (2)	0					Grade 3 chemistry or more, 7 (13)
	HU (high dose) with/without ddI	50			20 (40)*	9 (18)†	3 (6)					Grade 3 chemistry or more, 4 (8)
Havlir, 2001 [189]	IDV, ddI, d4T, + HU	68	F: 40 weeks	3								GI upset, 2 Pancreatitis, 4 Asymptomatic amylase elevation, 2
	IDV, ddI, d4T + placebo	68		0								GI upset, 1 Pancreatitis, 3
	IDV, ZDV (or d4T), 3TC	66		0								
Swindells, 2005 [111]	ABC, EFV, ddI + HU	30	F: 48 weeks								5	GI upset, 28 Neurological/psychiatric, 23 Endocrine or metabolic, 7 Arthralgia, 2 Fatigue, 6 Neuropathy, 4
	ABC, EFV, ddI	24									3	GI upset, 10 Neurological/psychiatric, 12 Nasal symptoms, 2 Endocrine or metabolic, 3 Arthralgia, 1 Fatigue, 2 Neuropathy, 1

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
HIV												
Seminari, 1999 [108]	ddI + HU	40	F: 40 weeks		1	1	1					Hair loss, 2 hyperamylasemia, 1 hypertryglyceridemia, 1
	ddI	21	D: 24 weeks		0	0	0					GI upset, 1 Hyperamylasemia, 1 Hypertryglyceridemia, 1
Bloch, 2006 [191]	Indinavir, ritonavir, ddI, and either stavudine or lamiduvine + HU	35					1					CMV esophagitis, (3) renal colic, (20) pneumonia, (3)
	Indinavir, ritonavir, ddI, and either stavudine or lamiduvine	33					0					Neuropathy, (3) rectal tear, (3) renal colic, (3)
Rutschmann Cluster/ HIV												
Rutschmann, 1998 [109]	ddI, stavudine + HU	72	F: 24 weeks		14‡	8§					5‖	GI upset, 16 Fatigue, 10 Neuropathy, 18¶ Diarrhea, 15
	ddI, stavudine + placebo	72			3/ 25	3					4	GI upset, 11 Fatigue, 2 Neuropathy, 10 Diarrhea, 9
Rutschmann, 1998[102#]	ddI, stavudine + HU	72	D: 12-48 weeks F: 48 weeks		11/ un-clear	7						Fatigue, 10 Diarrhea, 15 Paraesthesia, 29
	ddI, stavudine + placebo	72			3**	1††						Fatigue, 2‡‡ Diarrhea, 9§§ Paraesthesia, 14‖‖

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Rutschmann Cluster/ HIV (continued)												
Rutschmann, 2000[110#]	ddI, stavudine + HU	72	F: 24 months		18[¶¶]	29[##]			4 Kaposis' sarcoma***		8	GI upset, 20[†††] Hair loss, 1 Fatigue,16 Neuropathy, 28[‡‡] Diarrhea, 23 Mucositis, 5
	ddI, stavudine + placebo	72			8	8			1 Kaposi's sarcoma		5	GI upset, 6 Hair loss, 1 Fatigue, 5 Neuropathy, 10 Diarrhea, 15
CML												
Hehlmann, 2003 [114]	HU	308	F: 7.3 years								29/30 (9.4)	GI upset, 60 (19.5) (denominator= 304) Flu-like, 38 (12.3) Neurological/psychiatric, 19 (6.2) Cardiac/pulmonary symptoms, infections, wt. loss, Lab findings, BM aplasia, 53 (17.2)
	IFN + HU	226	Follow-up: 7.9 years								64/22 (28.3)	GI upset, 88 (38.9) (denominator=222) Flu-like, 146 (64.6) Neurological/psychiatric, 82 (36.3) Cardiac/pulmonary symptoms, infections, wt. loss, lab findings, BM aplasia, 92 (40.7)

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
CML (continued)												
No author, 1998[115]	HU alone	95	F: 51 months								1	Fever, 2 Accelerated disease/blast crisis, 52
	IFN and HU if needed	100									3	Flu-like, 7 Neurological/psychiatric,6 Vasculitis, 1 Accelerated diesease/blast crisis, 37
Hehlmann, 1994 [113]	HU	194	Median F: 3.4 years						1 (0.5)			Fever, 1 (0.5)
	IFN	133							2 (1.5)			
	Busulfan	186							2 (1.0)			
Broustet, 1991 [116]	HU	26	D: 20.4 months				0				0	
	IFN	24	D: 13.9 months				1				1	Flu-like, 1 CNS disturbance, 2 Thyroid insufficiency, 2
Hehlmann, 1993 [112]	HU	216	Median F: 2.03 years									Long lasting bone marrow aplasia, 0 (denominator=209)
	Busulfan	225										Long lasting bone marrow aplasia, unknown (denominator= 204)

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
Solid Tumor												
Stephens, 1984[121]	HU	69	NR			11/68 (16)						
	Adriamycin + cyclophosphamide	68	NR			9/68 (14)						
Loening, 1981[122]	HU	40	NR			2/28 (7)	8/28 (29)					GI upset, 13 (46) (denominator=28)
	Cyclophosph-amide	43				2/34 (5)	11/34 (26)					GI upset, 20 (46) (denominator=43)
	Methyl-CCNU	38				11/27 (41)	9/27 (33)					GI upset, 11(41) (denominator=27)
Najean Cluster/ PV												
Najean, 1997[123]	HU	150	F: 1 - 17 years					NR by arm§§§	10‖‖‖	12 (9)	10 (7)	GI upset, 9 (7) Myelofibrosis, 26, 40% at the 16th year Cystitis, 3 (2) Stomatitis, 13 (10)
	Pipobroman	142						NR by arm¶¶¶	6###	1	5 (4)	GI upset, 19 (17) Myelofibrosis, 3 Stomatitis, 4 (4)
Kiladjian, 2006[103]	HU	123§§§	Followup: 14 years					15††††				
	Pipobroman	134§§§	Followup: 11 years					25††††				

Evidence Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Intervention	N	Mean drug (D) or followup (F) duration	Death, n (%)	Neutropenia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
ET												
Harrison, 2005 [131]	Aspirin + HU	404	Median F: 39 months (12-72)	4§§§§				6				Myelofibrosis, 5
	Anagrelide + aspirin	405		3¶¶¶¶				4¶¶¶¶				Myelofibrosis, 16####
Finazzi Cluster/ ET												
Finazzi, 2000[130]	HU	56	Median F: 73 months (3-93)						7 (13)			
	No myelosuppressive agent at randomization	58	Median F: 73 months (12-94)						1 (1.7)*****			
Cortelazzo, 1995[129]	HU	56	D: 27 months			0		0			0	
	None	58				0		0			0	

Table 18. Toxicity Results in Randomized Controlled Trials on Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

* p = 0.007 (comparing arms 2 and 3)
† p = NS
‡ p = 0.04 for grade 1, ns for 2, 3, (denominator=36)
§ p = 0.03 for grade 1, ns for 2 and 3
‖ p = 0.7
¶ p = 0.09
# n = original assignments, please see associated text for number of patients that crossed over.
** p = 0.04, (denominator for this outcome unclear given crossover)
†† p = 0.03
‡‡ p = 0.02
§§ p = 0.2
‖‖ p = 0.008
¶¶ p = 0.08
p = 0.001
*** p = 0.2
††† p = 0.006
§§§ Risk = 10% at 13th year (denominator=150)
‖‖‖ Risk = 15% at 14th year, Risk = 1.1% per year
¶¶¶ Risk = 10% at 13th year (denominator =142)
Risk = 15% at 14th year, Risk = 1.1% per year
**** p = 0.0321 (this symbol doesn't appear in the table)
†††† 6 (40%) occurred after the 12th yr of f/u, (denominator =123)
‡‡‡‡ 11 (44%) after the 12th yr of follow-up (denominator=134)
§§§§ Death from transformation
‖‖‖‖ It is unclear why this only represents 157 patients when it is a follow-up of the original study [123]. No information on patients lost to follow-up is given
¶¶¶¶ (OR 0.67, CI, 0.20-0.33) p = NS
(OR 2.92, CI, 1.24 - 6.86) p = 0.01
***** p = 0.0321

3TC = lamivudine; ABC = abacavir ; ARV = antiretroviral; BM = bone marrow; CCNU = lomustine; CI = confidence interval; CMV = cytomegalovirus; CNS = central nervous system; d4T= didehydrodeoxythymidine; ddI = didanosine; EFV = efavirenz; ET = essential thrombocytopenia; GI = gastrointestinal; HU = hydroxyurea; IDV = indinavir; IFN = interferon; NR = not reported; NS = not significant; OR = odds ratio; PV = polycythemia vera; wt = weight; ZDV = zidovudine.

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
CML/AML									
Yin, 2006 [117]	North America	Case series	CML	Jan 1997 - Sep 2004	**Inclusion:** t (3;21) translocation	15 -HU, 1 -imatinib		2 weeks to 31 months/ last observation, median 3 months	65
			AML			8 varieties of prior chemo: two patients had no prior therapy			
Urabe, 1990 [119]	Asia	Case series	CML	May 1988 - NA	**Inclusion:** CML	HU	NR	Last observation mean, 20.1 months*	30
Vassallo, 2001 [118]	Europe	Case series	CML	1977 - 1998	**Exclusion:** diabetes; peripheral venous insufficiency; condylomata acuminata; cancer/ precancerous lesions; exposure to carcinogens/ radiation; previously treated with anything but HU; rheumatological and autoimmune disorders	HU	1500-2000 mg/d; reported maintenance doses of 500 to 1000 mg/d based on response		54

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
CML/AML (continued)									
Duletic-Nacinovic, 2000 [120]	Europe	Cohort with comparison arm	CML	Jan 1986 - Jun 1997	**Inclusion**: CML 1st chronic phase	HU	40 mg/kg/d: dose decreased to 20 mg/kg when WBC decreased to 20,000		63
						Busulfan	0.1 mg/kg/d: dose decreased by 50% when WBC decreased by 50%, discontinued when WBC dropped below 20,000		
PV/ET/MF/unspecified MPD									
Nielsen, 2003 [134]	Europe	Cohort with comparison arm	PV, ET, IMF un-classified MPD†	Jan1993 - Dec 2000	**Inclusion**: chronic MPD, Philadelphia chromosome negative	HU	650.1 g HU (range 1–3,200 g)		64
						No drug treatment			
						Busulfan alone			
						Busulfan + HU			
						Anagrelide + HU			
						Busulfan, IFN + HU			
						Busulfan, Anagrelide + HU			
						IFN + HU			

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
PV/ET/MF/unspecified MPD (continued)									
Weinfeld, 1994 [135]	NR	Other pro-spective cohort	PV, ET, IMF	1976 - NR	**Inclusion**: myeloproliferative disorders	PV/HU	30 mg/kg/d: day 8 reduced by 50% and adjusted to blood counts maintenance dose of 0.5 to 1.5 g/d)	NR	23
				1976 - NR		ET/HU	30 mg/kg/d: day 8 reduced by 50% and day 8 reduced by 50% and adjusted to blood counts (maintenance dose of .5 to 1.5 g/d)		
				1976 - NR		MF/HU	30 mg/kg/d: day 8 reduced by 50% and day 8 reduced by 50% and adjusted to blood counts (maintenance dose of .5 to 1.5 g/d)		
Randi, 2005‡ [136]	Europe	Case series	PV, ET		**Inclusion**: Age >60; PV or ET diagnosed by PVSG criteria; previous thrombotic event (n=72); plt count >1,500K/ml	HU	30 mg/kg per day	4.33 years	46
Randi, 2005 [137]	Europe	Case series	PV, ET		**Inclusion**: Age >60 years; previous major thrombotic event; platelet count over $1500x10^9$/L	HU	30mg/kg/day: maintenance dose 15mg/kg/day	Patients observed over a period of 20 years	31

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
PV/ET/MF/unspecified MPD (continued)									
Mavrogianni, 2002 [196]	Europe	Cohort with a compa-rison arm	PV, ET	NR	NR	PV: HU therapy ET: HU therapy PV: busulfan ET: alpha IFN	NR	86 (range, 36-195) months	57
PV									
Finazzi, 2005 [124]	Europe	Case series	PV	1997 - 2001	**Inclusion:** diagnosis of PV by PVSG	HU Any other cytoreductive drug No drug or alpha IFN only			63
West, 1987 [128]	North America	Case series	PV	1963 - 1983	**Inclusion**: PV	HU	500 mg: based on blood counts, mean daily dose of 720mg	64.9 months	33
Donovan, 1984 [127]	North America	Case series	PV		**Inclusion:** PV; off all therapy for four months prior to starting HU	HU no prior treatment HU and prior myelosuppressive therapy	30 mg/kg day x 1 week then 15 mg/kg: 5/mg/kg/d changes to keep HCT controlled 30 mg/kg day x 1 week then 15 mg/kg: 5/mg/kg/d changes to keep HCT controlled		53

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
PV (continued)									
Najean, 1996 [105]	Europe	Cohort with a comparison arm	PV			HU	30mg/kg/d (initial dose) 8mg/kg/d (maintenance dose)		28
						Pipobroman	1.5mg/kg/d (initial dose) 0.4 mg/kg/d (maintenance dose)		
						^{32}P +HU	NR		
						^{32}P without maintenance	NR		
Wasserman Cluster/PV									
Kaplan, 1986 [125]	North America	Cohort with a comparison arm[§]	PV		**Exclusion:** previously treated with myelosuppresive agents	HU		61 (245 weeks)	44
						Phlebotomy			
Fruchtman, 1997 [126]	North America	Cohort with a comparison arm	PV		**Inclusion**: PV **Exclusion:** prior chemo	HU		Last observation: 198.75 months	60
						Phlebotomy			

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author, year	Location	Design	Disease	Recruitment start date - end date	Inclusion & exclusion criteria	Intervention	Starting dose: Titration Dose	Planned duration/ last observation	Total Q score
ET									
Chim, 2005 [133]	Southeast Asia	Case series	ET		**Inclusion**: Essential Thrombocytosis	HU alone Melphalan + HU ^{32}P + HU			67
Bernasconi, 2002 [107]	Europe	Case series	ET	1985 - 1995		HU alone Pipobroman None	15 mg/kg/d 1 mg/kg/d		67
Gangat, 2007 [106]	North America	Cohort with a comparison arm	ET	Jul 1956 - Dec 2005		HU Anagrelide or IFN only Exposure to single agent cytotoxics other than HU No drug exposure Anagrelide or IFN-alpha + HU Other cytotoxics (busulfan, chlorambucil, ^{32}P) + HU		median follow-up for the entire study population: 84 months (range, 0-424)	73
Sterkers, 1998[132]	Europe	Case series	ET	1970 - Jan 1991	**Inclusion**: ET	HU alone HU with other agents ^{32}P alone ^{32}P with other agents Busulfan alone Busulfan with other agents Pipobroman alone Pipobroman with other agents No treatment	1.5 g/d 0.1 mCi/kg 6 mg/d 1 mg/kg/day 	Fourteen patients had received HU, during a median period of 53 months (range, 3 to 96); seven of them had received HU alone, and seven had also received other treatments	

Evidence Table 19. Description of Large Observational Toxicity Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

* No data was given on the average time each patient was treated, and no info on demographics was reported.
† No demographic information reported based on chemo. Data only given only by disease type.
‡ Four patients with short-time toxicity; 12 patients with long-term side effects needing drug withdrawal; 65 patients with minor side-effects (black nail pigmentation; asymptomatic macrocytosis).
§ Compared two population groups from different studies.

