

Hydroxyurea for the Treatment of Sickle Cell Disease

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Prepared by:

The Johns Hopkins University Evidence-based Practice Center, Baltimore, MD

Investigators

Jodi B. Segal, M.D., M.P.H.
John J. Strouse, M.D.
Mary Catherine Beach, M.D., M.P.H.
Carlton Haywood, M.A.
Catherine Witkop, M.D., M.P.H.
Haeseong Park, M.D., M.P.H.
Renee F. Wilson, M.Sc.
Eric B. Bass, M.D., M.P.H.
Sophie Lanzkron, M.D.

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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.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Barry Kramer, M.D.
Director, Office of Medical Applications
of Research, NIH

Beth A. Collins Sharp, R.N., Ph.D.
Director, EPC Program
Agency for Healthcare Research and Quality

Ernestine W. Murray, B.S.N., R.N., M.A.S.
Task Order Officer
Agency for Healthcare Research and Quality

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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 MEDLINE[®], 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.

Contents

Executive Summary	1
Evidence Report	13
Chapter 1. Introduction	15
Sickle Cell Disease	15
Clinical Characteristics	15
Established Treatments	16
A Brief History of Hydroxyurea	16
Mechanism of Action	17
Pharmacokinetics	17
Current Labeling	18
Purpose of Evidence Report	18
Chapter 2. Methods	21
Recruitment of Technical Experts and Peer Reviewers	21
Key Questions	21
Literature Search Methods	23
Sources	25
Search Terms and Strategies	25
Organization and Tracking of Literature Search	25
Title Review	25
Abstract Review	26
Article Review	26
Data Abstraction	26
Quality Assessment	27
Data Synthesis	28
Data Entry and Quality Control	28
Grading of the Evidence	28
Peer Review	30
Chapter 3. Results	31
Literature Search/Abstract/Article Review	31
Description of Types of Studies Retrieved	31
Key Question 1: What is the Efficacy (results from clinical studies)of Hydroxyurea Treatment for Patients who have Sickle Cell Disease?	33
Key Question 2: What is the Effectiveness (in everyday practice) of Hydroxyurea Treatment for Patients who have Sickle Cell Disease?	33
Description of Randomized Trials	33
Description of Observational Studies	34
Efficacy and Effectiveness of Hydroxyurea in Children	36
Efficacy and Effectiveness of Hydroxyurea in Adults	38
Key Question 3: What are the Short- and Long-term Harms of Hydroxyurea Treatment?.....	43

Report by Center for the Evaluation of Risks to Human Reproduction (CERHR)	43
Results from Randomized Trials in Sickle Cell Disease	46
Results from Observational Studies in Sickle Cell Disease Including Case Reports	47
Results from Studies in Other Diseases	50
Key Question 4. B 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?.....	58
Characteristics of Studies Addressing Interventions to Overcome Barriers to the Appropriate use of Therapies.....	58
Results of Studies Addressing Barriers to use of Therapies for Sickle Cell Disease	59
Characteristics of Studies Addressing Interventions to Overcome Barriers to the Appropriate Use of Therapies	63
Results of Studies Addressing Interventions to Overcome Barriers to the Appropriate Use of Therapies	64
Chapter 4. Discussion	67
Summary of Key Findings	67
Key Questions 1 and 2	67
Efficacy and Effectiveness of Hydroxyurea in Children	67
Efficacy and Effectiveness of Hydroxyurea in Adults	68
Key Question 3	69
Toxicities of Hydroxyurea in Children and Adults.....	69
Key Question 4	71
Barriers to use of Hydroxyurea and Other Treatments for Managing Sickle Cell Disease	71
Limitations	72
Research in Progress	74
Future Research Needs	75
Implications.....	76
References and Included Studies	77
List of Acronyms	79
Figures	
Figure 1. Analytic Framework	22
Figure 2. Conceptual Model: Hydroxyurea Treatment For Sickle Cell Disease (Adapted From The Aday & Andersen Expanded Behavioral Model).....	24
Figure 3. Summary of literature search and review process.....	32
Summary Tables	
Table 1. Efficacy of Hydroxyurea in Observational Studies on Children with Sickle Cell Disease	36

Table 2. Efficacy of Hydroxyurea in Observational Studies on Adults with Sickle Cell Disease	39
Table 3. Predictors of Benefit from Hydroxyurea in Studies of Sickle Cell Disease	41
Table 4. Outcomes of Hydroxyurea Use in Sickle Cell Disease Reported by Genotype	42
Table 5. Summary of the Evidence.....	45
Table 6. Major Toxicities of Hydroxyurea in Other Diseases	48
Table 7. Predictors of Toxicity from Hydroxyurea in Studies of Sickle Cell Disease	58
Table 8. Patient, Provider, and Societal Barriers and Facilitators Shown to be Associated with Treatment for Patients with Sickle Cell Disease	61
Table 9. Summary of Barriers to Treatment of Sickle Cell Disease Reported by Patients and Providers	63
Table 10. Results of Studies which have 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.....	66

Appendixes

- Appendix A: Detailed Search Strategies
- Appendix B: Screen and Data Abstraction Forms
- Appendix C: Evidence Tables
- Appendix D: Excluded Articles
- Appendix E: Evidence Grading
- Appendix F: Technical Experts and Peer Reviewers

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 thrombocytopenia. 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 used 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 S β 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 to 15 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 (<i>in utero</i>)	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 interventions 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 β^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 Powars⁷ 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 Powars⁷ 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 β^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/mm³, platelets greater than or equal to 95,000/mm³, hemoglobin greater than 5.3 g/dl, and reticulocytes greater than or equal to 95,000/mm³ if the hemoglobin concentration is less than 9 g/dl. Counts considered to be toxic are: neutrophils less than 2000 cells/mm³, platelets less than 80,000/mm³, hemoglobin less than 4.5 g/dl, and reticulocytes less than 80,000/mm³ 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 drugs¹⁵; 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 guidelines²⁴ 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>

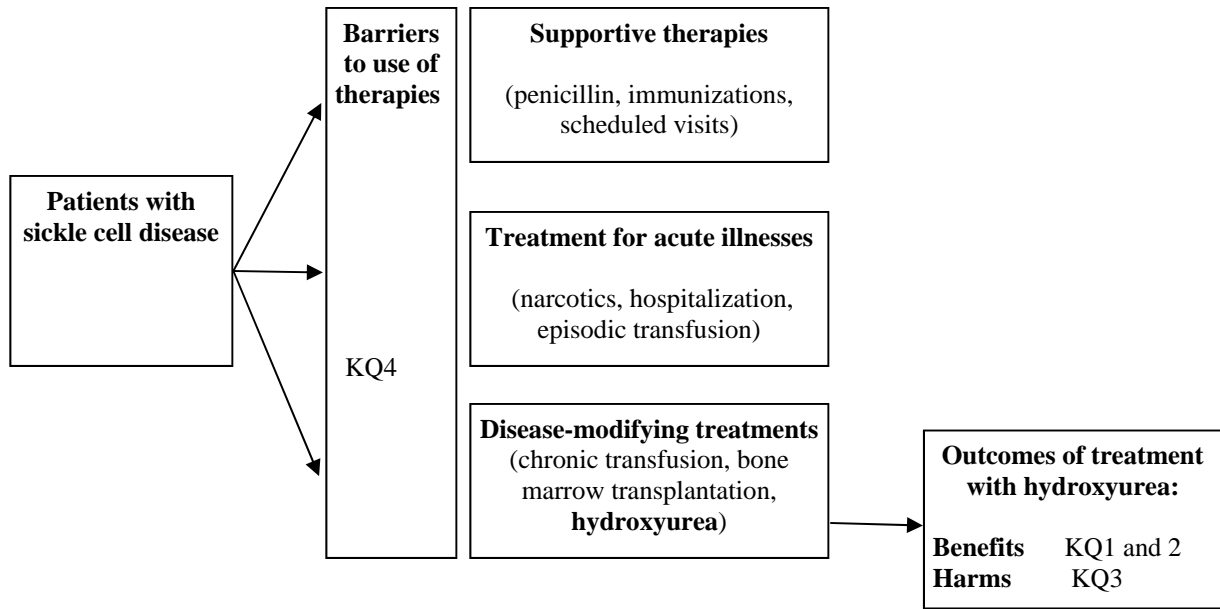


Figure 1. Analytic Framework

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 CERHR²⁶ 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.