^{32}P = radioactive phosphorus; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; ET = Essential thrombocytopenia; HCT = hematocrit; HU = hydroxyurea; IFN = interferon; IMF = idiopathic myelofibrosis; MF = Myelofibrosis; MPD = myeloproliferative disorder; NA = not applicable; NR = not reported; plt = platelets; Pts = patients; PV = Polycythemia vera; PVSG = Polycythemia Vera Study Group; Q = quality; WBC = white blood cells.

Evidence Table 20. Description of Patient Populations in Large Observational Toxicity Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease

Author, year	Patient groups: intervention	N	Age, mean (SD) [range]*	Male n (%)	Race (%)
CML/AML					
Yin, 2006 [117†]	15 -HU, 1 -imatinib	16	Median, 53; [21-76]	13	NR
	8 varieties prior chemo: two patients had no prior therapy	10	Median, 65; [53-76]	3	
Urabe, 1990 [119]	HU	134	NR	NR	NR
Vassallo, 2001 [118]	HU	158	Median, 58; [25-79]	m/f ratio=3.5:1	NR
Duletic-Nacinovic, 2000 [120]	HU	72	Median, 42.69; [10-81]	(52.8)	NR
	Busulfan	109	Median, 47.54; [7-84]	(59.6)	
PV/ET/MF/unclassified MPD					
Nielsen, 2003 [134]	HU	36	64.4 for arms 1,4,5,6,7,8	22 (38) for arms 1,3,4	NR
	No drug treatment	21	62.3 for arms 2,3		
	Busulfan alone	4	NR		
	Busulfan + HU	18	NR		
	Anagrelide + HU	1	NR		
	Busulfan, IFN + HU,	1	NR	17 (68)	
	Busulfan, Anagrelide, + HU	1	NR	NR	
	IFN + HU	1	NR	NR	
Weinfeld, 1994 [135]	PV: HU	30	61	NR	NR
	ET: HU	10	60		
	MF: HU	10	66		
Randi, 2005 [136]	HU	152	58.12 ± 14.68 (at diagnosis)	62	
Randi, 2005 [137]	HU	129	NR	53	
Mavrogianni, 2002 [196]	PV: HU therapy	34	62 [38-80]	15 out of 35 PV patients	NR
	ET: HU therapy	30	64 [18-83]	20 out of 34 ET patients	
	PV: HU/busulfan	1	NR	NR	
	ET: IFN alpha	4	NR	NR	

Evidence Table 20. Description of Patient Populations in Large Observational Toxicity Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease (continued)

Author, year	Patient groups: intervention	N	Age, mean (SD) [range]*	Male n (%)	Race (%)
PV					
Finazzi, 2005 [124]	HU	742	Median, 67.3	NR	NR
	Any other cytoreductive drug	227	NR		
	Either no drug, or IFN alpha only	669	NR		
West, 1987 [128]	HU	100	54.6; [24-88]	78	White 99; Black 1
Donovan, 1984 [127]	HU no prior treatment	59	NR	(56)	NR
	HU and prior myelosuppressive therapy	59		(51)	
Najean, 1996 [105]	HU	104	Median, 58 (combined with Arm2)	NR	NR
	Pipobroman	98	Median, 58 (combined with Arm1)		
	^{32}P+HU	174	74 (at diagnosis, combined with Arm 4)		
	^{32}P without maintenance	221	74 (at diagnosis, combined with Arm 3)		
Wasserman Cluster/ PV					
Kaplan, 1986 [125]	HU	51	NR	(53)	NR
	Phlebotomy	134		(55)	
Fruchtman, 1997 [126]	HU	51	NR	(53)	NR
	Phlebotomy	134		(55)	

Evidence Table 20. Description of Patient Populations in Large Observational Toxicity Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease (continued)

Author, year	Patient groups: intervention	N	Age, mean (SD) [range]*	Male n (%)	Race (%)
ET					
Chim, 2005 [133]	HU alone	222	Median, 65; [18-90]	(49)	Asian/Pacific Islander, (100)
	Melphalan + HU	3			
	^{32}P + HU	4			
Bernasconi, 2002 [107]	HU	23	Median, 55; [15-86] ‡	68: out of 155 ‡	NR
	Pipobroman	106			
	None	26			
Gangat, 2007 [106]	HU only	165	Median, 57; [5-96] ‡	206: out of 605‡	NR
	Anegralide or IFN only	63			
	Exposure to single agent cytotoxics other than HU	21			
	No drug exposure	181			
	Anagrelide or IFN alpha + HU	128			
	Other cytotoxics + HU	47			
Sterkers, 1998[132]	HU alone	201	NR	NR	NR
	Other agents + HU	50			
	^{32}P alone	29			
	Other agents + ^{32}P	11			
	Busulfan alone	35			
	Other agents + busulfan	6			
	Pipobroman alone	12			
	Other agents + pipobroman	31			
	No treatment	31			

* Unless otherwise specified
† Median 3 months for last observation
‡ These are the characteristics of entire cohort, no subgroup data were reported.

^{32}P= radioactive phosphorus; ACL = acute myelogenous leukemia; CML = chronic myelogenous leukemia; ET = Essential thrombocytopenia; HU = hydroxyurea; IFN = interferon; m/f = male to female ratio; MF = Myelofibrosis; MPD = myeloproliferative disorder; NR= not reported; PV= Polycythemia vera; SD = standard deviation.

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease*

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
CML/AML												
Yin, 2006 [117]	15 -HU 1 -imatinib	16	D: HU, 2 weeks-31 months before translocation; D: imatinib alone, 3 months	8/15								
	8 varieties prior chemo: two patients had no prior therapy	10		7/9								
Urabe, 1990 [119]	HU	134	NR								1	Liver dysfunction, 1 GI upset, 1
Vassallo, 2001 [118]	HU	158	D: Median = 38 months						5		21‡	
Duletic-Nacinovic, 2000 [120]	HU	72	F: Median = 32 months		2		0				0	
	Busulfan	109	F: Median = 31 months		8		2				2	Lung fibrosis, 3 Amenorrhea, 2

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease * (continued)

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
PV/ET/IMF/unspecified MPD												
Nielsen, 2003 [134]	HU	36	F: 7.8 years (follow-up for all patients that received HU)					5				
	No drug treatment	21	F: 10.5 years (this is follow-up for all patients that did not receive HU)					1				
	Busulfan alone	4						0				
	Busulfan + HU	18						4				
	Anagrelide + HU	1						0				
	Busulfan, IFN + HU	1	62					1				
	Busulfan, anagrelide + HU	1	84					1				
	IFN + HU	1	21					1				
Weinfeld, 1994 [135]	PV: HU	30	NR			(30)		3				Chromosomal anomalies, 4/11; platelet count >6x10^9/l
	ET: HU	10				(30)		1				Chromosomal anomalies, 1/5; platelet count >6x10^9/l
	MF: HU	10						3				Chromosomal anomalies, 2/3
Randi, 2005§ [136]	HU	152	Median 4.33 years aspirin (n=88), ticlopicine (n=11), oral anticoagulants (n=12), 8.13 years	3 (1.97)			5 (0.03 29)	3, (1.97)		4 (2.6)		Cutaneous allergic reaction and mild pancytopenia, 1; Allergic reaction and transient liver failure, 1; Fever above 39^{o}C, 2

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease * (continued)

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
PV,ET/IMF/unspecified MPD (continued)												
Randi, 2005 [137]	HU	129	F: 7.18 years				2/129	3	1	4	3	CV complications, 4 Coronary complications, 5 Fever above 39°C, 2
Mavrogianni, 2002 [196]	PV: HU therapy	34	D: 86 [36-195] months					2 (5.7)				
	ET: HU therapy	30	D: 79 [36-162] months					1 (3.3)				
	PV: HU and busulfan	1	D: 44 months on HU followed by 86 months on busulfan								1	
	ET: INF α	4	D: 105 [91-123] months									
PV												
Finazzi, 2005 [124]	HU only	742						6				
	Any other cyto-reductive drug	227						11				
	No drug or interferon α only	669						5				
West, 1987 [128]	HU only	100	D: 3-216 months, mean 64.9 [3-21] F: 20 year observation					2 (2)	1 (1)		1	Splenic infarction, 1 Myelofibrosis, 6
Donovan, 1984 [127]	HU no prior treatment	59	F: 61 weeks to 171 weeks					2				
	HU after prior myelo-suppressive therapy	59	F: 193 weeks					1				

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease * (continued)

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
PV (continued)												
Najean, 1996 [105]	HU only§	104	Median followup: 6.7 years					13% at 12y f/u‖	9% at 10y f/u¶			Myelofibrosis, 17% at 12 year f/u
	pipobroman	98	Median followup: 6.7 years					14% at 12y f/u‖	9% at 10y f/u¶			
	^{32}P+HU maintenance	174	D: 1-15 years Median 10.5 years					19% at 10y f/u#	29% at 12y f/u‖			Myelofibrosis, 16% at 10 year f/u; 23% at 14 year f/u
	^{32}P without maintenance	221	D: 1-15 years, Median 10.5 years					10% at 10y f/u	15% at 12y f/u‖ **			Myelofibrosis, 10% at 10 year f/u; 19 at 14 year f/u
Wasserman Cluster/PV												
Kaplan, 1986 [125]	HU	51	D: Median 245 weeks (range: 5-389 weeks)					3 (5.9)				
	Phlebotomy	134	NR					2 (1.5)††				
Fruchtman, 1997 [126]	HU	51	F: 795 weeks	16 (31.4)‡‡				5 (9.8)§§				Spent phase, 4
	Phlebotomy	134	NR	54 (40.3)				5 (3.7)				Spent phase, 15

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease * (continued)

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
ET												
Chim, 2005 [133]	HU alone	224	F: 10 years					3 (1.3)				Myelofibrosis, 6
	Melphalan + HU	4						2				Myelofibrosis, 1
	Phosphorus + HU	3						0				
Bernasconi, 2002 [107]	HU only	23	Median F: 104 months (range, 8-240) for all three groups					4‖‖				
	Pipobroman	106						4¶¶				
	No treatment	26						0				
Gangat, 2007 [106]	HU only	165	Median F: 84 months (0-424)					5				
	Anegralide or IFN α only	63						1				
	Exposure to single agent cytotoxics other than HU	21						3				
	No drug exposure	181						4				
	Anagrelide or IFN + HU	128						2				
	Other cytotoxics + HU	47						5				

Evidence Table 21. Toxicity Results of Observational Studies of Hydroxyurea in Diseases Other than Sickle Cell Disease * (continued)

Author, year	Intervention	N	Mean duration of drug (D) or followup (F) in months†	Death, n (%)	Neutro-penia, n (%)	Thrombo-cytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
ET (continued)												
Sterkers, 1998 [132]	HU alone	201	Median F: 98 months (22 - 265)					7 (3.5)				
	HU + other agents	50						7 (14)				
	^{32}P alone	29						2 (7)				
	^{32}P + other agents	11						1 (9)				
	Busulfan alone	35						1 (3)				
	Busulfan + other agents	6						1 (17)				
	Pipobroman alone	12						0				
	Pipobroman + other agents	31						5 (16)				
	No treatment	31						0				

* Denominators = N unless otherwise specified.
† Unless otherwise specified
‡ HU therapy was discontinued in all 21 patients showing toxicity, and all cutaneous ulcers healed within a median period of 9 months.
§ 12 patients originally assigned to the HU arm were switched to pipobroman, and 5 patients on the pipobroman arm were switched to the HU arm.
‖ Actuarial risk
¶ Observed risk
# Reported as "significant" when compared to no maintenance arm
** $p < 0.01$ at 10 year f/u compared to Arm 3
†† $p > 0.25$
‡‡ $p = 0.0718$
§§ $p = 0.0973$
‖‖ Incidence rate ratio HU v PI 6.15, CI, 1.4-26.99, 5-year CI = 8.09%, 10-year CI = 15.53%, 15-year CI = 22.37% (where CuI is cumulative incidence, p for IRR = 0.0198
¶¶ 5-year CuI = 1.97%, 10-year CuI = 3.89%, 15-year CuI = 5.78%
^{32}P = radioactive phosphorus; CV = Cardiovascular; ET = Essential thrombocytopenia; f/u = followup; GI = Gastrointestinal; HU = Hydroxyurea; IFN = Interferon; MF = Myelofibrosis; MPD = Myeloproliferative Disorder; NR = Not reported; PV = Polycythemia vera.

Evidence Table 22. Adequacy of Reporting in Controlled Trials on Hydroxyurea Treatment in Diseases Other the Sickle Cell Disease*

Author/year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Quality score
Frank, 2004 [104]						
Havlir, 2001 [189]	1		0		1	2
Swindells, 2005 [111]	1		0		1	2
Beeson, 1999 [108]						
Bloch, 2006 [191]						
Rutschmann, 1998 [109]						
Rutschmann, 1998 [102]	1		0		0	1
Rutschmann, 2000‖ [110]	1		0		1	2
Hehlmann, 2003 [114]						
The Benelux CML Study Group, 1998 [115]	1		0		1	2
Hehlmann, 1994 [113]	1	1	0		1	3
Broustet, 1991 [116]	1	1	0		1	3
Hehlmann, 1993 [112]	1		0		1	2
Stephens, 1984 [121]	1		0		1	2
Loening, 1981 [122]						
Najean, 1997 [123]	1		0		1	2
Kiladjian, 2006 [103]						
Harrison, 2005 [103]						
Finazzi, 2000 [130]	1		0		1	2
Cortelazzo, 1995 [129]	1		0		1	2

*Blank cells represent categories that were not applicable to the question

Evidence Table 23. Adequacy of Reporting in Observational Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease*

Author/year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Adjustment for outcome comparison reporting	Objective outcome	Losses to follow-up	Overall assessment (% of total)
Yin, 2006 [117]	1.5	1	1.5				2		65
Urabe, 1990 [119]	1.5	0	0	1	0		2	0	30
Vassallo, 2001 [118]	2	1	0.5	1.5	0		2		54
Duletic-Nacinovic, 2000 [120]	2	0.5	2	2	0	0.5	2	1	63
Nielsen, 2003 [134]	2	2	1.5	1	0	0.5	2		64
Weinfeld, 94 [135]	1	0	0.5		0		1	0	23
Randi, 2005‡ [136]	1	1	1	1.5	0		1.5		46
Randi, 2005 [137]	0.5	0.5	1		0		1.5	0	31
Mavrogianni, 2002 [196]	1	2	2	1	0		2	0	57
Finazzi, 2005 [124]	1.5	1.5	1.5	1	0	2	2		63
West, 87 [128]	1	0.5	1	1	0		1.5	0	33
Donovan, 1984 [127]	1.5	1.5	1.5	1.5	0		2	0	53
Najean, 96 [105]	0.5	0.5	0.5	1	0	0	1	1	28
Kaplan, 86 [125]	1	0.5	1	0.5	0.5	1.5	1.5		53
Fruchtman, 1997 [126]	1.5	1.5	2	2	0	0	2		60
Chim, 2005 [133]	1.5	1.5	2	1	0	2	2		67
Bernasconi, 2002 [107]	2	2	1.5	2	1		1.5	0	67

Evidence Table 23. Adequacy of Reporting in Observational Studies of Hydroxyurea Treatment in Diseases Other than Sickle Cell Disease (continued)

Author/year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Adjustment for outcome comparison reporting	Objective outcome	Losses to follow-up	Overall assessment (% of total)
Gangat, 2007 [106]	2	2	2	1	0	2	2		73
Sterkers 1999 [132]	1	2	1	2	0	1	2		64

* Blank cells represent categories that were not applicable to the question.

Evidence Table 24. Hydroxyurea Toxicity Results from Case Reports in Disease Other than Sickle Cell Disease

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality	Evidence level for outcome* (1, 2, 3)
Alopecia	1	1/0	CML 100	16			1		3
Alveolitis	2	0/2	CML 50; MPD 50	4		1	1		2
Arthritis	1	0/1	CML 100	12			1		3
Azosperm or decreased sperm motility	2	0/2	ET 50; PV 50	470	1		1		1
Behcet's disease	2	2/0	CML 100	91			1	1	3
Colitis	1	0/1	CML 100	2		1			2
Cytopenia	2	0/2	HIV 100	12		1	1		2
Eyelid changes	1	0/1	CML 100	NR		1			2
Falsely elevated HbA1c	1	0/1	PV 100	NR				1	0
Fever	15	6/9	ET 73; CML 13; other 16	3	14		1		1
Gangrene of toes	2	1/1	CML 100	175			2		3
Glioblastoma multiforme	1	1/0	MPD 100	150			1		3
Hemolytic anemia	1	0/1	ET 100	150		1			2
Hepatitis	6	2/4	ET 33; PV 33; Psoriasis 33	27	3	1	2		1
Interstitial Pneumonitis	5	1/4	CML 40; ET 40; MPD 20	16	1	3	1		1
Leg ulcer	66	27/39	CML 48; ET 20; PV 27; MPD 4	220	4	31	31		1
Leukemia	33	15/18	ET 57; PV 24; MPD 6; Hyper-eosinophilia 6	300			30	3	3

Evidence Table 24. Hydroxyurea Toxicity Results from Case Reports in Disease Other than Sickle Cell Disease (continued)

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality	Evidence level for outcome* (1, 2, 3)
Limbal stem cell deficiency (cornea)	1	0/1	CML 100	104	1				1
Lymphoma	2	1/1	ET 50; Hyper-eosinophilia 50	450			2		3
Melanoma	1	0/1	ET 100	64			1		3
Meningioma	1	1/0	ET 100	520			1		3
Multiple myeloma	1	1/0	ET 100	360			1		3
Nail change	9	8/1	CML 55; ET 33; Psoriasis 11	104		2	7		2
Neuromuscular disorder	1	0/1	CML 100	4			1		3
Oral ulcers	4	0/4	ET25; Leukemia 75	116		2	2		2
Pruritis	1	1/0	PV 100	5	1				1
Pulmonary Fibrosis	1	1/0	PV 100	16			1		3
Dermatological changes	34	19/15	CML 68; ET 6; PV 26; Leukemia 3	222		19	15		2
Sarcoidosis	1	0/1	ET 100	16			1		3
Sarcoma	1	0/1	ET 100				1		3
Skin cancer	27	9/18	CML 41; ET 29; PV 29	376	1	6	20		1
SLE	1	1/0	Psoriasis 100	160		1			2
Soft-tissue Nodule	1	0/1	MPD 100	32		1			2
Thrombotic microangiopathy	1	1/0	CML 100	72			1		3

Evidence Table 24. Hydroxyurea Toxicity Results from Case Reports in Disease Other than Sickle Cell Disease (continued)

Outcome	# of case reports	Females/ males	Underlying disease %	Median weeks on HU until toxicity	# of case reports with certain causality	# of reports with probable causality	# of reports with possible causality	# of reports with unlikely causality	Evidence level for outcome* (1, 2, 3)
Tumor lysis	4	1/3	CML 25; Leukemia 50; PV 25	0.56			4		3
Ulcer (surgical site)	1	1/0	PV 100	300		1			2

* Level 1 evidence had to have at least 1 "certain" case report, level 2 evidence had to have at least 1 "probable" but no "certain" report, and level 3 evidence had to have at least 1 "possible" report but no "certain" or "probable" case report.

CML= chronic myelogenous leukemia; ET=essential thrombocytopenia; HIV = human immunodeficiency virus HU=hydroxyurea; MPD= myeloproliferative disorders; NR=not reported; PV= polycythemia vera; SLE= Systemic lupus erythematosus.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies Concerning Barriers to Receipt of Treatment to Increase Hemoglobin F							
Hankins, 2007 [138]	Patient decision to initiate HU Patient report, family report	Patients (Children, caregivers)/ Memphis, TN	30		Perceived safety and efficacy	Parental age, sex, # of children, parent's rating of child's HRQOL, frequency of VOC in prior 2 years	In this study of patient and parental treatment decisions, after hearing non-biased information about all three potential treatments, the majority of patients and parents (70%) chose HU therapy over chronic transfusion (17%) and stem cell transplantation (10%) ($p < 0.001$). The perceived efficacy and perceived safety of potential treatment options were the two most commonly cited factors affecting parental treatment preferences for their kids (~80% of respondents each). Health related quality of life (HRQOL) and number of vaso-occlusive crisis events were not associated with treatment preference. There was disagreement over treatment preference in 3 out of 7 patient-parent dyads.
Studies Concerning Barriers to Patient Adherence to Established Therapies for Disease Management							
Treadwell, 2005 [139]	Patient adherence to chelation therapy Patient or caregiver report, physical examination, administrative records	Patients (Children, Caregivers) California	15	Family stress	Child-parent shares responsibility	Convenience of the regimen, behavioral/ psychological adjustment, patient/ caregiver knowledge, satisfaction with regimen, child cognitive disability	The developmentally appropriate sharing of responsibilities for chelation therapy between parents and their children with SCD contributes to better adherence to home deferoxamine administration ($p<0.05$). Low family stress was marginally related to better adherence ($p = 0.07$). There was no difference between the most and least adherent group in the perception of the inconvenience of the deferoxamine regimen (significance not shown). The child's behavioral and psychological adjustment was not associated with adherence (significance not shown). The primary hypothesis, that greater child cognitive disability would be a risk factor for non-adherence, was not supported by the data (significance not shown).

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Patient Adherence to Established Therapies for Disease-Management (continued)							
Wurst, 2004 [140]	Provider provision of prophylactic antibiotics/ Provider report	Physicians (hematologists, heme/ onc, pediatricians)/ North Carolina	142	Academic medical center setting	Provider knowledge, provider specialty	Provider years in practice, provider gender	Pediatricians were more likely than hematologists to answer correctly 5 or 6 out of 6 questions on SCD antibiotics guidelines ($p<0.001$). Pediatricians were significantly more likely than hematologists to be 100% adherent in prescribing antibiotics prophylaxis ($p=0.001$). Physician knowledge of antibiotic prophylaxis prescribing guidelines was associated with better physician adherence to prescribing antibiotics ($p=0.031$). Physicians in a medical school or university setting were significantly less likely than physicians in other settings to be 100% adherent ($p=0.033$).
Sox, 2003 [141]	Receipt of prophylactic antibiotics Administrative data	Patients (Children/ Caregivers) Tennessee, Washington State	261	NR	Private insurance, hospital visits	Patient sex, patient age, urban residence, cost-sharing, non-preventive outpatient care visits	Publicly insured children may receive an inadequate amount of prophylactic antibiotics against pneumococcal infections, as the children in this sample were dispensed an average of only 148.4 days of coverage out of a 365 day period (SD: 121.4, median:114, IQR 39 - 247). The number of outpatient visits for preventive care and the number of emergency department visits experienced by children were significantly associated with increased provision of prophylactic antibiotics. Each visit for preventive care was associated with 12 additional days of prophylactic antibiotic coverage (95%CI 2.3 - 21.7). Each emergency department visit was associated with 10 additional days of coverage (95% CI 1.2 - 18.8).

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Patient Adherence to Established Therapies for Disease-Management (continued)							
Elliot, 2001 [142]	Patient adherence to prophylactic antibiotics Family report, Administrative records	Patients (Children/ Caregivers) Unknown location	50	More children at home	More adults at home, having a car	Patient age, parental education	A higher number of adults living in the home and having a car were positively associated with compliance (p<0.01). A higher number of children in the home was negatively associated with compliance (p<0.01). The number of days between refills tended to increase as the child's age increased (p = 0.15). Maternal education was not significantly associated with compliance (p = 0.25). The authors assessed the utility of the Health Belief Model (HBM) in predicting parental compliance with prophylactic penicillin administration and did not find that any of the assessed variables (parent's perceptions of the seriousness of infection in young children with SCD, the perceived susceptibility of their child to infection, the perceived benefit of prophylactic penicillin in preventing infection, and the perceived burden of penicillin administration) were significantly associated with compliance after adjustment for demographic factors (p = 0.61).
Teach, 1998 [143]	Patient adherence to prophylactic antibiotics Patient report, family report, biologic outcome (urine assay)	Patients (Children/ Caregivers) Buffalo, NY	123	NR	Private insurance, younger patient age	Patient sex, SCD type	Measured compliance was significantly greater in patients <5 years of age than in those >5 (64% vs. 34%, p=0.004). Patients with private insurance (p=0.02) had better measured compliance than patients with public insurance. Sex, type of hemoglobinopathy, recruitment site (ED vs. clinic), and chief complaint in ED (fever vs. VOC) were not significantly associated with measured compliance.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Patient Adherence to Established Therapies for Disease-Management (continued)							
Witherspoon, 2006 [169]	Patient adherence to prophylactic antibiotics Provider report, family report, administrative data	Patients (Children/ Caregivers) USA	30	NR	Caregiver knowledge, intent to adhere, perceived benefits, family employment	NR	Based on pharmacy records, one-third of caregivers had poor (14-30 days/month not 'covered' with antibiotic) and one-third had less than optimal (2-7 days/ month 'uncovered' with antibiotics) levels of adherence to penicillin prophylaxis. Caregiver knowledge of infection and intent to adhere positively predict adherence. Caregivers with better adherence had more knowledge of infection, greater intent to adhere or greater belief in the importance of the medication ($p<0.05$), and reported fewer barriers to adherence ($p<0.01$). Families with better adherence rates were more likely to be employed ($p<0.01$), and reported fewer barriers to adherence ($p <0.05$).
Pejaver, 1997 [170]	Patient adherence to prophylactic antibiotics Family report, presence of penicillin in urine	Patients (Children/ Caregivers) Saudi Arabia (armed forces hospital)	41	NR	NR	Patient/ caregiver knowledge, patient age, patient sex, # of children in family, years on therapy, # of inpatient admissions	One quarter (24%) of parents demonstrated good knowledge of the reasons and need for penicillin prophylaxis, however knowledge was not associated with compliance levels in this study.
Jensen, 2005 [144]	Patient adherence to prophylactic antibiotics Family report	Patients (Children/ Caregivers) USA	97	NR	Caregiver knowledge for children <11 yrs, no child history of transfusions	History of stroke, hospital visits, # of missed appointments	In the overall sample, caregiver knowledge of SCD did not correlate with adherence with recommended SCD preventative behaviors ($r=0.16$, $p=0.12$). In post-hoc analyses, however, the authors found that caregiver knowledge of SCD was positively associated with adherence for children 11 years of age and younger, but not for children 12 and older ($p<0.05$).