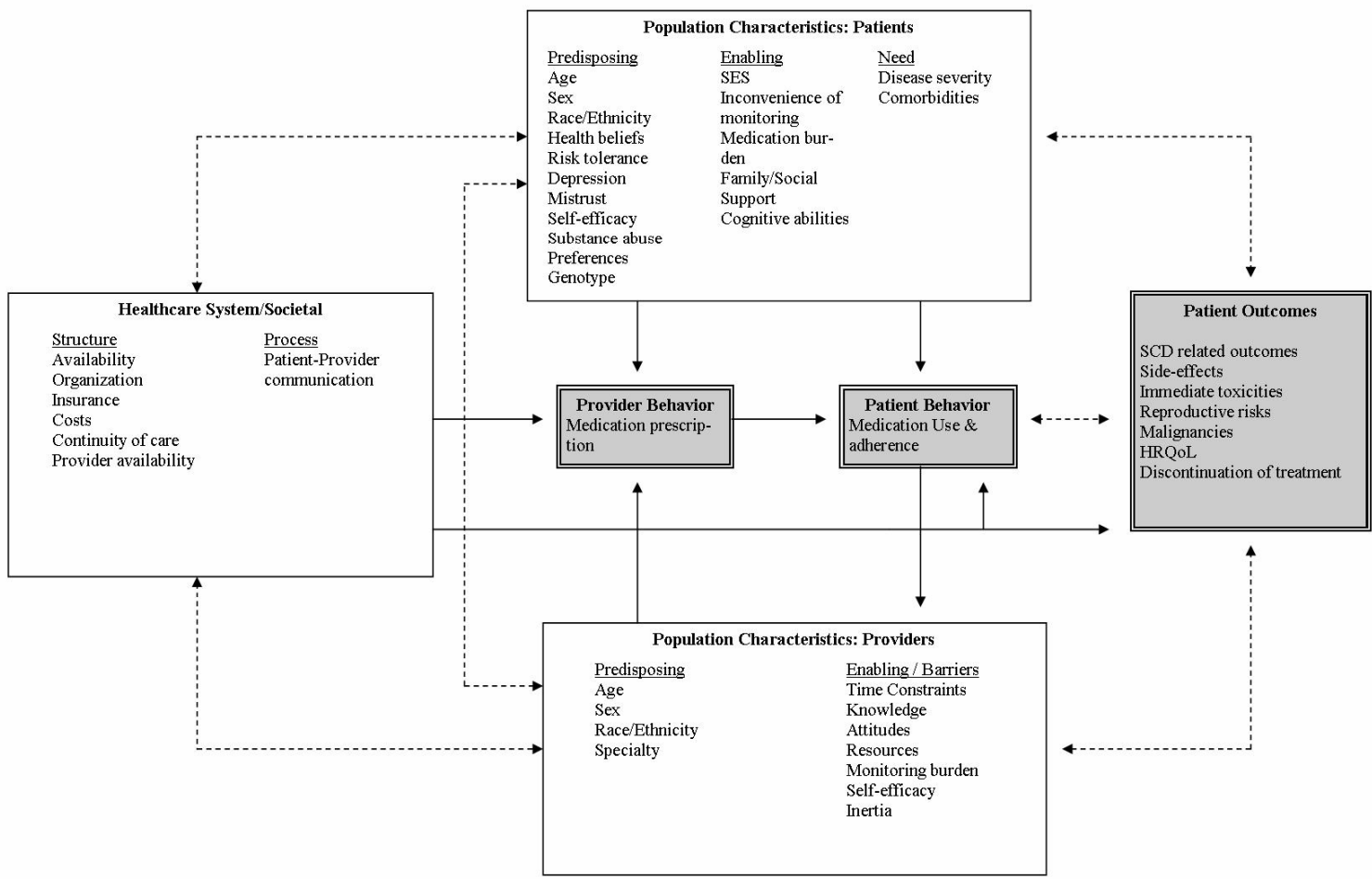


Figure 2. Conceptual Model: Hydroxyurea Treatment For Sickle Cell Disease (Adapted From The Aday & Andersen Expanded Behavioral Model)²⁶

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/hydsdtp.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/hydsdtp.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 below²⁸ (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/hydsdctp.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 Group³⁷ 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/hydsdtp.htm>

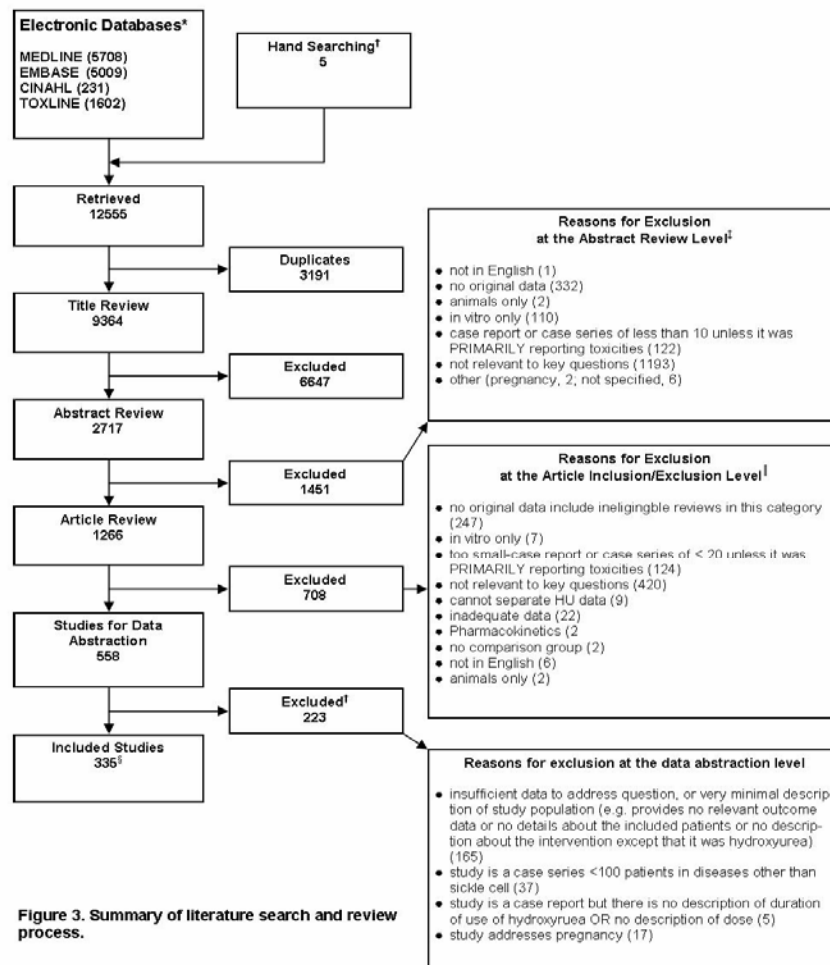


Figure 3. Summary of literature search and review process.

* 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 study⁴⁷ 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/hydsdtp.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 study⁴⁸ 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 percent⁴⁷ and 93 percent⁷⁷ 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 percent⁷⁷ to 74 percent.⁷⁶ The majority of the studies included patients with Hb S β 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 microalbuminuria⁴⁹: 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 Sβ⁺ thalassemia and Hb Sβ⁰ 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 Sβ⁺ thalassemia and Hb Sβ⁰ 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≤0.05), 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 HbSB⁰ or SB⁺thalassemia, 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/hydsdtp.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/ μ l, F reticulocytes greater than 12 percent, absolute neutrophil count (ANC) greater than 7500/ μ l, 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 baseline⁷⁵ 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 haplotype⁷⁵ 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 β^0 thalassemia or Hb S β^+ 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 ⁸⁹	More marked improvement in splenic function in patients with Hb SS than in patients with HbS β^0 -thalassemia. Thought to be due to less severely impaired splenic function at baseline in patients with Hb S β^0 -thalassemia
Loukopoulos, 2000 ⁹³	No increase in Hb among patients with Hb S β^+ thalassemia; increase in the Hb SS and HbS β^0 -thalassemia 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 β^+ 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 β^0 -thalassemia
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/hydsdtp.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 (<i>in utero</i>)	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 of hydroxyurea, 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 to 15 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/ μ l vs 6400/ μ l) 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, lymphadenopathy, 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/ μ l ($p < 0.001$), 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 V γ -J β 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/hydsdtp.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 malignancies, n	Comments
HIV	RCT: 6 Other: 0	0	0	0	RCT: 1	4 cases of Kaposi's 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 myelosuppressive 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 a 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/ μ l, including 6 with an absolute neutrophil count of less than 500/ μ l.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/ μ l. 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/hydsdctp.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 with AML; 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 4¹⁰⁴ (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 percent¹⁰⁵ and 73 percent¹⁰⁶ 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/hydsdtp.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 Group¹¹⁵ 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 ³²P 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 ³²P 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) ³²P and hydroxyurea maintenance therapy, and (4) ³²P without hydroxyurea maintenance. The patients treated with ³²P 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 ³²P arm receiving maintenance hydroxyurea, versus 10 percent at 10 years for the ³²P 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 ³²P group who received maintenance hydroxyurea was 29 percent at 12 years of followup; it was 15 percent at 12 years for those who received ³²P 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 ³²P with maintenance versus the arm receiving ³²P 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 publication¹²⁵ 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 $1000 \times 10^9/l$ 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 thrombocytosis being highest, despite a lack of FDA approval of this drug for the treatment of essential thrombocytosis (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 thrombocytosis, 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 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, 1992 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 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 Arabia¹⁷⁰ and five did not specify a location.

* Appendixes cited in this report are provided electronically at: <http://www.ahrq.gov/clinic/tp/hydsdctp.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	<i>Barriers</i>		NR	NR
	<i>Facilitators</i>	Perceived efficacy (1) Perceived safety (1)	NR	NR
	<i>Neither</i>	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	<i>Barriers</i>	Family stress (1) More children at home (1)	NR	Academic medical setting (1)
	<i>Facilitators</i>	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
	<i>Neither</i>	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-occlusive crisis	<i>Barriers</i>	Hospital visits (1)	Negative attitudes (1)	
	<i>Facilitators</i>	Dispositional optimism (1)	Female sex (1) Fewer years in practice (1)	NR
	<i>Neither</i>	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	<i>Barriers</i>	Greater community socioeconomic distress (1)	NR	NR
	<i>Facilitators</i>	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
	<i>Neither</i>	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 disease¹⁴⁷⁻¹⁵² 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-occlusive 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 activities¹⁸³), 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 hospital¹⁷⁶ 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 desferoxime¹⁸¹ 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/hydsdtp.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-occlusive 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 to 15 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, erythropoietin 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/hydsdtp.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.

References and Included Studies*

1. Platt OS, Brambilla DJ, Rosse WF et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330(23):1639-44.
2. U.S. Preventive Services Task Force. Screening for Hemoglobinopathies U.S. Preventive Services Task Force, Guidelines from Guide to Clinical Preventive Services. second. 1996 Williams and Wilkens. 1996.
3. McClish DK, Penberthy LT, Bovbjerg VE et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health Qual Life Outcomes* 2005;3:50.
4. Shapiro BS, Benjamin LJ, Payne R et al. Sickle cell-related pain: perceptions of medical practitioners. *J Pain Symptom Management* 1997;14:168-174.
5. Gaston M and Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. *Am J Pediatr Hematol Oncol* 1982;4(2):197-201.
6. Platt OS, Thorington BD, Brambilla DJ et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med* 1991;325(1):11-6.
7. Powars DR, Chan LS, Hiti A et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine (Baltimore)* 2005;84(6):363-76.
8. Vichinsky EP, Neumayr LD, Earles AN et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;342(25):1855-65.
9. Castro O, Brambilla DJ, Thorington B et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood* 1994;84(2):643-9.
10. Eckman JR. Leg ulcers in sickle cell disease. *Hematol Oncol Clin North Am* 1996;10(6):1333-44.
11. Quinn CT, Rogers ZR, and Buchanan GR. Survival of children with sickle cell disease. *Blood* 2004;103(11):4023-7.
12. Kirkham FJ. Therapy insight: stroke risk and its management in patients with sickle cell disease. *Nat Clin Pract Neurol* 2007;3(5).
13. Dressler WFC and Sterin R. Uber den Hydroxylharnstoff. *Jusutus Liebig's Ann Chem Pharm* 1869;150: 242-252.
14. Stevens MR. Hydroxyurea: An overview. *J. Biol. Regul. Homeostatic Agents* 1999;13(3):172-175.
15. Food and Drug Administration. Med watch. <http://www.fda.gov/medwatch/safety/2006/safety06.htm#Hydrea>.
16. Krakoff IH, Brown NC, and Reichard P. Inhibition of ribonucleoside diphosphate reductase by hydroxyurea. *Cancer Res* 1968;28(8):1559-65.
17. Dover GJ and Charache S. Hydroxyurea induction of fetal hemoglobin synthesis in sickle-cell disease. *Semin Oncol* 1992;19(3 Suppl 9):61-6.
18. Cokic VP, Smith RD, Beleslin-Cokic BB et al. Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase. *J Clin Invest* 2003;111(2):231-9.
19. Ho JA, Pickens CV, Gamcsik MP et al. In vitro induction of fetal hemoglobin in human erythroid progenitor cells. *Exp Hematol* 2003;31(7):586-91.
20. http://www.bms.com/cgi-bin/anybin.pl?sql=PI_SEQ=72. 2006.
21. Charache S, Terrin ML, Moore RD et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;332(20):1317-22.
22. Moore RD, Charache S, Terrin ML et al. Cost-effectiveness of hydroxyurea in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *Am J Hematol* 2000;64 (1):26-31.
23. The Management of Sickle Cell Disease, 4th. NIH Publication No. 02-2117 2002.
24. Stafford RS, Furberg CD, Finkelstein SN et al. Impact of clinical trial results on national trends in alpha-blocker prescribing, 1996-2002. *JAMA* 2004;291(1):54-62.
25. Cabana MD, Rand CS, Powe NR et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282(15):1458-65.