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis							
Labbe, 2005 [155]	Provider provision of pain medication Provider report	Physicians 7 federally funded comprehensive SCD centers in the USA	109	Negative provider attitudes	Fewer provider years in practice, provider female gender		Physician characteristics and attitudes may affect the quality of pain management delivered to patients with SCD. The earlier the year of graduation from medical school, the more likely a physician was to believe that opioids play major role in the development of addiction (r = -0.32, p<0.001), and also that drug addiction should be a primary concern when treating SCD patients (r = -0.26, p<0.008). Female physicians were more likely than male physicians to believe that the primary focus of treatment for a sickle cell crisis should be adequate pain relief (r = -0.20, p <0.04). Physicians who believed drug addiction should be a primary concern were less likely to believe the primary focus of treatment should be adequate pain relief (r = -0.20, p < 0.0037).
Armstrong, 1992 [145]	Provider provision of pain medication Provider report	Physicians (pediatric residents), Nurses Unknown	92	Hospital visits	NR	Provider attitudes, professional experience and training	Nurses, but not pediatric residents, recommended lower pain medication doses for frequently, as opposed to occasionally, hospitalized children as described in hypothetical history vignettes. However, there were no differences in pain ratings between nurses and residents across the vignettes. There were no significant correlations between nurse or resident pain ratings or medication decisions and their attitudes and beliefs about pain in children.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)							
Pence, 2007 [146]	Patient use of pain medication Patient report, family report	Patients (Children/ Caregivers) North Carolina	27	NR	Dispositional optimism	Patient age, patient sex, parent education	For adolescent patients with SCD, pain severity was positively associated with opioid use such that high pain predicted higher use ($p<0.001$), and pain severity uniquely accounted for the largest proportion of the variance in opioid use (partial r-squared = 0.19). Dispositional optimism was found to moderate the relationship between pain severity and use of opioids ($p<0.05$). Specifically, at medium and high levels of optimism, pain severity was positively associated with opioid use. At low levels of optimism, pain severity was not associated with opioid use. At low levels of optimism, an intermediate level of opioids was used consistently regardless of whether pain severity was low or high. Additionally, maternal education was found to be marginally associated with adolescent opioid use ($p = 0.08$). Higher maternal education predicted more opioid use, while lower maternal education predicted more non-opioid use.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Receipt of Routine, Scheduled Care							
Telfair, 2003 [147]	Use of routine health services Patient report, administrative data	Patients (Adults and Children/ Caregivers) Alabama	662	NR	Rural geographic region	Community socioeconomic distress, physical functioning, # of medical problems, distance to a clinic	In bivariate analyses, patients with SCD living in rural areas had lower utilization of comprehensive sickle cell services than patients living in urban areas (significance not reported). However, utilization of comprehensive sickle cell services is predicted to be higher for SCD patients in rural areas compared to those in urban areas after adjustment for distance to a clinic, community socioeconomic distress, physical functioning, and a medical problem index (p=0.003). While the model results suggested that utilization of services increased with increasing socioeconomic distress, the p-value for the result (p = 0.011) did not reach the author's threshold for statistical significance.
Logan, 2002 [148]	Use of routine health services Patient report, family report, administrative data	Patients (Children/ Caregivers) Unknown	70	NR	Illness-related stress, greater parental/ family knowledge	Parent/ adolescent relationship, disease severity, stressful life events, clinical mal-adjustment	The authors developed a multivariate model predicting the use of routine health services (scheduled clinic visits, calls to clinic, information seeking from clinic, management of pain symptoms at home). The frequency of illness-related stress accounted for the largest individual portion of the explained variance in routine service use (partial r=0.41, p<0.001). Having more frequent illness-related stress was associated with greater use of routine services. Greater parental knowledge of SCD also accounted for a significant portion of the variance in routine service use and predicted more use of routine services (partial r=0.33, p<0.001). Parental reports of the parent-adolescent relationship, disease severity, stressful life events, and clinical maladjustment were not significant predictors of routine service use.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Receipt of Routine, Scheduled Care (continued)							
Wojciechowski, 2002 [149]	Transition to adult care Patient report, provider report	Patients (Adults and Children/ Caregivers) Unknown	18	NR	Self-efficacy, female sex	Receipt of preparation for the transfer to adult care	In this study of adolescents and young adults making the transition to adult-centered care, patients with greater SCD self-efficacy kept a higher percentage of their care appointments ($p<0.05$ using Spearman rho test). Females exhibited better compliance with medical regimens than did males as indicated by higher scores on a scale assessing compliance. There was no significant association between receipt of preparation for the transfer to adult-centered care and compliance with medical regimens.
Haque, 2000 [150]	Use of routine health services Patient report, administrative data	Patients (Adults and Children/ Caregivers) North Carolina	1189	Greater community socio-economic distress	Rural geographic region	Distance to clinic, interference of disease in daily life, level of medical problems	Patients living in rural areas were estimated to have greater utilization of comprehensive sickle cell services than patients living in urban areas after adjustment for socioeconomic distress, interference of sickle cell disease in their daily lives, their self-reported level of medical problems, their distance to a comprehensive clinic, and a term representing the interaction of distance to a clinic and their level of socioeconomic distress ($p <0.001$). In this same model, patients living in areas with more socioeconomic distress were estimated to have less utilization of services ($p = 0.04$) after adjustment for the other factors. None of the other variables in the model were significantly associated with utilization.

Evidence Table 25. Barriers and Facilitators (Patient, Provider, and Societal) Shown to be Associated with Treatment for Patients with Sickle Cell Disease (continued)

Author, year	Outcome Measurement	Study population Location	N	Barriers	Facilitators	Neither	Primary results
Studies on Barriers to Receipt of Routine, Scheduled Care (continued)							
Barakat, 2002 [151]	General adherence to treatment regimens Provider report, patient report, family report, administrative data	Patients (Children/ Caregivers) Unknown	81	NR	Greater parental/ family knowledge, family problem-solving effort, higher family income	NR	In multivariate models, greater SCD knowledge (p = 0.032) and greater family effort in solving family problems (p = 0.037) were significantly associated with higher medical staff rating of patient/ family adherence to treatment regimens. Greater family income was marginally associated with higher medical staff ratings of adherence (p = 0.053).
Belgrave, 1994 [152]	Appointment-keeping Patient report	Patients (Adults) Washington, DC	49	NR	Social support	NR	Social support, defined in this study as the frequency of supportive and helpful behaviors performed by others, was positively correlated with self-report of medical appointment keeping (r = 0.47, p 0.05). Patients with greater social support had better self-reported rates of keeping medical appointments

CI = confidence interval; ED = emergency department; HBM = Health Belief Model; HRQOL = health-related quality of life; HU = hydroxyurea; IQR = interquartile range; NR = not reported; SCD = sickle cell disease; SD = standard deviation; VOC = vaso-occlusive crisis.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Treatments to Increase Hemoglobin F					
Zumberg, 2005 [93]	Quantitative: questionnaires (27-item, 4-page self-administered questionnaire)	Doctors (hematologists) Florida, North Carolina	184	Patient compliance, lack of contraception, patient anticipation of side effects, patient age, provider concern about side effects, provider doubting effectiveness, cost	There were differences in HU prescribing between community and academic physicians showed differences in HU prescribing in the treatment of ACS (43% vs. 70%, p=0.006), stroke (40% vs. 60%, p=0.04), and pulmonary hypertension (7% vs. 23%, p=0.008). Community physicians less frequently monitored compliance by pill count (7% vs. 20% in academic physicians, p=0.03) and MCV measurements (36% vs. 90%, p<0.0001). Concerns that were identified as "important" or "very important" barriers to the use of HU were patient compliance (90%), lack of contraception (79%), patients' anticipation of side effects (82%), patient's age (50%), cost (59%), concern about carcinogenic potential (40%) and doubting effectiveness (40%).
Studies on barriers to patient adherence to established therapies for disease-management					
Witherspoon, 2006 [169]	Quantitative: questionnaires	Patients (children/caregivers) USA	30	Caregiver being busy, forgetting to administer medications, child falling asleep, running out of medication	Commonly reported barriers to adherence were: the caregiver being busy (26.7%), forgetting to administer the medication (23%), the child falling asleep (20%), and running out of medication (16.7%)
Pejaver, 1997 [170]	Quantitative: questionnaires	Patients (children/caregivers) Saudi Arabia	41	Forgetting, disliking taste, concern about side effects	Common reasons given for non-compliance with penicillin were forgetting to give the medicine, forgetting to renew the supply of medicine, the child not liking the medicine, and the feeling that daily medication could have ill effects.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis					
Booker, 2006 [159]	Qualitative: focus groups	Patients (adults) UK	10	Negative provider attitudes	Participants likened dealing with healthcare professionals to a battle. They felt that they had to work hard to convince the doctors that they were in genuine pain and need of help. Some patients felt so disbelieved that they actively avoided consulting when in crisis, for fear of being perceived as opioid dependent. Many patients felt that doctors did not have sufficient knowledge of sickle cell disease to make valid treatment decisions.
Rouse, 2004 [160]	Qualitative: observations made while performing anthropological research on two children's hospitals	Nurses, doctors, patients (adults) California and Pennsylvania	NR	Negative provider attitudes	In the wards, residents and nurses dismissed patients' demands for pain relief as drug addiction, malingering, or manipulation. Furthermore, several staff members stated that "patients were being denied proper medical care, unfairly accused of drug use or criminal behavior, transferred to adult care clinics at an early age, and generally treated with less respect than the cancer patients who occupied the same floor in the hospital." With few exceptions, the nurses' perceptions of their sickle cell patients were overwhelmingly negative. During one session, it was revealed that while nurses believe cancer patients' self-reporting of pain, they generally believed that their sickle cell patients inflated their level of pain. One nurse said, "One of the problems with sickle patients, I believe, is that healthcare professionals make a connection between African-Americans using drugs and existing stereotypes; and that is coupled with {health care professionals'} lack of knowledge about sickle cell disease."

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Pack-Mabien, 2001 [153]	Quantitative: questionnaires (written 31-item multiple choice survey about nurses' attitudes and perceived barriers to opioid pain management of sickle cell patient pain episodes)	Nurses USA	200	Negative provider attitudes, lack of provider knowledge, lack of time, inadequate pain assessment tools	Many nurses believed that drug addiction frequently develops in sickle cell patients (63%) and reported (49%) that they did not have broad knowledge of sickle cell disease. 59% reported Inadequate pain assessment tools were reported by 59% as the greatest barrier in the management of pain episodes. Lack of time for psychological support of patients (58%), nurse reluctance to provide opioids (37%), a narrow range of available analgesics (37%), physicians' reluctance to prescribe opioids (33%), and the belief that most sickle cell patients are drug addicts (32%) also reported barriers.
Maxwell, 1999 [161]	Qualitative: 18 semistructured interviews with 15 individuals and 8 focus groups	Patients (adults) London	57	Negative provider attitudes	In focus groups, patients reported negative experiences with hospital care. These were characterized by mistrust (being suspected by health professionals of exaggerating pain), stigmatization (treated differently from other inpatients--"drug addicts"), control (health professionals exerted control and failed to involve patients in decision-making), neglect (of personal care, monitoring of vital signs, and psychosocial support due to understaffing or low priority). A minority of patients responded to unsatisfactory care by self-discharging from one hospital and going to another.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Waters, 1995 [168]	Mixed: questionnaires (self-administered in presence of research coordinator) with qualitative analysis of open-ended responses.	Nurses (inpatient), patients (adults) UK	26*	Negative provider attitudes, lack of provider knowledge, lack of time	Factors reported by the subset of 13 nurses who felt they could better relieve sickle cell pain were time (4/13), lack of knowledge of narcotic analgesia (4/13), fears of overdosing and addiction (4/13), and lack of experience with sickle cell patients (2/13). Most patients (7/9) felt less in control of pain while in the hospital as compared to at home and wanted to be more involved in management of pain while on the ward. All patients stated they had to ask if they wanted more analgesia although the "majority" of nurses said they assessed pain continually. The majority of patients considered nurses' knowledge of sickle cell crisis and sympathy towards them as a patient group to be poor. Evidence of unsatisfactory pain management evidenced by comment from patient: ". . . You can just tell sometimes that they don't agree with having to give you the injection"
Tucker, 1995 [162]	Qualitative: focus groups	Patients (adults) California	NR	Negative provider attitudes, lack of provider knowledge	In 12 support group sessions of 2-8 patients each, patients all agreed on two major problem areas: (1) obtaining appropriate medical care in the ER (time to admission, feeling "forgotten", would delay hospital visits out of "dread") and (2) difficulty relating to members of the health care team (poor communication, "providers did not believe them", pain medication "not strong enough", discharged "too soon", being told "the pain is all in your head." Also, patients noted lack of knowledge by providers, felt "they are encouraged to 'act out' the pain in order to be taken seriously and medicated appropriately. Several group members said that "they would do everything possible" to keep from coming to the hospital because they dreaded the admission procedures.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Alleyne, 1995 [163]	Qualitative: in-depth semi-structured individual and group interviews	Nurses (inpatient), patients (adults) UK	20 †	Negative provider attitudes, patient race	All 10 patients and 4 nurses expressed dissatisfaction with pain management. Patients (7) reported they had to demand painkillers and wait at least 30 minutes. Patients (8) believed the nurses doubt the genuine nature of the pain, all patients reported lack of involvement in pain control, and all reported that nurses were not sympathetic to pain, telling them, "you'll have to wait." One patient said, "I've got the feeling that some of them purposely prolong it." One nurse suggested that there might be a link between young black people and drug-taking which caused nursing staff to be suspicious of the patients' request for pethidine. Nurses reported frustration with relying on physician orders for narcotics and 2 nurses reported that patients could not be "trusted to be responsible" with patient-controlled analgesia.
Shelley, 1994 [164]	Qualitative: phone interviews	Patients (adults, SCD self-help group leaders) USA	11	Negative provider attitudes, lack of provider knowledge	Patients perceived problems in health care services delivery. Inadequate staff training and high turnover in the ED, health providers' fears of drug addiction, negative attitudes of physicians to patients, delays in ED, unfamiliarity of staff with SCD, routine accusations of drug-seeking, insensitivity of physicians to patients' pain, and negative reactions by physicians to patient attempts to be involved in the course of their own care were all reported. Most group leaders cited the unfamiliarity of ER staff with SCD as a factor which contributes to delays in treatment of VOCs. Several group leaders also cited provider insensitivity to patients' pain as a problem. Almost half of group leaders reported negative reactions on the part of some physicians to patients, including ignoring a patient, blunt remarks about the doctor's amount of knowledge vs. the 'lay' patient. Group leaders reported that these sorts of incidents keep some SCD patients from the ED, even when they are in pain.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population/ location	N	Barriers identified	Main results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Strickland, 2001 [165]	Qualitative: focus groups	Patients (adults), family members USA	21‡	Negative provider attitudes	In focus group sessions, adults with SCD stated the belief that nurses would not give them pain medications when needed because the nurses believed that persons with SCD are addicts. Adults with SCD also stated the belief that some medical providers are intimidated when patients demonstrate knowledge about their disease or their pain control.
Murray, 1988 [154]	Quantitative: questionnaires	Patients (adults) UK	102	Negative provider attitudes	Of the 88 patients who went to the hospital for care, 18 thought they were seen quickly, 33 thought the delay was too long, 17 were concerned about side effects of medications, 40 said pain relief "was there when needed", but only 23 routinely received analgesics on demand, and 57 patients thought staff did not appreciate the amount of pain they were having.
Harris, 1998 [166]	Qualitative: standardized, structured open-ended interviews	Patients (adults) UK	27	Negative provider attitudes	Study participants were satisfied with pain relief (78%), but 30% stated pain control would be improved with more prompt administration of meds. Overall hospital service was reported as "satisfactory to good" by 63%, but 44% made a complaint about the staff's negative attitude to people with SCD, 26% felt staff generally lacked knowledge and understanding of SCD and pain crises, 22% said staff did not believe or appreciate that they were in pain ("they treat us like liars") and 19% said nurses were slow to give analgesia and attended to other "less urgent" tasks (such as "pillows").