26. Center for the Evaluation of Risks to Human Reproduction. [Http://Cerhr.Niehs.Nih.Gov/?](http://Cerhr.Niehs.Nih.Gov/)
27. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet* 1997;350(9072):185-6.
28. WHO Collaborating Center for International Drug Monitorin. [Http://Www.Who-Umc.Org/DynPage.Asp?Id=22682](http://Www.Who-Umc.Org/DynPage.Asp?Id=22682) .
29. 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.
30. Normand SL, Sykora K, Li P et al. Readers guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding. *BMJ* 2005;330(7498):1021-3.
31. Mamdani M, Sykora K, Li P et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ* 2005;330(7497):960-2.
32. Rochon PA, Gurwitz JH, Sykora K et al. Reader's guide to critical appraisal of cohort studies: 1. Role and design. *BMJ* 2005;330(7496):895-7.
33. Lincoln TM and Reif W. How much do sample characteristics affect the effect size? An investigation of studies testing the treatment effects for social phobia. *J Anxiety Disord* 2004;18(4).
34. Tobin GA and Begley CM. Methodological rigour within a qualitative framework. *J Adv Nurs* 2004;48(4):388-96.
35. Horsburgh D. Evaluation of qualitative research. *J Clin Nurs* 2003;12(2):307-12.
36. Ratanawongsa N, Thomas PA, Marinopoulos SS et al. and Reliability of Methods for Evaluating Continuing Medical Education: A Systematic Review. *Acad Med in press*.
37. Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490.
38. Jones J. K. Determining causation from case reports. In: *Pharmacoevidence 4th ED*. Brian Strom (Ed) 2005;John Wiley and Sons, West Sussex, England.
39. Charache S, Barton FB, Moore RD et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *Medicine (Baltimore)* 1996;75(6):300-26.
40. Steinberg MH, Lu ZH, Barton FB et al. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea. Multicenter Study of Hydroxyurea. *Blood* 1997;89(3):1078-88.
41. Hackney AC, Hezier W, Gullidge TP et al. Effects of hydroxyurea administration on the body weight, body composition and exercise performance of patients with sickle-cell anaemia. *Clin Sci (Lond)* 1997;92(5):481-6.
42. Ballas SK, Barton FB, Waclawiw MA et al. Hydroxyurea and sickle cell anemia: effect on quality of life. *Health Qual Life Outcomes* 2006; 4:59.
43. Steinberg MH, Barton F, Castro O et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003;289(13):1645-51.
44. Ferster A, Vermeylen C, Cornu G et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood* 1996;88(6):1960-4.
45. el-Hazmi MA, Warsy AS, al-Momen A et al. Hydroxyurea for the treatment of sickle cell disease. *Acta Haematol* 1992;88(4):170-4.
46. Charache S, Dover GJ, Moore RD et al. Hydroxyurea: effects on hemoglobin F production in patients with sickle cell anemia. *Blood* 1992;79(10):2555-65.
47. Khayat AS, Antunes LM, Guimaraes AC et al. Cytotoxic and genotoxic monitoring of sickle cell anaemia patients treated with hydroxyurea. *Clin Exp Med* 2006 ;6(1):33-7.
48. de Montalembert M, Brousse V, Elie C et al. Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes. *Haematologica* 2006;91(1):125-8.
49. McKie KT, Hanevold CD, Hernandez C et al. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. *J Pediatr Hematol Oncol* 2007;29(3):140-4.

50. Svarch E, Machin S, Nieves RM et al. Hydroxyurea treatment in children with sickle cell anemia in Central America and the Caribbean countries. *Pediatr Blood Cancer* 2006;47(1):111-2.
51. Bakanay SM, Dainer E, Clair B et al. Mortality in sickle cell patients on hydroxyurea therapy. *Blood* 2005;105(2):545-7.
52. Ferguson RP, Arun A, Carter C et al. Hydroxyurea treatment of sickle cell anemia in hospital-based practices. *Am J Hematol* 2002;70(4):326-8.
53. Schultz WH and Ware RE. Malignancy in patients with sickle cell disease. *Am J Hematol* 2003;74(4):249-53.
54. Gergen PJ, Macri CJ, and Murrillo S. The need for sickle cell screening among pediatric latino immigrants. *Arch Pediatr Adolesc Med* 2002;156(7):729.
55. de Montalembert M, Begue P, Bernaudin F et al. Preliminary report of a toxicity study of hydroxyurea in sickle cell disease. French Study Group on Sickle Cell Disease. *Arch Dis Child* 1999;81(5):437-9.
56. Harrod VL, Howard TA, Zimmerman SA et al. Quantitative analysis of Howell-Jolly bodies in children with sickle cell disease. *Exp Hematol* 2007;35(2):179-83.
57. Hanft VN, Fruchtman SR, Pickens CV et al. Acquired DNA mutations associated with in vivo hydroxyurea exposure. *Blood* 2000;95(11):3589-93.
58. Ferster A, Tahriri P, Vermynen C et al. Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood* 2001;97(11):3628-32.
59. Santos A, Pinheiro V, Anjos C et al. Scintigraphic follow-up of the effects of therapy with hydroxyurea on splenic function in patients with sickle cell disease. *Eur J Nucl Med Mol Imaging* 2002;29(4):536-41.
60. Wang WC, Wynn LW, Rogers ZR et al. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001;139(6):790-6.
61. Cummins O and Anie KA. A comparison of the outcome of cognitive behaviour therapy and hydroxyurea in sickle cell disease. *Psychol. Health Med.* 2003;8(2):199-204.
62. Kratovil T, Bulas D, Driscoll MC et al. Hydroxyurea therapy lowers TCD velocities in children with sickle cell disease. *Pediatr Blood Cancer* 2006;47(7):894-900.
63. Zimmerman SA, Schultz WH, Burgett S et al. Hydroxyurea therapy lowers transcranial doppler flow velocities in children with sickle cell anemia. *Blood* 2007.
64. Olivieri NF and Vichinsky EP. Hydroxyurea in children with sickle cell disease: impact on splenic function and compliance with therapy. *J Pediatr Hematol Oncol* 1998;20(1):26-31.
65. Hankins JS, Helton KJ, McCarville MB et al. Preservation of spleen and brain function in children with sickle cell anemia treated with hydroxyurea. *Pediatr Blood Cancer* 2007.
66. Chaîne B, Neonato MG, Girot R et al. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001;137(4):467-70.
67. Ware RE, Zimmerman SA, Sylvestre PB et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004;145(3):346-52.
68. Kinney TR, Helms RW, O'Branski EE et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Pediatric Hydroxyurea Group. Blood* 1999;94(5):1550-4.
69. Loukopoulos D, Voskaridou E, Stamoulakatou A et al. Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998;850:120-8.
70. Al-Jam'a AH and Al-Dabbous IA. Hydroxyurea in sickle cell disease patients from Eastern Saudi Arabia. *Saudi Med J* 2002;23(3):277-81.
71. Rigano P, Rodgers GP, Renda D et al. Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/beta-thalassemia. *Hemoglobin* 2001;25(1):9-17.
72. Hankins JS, Ware RE, Rogers ZR et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood* 2005;106(7):2269-75.
73. Ware RE, Eggleston B, Redding-Lallinger R et al. Predictors of fetal hemoglobin response in children with sickle cell anemia receiving hydroxyurea therapy. *Blood* 2002;99(1):10-4.
74. Loukopoulos D, Voskaridou E, Kalotychoy V et al. Reduction of the clinical severity of sickle cell/beta-

- thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000;26(5):453-66.
75. Maier-Redelsperger M, de Montalembert M, Flahault A et al. Fetal hemoglobin and F-cell responses to long-term hydroxyurea treatment in young sickle cell patients. The French Study Group on Sickle Cell Disease. *Blood* 1998;91(12):4472-9.
 76. de Montalembert M, Belloy M, Bernaudin F et al. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. *J Pediatr Hematol Oncol* 1997;19(4):313-8.
 77. Scott JP, Hillery CA, Brown ER et al. Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996;128(6):820-8.
 78. Voskaridou E, Kalotychoy V, and Loukopoulos D. Clinical and laboratory effects of long-term administration of hydroxyurea to patients with sickle-cell/beta-thalassaemia. *Br J Haematol* 1995;89(3):479-84.
 79. Ataga KI, Moore CG, Jones S et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *Br J Haematol* 2006; 134(1):109-15.
 80. Vicari P, Barretto de Mello A, and Figueiredo MS. Effects of hydroxyurea in a population of Brazilian patients with sickle cell anemia. *Am J Hematol* 2005 ;78(3):243-4.
 81. Zimmerman SA, Schultz WH, Davis JS et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004;103(6):2039-45.
 82. Gulbis B, Haberman D, Dufour D et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005;105(7):2685-90.
 83. Scothorn DJ, Price C, Schwartz D et al. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *J Pediatr* 2002;140(3):348-54.
 84. Wilimas J, Goff JR, Anderson HR Jr et al. Efficacy of transfusion therapy for one to two years in patients with sickle cell disease and cerebrovascular accidents. *J Pediatr* 1980;96(2):205-8.
 85. Athanassiou G, Moutzouri A, Kourakli A et al. Effect of hydroxyurea on the deformability of the red blood cell membrane in patients with sickle cell anemia. *Clin Hemorheol Microcirc* 2006;35(1-2):291-5.
 86. Iyamu EW, Cecil R, Parkin L et al. Modulation of erythrocyte arginase activity in sickle cell disease patients during hydroxyurea therapy. *Br J Haematol* 2005;131(3):389-94.
 87. Nahavandi M, Tavakkoli F, Wyche MQ et al. Nitric oxide and cyclic GMP levels in sickle cell patients receiving hydroxyurea. *Br J Haematol* 2002;119(3):855-7.
 88. Lapoumeroulie C, Benkerrou M, Odievre MH et al. Decreased plasma endothelin-1 levels in children with sickle cell disease treated with hydroxyurea. *Haematologica* 2005;90(3):401-3.
 89. Tavakkoli F, Nahavandi M, Wyche MQ et al. Plasma levels of TNF-alpha in sickle cell patients receiving hydroxyurea. *Hematology* 2004;9(1): 61-4.
 90. Heeney MM, Howard TA, Zimmerman SA et al. UGT1A promoter polymorphisms influence bilirubin response to hydroxyurea therapy in sickle cell anemia. *J Lab Clin Med* 2003;141(4):279-82.
 91. Nahavandi M, Tavakkoli F, Wyche MQ et al. Arterialization of venous blood for differentiation of sickle cell subjects in vaso-occlusive crisis. *Hematology* 2003;8(6):421-428.
 92. Teixeira SM, Cortellazzi LC, and Grotto HZ. Effect of hydroxyurea on G gamma chain fetal hemoglobin synthesis by sickle-cell disease patients. *Braz J Med Biol Res* 2003;36(10):1289-92.
 93. Zumberg MS, Reddy S, Boyette RL et al. Hydroxyurea therapy for sickle cell disease in community-based practices: a survey of Florida and North Carolina hematologists/oncologists. *Am J Hematol* 2005;79(2):107-13.
 94. Thauvin-Robinet C, Maingueneau C, Robert E et al. Exposure to hydroxyurea during pregnancy: a case series. *Leukemia* 2001;15(8):1309-11.
 95. Dilek I, Topcu N, Demir C et al. Hematological malignancy and pregnancy: A single-institution experience of 21 cases. *Clin. Lab. Haematol.* 2006;28(3):170-176.
 96. Moschovi M, Psychou F, Menegas D et al. Hodgkin's disease in a child with sickle cell disease treated with hydroxyurea. *Pediatr Hematol Oncol* 2001;18(6):371-6.

97. Kattamis A, Lagona E, Orfanou I et al. Clinical response and adverse events in young patients with sickle cell disease treated with hydroxyurea. *Pediatr Hematol Oncol* 2004;21(4):335-42.
98. 3Fenster A, Sariban E, and Meuleman N. Malignancies in sickle cell disease patients treated with hydroxyurea. *Br J Haematol* 2003;123(2):368-9.
99. Al-Jam'a AH, Al-Dabbous IA, Al-Khatti AA et al. Are we underestimating the leukemogenic risk of hydroxyurea. *Saudi Med J* 2002;23(11):1411-3.
100. Wilson S. Acute leukemia in a patient with sickle-cell anemia treated with hydroxyurea. *Ann Intern Med* 2000;133(11):925-6.
101. Rauch A, Borromeo M, Ghafoor A et al. Leukemogenesis of hydroxyurea in the treatment of sickle cell anemia [abstract]. *Blood* 1999;94 (Suppl 1).
102. Rutschmann OT, Opravil M, Iten A et al. Didanosine plus stavudine with or without hydroxyurea in HIV-1-infected patients: 1 year follow-up. *Antiviral Ther.* 1998;3(SUPPL. 4):65-67.
103. Kiladjian JJ, Rain JD, Bernard JF et al. Long-term incidence of hematological evolution in three French prospective studies of hydroxyurea and pipobroman in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 2006.
104. Frank I, Bosch RJ, Fiscus S et al. Activity, safety, and immunological effects of hydroxyurea added to didanosine in antiretroviral-naïve and experienced HIV type 1-infected subjects: a randomized, placebo-controlled trial, ACTG 307. *AIDS Res Hum Retroviruses* 2004;20(9):916-26.
105. Najean Y, Rain J-D, Dresch C et al. Risk of leukaemia, carcinoma, and myelofibrosis in 32P- or chemotherapy-treated patients with polycythaemia vera: A prospective analysis of 682 cases. *LEUK. LYMPHOMA* 1996;22(SUPPL. 1):111-119.
106. Gangat N, Wolanskyj AP, McClure RF et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: A single institutional study of 605 patients. *Leukemia* 2007;21 (2):270-276.
107. Bernasconi P, Boni M, Cavigliano PM et al. Acute myeloid leukemia (AML) having evolved from essential thrombocythemia (ET): distinctive chromosome abnormalities in patients treated with pipobroman or hydroxyurea. *Leukemia* 2002;16(10):2078-83.
108. Seminari E, Lisziewicz J, Tinelli C et al. Hydroxyurea toxicity combined with didanosine (ddI) in HIV-1-seropositive asymptomatic individuals. *Int. J. Clin. Pharmacol. Ther.* 1999;37(10):514-518.
109. Rutschmann OT, Opravil M, Iten A et al. A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. The Swiss HIV Cohort Study. *AIDS* 1998.
110. Rutschmann OT, Vernazza PL, Bucher HC et al. Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000;14(14):2145-2151.
111. Swindells S, Cohen CJ, Berger DS et al. Abacavir, efavirenz, didanosine, with or without hydroxyurea, in HIV-infected adults failing initial nucleoside/protease inhibitor-containing regimens. *BMC Infect. Dis.* 2005; 5(-):13p.
112. Hehlmann R, Heimpel H, Hasford J et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. *Blood* 1993;82(2):398-407.
113. Hehlmann R, Heimpel H, Hasford J et al. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood* 1994;84(12):4064-77.
114. Hehlmann R, Berger U, Pfirrmann M et al. Randomized comparison of interferon alpha and hydroxyurea with hydroxyurea monotherapy in chronic myeloid leukemia (CML-study II): prolongation of survival by the combination of interferon alpha and hydroxyurea. *Leukemia* 2003;17(8):1529-37.
115. Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-alpha 2b for chronic myeloid leukemia. The Benelux CML Study Group. *Blood* 1998;91(8):2713-21.
116. Broustet A, Reiffers J, Marit G et al. Hydroxyurea versus interferon alfa-2b in chronic myelogenous leukaemia: preliminary results of an open French multicentre randomized study. *Eur J Cancer* 1991;27 Suppl 4:S18-21.
117. Yin CC, Cortes J, Barkoh B et al. t(3;21)(q26;q22) in myeloid leukemia: an aggressive syndrome of blast transformation associated with hydroxyurea or antimetabolite therapy. *Cancer* 2006;106(8):1730-8.

118. Vassallo C, Passamonti F, Merante S et al. Mucocutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin. Exp. Dermatol.* 2001;26(2):141-148.
119. Urabe A, Mizoguchi H, and Takaku F. Hydroxyurea in the therapy of chronic myelogenous leukemia. *ACTA HAEMATOL. JPN.* 1990;53(8):1589-1593.
120. Duletic-Nacinovic A, Labar B, and Sever-Prebilic M. Busulfan versus hydroxyurea in therapy of chronic myelogenous leukemia in 1(st) chronic phase. *Cancer Res. Ther. Control* 2000;10(4):251-261.
121. Stephens RL, Vaughn C, Lane M et al. Adriamycin and cyclophosphamide versus hydroxyurea in advanced prostatic cancer. A randomized Southwest Oncology Group study. *Cancer* 1984;53(3):406-10.
122. Loening SA, Scott WW, deKernion J et al. A comparison of hydroxyurea, methyl-chloroethyl-cyclohexy-nitrosourea and cyclophosphamide in patients with advanced carcinoma of the prostate. *J Urol* 1981;125(6):812-6.
123. Najean Y and Rain JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. *Blood* 1997;90(9):3370-7.
124. Finazzi G, Caruso V, Marchioli R et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood* 2005;105(7):2664-70.
125. Kaplan ME, Mack K, Goldberg JD et al. Long-term management of polycythemia vera with hydroxyurea: a progress report. *Semin Hematol* 1986;23(3):167-71.
126. Fruchtman SM, Mack K, Kaplan ME et al. From efficacy to safety: A Polycythemia Vera Study Group report on hydroxyurea in patients with polycythemia vera. *SEMIN. HEMATOL.* 1997;34(1):17-23.
127. Donovan PB, Kaplan ME, Goldberg JD et al. Treatment of polycythemia vera with hydroxyurea. *Am J Hematol* 1984;17(4):329-34.
128. West WO. Hydroxyurea in the treatment of polycythemia vera: a prospective study of 100 patients over a 20-year period. *South Med J* 1987;80(3):323-7.
129. Cortelazzo S, Finazzi G, Ruggeri M et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *NEW ENGL. J. MED.* 1995;332(17):1132-1136.
130. Finazzi G, Ruggeri M, Rodeghiero F et al. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. *Br J Haematol* 2000;110(3):577-83.
131. Harrison CN, Campbell PJ, Buck G et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005;353(1):33-45.
132. Sterkers Y, Preudhomme C, Lai JL et al. Acute myeloid leukemia and myelodysplastic syndromes following essential thrombocythemia treated with hydroxyurea: high proportion of cases with 17p deletion. *Blood* 1998;91(2):616-22.
133. Chim CS, Kwong YL, Lie AK et al. Long-term outcome of 231 patients with essential thrombocythemia: prognostic factors for thrombosis, bleeding, myelofibrosis, and leukemia. *Arch Intern Med* 2005;165(22):2651-8.
134. Nielsen I and Hasselbalch HC. Acute leukemia and myelodysplasia in patients with a Philadelphia chromosome negative chronic myeloproliferative disorder treated with hydroxyurea alone or with hydroxyurea after busulphan. *Am J Hematol* 2003;74(1):26-31.
135. Weinfeld A, Swolin B, and Westin J. Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications. *Eur J Haematol* 1994;52(3):134-9.
136. Randi ML, Ruzzon E, Tezza F et al. Toxicity and side effects of hydroxyurea used for primary thrombocythemia. *Platelets* 2005;16(3-4):181-4.
137. Randi ML, Ruzzon E, Luzzatto G et al. Safety profile of hydroxyurea in the treatment of patients with Philadelphia-negative chronic myeloproliferative disorders. *Haematologica* 2005;90(2):261-2.
138. Hankins J, Hinds P, Day S et al. Therapy preference and decision-making among patients with severe sickle cell anemia and their families. *Pediatr Blood Cancer* 2007;48(7):705-10.
139. Treadwell MJ, Law AW, Sung J et al. Barriers to adherence of deferoxamine usage in sickle cell disease. *Pediatr Blood Cancer* 2005; 44(5):500-7.