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Labbe, 2005 [155]	Quantitative: questionnaires	Doctors Alabama	109	Negative provider attitudes, inadequate pain assessment tools	Physicians hold a number of beliefs and attitudes which may affect the quality of pain management delivered to patients with SCD. While the patient's self-report of pain was the tool most commonly used by physicians in assessing the severity of pain (92% of respondents), 86% of the physicians "somewhat disagreed to disagreed" that the most reliable indicator of the existence and intensity of pain is the patient's self-report. Physiological and behavioral measures were also commonly cited tools used to assess pain severity. The top 5 barriers to optimal pain management in SCD as reported by these physicians were lack of psychological support from patient's family and the medical profession, fear that the patient is a drug abuser, reluctance to prescribe opioids, disbelief in patient's report of pain severity, and inadequate pain assessment tools.
Butler, 1993 [167]	Qualitative: authors' reports of themes that arose in a SCD support group that included medical residents	Patients (adults) USA	24	Negative provider attitudes	During their lives, each member of the group had experienced many negative interactions with health care providers, including routinely being treated with suspicion and distrust. Patients expressed extreme frustration in attempting to convince health professionals of their distress.
Studies on Barriers to Bone Marrow Transplantation					
Walters, 1996 [158]	Quantitative: questionnaires (bone marrow consortium participants were asked to report on barriers at their institutions)	Physicians USA (multi-center study)	315	Lack of donor, lack of financial/ psychosocial support, parental refusal, physician refusal, history of non-compliance	315 out of 4,848 patients from 22 centers were reported to be eligible for bone marrow transplantation (BMT). Of the 315, 187 did not undergo HLA typing. The reasons for this included lack of HLA matching donor (76/187), lack of support (33/187), parental refusal (30/187), and physician refusal (13/187). Among those who had an HLA-identical donor (44), parental refusal was the most frequent reason for not performing a BMT.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Non-specific 'Treatment' or Healthcare 'Quality'					
Telfair, 1998 [156]	Quantitative: questionnaires (providers were asked to agree or disagree with 3 questions about (1) quality of health care provided to persons with SCD, (2) decisions about the administration of pain medication, (3) quality of interpersonal relationships between health care providers and patients)	Nurses, doctors, physician assistants, social workers USA	227	Patient race	Providers generally disagreed that race influences delivery of health care to individuals with SCD (52% disagree that quality is influenced, 77% disagree that pain medication decisions are influenced, 52% disagree that quality of interpersonal relationships are influenced). In bivariate analyses, 76% African-American vs. 35% Caucasians (p<0.00) agreed that race is an influence on quality, and 30-54% females vs. 12-37% males (p<0.01) agreed with all three statements regarding race as an influence on health care provision. More urban providers (26%) vs. rural providers (11%) agree that race influences pain medication decisions (p<0.02). In multivariate analysis, AA provider race was associated with all three questions (p<0.01): quality (or 5.6, 95% CI: 2.80,11.22); pain medication decisions (or 3.1, 95%CI: 1.54,6.19); quality of relationships (or 3.9, 95%CI: 2.02,7.38)
Chestnut, 1994 [171]	Qualitative: structured interview and service perception test (spt) in which subjects had to choose patients (via pictures) who they felt would receive better care	Nurses, doctors (hematologists), medical staff, patients (children/caregivers) USA	29 [§]	Patient race, patient sex, patient age	Family respondents perceived that younger children get the best care (regardless of gender or race), that whites get better service than blacks (regardless of age or gender), and that females get better care than males. Medical staff also perceived that children, whites, and females get better care than adults, blacks, and males.

Evidence Table 26. Barriers to Care of Sickle Cell Disease Reported by Patients and Providers (continued)

Author, year	Study design	Study population Location	N	Barriers identified	Primary results
Studies on Barriers to Non-specific 'Treatment' or Healthcare 'Quality'					
Vichinsky, 1999 [157]	Quantative: questionnaires (directors and associates of SCD centers were asked to comment on provision of care by community physicians using a survey tool developed for this study)	Directors and associates of sickle cell disease centers USA, Canada	21	Lack of provider knowledge	In most categories, over 90% of respondents stated that care provided by physicians from their centers complied with NIH guidelines, as compared to many fewer (50% or less) who reported that care by community physicians complied with NIH guidelines in all categories except care related to infection (60%) and contraception and pregnancy care (59%). Most respondents (72%) believed that lack of knowledge or training was the reason that community physicians failed to follow NIH guidelines.

* 9 patients and 17 nurses
† 10 nurses and 10 patients
‡ 10 patients and 11 family members
§ 22 patients and 7 staff

AA = African American; ACS = acute chest syndrome; BMT = bone marrow transplant; CI = confidence interval; ED = emergency department; ER = emergency room; HU = hydroxyurea; MCV = mean corpuscular volumes; NIH=National Institutes of Health; NR = not reported; OR = odds ratio; SCD = sickle cell disease; SPT = service perception test; VOC = vaso-occlusive crisis.

Evidence Table 27. Description of Interventions to Improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Studies on Interventions to Improve Receipt of Appropriate Pain Medication during Vaso-occusive Crisis					
Mitchell, 2002 [172]	Pre-post	Nurses, doctors, social workers, patients Philadelphia, PA	27	To improve the consistency and quality of care for patients with SCD having a VOC at a 200-bed community hospital. **Clinical protocol/pathway**	Implementation of new mandatory pain management protocol emphasizing aggressive pain management in the ED (using morphine sulfate or dilaudid rather than meperedine), admission to medical-surgical unit if crisis not resolved in 8 hours, and continued PCA, IV fluids, and oxygen. Physicians and nurses received in-service training related to the new protocol. One case manager was also assigned to coordinate all care.
Co, 2003 [173]	Pre-post, CCT	Patients (children/caregivers) Baltimore, MD	369	To improve the care for pediatric SC VOCs **Clinical protocol/pathway**	Clinical pathway for the treatment of children aged 2 – 19 years with VOC requiring hospitalization. Use of IV fluids, incentive spirometry, and pain service consultation were main check points for the pathway.
Jamison, 2002 [174]	Pre-post	Nurses, doctors, patients Greensboro, NC	204	1) To improve overall satisfaction of patients with SCD who were cared for at the study hospital (tertiary care hospital in the southeast) 2) To reduce the length of stay of patients with SCD 3) To reduce the costs associated with hospital treatment of patients with SCD. **Clinical protocol/pathway with sensitivity training**	Intervention included staff education (sensitivity training, information about SCD, pain management and other treatment interventions), nurse education about complementary therapies and other diversional activities, and a protocol to be used which included standing orders to evaluate and treat crises. Patients who did not have adequate control within 8 hours and who were moved to inpatient area were all admitted to oncology ward rather than diverse departments. Patient education materials, safety guidelines for admission, identification cards and discharge instructions (including document with education and resources) were developed.

Evidence Table 27. Description of Interventions to Improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Studies on Interventions to Improve Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Cooper, 2000[175]	CCT, Pre-post	Nurses, doctors Cleveland, OH	67	1) Develop individualized pain management protocols 2) Discourage the use of meperedine in favor of morphine, hydromorphone, and levorphanol 3) To use buprenorphine for patients with known or suspected narcotic dependence. **Clinical protocol/pathway**	The intervention was developed by establishing consensus concerning guidelines for care of SCD patients, and then educating physicians, nurses and house staff on new guidelines via Grand Rounds, conferences, medical management conferences, informal presentations, audiotapes and mailings. Patients were identified via admitting diagnosis and a care manager or physician made recommendations based on guidelines. Individualized care plans were constructed for "frequently admitted" sickle cell patients and were entered into mainframe for access by all physicians.
Benjamin, 2000 [176]	CCT, Pre-Post	Nurses, doctors, social workers, patients Bronx, NY	144	To decrease the load of the ED and to study the value of a dedicated facility with knowledgeable staff applying principle-based individualized care. **Establishment of Day Hospital**	Establishment of a Day Hospital with comprehensive assessment and treatment protocol (assessment and initial treatment within 15-20 minutes of arrival followed by assessment with established instruments every 30 minutes). Protocol included assessment, individualized drug management, medication titration to relief, maintenance of relief, use of combination drugs to enhance efficacy/toxicity ratio, monitoring of adverse events, identifying and treating precipitating factors, and appropriate disposition.
Day, 1997 [177]	Pre-post	Nurses, doctors, patients UK	18	To retrospectively audit admissions of SCD patients to identify problems with pain management and look for improvements after the care guidelines were introduced to department. **Audit and Feedback**	One nurse audited 10 admissions prior to implementation and 8 admissions after implementation to evaluate time to receive analgesia, what was prescribed, dose and method of administration, whether the pain management team was called, whether patient-controlled analgesia was used, and to which ward patient admitted. Data from the initial audit were shared with providers.

Evidence Table 27. Description of Interventions to Improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Studies on Interventions to Improve Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)					
Brookoff, 1992 [178]	Pre-post	Nurses, doctors, patients (adults) Philadelphia, PA	50/ year	To determine if providing adequate pain control (using continuous morphine infusions and sustained courses of orally administered controlled-release morphine) for the treatment of SCD in adults can decrease hospital visits and admissions for sickle cell pain. **Clinical protocol/pathway**	Intravenous and oral controlled-release morphine was used instead of intramuscular meperidone and short-acting opiods in treatment of pain.
Fertleman, 1992 [179]	Pre-post	Nurses, doctors, patients (children/caregivers) London, UK	72	To evaluate the efficacy of fast track system in which children with SCD are directly admitted to the ward after a telephone call from parent, assessed immediately, and given intramuscular pethidine if indicated (dose pre-prescribed). **Establishment of fast track admission procedures**	Fast track system in which children with SCD are directly admitted to the ward after a telephone call from parent, assessed immediately, and given a (pre-prescribed, documented) dose of intramuscular pethidine if indicated. Time to treatment pre- (1994) and post-implementation (1995) were compared. Parents (25) whose children had used both systems completed questionnaires about both.
Treadwell, 2002 [180]	Pre-post	Hospital staff, patients (children/caregivers) USA	235	To implement developmentally appropriate pain assessment guidelines for pediatric inpatients **Clinical protocol/pathway**	Staff were educated on the use of pediatric pain assessment tools and a standardized pain assessment protocol was put into practice.

Evidence Table 27. Description of Interventions to Improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Studies on Interventions to Improve Patient Adherence to Therapies					
Treadwell, 2001[181]	Pre-post	Patients (children/caregivers) California	11	To increase patients' knowledge of the disease and treatment regimen within a setting that encouraged and assisted peer interactions, and ultimately to enhance treatment adherence. **Education and peer support**	Desferel Day Camp - provided peer support and education for 4 days each summer.
Berkovitch, 1998[182]	RCT	Patients (children/caregivers) Toronto,Canada	23	To establish a simple method of improving compliance with antibiotics in children with SCD. **Education and follow-up by medical professionals**	Intervention subjects attended slide show (describing pathophysiology of SCD, risk of infections, importance of antibiotics), received stickers and a calendar to document compliance, and got a weekly phone call from social worker (asking questions about treatment, general health, other meds, family problems). Control and intervention subjects were invited to clinics every 8 weeks, where meds were dispensed and compliance evaluated. At end of 6 months, parents in both groups completed a questionnaire to determine knowledge and understanding of SCD.
Ketchen, 2006[183]	RCT	Patients (children/caregivers) US, Canada	37	To evaluate the efficacy of the home version of Starbright World, a Web-based computer network designed to connect chronically ill children, on increasing knowledge of SCD, increasing engagement in health-promoting activities, and improving psychosocial functioning. **Education and peer support**	Access to Starbright World with weekly assignments (educational and social activities and those that encouraged child-parent participation). Staff member called caregiver weekly.

Evidence Table 27. Description of Interventions to Improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Study design	Study population Study location	N	Intervention objective Main intervention components	Intervention description
Studies on Interventions to Improve Patient Receipt of Routine, Scheduled Care					
Patik, 2006[184]	Pre-post	Patients (children/caregivers) Pittsburgh, PA	202	To determine the feasibility and acceptance of the intervention for families with a child with SCD and the impact of the intervention on adherence to comprehensive care. **Education and non-medical follow up support**	Telephone-delivered structured follow-up, support and education by non-medical personnel (graduate student researcher). The semi-structured script included questions related to patient's well-being and health-related behaviors and was administered at 3-month intervals from the last contact.