140. Wurst KE and Sleath BL. Physician knowledge and adherence to prescribing antibiotic prophylaxis for sickle cell disease. *Int J Qual Health Care* 2004;16(3):245-51.
141. Sox CM, Cooper WO, Koepsell TD et al. Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease. *JAMA* 2003;290(8):1057-61.
142. Elliott V, Morgan S, Day S et al. Parental health beliefs and compliance with prophylactic penicillin administration in children with sickle cell disease. *J Pediatr Hematol Oncol* 2001;23(2):112-6.
143. Teach SJ, Lillis KA, and Grossi M. Compliance with penicillin prophylaxis in patients with sickle cell disease. *Arch Pediatr Adolesc Med* 1998;152(3):274-8.
144. Jensen SA, Elkin DT, Hilker K et al. Caregiver knowledge and adherence in children with sickle cell disease: Knowing is not doing. *J. Clin. Psychol. Med. Settings* 2005;12(4):333-337.
145. Armstrong FD, Pegelow CH, Gonzalez JC et al. Impact of children's sickle cell history on nurse and physician ratings of pain and medication decisions. *J Pediatr Psychol* 1992;17(5):651-64.
146. Pence L, Valrie CR, Gil KM et al. Optimism Predicting Daily Pain Medication Use in Adolescents with Sickle Cell Disease. *J. Pain Symptom Manage.* 2007;33(3):302-309.
147. Telfair J, Haque A, Etienne M et al. Rural/urban differences in access to and utilization of services among people in Alabama with sickle cell disease. *Public Health Rep* 2003;118(1):27-36.
148. Logan DE, Radcliffe J, and Smith-Whitley K. Parent factors and adolescent sickle cell disease: associations with patterns of health service use. *J Pediatr Psychol* 2002;27(5):475-84.
149. Wojciechowski EA, Hurtig A, and Dorn L. A natural history study of adolescents and young adults with sickle cell disease as they transfer to adult care: a need for case management services. *J Pediatr Nurs* 2002;17(1):18-27.
150. Haque A and Telfair J. Socioeconomic distress and health status: the urban-rural dichotomy of services utilization for people with sickle cell disorder in North Carolina. *J Rural Health* 2000;16 (1):43-55.
151. Barakat LP, Smith-Whitley K, and Ohene-Frempong K. Treatment adherence in children with sickle cell disease: Disease-related risk and psychosocial resistance factors. *J. Clin. Psychol. Med. Settings* 2002;9(3):201-209.
152. Belgrave FZ and Lewis DM. The role of social support in compliance and other health behaviors for African Americans with chronic illnesses. *J Health Soc Policy* 1994;5(3-4):55-68.
153. Pack-Mabien A, Labbe E, Herbert D et al. Nurses' attitudes and practices in sickle cell pain management. *Appl Nurs Res* 2001;14(4):187-92.
154. Murray N and May A. Painful crises in sickle cell disease--patients' perspectives. *BMJ* 1988;297(6646):452-4.
155. Labbe E, Herbert D, and Haynes J. Physicians' attitude and practices in sickle cell disease pain management. *J Palliat Care* 2005;21(4):246-51.
156. Telfair J, Myers J, and Drezner S. Does race influence the provision of care to persons with sickle cell disease? Perceptions of multidisciplinary providers. *J Health Care Poor Underserved* 1998;9(2):184-95.
157. Vichinsky E, Rust D, and Lubin B. A possible disparity between standard of care and delivery of care in sickle cell disease, as assessed from sickle cell centers. *Int. J. Pediatr. Hematol. Oncol.* 1999;6(3):189-197.
158. Walters MC, Patience M, Leisenring W et al. Barriers to bone marrow transplantation for sickle cell anemia. *Biol Blood Marrow Transplant* 1996;2(2):100-4.
159. Booker MJ, Blethyn KL, Wright CJ et al. Pain management in sickle cell disease. *Chronic Illn* 2006;2(1):39-50.
160. Rouse CM. Paradigms and politics: shaping health care access for sickle cell patients through the discursive regimes of biomedicine. *Cult Med Psychiatry* 2004;28(3):369-99.
161. Maxwell K, Streetly A, and Bevan D. Experiences of hospital care and treatment seeking for pain from sickle cell disease: qualitative study. *BMJ* 1999;318(7198):1585-90.
162. Tucker C, Spencer J, Dowling PT et al. Developing a community for patients with sickle cell anemia at Harbor-UCLA. *Emphasis Nurs* 1995;5(1):19-27.

163. Alleyne J and Thomas VJ. The management of sickle cell crisis pain as experienced by patients and their carers. *J Adv Nurs* 1994;19(4):725-32.
164. Shelley B, Kramer KD, and Nash KB. Sickle cell mutual assistance groups and the health services delivery system. *J Health Soc Policy* 1994;5(3-4):243-59.
165. Strickland OL, Jackson G, Gilead M et al. Use of focus groups for pain and quality of life assessment in adults with sickle cell disease. *J Natl Black Nurses Assoc* 2001;12(2):36-43.
166. Harris A, Parker N, and Barker C. Adults with sickle cell disease: Psychological impact and experience of hospital services. *Psychol. Health Med.* 1998;3(2):171-179.
167. Butler DJ and Beltran LR. Functions of an adult sickle cell group: education, task orientation, and support. *Health Soc Work* 1993;18(1):49-56.
168. Waters J and Thomas V. Pain from sickle-cell crisis. *Nurs Times* 1995;91(16):29-31.
169. Witherspoon D and Drotar D. Correlates of adherence to prophylactic penicillin therapy in children with sickle cell disease. *Child. Health Care* 2006;35(4):281-296.
170. Pejaver RK, Ahmed FE, and Al Hifzi I. Compliance to penicillin prophylaxis amongst Saudi children with sickle cell disease. *J. IR. COLL. PHYS. SURG.* 1997;26(4):268-270.
171. Chestnut DE. Perceptions of ethnic and cultural factors in the delivery of services in the treatment of sickle cell disease. *J Health Soc Policy* 1994;5(3-4):215-42.
172. Mitchell MB, Lambright WD, Breish R et al. Meeting the challenge of managing vaso-occlusive crisis. *J Healthc Qual* 2002;24(3):4-8, 56.
173. Co JP, Johnson KB, Duggan AK et al. Does a clinical pathway improve the quality of care for sickle cell anemia? *Jt Comm J Qual Saf* 2003;29(4):181-90.
174. Jamison C and Brown HN. A special treatment program for patients with sickle cell crisis. *Nurs Econ* 2002;20(3):126-32.
175. Cooper GS, Armitage KB, Ashar B et al. Design and implementation of an inpatient disease management program. *Am J Manag Care* 2000;6(7): 793-801.
176. Benjamin LJ, Swinson GI, and Nagel RL. Sickle cell anemia day hospital: an approach for the management of uncomplicated painful crises. *Blood* 2000;95(4):1130-6.
177. Day J. An audit of pain management in acute sickle cell crisis. *Nurs Times* 1997;93(2):33-4.
178. Brookoff D and Polomano R. Treating sickle cell pain like cancer pain. *Ann Intern Med* 1992;116(5):364-8.
179. Fertleman CR, Gallagher A, and Rossiter MA. Evaluation of fast track admission policy for children with sickle cell crises: questionnaire survey of parents' preferences. *BMJ* 1997;315(7109):650.
180. Treadwell MJ, Franck LS, and Vichinsky E. Using quality improvement strategies to enhance pediatric pain assessment. *Int J Qual Health Care* 2002;14(1):39-47.
181. Treadwell MJ and Weissman L. Improving adherence with deferoxamine regimens for patients receiving chronic transfusion therapy. *Semin Hematol* 2001;38(1 Suppl 1):77-84.
182. Berkovitch M, Papadouris D, Shaw D et al. Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease. *Br J Clin Pharmacol* 1998;45(6):605-7.
183. Ketchen B, Hazzard A, Lassiter S et al. STARBRIGHT World: A pilot study of a home-based sickle cell psychoeducational intervention. *Child. Health Care* 2006;35(4):321-338.
184. Patik M, Phillips L, Kladny B et al. Structured telephone-based outreach using nonmedical personnel can improve adherence to comprehensive care in families of children with sickle cell disease. *Am J Hematol* 2006;81(6):462-4.
185. Woods KF, Johnson JA, Kutlar A et al. Sickle cell disease telemedicine network for rural outreach. *J Telemed Telecare* 2000;6(5):285-90.
186. Smith LA, Oyeku SO, Homer C et al. Sickle cell disease: a question of equity and quality. *Pediatrics* 2006;117(5):1763-70.
187. Sumoza A, de Bisotti R, Sumoza D et al. Hydroxyurea (HU) for prevention of recurrent stroke in sickle cell anemia (SCA). *Am J Hematol* 2002;71(3):161-5.
188. Yan JH, Ataga K, Kaul S et al. The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005;45(4):434-45.

189. Havlir DV, Gilbert PB, Bennett K et al. Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001;15(11):1379-88.
190. Seminari E, Lisziewicz J, Tinelli C et al. Hydroxyurea toxicity combined with didanosine (ddl) in HIV-1-seropositive asymptomatic individuals. *Int J Clin Pharmacol Ther* 1999;37(10):514-8.
191. Bloch MT, Smith DE, Quan D et al. The role of hydroxyurea in enhancing the virologic control achieved through structured treatment interruption in primary HIV infection: final results from a randomized clinical trial (Pulse). *J Acquir Immune Defic Syndr* 2006.
192. Rutschmann OT, Opravil M, Iten A et al. A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998;12(8):F71-F77.
193. Rutschmann OT, Opravil M, Iten A et al. Didanosine plus stavudine with or without hydroxyurea in HIV-1-infected patients: 1 year follow-up. *Swiss HIV Cohort Study. Antivir Ther* 1998;3 Suppl 4:65-7.
194. Rutschmann OT, Vernazza PL, Bucher HC et al. Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *Swiss HIV Cohort Study. AIDS* 2000;14(14):2145-51.
195. Hehlmann R, Heimpel H, Hasford J et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: prolongation of survival by hydroxyurea. The German CML Study Group. *Blood* 1993;82(2):398-407.
196. Mavrogianni D, Viniou N, Michali E et al. Leukemogenic risk of hydroxyurea therapy as a single agent in polycythemia vera and essential thrombocythemia: N- and K-ras mutations and microsatellite instability in chromosomes 5 and 7 in 69 patients. *Int J Hematol* 2002;75(4):394-400.

* Included references not cited in the report (primarily case reports and case studies).

- Abhyankar D, Shende C, Saikia T et al. Hydroxyurea induced leg ulcers. *J Assoc Physicians India* 2000;48(9):926-7
- Akinci B, Yesil S, Atabey A et al. Hydroxyurea associated leg ulcer successfully treated with hyperbaric oxygen in a diabetic patient. *Exp Clin Endocrinol Diabetes* 2007;115(2):143-5
- Aragane Y, Okamoto T, Yajima A et al. Hydroxyurea-induced foot ulcer successfully treated with a topical basic fibroblast growth factor product. *Br J Dermatol* 2003;148(3):599-600
- Aste N, Fumo G, Biggio P. Multiple squamous epitheliomas during long-term treatment with hydroxyurea. *J Eur Acad Dermatol Venereol* 2001;15(1):89-90
- Au W Y, Hung K N, Loong F et al. Patients presenting with CNS lesions. Case 3. Sequential myeloproliferative disease and glioblastoma multiforme in a renal transplant recipient. *J Clin Oncol* 2003;21(21):4062-3
- Azagury M, Martelli J M, Morcelet M et al. Development of hairy cell leukemia in a patient treated with cytoreductive agents for essential thrombocythemia. *Leuk Lymphoma* 2003;44(6):1067-9
- Bacher U, Haferlach T, Kern W et al. A case of chronic myeloproliferative syndrome followed by precursor T-cell acute lymphoblastic leukemia. *Cancer Genet. Cytogenet.* 2007;175(1):52-56
- Bader U, Banyai M, Boni R et al. Leg ulcers in patients with myeloproliferative disorders: Disease- or treatment-related?. *Dermatology* 2000;200(1):45-48
- Bahadoran P, Castanet J, Lacour J P et al. Pseudo-dermatomyositis induced by long-term hydroxyurea therapy: report of two cases. *Br J Dermatol* 96;134(6):1161-3
- Barnhill R L, Wiles J C. Malignant melanoma associated with multiple therapies for psoriasis. *J Am Acad Dermatol* 89;21(1):148-50
- Battle M, Fernandez-Aviles F, Ribera J M et al. Acute promyelocytic leukemia in a patient with idiopathic myelofibrosis. *Leukemia* 99;13(3):492-4
- Beeson M, Antwi E K, Vesely D L. Hydroxyurea-induced hypogonadism. *Endocrinologist* 99;9(5):389-390
- Bergin P S, Gale A N. Complex neuromuscular disorder in a patient with chronic myeloid leukaemia. *Postgrad Med J* 93;69(810):312-4
- Berkahn L C, Nelson J, Ockelford P A et al. Transformation of essential thrombocythaemia to T cell acute lymphoblastic leukaemia. *Leuk Lymphoma* 96;20(3-4):347-9
- Best P J, Petitt R M. Multiple skin cancers associated with hydroxyurea therapy. *Mayo Clin Proc* 98;73(10):961-3
- Best P J, Daoud M S, Pittelkow M R et al. Hydroxyurea-induced leg ulceration in 14 patients. *Ann. Intern. Med.* 98;128(1):29-32
- Beylot-Barry M, Vergier B, Beylot C et al. Multiple squamous cell carcinomas after prolonged treatment with hydroxyurea. *EUR. J. DERMATOL.* 95;5(3):227-230
- Blonk M C, Ossenkoppele G J. Hydroxyurea as a cause of drug fever in chronic myeloid leukaemia. *Neth J Med* 88;32(5-6):240-2
- Bohn J, Hansen J P, Menne T. Ulcerative lichen planus-like dermatitis due to long-term hydroxyurea therapy. *J Eur Acad Dermatol Venereol* 98;10(2):187-9
- Bouldouyre M A, Avril M F, Gaulier A et al. Association of cutaneous side-effects of hydroxyurea and neuroendocrine carcinoma. *Eur J Dermatol* 2005;15(4):268-70
- Braester A, Quitt M. Hydroxyurea as a cause of drug fever. *Acta Haematol.* 2000;104(1):50-51
- Brazzelli V, Bellani E, Barbagallo T et al. Melanonychia due to hydroxyurea therapy. *G. Ital. Dermatol. Venereol.* 2005;140(6):723-726
- Brincker H, Christensen B E. Acute mucocutaneous toxicity following high-dose hydroxyurea. *Cancer Chemother Pharmacol* 93;32(6):496-7
- Budny A M, Forman M. Cutaneous ulceration secondary to hydroxyurea treatment. *J Am Podiatr Med Assoc* 2006;96(6):525-7
- Burns D A, Sarkany I, Gaylarde P. Effects of hydroxyurea therapy on normal skin: a case report. *Clin Exp Dermatol* 80;5(4):447-9
- Cacciola E, Cacciola R R, Guglielmo P et al. Acute myeloid leukemia occurring in a patient with polycythemia vera in treatment with hydroxyurea. *Haematologica* 99;84(8):755-6
- Cakir B, Sucak G, Haznedar R. Longitudinal pigmented nail bands during hydroxyurea therapy. *Int J Dermatol* 97;36(3):236-7
- Callot-Mellot C, Bodemer C, Chosidow O et al. Cutaneous carcinoma during long-term hydroxyurea therapy: A report of 5 cases. *Arch Dermatol.* 96 ;132(11):1395-7

- Camos M, Cervantes F, Montoto S et al. Acute lymphoid leukemia following polycythemia vera. *Leuk. Lymphoma* 99;32(3-4):395-398
- Chim C S, Ma S K. Der(8)t(1;8) in myeloblastic transformation of ET with hydroxyurea as the sole prior treatment. *Hematol Oncol* 2005;23(2):57-60
- Chim C S, Ma S K. Eosinophilic leukemic transformation in polycythemia rubra vera (PRV). *Leuk Lymphoma* 2005;46(3):447-50
- Chowdhury M M, Patel G K, Inaloz H S et al. Hydroxyurea-induced skin disease mimicking the baboon syndrome. *Clin Exp Dermatol* 99;24(4):336-7
- Cohen A D, Hallel-Halevy D, Hatskelzon L et al. Longitudinal melanonychia associated with hydroxyurea therapy in a patient with essential thrombocytosis. *J Eur Acad Dermatol Venereol.* 99;13(2):137-9
- Cox C, Nowicky D, Young R. Hydroxyurea-related ankle ulcers in patients with myeloproliferative disorders: a case report and review of the literature. *Ann Plast Surg* 97;39(5):546-9
- Dacey M J, Callen J P. Hydroxyurea-induced dermatomyositis-like eruption. *J. Am. Acad. Dermatol.* 2003;48(3):439-441
- Daoud M S, Gibson L E, Pittelkow M R. Hydroxyurea dermatopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 97;36(2 Pt 1):178-82
- De Benedittis M, Petruzzi M, Giardina C et al. Oral squamous cell carcinoma during long-term treatment with hydroxyurea. *Clin. Exp. Dermatol.* 2004;29(6):605-607
- De Simone C, Guerriero C, Guidi B et al. Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. *Eur J Dermatol* 98;8(2):114-5
- Delmas-Marsalet B, Beaulieu P, Teillet-Thiebaud F et al. Longitudinal melanonychia induced by hydroxyurea: Four case reports and review of the literature. *NOUV. REV. FR. HEMATOL.* 95;37(3):205-210
- Demircay Z, Comert A, Adiguzel C. Leg ulcers and hydroxyurea: report of three cases with essential thrombocytopenia. *Int J Dermatol* 2002;41(12):872-4
- Disla E, D'Eamour L, Cioriou M. Hydroxyurea-associated leg ulceration. *Ann Intern Med* 98;129(3):252-3
- Dissemond J, Hoeft D, Knab J et al. Leg ulcer in a patient associated with hydroxyurea therapy. *Int J Dermatol* 2006;45(2):158-60
- Ellies P, Anderson D F, Topuhami A et al. Limbal stem cell deficiency arising from systemic chemotherapy. *Br J Ophthalmol* 2001;85(3):373-4
- Elliott R, Davies M, Harmse D. Dermatomyositis-like eruption with long-term hydroxyurea. *J Dermatolog Treat* 2006;17(1):59-60
- Elliott R, Davies M, Harmse D. Dermatomyositis-like eruption with long-term hydroxyurea [2]. *J. Dermatol. Treat.* 2006;17(1):59-60
- Ellis A K, Lee D H. Tumor lysis syndrome induced by hydroxyurea therapy for leukemic transformation of polycythemia vera. *Am J Hematol* 2002;71(3):237-8
- Famoso G, Ponzoni M, Freschi M et al. Megakaryoblastic differentiation of myeloid sarcoma in a patient with essential thrombocytopenia +AFs-4+AF0-. *Leuk. Lymphoma* 2006;47(11):2414-2417
- Ferrari D, Ticozzelli G, De Vizzi M et al. Essential thrombocytopenia and acute leukemia. *Haematologica* 93;78(6):401-2
- Flamm M J, Murty V V, Rao P H et al. Coexistence of independent myelodysplastic and Philadelphia chromosome positive clones in a patient treated with hydroxyurea. *Leuk Res* 2002;26(4):417-20
- Folan D W. Severe reaction to hydroxyurea. *Cutis*Drug Hypersensitivity/Humans/Hydroxyurea: *adverse effects: therapeutic use/Male/Middle Aged/Psoriasis: drug therapy/Thrombocytopenia: *chemically induced*
- Friedrich S, Raff K, Landthaler M et al. Cutaneous ulcerations on hands and heels secondary to long-term hydroxyurea treatment. *Eur J Dermatol* 2004;14(5):343-6
- Furgerson J L, Vukelja S J, Baker W J et al. Acute myeloid leukemia evolving from essential thrombocytopenia in two patients treated with hydroxyurea. *Am J Hematol* 96;51(2):137-40
- Garozzo G, Disca S, Fidone C et al. Azoospermia in a patient with sickle cell disease treated with hydroxyurea. *Haematologica* 2000;85(11):1216-8
- Giordano F, Savarino A, Pagni C A. Spinal meningioma during hydroxyurea therapy. A paradoxical case report. *Neurol Sci* 2002;23(3):127-9
- Goodrich J, Khardori N. Hydroxyurea toxicity in human immunodeficiency virus-positive patients. *Clin Infect Dis* 99;29(3):692-3
- Grace R F, Shenfield G M, Grant J et al. Recurrent pyrexia, cough and dyspnoea with hydroxyurea. *Aust. New Zealand J. Med.* 98;28(3):347
- Gropper C A, Don P C, Sadjadi M M. Nail and skin hyperpigmentation associated with hydroxyurea therapy for polycythemia vera *Int J Dermatol.* 93;32(10):731-3
- Gupta A K, Rohatgi N, Rohatgi A. Hydroxyurea induced nail pigmentation. *JK Science* 2003;5(1):43