CCT = clinically controlled trial; ED = Emergency department; IV = intravenous; LOS = length of stay; PCA = patient controlled analgesia; RCT = randomized controlled trial. SCD = sickle cell disease; VOC = vaso-occlusive crisis.

Evidence Table 28. Results of Interventions to improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Studies on Interventions to Improve Receipt of Appropriate Pain Medication during Vaso-occusive Crisis				
Mitchell, 2002 [172]	Utilization (indirect)	Administrative data were used. Outcomes were measured 6 months before and 6 months after protocol.	There were 235 visits to the ED with 76 admissions (68% treat-and-release) pre-intervention compared to 188 visits to the ED with 46 admissions (76% treat-and-release) post intervention. The average length of stay decreased from 4.9 days to 3.8 days. The authors report that there were no patient complaints during the intervention and that patients commented that "pain was being managed more efficiently." There was no significance testing reported in the article.	Potential improvement
Co, 2003 [173]	Pain management quality (direct)	Administrative data (use of IV fluids, incentive spirometry, and pain service consultation) were used.	Of 369 patients, 139 were admitted before the pathway, and 230 were admitted after the pathway. Physicians used the pathway 43% of the time after the pathway became available. Pathway patients were more likely than non-pathway patients to have received IV fluids (OR=1.15, 95% CI 1.07 -1.23), incentive spirometry (OR=2.49, 95% CI 2.02-3.07), and pain service consult (OR=1.33, 95% CI 1.18 -1.50). Pathway patients had longer length of stay (p=0.01) and time to oral pain medication (p<0.001) than non-pathway admissions. No difference in readmission rates.	Improvement
Jamison, 2002 [174]	Patient ratings, utilization, costs (direct)	Patient reports, administrative data were used	A pain management questionnaire administered to 9 patients at the beginning of implementation and to 10 patients 6 months later showed "marked improvement in the follow-up 6 month survey." Patient satisfaction post questionnaire that asked patients about satisfaction pre and post implementation was administered to 18 patients, and suggested that satisfaction overall improved. There was an overall trend in decreasing LOS post-implementation. Admissions to the ED or inpatient departments decreased >50% post-implementation. There was an 18.5% decrease in inpatient costs and 29.6% decrease in costs of observation stays. There was no significance testing reported in the article.	Potential improvement
Cooper, 2000 [175]	Utilization, costs, pain management quality (direct)	Administrative data were used	Of 58 care-managed admissions (study group) and 9 non-care-managed admissions (control group), the median unadjusted hospital length of stay was 3.5 days in the study group versus 4 days in the control group (p=0.54). Costs were $2,920 in study group versus $3,157 in control group (p=0.32). The use of non-guideline narcotic meperedine decreased from 82% pre-implementation to 18% post-implementation. (p<0.001).	Improvement

Evidence Table 28. Results of Interventions to improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Studies on Interventions to Improve Receipt of Appropriate Pain Medication during Vaso-occusive Crisis (continued)				
Benjamin, 2000 [176]	Utilization, pain management quality (direct)	Administrative data were used.	Walk-in DH patients discharged to home increased from 70% in first 2 years to 90-94% in last 3 years. The average length of stay in DH was 4.5 hours (range 2 to 7 hours) vs.13 hours (range 11 minutes to 90 hours) in the ED. Treatment time in the ED before transfer to DH was 16 hours in year 1 vs. 8 hours in year 5. Visits resulting in admission were lower for DH patients (8%) vs. ED patients (51%). Admission rate in patients with uncomplicated pain was 776/1818 (42.7%) ED patients vs. 168/2033 (8.3%) DH patients. The use of meperidine decreased from 90% in year 1 to 63% in year 5, while the use of hydromorphone increased from 3% (Year 1) to 33% (Year 5). There were no p-values reported.	Potential improvement
Day, 1997 [177]	Pain management quality (direct)	Administrative data were used.	After the intervention, the use of intramuscular pethidine decreased from 8/10 to 0/8 and the use of patient-controlled analgesia with morphine increased from 1/10 to 7/8. The incidence of calling the pain team promptly at admission increased from 1/10 to 8/8. The author reports that the time to see physician was "often. . .not immediate" prior to the intervention, but changed to "all. . . seen by a doctor immediately upon arrival" after the intervention.	Potential improvement
Brookoff, 1992 [178]	Utilization (indirect)	Administrative data and patient reports were used. Data on admissions and duration of hospital stay were collected for patients with SCD for all admissions from Jan 1 to June 30 in the years 1985 to 1990. ED visit data was collected for Jan 1 to June 30, 1988-1990. The new protocol was implemented in 1989.	Following this intervention, the total number of emergency department visits declined by 67% (426 to 138), the number of admissions declined by 44% (115 to 65), and the duration of hospital stay decreased by 23% (7.12 days to 5.45 days). There were no p-values reported. New protocol "met with strong resistance by a few patients" but this was eased by allowing these patients to "participate in developing their own analgesic plan."	Potential improvement
Fertleman, 1992[179]	Pain management quality, patient ratings (direct)	Family reports and administrative data were used.	Median time to pethidine decreased from 38 min to 5 min ($p<0.001$). 21 of 25 questionnaires were returned and all parents preferred the fast track system. Parents "added that the ward staff knew more about SCD, knew their children, and did not ask irrelevant questions before giving pethidine"	Improvement
Treadwell, 2002 [180]	Pain management quality, patient ratings (direct)	Patient report, family report, administrative data	Patients, families, and staff reported increased pain assessment, improved staff responsiveness to patients' pain and greater satisfaction with assessment tools post-intervention (all p-values <0.05). Increased compliance with the assessment guidelines was confirmed by chart audit.	Improvement

Evidence Table 28. Results of Interventions to improve the Receipt of Routine Care, and Appropriate Medications for Sickle Cell Disease (continued)

Author, year	Primary outcome (directness)	Outcome measurement	Primary results	Summary
Studies on Interventions to Improve Patient Adherence to Therapies				
Treadwell, 2001 [181]	Patient adherence (direct)	Patient reports were used.	Participation in Desferel Day Camp did not result in increases in measures of patient knowledge, peer support, or adherence to therapy.	No improvement
Berkovitch, 1998 [182]	Patient adherence (direct)	Family reports, administrative data, and medication event monitoring system were used. At 6 months, parents in both groups completed questionnaire.	Compliance at 2-4 months was 79.0% (±31.4%) in intervention group vs. 66.0 (±20.2%) in control group (p=0.297). Compliance at 4-6 months was 82.0 (±34.7%) in intervention group vs. 65.8 (±25.3) in control group (p=0.366). There were no significant differences in admission rates, or in measures of parent knowledge of SCD.	No improvement
Ketchen, 2006 [183]	Health promotion activities, parent-child relationships, child quality of life, child depression (direct)	Patient/family reports were used. Data collection occurred pre-intervention and 2 months post-intervention of SCD.	Intervention and control groups did not differ with respect to demographic, disease severity, pre-study computer ownership, or exposure to health education programs. Children in the intervention group had significant improvements in quality of life [child quality of life (lower scores better): pre: 32.70 (17.64) in intervention vs. 35.27 (17.08) in control Post: 29.90 (15.34) in intervention vs. 31.44 (25.05) in control time. Children in intervention group showed improvements in parent-child relationships [pre: 14.50 (6.19) in intervention vs. 17.82 (4.28) in control and post: 16.04 (4.75) in intervention vs. 17.18 (5.00) in control time. There was a non-significant trend towards children in the intervention group having improvements in depression scores. There were no significant differences between intervention and control groups in health promotion activities or child knowledge of SCD.	Partial Improvement
Studies on Interventions to Improve Patient Receipt of Routine, Scheduled Care				
Patick, 2006 [184]	Rate of patient non-attendance at clinic for 2 years (direct)	Cross-sectional patient survey prior to the start of the intervention and repeated 18 months later.	147 of the 202 patients (73.6%) were available and willing to talk. 64% of patients requested a service during the phone call (e.g. prescription refill, information, appointment scheduling). The proportion of patients who had not attended clinic for >2 years decreased from 19.7% to 9.9% (p=0.002) following intervention, and transcranial doppler compliance increased from 34% to 49% (p= 0.05).	Improvement

CI = confidence interval; DH = day hospital; ED = emergency department; IV = intravenous; LOS = length of stay; OR = odds ration; SCD = sickle cell disease.

Evidence Table 29. In Progress or Planned Trials involving Hydroxyurea from Clinicaltrials.gov (continued)

Title	Sponsor	Design, Intervention	Target N	Study start-end	Inclusion and exclusion criteria	Objective
Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)	National Heart, Lung, and Blood Institute	Interventional, efficacy, randomized trial of transfusions and chelation versus HU and phlebotomy (Phase III)	130	Jul 2006-NR	**Inclusion:** 5.0-18.9 years; HbSS; HbSß^0 thalassemia; Hb S/O Arab; overt clinical stroke after the age of one year with documented infarction on imaging; ≥18 months of chronic monthly transfusions since stroke; transfusional iron overload; average hemoglobinS ≤ 45% in the 6 months prior to study entry **Exclusion:** Inability to receive or tolerate chronic red blood cell transfusion therapy due to the following: multiple red blood cell alloantibodies or autoantibodies, religious objection to transfusions, non-compliance with transfusions in the 6 months prior to study entry; inability to take or tolerate daily oral HU; HIV infection; cancer; pregnant or breastfeeding; previous stem cell transplant or other myelosuppressive therapy; clinical and laboratory evidence of hypersplenism; transfusion requirement greater than 250 mL/kg in the 12 months prior to study entry; abnormal laboratory value at initial evaluation including: pre-transfusion hemoglobin concentration less than 7.0 gm/dL; white blood cell count less than 3.0 x 10^9/L; absolute neutrophil count less than 1.5 x 10^9/L;, platelet count less than 100 x 10^9/L; serum creatinine more than twice the upper limit for age OR greater than or equal to 1.0 mg/dL; current participation in other therapeutic trials; current use of other therapeutic agents for sickling	Aimed at demonstrating prevention of secondary stroke and management of iron overload.

eGFR = estimated glomerular filtration rate; Hb = hemoglobin; NR = not reported; S ß^0 thal = Sickle ß^0 thalassemia; Hb S/O Arab = hemoglobin SO Arab; SC = Sickle-Hemoglobin C Disease; SCA = sickle cell anemia; SS = Sickle Hemoglobin SS Disease; SWiTCH = Stroke With Transfusions Changing to Hydroxyurea; VOC = vaso-occlusive crisis.

Evidence Table 30. Analyses in Progress from the Multicenter Study of Hydroxyurea

Analysis	Investigators
Treatment effect on daily pain / D-02 (Measurement of pain in sickle cell anemia) / D22 (Pattern of utilization of health care facilities by adult patients with SS) / D-08 (Effect of weather on sickle cell)	Smith, Ballas, McCarthy, and the MSH Investigators
Analgesia usage in sickle cell patients	Ballas, Smith, Castro, Bellevue, B. Barton and MSH Investigators
A surrogate end point for sickle cell crisis from pain diaries / Development of multivariate predictive model of painful episodes in sickle cell anemia	Swerdlow, Smith, Ataga and the MSH Investigators.
Long-term mortality in sickle cell patients using HU	Saunthararajah, Ataga, Barton, McCarthy, other investigators
Pulmonary hypertension in sickle cell patients using HU	Castro, Ataga, B. Barton
Effect of discontinuation of HU on effectiveness / D-17 Non-response to HU therapy	Ballas, Swerdlow, Orringer and the MSH Investigators.
Long-term effects of hydroxyurea usage on laboratory measurements	Kutlar, Eckman, B. Barton
Dense cells and reticulocytes in sickle cell patients / A-02 (Effects of HU on RBCs in sickle cell anemia / D-19 (Technicon data)	Ballas, Orringer, Dover, B. Barton
Iron deficiency and the response to HU	Castro, Ballas, Barton, and the MSH Investigators.
Reproductive outcomes in sickle cell patients using HU	DeCastro, McCarthy, and the MSH Investigators
Results of the Vineland survey administered to sickle cell patients	Armstrong, Kutlar, B. Barton
Cytogenetic abnormalities in sickle cell patients / D-05 (Unusual alpha globin gene haplotypes in sickle cell anemia / A-08 (Analysis of DNA mutations associated with HU therapy	Kutlar, Saunthararajah, B. Barton
Clinical manifestations of sickle cell disease / D-10 (Defining a sickle cell crisis) / D-15 (GU Complications) / D-16 (AE of HU on liver and kidney function)	Ballas and the MSH Investigators.
Factors affecting compliance	Earles A, Jones S, Barton F.
Leg ulcers and HU	Kutlar, Ballas, Barton
Career and employment in Hb SS before and after HU treatment	Ballas, Barton
Objective laboratory parameters in SCD patients that predict chronic organ damage or survival	Saunthararajah, Ataga, Barton

AE = adverse event; DNA = deoxyribonucleic acid; GU = genitourinary; Hb = hemoglobin; Hb SS = sickle hemoglobin SS disease; HU = hydroxyurea; MSH = Multicenter Study of Hydroxyurea; SCD = sickle cell disease.

Appendix D

Appendix D: Excluded Articles

"Frequent flier" patients. Br. Med. J. 2005;330(7496):869 **Not relevant to key questions**

A prospective comparison of alpha-IFN and conventional chemotherapy in Ph+ chronic myeloid leukemia. Clinical and cytogenetic results at 2 years in 322 patients. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Haematologica 92;77(3):204-14 **Not relevant to key questions**

A quantitative method of assessing the health impact of different diseases in less developed countries. Ghana Health Assessment Project Team. Int J Epidemiol 81;10(1):73-80 **Not relevant to key questions**

Aboulafia D M, Meneses M, Ginsberg S et al. Acute myeloid leukemia in patients infected with HIV-1. AIDS 2002;16(6):865-876 **Not relevant to key questions**, **other, study size too small**

Adamson J W. Hemoglobin--from F to A, and back. N Engl J Med 84;310(14):917-9 **No Original Data**

Adamson R H. Activity Of Congeners Of Hydroxyurea Against Advanced Leukemia L1210. Proc Soc Exp Biol Med **Not relevant to key questions**, **Invitro only**

Adeodu O O, Alimi T, Adekile A D. A comparative study of perception of sickle cell anaemia by married Nigeria rural and urban women. West Afr J Med 2000;19(1):1-5 **Not relevant to key questions**

Advani S H, Venugopal P, Charak B S et al. Effect of hydroxyurea on foetal haemoglobin in myeloproliferative and myelodysplastic syndromes. Indian J. Med. Res. Sect. B Biomed. Res. Other Than Infect. Dis. 90;92(APR.):83-85 **Not relevant to key questions**

Ahmad A. Hydroxyurea and bronchogenic carcinoma. Australas Radiol 74;18(4):393-7 **Not relevant to key questions**

Ahmed S, Anwar M, Siddiqui S A et al. Granulocyte sarcoma in patients with chronic myeloid leukaemia. J. PAK. MED. ASSOC. 95;45(7):180-181 **Not relevant to key questions**, **study size too small**

Akinyanju O O, Anionwu E N. Training of counsellors on sickle-cell disorders in Africa. LANCET 89;1(8639):653-654 **Not relevant to key questions**, **No Original Data**, **other, Not relevant to key questions**

Al Jam"a A H, Al Dabbous I A. Hydroxyurea in the treatment of sickle cell associated priapism. J Urol 98;159(5):1642 **Study size too small**

Al Nasir F A, Niazi G. Sickle cell disease: Patients" awareness and management. Ann. Saudi Med. 98;18(1):63-65 **Not relevant to key questions**

Al-Arrayed S, Hafadh N, Amin S et al. Student screening for inherited blood disorders in Bahrain. East Mediterr Health J 2003;9(3):344-52 **Not relevant to key questions**

Albain K S, Swinnen L J, Erickson L C et al. Cisplatin preceded by concurrent cytarabine and hydroxyurea: A pilot study based on in vitro model. CANCER Chemother. Pharmacol. 90;27(1):33-40 **Not relevant to key questions**

Alberts D S, Durie B G, Salmon S E. Treatment of multiple myeloma in remission with anticancer drugs having cell cycle specific characteristics. Cancer Treat Rep 77;61(3):381-8 **Study size too small**

Alfrey C P, Karjala R J, Dale S C Et Al. Erythrokinetic Abnormalities With Administration Of Hydroxyurea (Nsc-32065). Cancer Chemother Rep **Not relevant to key questions**, **study size too small**

Aliyu Z Y, Tumblin A R, Kato G J. Current therapy of sickle cell disease. Haematologica 2006;91(1):7-10 **No Original Data**

Allan N C, Richards S M, Shepherd P C. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukaemia: improved survival irrespective of cytogenetic response. The UK Medical Research Council's Working Parties for Therapeutic Trials in Adult Leukaemia. Lancet 95;345(8962):1392-7 **Not relevant to key questions**

Allan N C, Shepherd P C A, Brackenridge I et al. United Kingdom Medical Research Council randomized trial of interferon alfa in chronic-phase chronic myelogenous leukemia. SEMIN. HEMATOL. 93;30(3 SUPPL. 3):20-21 **Not relevant to key questions**

Allen A, Scoble J, Snowden S et al. Hydroxyurea, sickle cell disease and renal transplantation. Nephron 97;75(1):106-7 **Study size too small**

Alleyne S I, Wint E, Serjeant G R. Psychosocial aspects of sickle cell disease. Health Soc Work 76;1(4):104-19 **Not relevant to key questions**

al-Momen A K. Recombinant human erythropoietin induced rapid healing of a chronic leg ulcer in a patient with sickle cell disease. Acta Haematol 91;86(1):46-8 **Not relevant to key questions**

Alnasir F A, Skerman J H. Schoolteachers' knowledge of common health problems in Bahrain. East Mediterr Health J 2004;10(4-5):537-46 **Not relevant to key questions**

Al-Suliman A, Elsarraf N A, Baqishi M et al. Patterns of mortality in adult sickle cell disease in the Al-Hasa region of Saudi Arabia. Ann Saudi Med 2006;26(6):487-8 **Not relevant to key questions**

Alter B P, Gilbert H S. The effect of hydroxyurea on hemoglobin F in patients with myeloproliferative syndromes. Blood 85;66(2):373-9 **Study size too small**

Alvarez-Larran A, Cervantes F, Bellosillo B et al. Essential thrombocythemia in young individuals: Frequency and risk factors for vascular events and evolution to myelofibrosis in 126 patients. Leukemia 2007;21(6):1218-1223 **Study size too small**, other

Anderson-Shaw L, Orfali K. Child-to-parent bone marrow donation for treatment of sickle cell disease. J Clin Ethics 2006;17(1):53-61 **Not relevant to key questions**, **No Original Data**

Angeli-Besson C, Koeppel M C, Jacquet P et al. Multiple squamous-cell carcinomas of the scalp and chronic myeloid leukemia. Dermatology 95;191(4):321-2 **Not relevant to key questions**

Anie K A, Green J, Tata P et al. Self-help manual-assisted cognitive behavioural therapy for sickle cell disease. Behav. Cognitive Psychother. 2002;30(4):451-458 **Not relevant to key questions**

Anie K A, Steptoe A. Pain, mood and opioid medication use in sickle cell disease. Hematol J 2003;4(1):71-3 **Not relevant to key questions**

Anie K A. Coping with sickle cell disease: a self help manual. Arch Dis Child 2002;86(5):385 **No Original Data**

Anionwu E. Ethnic minority health. Fair provision. Nurs Stand 95-96;10(12-14):45 **No Original Data**

Anti-cancer agents. Hydroxyurea as anti-viral therapy for brain lymphoma. TreatmentUpdate 2000;12(6):6 **Not relevant to key questions**, **study size too small**

Anti-HIV agents. Long-term use of hydroxyurea. TreatmentUpdateAnti-HIV Agents: administration & dosage: adverse effects: **No Original Data**

Apte S V. Preventive hematology.. Indian J Med Sci 93;47(7):185-190 **Not relevant to key questions**

Aranha G V, Grage T B. Single drug and combination chemotherapy in the treatment. Disseminated malignant melanoma. Minn Med 77;60(8):543-8 **Not relevant to key questions**

Ariel I M. Anticancer therapy with hydrea: comparative study of daily vs. intermittent oral dosage. J Surg Oncol 74;6(1):73-8 **Not relevant to key questions**

Ariel I M. Treatment of disseminated cancer by intravenous hydroxyurea and autogenous bone-marrow transplants: experience with 35 patients. J Surg Oncol 75;7(5):331-5 **Not relevant to key questions**

Arpaci A, Aytac N, Yuregir G T et al. An education programme on sickle cell anemia and (beta)-thalassemia for the 8th grade students. Turk. J. Haematol. 2003;20(1):19-24 **Not relevant to key questions**

Ballas S K, Marcolina M J, Dover G J et al. Erythropoietic activity in patients with sickle cell anaemia before and after treatment with hydroxyurea. Br J Haematol 99;105(2):491-6 **Study size too small**

Ballas S K. Attitudes toward adult patients with sickle cell disease: silent prejudice or benign neglect?. J Assoc Acad Minor Phys 96;7(3):62 **No Original Data**

Ballas S K. Bone-marrow transplantation in sickle-cell anaemia: why so few so late?. Lancet 92;340(8829):1226 **Not relevant to key questions**

Bamisaiye A, Bakare C G, Olatawura M O. Some social-psychologic dimensions of sickle cell anemia among Nigerians. Clin Pediatr (Phila) 74;13(1):56-9 **Not relevant to key questions**

Barakat L P, Lutz M J, Nicolaou D C et al. Parental locus of control and family functioning in the quality of life of children with sickle cell disease. J. Clin. Psychol. Med. Settings 2005;12(4):323-331 **Not relevant to key questions**

Barakat L P, Lutz M, Smith-Whitley K et al. Is treatment adherence associated with better quality of life in children with sickle cell disease?. Qual Life Res 2005;14(2):407-14 **Not relevant to key questions**

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Foa P, Iurlo A, Saglio G et al. Chronic neutrophilic leukaemia associated with polycythemia vera: Pathogenetic implications and therapeutic approach. BR. J. HAEMATOL. 91;78(2):286-288 **Not relevant to key questions**

Foley K M, Portenoy R K, Rosenbloom B E et al. Treatment of pain in sickle-cell crisis +AFs-5+AF0-. NEW ENGL. J. MED. 94;331(5):334-335 **Not relevant to key questions**, **No Original Data**

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Hehlmann R, Heimpel H, Hasford J et al. Randomized comparison of interferon-(alpha) with busulfan and hydroxyurea in chronic myelogenous leukemia. Blood 94;84(12):4064-4077 **Not relevant to key questions**

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Hermans P, De Wit S, Sommereijns B et al. Use of hydroxyurea in heavily pretreated patients with HIV infection. Antivir Ther 99;4 Suppl 319-22 **Not relevant to key questions**, other

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Hwang W-L, Gau J-P, Chen M-C et al. Treatment of acute promyelocytic leukemia with all-trans retinoic acid: Successful control of hyperleukocytosis and leukostasis syndrome with leukaphereses and hydroxyurea [2]. AM. J. HEMATOL. 93;43(4):323-324 **Not relevant to key questions**

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In re Cabrera. Atl Report 89;5521114-21 **Not relevant to key questions**

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Jayabose S, Tugal O, Sandoval C et al. Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. J Pediatr 96;129(4):559-65 **Study size too small**

Jensen A W, Tefferi A, Arndt C A S. Cerebral venous sinus thrombosis associated with essential thrombocytosis in a pediatric patient. J. Pediatr. Hematol. Oncol. 2007;29(3):156-159 **Not relevant to key questions**

Johansson P, Ricksten A, Wasslavik C et al. The effects of hydroxyurea on PRV-1 expression in patients with essential thrombocythemia and polycythemia vera. Haematologica 2004;89(10):1264-1266 **Not relevant to key questions**

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Johnson C S. Therapeutic manipulation of globin gene expression in the hemoglobinopathies. J. NATL. MED. ASSOC. 86;78(7):599-600 **No Original Data**

Johnson F D, Jacobs E M. Chemotherapy of metastatic malignant melanoma. Experience with 73 patients. Cancer 71;27(6):1306-12 **Study size too small**, **No Original Data**

Johnson L. Sickle cell disease patients and patient-controlled analgesia. Br J Nurs 2003;12(3):144-53 **Other, No Original Data**

Johnson R J, Owen R G, Child J A et al. Mobilization of Philadelphia-negative peripheral blood mononuclear cells in chronic myeloid leukaemia using hydroxyurea and G-CSF (filgrastim). Br J Haematol 96;93(4):863-8 **Not relevant to key questions**, **study size too small**

Johnson S, Kass N E, Natowicz M. Disclosure of personal medical information: differences among parents and affected adults for genetic and nongenetic conditions. Genet Test 2005;9(3):269-80 **Not relevant to key questions**

Jones F C, Broome M E. Focus groups with African American adolescents: enhancing recruitment and retention in intervention studies. J Pediatr Nurs 2001;16(2):88-96 **Not relevant to key questions**, **study size too small**

Jones J D, Kleiner D M. Awareness and Identification of Athletes With Sickle Cell Disorders at Historically Black Colleges and Universities. J Athl Train 96;31(3):220-222 **Not relevant to key questions**

Joyner S, Lee D, Hay P et al. Hydroxyurea-induced nail pigmentation in HIV patients. HIV **Study size too small**, **other**

Jusko W J. Pharmacodynamic principles in chemical teratology: dose-effect relationships. J Pharmacol Exp Ther 72;183(3):469-80 **Not relevant to key questions**, **No Original Data**

Kantarjian H M, Talpaz M. Questions raised by the Benelux CML Study Group: results from the randomized study with hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha2b for chronic myeloid leukemia. Blood 98;92(8):2984-7 **No Original Data**

Kaslow N J, Brown F. Culturally sensitive family interventions for chronically ill youth: Sickle cell disease as an example. Fam. Syst. Med. 95;13(2):201-213 **Not relevant to key questions**

Kaslow N J, Collins M H, Loundy M R et al. Empirically validated family interventions for pediatric psychology: sickle cell disease as an exemplar. J Pediatr Psychol 97;22(2):213-27 **Not relevant to key questions**

Kaslow N J, Collins M H, Rashid F L et al. The efficacy of a pilot family psychoeducational intervention for pediatric Sickle Cell Disease (SCD). Fam. Syst. Health 2000;18(4):381-404 **Not relevant to key questions**

Kato N, Kimura K, Yasukawa K et al. Hydroxyurea-related leg ulcers in a patient with chronic myelogenous leukemia: A case report and review of the literature. J. Dermatol. 99;26(1):56-62 **Not relevant to key questions**

Kaufman R E. Hydroxyurea: Specific therapy for sickle cell anemia?. BLOOD 92;79(10):2503-2506 **No Original Data**

Kav S, Bostanci H. Role of the nurse in patient education and follow-up of people receiving oral chemotherapy treatment in Turkey. Support Care Cancer 2006;14(12):1252-7 **Not relevant to key questions**

Kennedy B J, Yarbro J W. Metabolic and therapeutic effects of hydroxyurea in chronic myelogenous leukemia. Trans Assoc Am Physicians 65;78391-9 **Not relevant to key questions**, **No Original Data**

Kennedy B J. Cyclic leukocyte oscillations in chronic myelogenous leukemia during hydroxyurea therapy. Blood 70;35(6):751-60 **Not relevant to key questions**

Kennedy B J. Hydroxyurea-associated leg ulceration. Ann Intern Med 98;129(3):252; author reply 252-3 **Not relevant to key questions**, **No Original Data**

King A A, Tang S, Ferguson K L et al. An education program to increase teacher knowledge about sickle cell disease. J Sch Health 2005;75(1):11-4 **Not relevant to key questions**, **No Original Data**

Kirby B, Gibson L E, Rogers S et al. Dermatomyositis-like eruption and leg ulceration caused by hydroxyurea in a patient with psoriasis. Clin Exp Dermatol 2000;25(3):256-7 **Not relevant to key questions**, **No Original Data**

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Kirk S A. Sickle cell disease and health education. Midwife Health Visit Community Nurse 87;23(5):200-6 **Not relevant to key questions**, **No Original Data**