- Haniffa M A, Speight E L. Painful leg ulcers and a rash in a patient with polycythaemia rubra vera. *Clin. Exp. Dermatol.* 2006;31(5):733-734
- Hartmann K, Nagel S, Erichsen T et al. Cutaneous ulcers following hydroxyurea therapy. *Phlebologie* 2004;33(6):202-205
- Hawkins T E, Carter J M, Romeril K R et al. Lymphoma transformation in polycythaemia vera treated with hydroxyurea. *Am J Hematol* 93;44(4):290
- Heddle R, Calvert A F. Hydroxyurea induced hepatitis. *Med J Aust/Hepatitis, Toxic: *etiology/Humans/Hydroxyurea: *adverse effects: therapeutic use/Male/Middle Aged/Psoriasis: drug therapy*
- Hennemann B, Bross K J, Reichle A et al. Acute alveolitis induced by hydroxyurea in a patient with myeloproliferative syndrome. *Ann Hematol/Acute Disease/Aged/Alveolitis, Extrinsic Allergic: *chemically induced/Humans/Hydroxyurea: *adverse effects: *therapeutic use/Male/Myeloproliferative Disorders: *drug therapy/Pneumonia: chemically induced/*Pulmonary Alveoli*
- Henry L, Carillo S, Jourdan E et al. Association of essential thrombocythemia and chronic lymphocytic leukemia: Absence of the V617F JAK2 mutation in the lymphoid compartment [8]. *Am. J. Hematol.* 2007;82(6):500-501
- Higuchi W, Koike T, Ihizumi T et al. Hypereosinophilic syndrome terminating in acute myelogenous leukemia. *ACTA HAEMATOL.* 93;90(3):165-166
- Hirose Y, Masaki Y, Sugai S. Leukemic transformation with trisomy 8 in essential thrombocythemia: a report of four cases. *Eur J Haematol* 2002;68(2):112-6
- Hirri H M, Green P J. Skin lesion caused by hydroxyurea. *Eur J Haematol/Aged/Antineoplastic Agents: *adverse effects: therapeutic use/Fusion Proteins, bcr-abl/Humans/Hydroxyurea: *adverse effects: therapeutic use/Leg Dermatoses: *chemically induced: etiology/Male/Myeloproliferative Disorders: *drug therapy/Philadelphia Chromosome*
- Holcombe R F, Treseler P A, Rosenthal D S. Chronic myelomonocytic leukemia transformation in polycythemia vera. *Leukemia* 91;5(7):606-10
- In 'T, Veld B A, Slappendel A M et al. Fever attributed to the use of hydroxyurea. *NETH. J. MED.* 97;51(3):110-113
- Jabr F I, Shamseddine A, Taher A. Hydroxyurea-induced hemolytic anemia in a patient with essential thrombocythemia. *Am. J. Hematol.* 2004;77(4):374-376
- Jackson G H, Wallis J, Ledingham J et al. Hydroxyurea-induced acute alveolitis in a patient with chronic myeloid leukaemia. *Cancer Chemother Pharmacol* 90;27(2):168-9
- Jacobs P, Wood L, Foster J. Hydroxyurea hypersensitivity reaction. *S Afr Med J* 89;75(10):506
- Jain V, Gupta K, Nagpal N. Perimalleolar ulcers in hydroxyurea treated patients with concomitant chronic venous disease: Diagnostic pitfalls. *J. Coll. Phys. Surg. Pak.* 2005;15(10):658-660
- Jeevankumar B, Thappa D M. Blue lunula due to hydroxyurea. *J Dermatol.* 2003;30(8):628-30
- Karincaoglu Y, Kaya E, Esrefoglu M et al. Development of large genital ulcer due to hydroxyurea treatment in a patient with chronic myeloid leukemia and Behcet's disease. *Leuk. Lymphoma* 2003;44(6):1063-1065
- Karsegard J, Wicky J, Mensi N et al. Spurious glycohemoglobin values associated with hydroxyurea treatment. *Diabetes Care.* 1997;20(7):1211-2
- Kavuru M S, Gadsden T, Lichtin A et al. Hydroxyurea-induced acute interstitial lung disease. *South Med J* 94;87(7):767-9
- Kelly R I, Bull R H, Marsden A. Cutaneous manifestations of long-term hydroxyurea therapy. *Australas J Dermatol* 94;35(2):61-4
- Kelsey P R. Multiple longitudinal pigmented nail bands during hydroxyurea therapy. *Clin Lab Haematol* 92;14(4):337-8
- Kelsey P R, Patel K. Essential thrombocythaemia followed by multiple myeloma in the same patient. *Clin Lab Haematol* 95;17(4):349-51
- Kennedy B J, Smith L R, Goltz R W. Skin changes secondary to hydroxyurea therapy. *Arch Dermatol* 75;111(2):183-7
- Kido M, Tago O, Fujiwara H et al. Leg ulcer associated with hydroxyurea treatment in a patient with chronic myelogenous leukaemia: successful treatment with prostaglandin E1 and pentoxifylline. *Br J Dermatol* 98;139(6):1124-6
- Killick S, Matutes E, Swansbury J et al. Case 17: Essential thrombocythaemia with inversion 3 terminating in acute leukaemia. *Leuk. Lymphoma* 98;30(5-6):661-664
- Kreft A, Burg J, Fischer T et al. Essential thrombocythemia terminating in pure erythroleukemia. *Am J Hematol* 2004;77(2):140-3
- Krsnik I, Ferro T, Garcia Suarez J et al. Translocation t(4;6)(q21; q27) in a case of primary thrombocythaemia in transformation. *Clin Lab Haematol* 2001;23(4):259-60
- Kwong Y L. Hydroxyurea-induced nail pigmentation. *J. AM. ACAD. DERMATOL.* 96;35(2 I):275-276

- Lannemyr O, Kutti J. Hydroxyurea as a cause of drug fever in essential thrombocythaemia. *Eur J Haematol* Aged/Aged, 80 and over/Antisickling Agents: *adverse effects: therapeutic use/Female/Fever: *chemically induced/Humans/Hydroxyurea: *adverse effects: therapeutic use/Thrombocytosis: *drug therapy
- Lannemyr O, Kutti J. Hydroxyurea as a cause of drug fever in essential thrombocythaemia [4]. *Eur. J. Haematol.* 99;62(5):354-355
- Las Heras G, Junca P, Piera J. Nail changes after chemotherapy. *Haematologica* 98;83(8):748
- Layton A M, Cotterill J A, Tomlinson I W. Hydroxyurea-induced lupus erythematosus. *Br J Dermatol* Female/Humans/Hydroxyurea: *adverse effects/Lupus Erythematosus, Systemic: *chemically induced/Middle Aged/Psoriasis: *drug therapy
- Lazarevic V L j, Tomin D, Jankovic G M et al. A novel t(2;17) in transformation of essential thrombocythemia to acute myelocytic leukemia. *Cancer Genet Cytogenet* 2004;148(1):77-9
- Leo E, Kramer A, Hochhaus A et al. Gangrene of the toes in a patient with chronic myelogenous leukemia after long-term hydroxyurea therapy. *Ann Hematol* 2002;81(8):467-9
- Liozon E, Brigaudeau C, Trimoreau F et al. Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature. *Hematol Cell Ther* 97;39(1):11-8
- Liu T-C, Suti R. Multiple factors in the transformation of essential thrombocythemia to acute leukemia or myelodysplastic syndrome [9]. *Blood* 98;92(4):1465-1466
- Lossos I S, Matzner Y. Hydroxyurea-induced fever: Case report and review of the literature. *ANN. PHARMACOTHER.* 95;29(2):132-133
- Majumdar G, Heard S E, Slater N G P. Reversible hyperpigmentation associated with high dose hydroxyurea. *BR. MED. J.* 90;300(6737):1468
- Marie I, Joly P, Levesque H et al. Pseudo-dermatomyositis as a complication of hydroxyurea therapy. *Clin Exp Rheumatol* 2000;18(4):536-7
- McLintock C, Ockelford P A. Hydroxyurea induced skin ulceration in myeloproliferative disorders *Aust N Z J Med.* 2000;30(3):373-6
- Murphy J, Morley S M. Hydroxyurea-induced leg ulcers. *Hosp Med* 2000;61(7):510
- Najean Y. Unwanted side effect of hydroxyurea. *Ann Hematol* 96;72(2):101
- Nakahata J, Takahashi M, Fuse I et al. Paroxysmal nocturnal hemoglobinuria with myelofibrosis: progression to acute myeloblastic leukemia. *Leuk Lymphoma* 93;12(1-2):137-42
- Nath S, Westerman D, Campbell L et al. Clonal "devolution" in a case of essential thrombocythemia with transformation from refractory cytopenia with multilineage dysplasia to acute myeloid leukemia. *Leuk. Lymphoma* 2006;47(6):1160-1162
- Ng J M, Vahidassr. Yet another cause for drug-induced pulmonary fibrosis. *J Postgrad Med.* 2005;51(1):76-7
- Nguyen T V, Margolis D J. Hydroxyurea and lower leg ulcers. *Cutis* 93;52(4):217-9
- Obata A, Izumi T, Saitoh Y et al. Hypereosinophilic syndrome associated with obliterative left ventricular chamber and systemic obliterative arteriosclerosis. *Jpn Heart J* 91;32(5):723-30
- Oh S T, Lee D W, Lee J Y et al. Hydroxyurea-induced melanonychia concomitant with a dermatomyositis-like eruption. *J Am Acad Dermatol* 2003;49(2):339-41
- Oskay T, Kutluay L, Ozyilkan O. Dermatomyositis-like eruption after long-term hydroxyurea therapy for polycythemia vera. *Eur J Dermatol* 2002;12(6):586-8
- Otrock Z K, Taher A T, Mahfouz R A R et al. Acute tumor lysis syndrome secondary to hydroxycarbamide in chronic myelomonocytic leukemia [5]. *Am. J. Hematol.* 2006;81(3):220-221
- Paleri V, Lindsey L. Oral ulcers caused by hydroxyurea. *J. Laryngol. Otol.* 2000;114(12):976-977
- Pamuk G E, Turgut B, Vural O et al. Metastatic squamous cell carcinoma of the skin in chronic myeloid leukaemia: complication of hydroxyurea therapy. *Clin Lab Haematol* 2003;25(5):329-31
- Papi M, Didona B, DePita O et al. Multiple skin tumors on light-exposed areas during long-term treatment with hydroxyurea. *J Am Acad Dermatol* 93;28(3):485-6
- Prabhaskar K, Bapsy P P. Hydroxyurea induced non-healing leg ulcer. *Indian J Dermatol Venereol Leprol* 2005;71(1):50-2
- Pulik M, Lionnet F, Genet P et al. Acute myeloid leukemia evolving from polycythemia vera in a patient treated with hydroxyurea. *Am J Hematol* 96;53(3):207-8
- Puri P, Woodcock B E, O'Donnell N. Localised chronic eyelid disease resulting from long term hydroxyurea therapy. *Br J Ophthalmol* 2001;85(3):372-3
- Quintas-Cardama A, Perez-Encinas M, Gonzalez S et al. Hydroxyurea-induced acute interstitial pneumonitis in a