Klener P, Donner L. Hydroxyurea (Biosupressin-BIOGAL) for the treatment of chronic myelogenous leukaemia. Ther Hung 81;29(1):38-41 **Study size too small**

Kliewer W, Lewis H. Family influences on coping processes in children and adolescents with sickle cell disease. J Pediatr Psychol 95;20(4):511-25 **Not relevant to key questions**

Klingebiel T, Creutzig U, Dopfer R et al. Bone marrow transplantation in comparison with conventional therapy in children with adult type chronic myelogenous leukemia. Bone Marrow Transplant 90;5(5):317-20 **Not relevant to key questions**, **study size too small**

Kluin-Nelemans H C, Buck G, le Cessie S et al. Randomized comparison of low-dose versus high-dose interferon-alfa in chronic myeloid leukemia: prospective collaboration of 3 joint trials by the MRC and HOVON groups. Blood 2004;103(12):4408-15 **Not relevant to key questions**

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Koc A, Gumruk F, Gurgey A. The effect of hydroxyurea on the coagulation system in sickle cell anemia and beta-thalassemia intermedia patients: a preliminary study. Pediatr Hematol Oncol 2003;20(6):429-34 **Study size too small**

Kodish E, Lantos J, Siegler M et al. Bone marrow transplantation in sickle cell disease: the trade-off between early mortality and quality of life. Clin Res 90;38(4):694-700 **Not relevant to key questions**, **No Original Data**

Koh L-P, Kanagalingam D. Pregnancies in patients with chronic myeloid leukemia in the era of imatinib [1]. Int. J. Hematol. 2006;84(5):459-462 **Not relevant to key questions**

Kolitz J E, Kempin S J, Schluger A et al. A phase II pilot trial of high-dose hydroxyurea in chronic myelogenous leukemia. Semin Oncol 92;19(3 Suppl 9):27-33 **Study size too small**

Konior G S, Yarbro J W. Hydroxyurea in the treatment of chronic myeloid leukemia. South Med J 71;64(2):247-8 **Study size too small**, **Not relevant to key questions**

Konotey-Ahulu F I D. Opiates for sickle-cell crisis? [8]. Lancet 98;351(9113):1438 **No Original Data**

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Krakoff I H, Savel H, Murphy M L. Phase Ii Studies Of Hydroxyurea (Nsc-32065) In Adults: Clinical Evaluation. Cancer Chemother Rep 64;4053-5 **Not relevant to key questions**, **No Original Data**

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Kreft A, Nolde C, Busche G et al. Polycythaemia vera: Bone marrow histopathology under treatment with interferon, hydroxyurea and busulphan. Eur. J. Haematol. 2000;64(1):32-41 **Study size too small**

Kuhr T, Burgstaller S, Apfelbeck U et al. A randomized study comparing interferon (IFN alpha) plus low-dose cytarabine and interferon plus hydroxyurea (HU) in early chronic-phase chronic myeloid leukemia (CML). Leuk Res 2003;27(5):405-11 **Not relevant to key questions**, **other**

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Kwong Y L, Brandt L. Leukaemic risk in polycythaemia vera and essential thrombocytopenia [2]. EUR. J. HAEMATOL. 96;56(1-2):90-92 **No Original Data**

Kwong Y L, Liang R H, Chiu E K et al. Essential thrombocythemia: a retrospective analysis of 39 cases. Am J Hematol 95;49(1):39-42 **Study size too small**, **Not relevant to key questions**

Kwong Y L. Leukaemic risk in polycythaemia vera and essential thrombocytopenia. Eur J Haematol 96;56(1-2):90-2 **No Original Data**

Labropoulos N, Manalo D, Patel N P et al. Uncommon leg ulcers in the lower extremity. J Vasc Surg 2007;45(3):568-573 **Not relevant to key questions**

Lal A, Vichinsky E. The role of fetal hemoglobin-enhancing agents in thalassemia. Semin. Hematol. 2004;41(SUPPL. 6):17-22 **No Original Data**

Landau Hurtig A, Park K B. Adjustment and coping in adolescents with sickle cell disease. Ann. New York Acad. Sci. 89;565(-):172-182 **Not relevant to key questions**

Lane J C, Scott R B. Awareness of sickle cell anemia among negroes of Richmond, Va. Public Health Rep 69;84(11):949-53 **Not relevant to key questions**

Lanigan C, Justins D. Sickle cell crisis and pain management +AFs-14+AF0-. ANAESTHESIA 93;48(9):829-830 **Not relevant to key questions**

Lanzkron S, Haywood C, Segal J B et al. Hospitalization rates and costs of care of patients with sickle-cell anemia in the state of Maryland in the era of hydroxyurea. Am J Hematol 2006;81(12):927-32 **Not relevant to key questions**

Laughon S K, Shinn L L, Nunley J R. Melanonychia and mucocutaneous hyperpigmentation due to hydroxyurea use in an HIV-infected patient. Int J Dermatol **Not relevant to key questions**, **other**

Lawrence C, Bentley H P. Relief of sickle cell anemia pain. J Med Assoc State Ala 80;49(9):16-8 **Not relevant to key questions**

Layton A M, Cotterill J A. Immunological changes in hydroxyurea-induced collagen disease. Br J Dermatol **Other**

Lazzarino M, Morra E, Brusamolino E et al. Hydroxyurea and 6-mercaptopurine in the treatment of chronic granulocytic leukemia. Am J Clin Oncol 86;9(1):45-9 **Not relevant to key questions**

Leavell U W, Yarbro J W. Treatment of psoriasis by hydroxyurea. South Med J **Not relevant to key questions**, **No Original Data**

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Zuazu J, Julia A, Sierra J et al. Pregnancy outcome in hematologic malignancies. CANCER 91;67(3):703-709 **Not relevant to key questions**

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Appendix E

Appendix E: Evidence Grading

Score Sheet –Efficacy in Children with SCD

		Outcomes					
		Hb F% change	**Reduction in crises (pain/ACS)**	**Reduction in hospitalization**	**Reduction in neurological events**	**Reduction in transfusion**	
1	Protection against risk of bias (relates to study design, study quality, reporting bias)						
2	Did the studies have important **inconsistency**? (-1)						
3	Was there some (-1) or major (-2) uncertainty about the **directness** or extent to which the **people**, **interventions** and **outcomes** are similar to those of interest?						
4	Were the studies sparse or imprecise? (-1)						
5	Did the studies show strong evidence of **association between intervention and outcome**? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))						
6	Did the studies have evidence of a **dose-response gradient**? (+1)						
7	Did the studies have **unmeasured plausible confounders** that affected the magnitude of the observed association? (+1)						
	Overall grade of evidence (high, moderate, low, very low) (*insufficient* if no studies or evidence is too sparse or inconsistent to draw conclusions)						

* enter 0 if the studies evidence does not warrant a (-) or (+) score

Score Sheet –Efficacy in Adults with SCD

		Outcomes					
		Hb F% change	**Reduction in crises (pain/ACS)**	**Reduction in hospitalization**	**Reduction in neurological events**	**Reduction in transfusion**	**Mortality**
1	Protection against risk of bias						
2	Did the studies have important **inconsistency**? (-1)						
3	Was there some (-1) or major (-2) uncertainty about the **directness** or extent to which the **people**, **interventions** and **outcomes** are similar to those of interest?						
4	Were the studies sparse or imprecise? (-1)						
5	Did the studies show strong evidence of **association between intervention and outcome**? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))						
6	Did the studies have evidence of a **dose-response gradient**? (+1)						
7	Did the studies have **unmeasured plausible confounders** that affected the magnitude of the observed association? (+1)						
	Overall grade of evidence (high, moderate, low, very low) (*insufficient* if no studies or evidence is too sparse or inconsistent to draw conclusions)						

Score Sheet –Toxicity in Children with SCD

		Outcomes				
		Leukemia (MDS/AML/Cyto genetic abnromalities	**Developmental toxicities (in utero)**	**Leg ulcers**	**Growth delays**	**Developmental toxicities in next generation**
1	Protection against risk of bias (relates to study design, study quality, reporting bias)					
2	Did the studies have important **inconsistency**? (-1)					
3	Was there some (-1) or major (-2) uncertainty about the **directness** or extent to which the **people**, **interventions** and **outcomes** are similar to those of interest?					
4	Were the studies sparse or imprecise? (-1)					
5	Did the studies show strong evidence of **association between intervention and outcome**? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))					
6	Did the studies have evidence of a **dose-response gradient**? (+1)					
7	Did the studies have **unmeasured plausible confounders** that affected the magnitude of the observed association? (+1)					
	Overall grade of evidence (high,moderate, low, very low) (*insufficient* if no studies or evidence is too sparse or inconsistent to draw conclusions)					

Score Sheet –Toxicity in Adults with SCD

		Outcomes					
		Leukemia (MDS/AML/Cytogenetic abnormalities	**Leg ulcers**	**Skin neoplasms**	**Secondary malignancies**	**Adverse preg. Outcomes**	**Spermato-genesis defects**
1	Protection against risk of bias (relates to study design, study quality, reporting bias)						
2	Did the studies have important **inconsistency**? (-1)						
3	Was there some (-1) or major (-2) uncertainty about the **directness** or extent to which the **people**, **interventions** and **outcomes** are similar to those of interest?						
4	Was the data sparse or imprecise (-1)						
5	Did the studies show strong evidence of **association between intervention and outcome**? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))						
6	Did the studies have evidence of a **dose-response gradient**? (+1)						
7	Did the studies have **unmeasured plausible confounders** that affected the magnitude of the observed association? (+1)						
	Overall grade of evidence (high, moderate, low, very low) (*insufficient* if no studies or evidence is too sparse or inconsistent to draw conclusions)						

Score Sheet –Toxicity in Adults with Other Diseases

		Outcomes					
		Leukemia (MDS/AML/Cytogenetic abnormalities	**Leg ulcers**	**Skin neoplasms**	**Secondary malignancies**	**Adverse preg. Outcomes**	**Spermato-genesis defects**
1	Protection against risk of bias (relates to study design, study quality, reporting bias)						
2	Did the studies have important **inconsistency**? (-1)						
3	Was there some (-1) or major (-2) uncertainty about the **directness** or extent to which the **people**, **interventions** and **outcomes** are similar to those of interest?						
4	Was the data sparse or imprecise (-1)						
5	Did the studies show strong evidence of **association between intervention and outcome**? ("strong" if significant relative risk or odds ratio > 2 based on consistent evidence from 2 or more studies with no plausible confounders (+1); "very strong" if significant relative risk or odds ratio > 5 based on direct evidence with no major threats to validity (+2))						
6	Did the studies have evidence of a **dose-response gradient**? (+1)						
7	Did the studies have **unmeasured plausible confounders** that affected the magnitude of the observed association? (+1)						
	Overall grade of evidence (high, moderate, low, very low) (*insufficient* if no studies or evidence is too sparse or inconsistent to draw conclusions)						

Grading the Evidence for Key Question 4 – Barriers to Therapies

Grading the Evidence for the Cross-sectional and Descriptive Studies about the Presence of Barriers

After all of the articles were reviewed, the body of the evidence supporting the existence of particular barriers for each question was graded on the basis of the number of times the barrier was identified (quantity), protection against the bias in the studies (quality), and consistency.

First, the quantity of the evidence was initially judged as being Strong, Moderate, or Low on the basis of the following criteria: there had to be more than ten studies identifying a particular factor (i.e. potential barrier or facilitator) to meet criteria for a "High" grade, six to ten studies to meet criteria for a "Moderate" grade, three to five studies to meet the criteria for a "Poor" grade, and two or fewer studies to meet the criteria for an "Insufficient" grade.

The initial grade for the evidence was then *lowered* by one level (i.e., changing from High to Moderate or from Moderate to Low) if 75% or less of the studies reviewed for each question attempted to protect against the risk of bias through controlling for potential confounders in the cross-sectional studies OR if the reported barriers were not cited by the population that would be most knowledgeable about the barrier in the descriptive studies (e.g. healthcare providers themselves saying they had limited knowledge was considered greater protection against bias than if patients had reported the same finding). The initial quantity score was left unchanged if our criteria for protection against the risk of bias were met.

The resulting score was then revised further based on the consistency of the evidence, which was an assessment of the extent to which any particular factor (i.e. potential barrier or facilitator) was found across studies to be a barrier to, a facilitator of, or to have no association with the appropriate therapy of interest. The score was *lowered* by one level if less than 75%, and *lowered* by two levels if less than 50%, of the studies found an independent variable to be a barrier, facilitator, or have no association with the therapy of interest. The score was *raised* by one level (i.e., from Poor to Moderate or from Moderate to High) if 100% of the studies examining any particular independent variable found it to be a barrier, facilitator, or have no association with the therapy of interest.

Grading the Evidence for the Intervention Studies

Criteria to grade the body of the evidence for the intervention studies were similar to the criteria used earlier in the report, and therefore were different criteria than that presented above for KQ4a-e. For each therapy of interest, the evidence that an intervention could overcome barriers to that therapy of interest was given an initial grade of High if the evidence contained at least one randomized controlled trial, Moderate if there was at least one controlled trial (not randomized), and Low if the evidence contained no controlled trials. Grades of High or Moderate were then lowered by one level if there were serious concerns about the presence of bias in the findings.

Grades were *lowered* by one additional level in the presence of important inconsistencies in the findings across studies, any uncertainty about the directness or extent to which the people, interventions, and outcomes were similar to the sickle cell populations of interest, or if the findings were too imprecise or sparse to estimate an effect.

Grades were then *raised* by one additional level in the presence of strong evidence of association between the intervention and the outcome, evidence of a dose-response gradient, or if all plausible unmeasured confounders would have reduced the observed effect. Grades were raised by two levels in the presence of very strong evidence of association between the intervention and the outcome.

The overall grade of the body of this evidence was given as the final grade that resulted from the above assessments. A grade of Insufficient was given if there were no studies examining potential interventions to overcome barriers to an appropriate therapy of interest, or of the existing body of evidence was deemed to be too sparse or inconsistent to draw conclusions.

Appendix F

Appendix F: Technical Experts and Peer Reviewers

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