- patient with essential thrombocythemia. *Ann Hematol* 99;78(4):187-8
- Radaelli F, Calori R, Faccini P et al. Early cutaneous lesions secondary to hydroxyurea therapy. *Am J Hematol* 98;58(1):82-3
- Radaelli F, Calori R, Ripamonti C et al. Treatment of myeloproliferative syndrome with hydroxyurea +AFs-1+AF0-. *ANN. HEMATOL.* 96;73(4):205
- Ravandi-Kashani F, Cortes J, Cohen P et al. Cutaneous ulcers associated with hydroxyurea therapy in myeloproliferative disorders. *Leuk Lymphoma* 99;35(1-2):109-18
- Renfro L, Kamino H, Raphael B et al. Ulcerative lichen planus-like dermatitis associated with hydroxyurea. *J Am Acad Dermatol* 91;24(1):143-5
- Richard M, Truchet F, Friedel J et al. Skin lesions simulating chronic dermatomyositis during long-term hydroxyurea therapy. *J. AM. ACAD. DERMATOL.* 89;21(4 1):797-799
- Rocamora V, Puig L, Alomar A. Dermatomyositis-like eruption following hydroxyurea therapy. *J Eur Acad Dermatol Venereol* 2000;14(3):227-8
- Ruiz-Arguelles G J, Ruiz-Delgado G J, Ruiz-Reyes G et al. Anagrelide-induced relapse of a hydroxyurea-induced leg ulcer in a patient with primary thrombocythemia. *Mayo Clin Proc* 98;73(11):1125
- Ruzzon E, Randi M L, Tezza F et al. Leg ulcers in elderly on hydroxyurea: A single center experience in ph-myeloproliferative disorders and review of literature. *Aging Clin. Exp. Res.* 2006;18(3):187-190
- Sadamoto Y, Ueda T, Matsumoto M et al. A case of drug-induced colitis complicating the administration of hydroxycarbamide. *Endoscopy* 2002;34(6):511
- Salmon-Ehr V, Grosieux C, Potron G et al. Multiple actinic keratosis and skin tumors secondary to hydroxyurea treatment. *Dermatology* 98;196(2):274
- Sanchez-Palacios C, Guitart J. Hydroxyurea-associated squamous dysplasia. *J Am Acad Dermatol.* 2004;51(2):293-300
- Sandhu H S, Barnes P J, Hernandez P. Hydroxyurea-induced hypersensitivity pneumonitis: A case report and literature review. *Can. Respir. J.* 2000;7(6):491-495
- Saravu K, Velappan P, Lakshmi N et al. Hydroxyurea induced perimaleolar ulcers. *J Korean Med Sci* 2006;21(1):177-9
- Sastre J L, Bravo A, Tembras S et al. Leg ulcers associated with hydroxyurea therapy. *Haematologica* 2003;88(2):EIM01
- Saviola A, Fiorani C, Ferrara L et al. Transition of polycythemia vera to chronic myeloid leukaemia. *Eur J Haematol* 2005;75(3):264-6
- Sawhney M P S, Mishra D K. Sarcoidosis following chemotherapy of essential thrombocythemia with hydroxyurea. *Med. J. Armed Forces India* 2005;61(4):379-380
- Seki J T, Al-Omar H M, Amato D et al. Acute tumor lysis syndrome secondary to hydroxyurea in acute myeloid leukemia. *Ann Pharmacother* 2003;37(5):675-8
- Shammas F, Meyer P, Heikkila R et al. Thrombotic microangiopathy in a patient with chronic myelogenous leukemia on hydroxyurea. *Acta Haematol* 97;97(3):184-6
- Silver F S, Espinoza L R, Hartmann R C. Acral erythema and hydroxyurea. *Ann Intern Med* 83;98(5 Pt 1):675
- Slobodin G, Lurie M, Munichor M et al. Gottron's papules-like eruption developing under hydroxyurea therapy. *Rheumatol Int* 2006;26(8):768-70
- Soppi E, Lahtinen R. Salmonella-induced reactive arthritis in a chronic myeloid leukemia patient on hydroxyurea and interferon-alpha. *Clin Exp Rheumatol* 88;6(4):425-6
- Stagno F, Guglielmo P, Consoli U et al. Successful healing of hydroxyurea-related leg ulcers with topical granulocyte-macrophage colony-stimulating factor. *Blood* 99;94(4):1479-80
- Stahl R L, Silber R. Vasculitic leg ulcers in chronic myelogenous leukemia. *Am J Med* 85;78(5):869-72
- Starmans-Kool M J F, Fickers M M F, Pannebakker M A G. An unwanted side effect of hydroxyurea in a patient with idiopathic myelofibrosis. *ANN. HEMATOL.* 95;70(5):279-280
- Stasi R, Cantonetti M, Abruzzese E et al. Multiple skin tumors in long-term treatment with hydroxyurea. *Eur J Haematol* 92;48(2):121-2
- Suehiro M, Kishimoto S, Wakabayashi T et al. Hydroxyurea dermopathy with a dermatomyositis-like eruption and a large leg ulcer. *Br J Dermatol* 98;139(4):748-9
- Tajima Y, Miyazaki Y, Higashi T et al. Primary CD30/Ki-1 positive anaplastic large cell lymphoma of the central nervous system occurring in a patient with a seventeen-year history of essential thrombocythemia. *Leuk. Lymphoma* 2003;44(7):1243-1245
- Tarumoto T, Imagawa S, Hotta T et al. A case of bilateral heel ulcers associated with hydroxyurea therapy for chronic myelogenous leukemia. *Jpn. J. Clin. Oncol.* 2000;30(3):159-162

- Thomas L, Ferrier E, Moulin G. Dermatomyositis-like eruption complicating hydroxyurea therapy of chronic myelogenous leukemia: report of a case and literature review.
- Tothova E, Fricova M, Stecova N et al. Leukemic transformation of polycythemia vera after treatment with hydroxyurea with abnormalities of chromosome 17. *Neoplasma* 2001;48(5):389-92
- Tripathi A K, Ahmad R, Sawlani K K. Reversible leg ulcer due to hydroxyurea in a case of chronic myeloid leukemia. *J Assoc Physicians India* 2003;511014-5
- Tsurumi H, Goto H, Hara T et al. Hydroxyurea-induced fever in a patient with chronic myelogenous leukemia. *Int J Hematol* 2000;72(3):386-7
- Vaiopoulos G, Terpos E, Viniou N et al. Behcet's disease in a patient with chronic myelogenous leukemia under hydroxyurea treatment: a case report and review of the literature. *Am J Hematol* 2001;66(1):57-8
- Van den, Anker-Lugtenburg P J, Sizoo W. Letter to the editor: Myelodysplastic syndrome and secondary acute leukemia after treatment of essential thrombocythemia with hydroxyurea. *AM. J. HEMATOL.* 90;33(2):152
- Van Der, Klooster J M, Sucec P M et al. Fever caused by hydroxyurea: A report of three cases and review of the literature. *NETH. J. MED.* 97;51(3):114-118
- Vargas-Diez E, Abajo P, Fraga J et al. Chemotherapy-induced acral erythema [12]. *Acta Derm.-Venereol.* 99;79(2):173-175
- Varma S, Lanigan S W. Dermatomyositis-like eruption and leg ulceration caused by hydroxyurea in a patient with psoriasis. *Clin Exp Dermatol* 99;24(3):164-6
- Velez A, Garcia-Aranda J M, Moreno J C. Hydroxyurea-induced leg ulcers: is macroerythrocytosis a pathogenic factor?. *J Eur Acad Dermatol Venereol* 99;12(3):243-4
- Velez A, Lopez-Rubio F, Moreno J C. Chronic hydroxyurea-induced dermatomyositis-like eruption with severe dermal elastosis. *Clin Exp Dermatol* 98;23(2):94-5
- Venigalla P, Motwani B, Nallari A et al. A patient on hydroxyurea for sickle cell disease who developed an opportunistic infection [1]. *Blood* 2002;100(1):363
- Vichinsky E P, Lubin B H. A cautionary note regarding hydroxyurea in sickle cell disease. *Blood* 94;83(4):1124-8
- Vomvouras S, Pakula A S, Shaw J M. Multiple pigmented nail bands during hydroxyurea therapy: an uncommon finding. *J Am Acad Dermatol* 91;24(6 Pt 1):1016-7
- Vosburgh E. Pruritus secondary to hydroxyurea therapy in a woman with polycythemia vera. *Am J Hematol.* 92;41(1):70
- Wahlin A, Golovleva I. Emergence of Philadelphia positive chronic myeloid leukaemia during treatment with hydroxyurea for Philadelphia negative essential thrombocythaemia. *Eur J Haematol* 2003;70(4):240-1
- Weinlich G, Schuler G, Greil R et al. Leg ulcers associated with long-term hydroxyurea therapy. *J Am Acad Dermatol* 98;39(2 Pt 2):372-4
- Westerman D A, Schwarzer A, Grigg A P. Hydroxyurea-induced fever and hepatitis. *Aust N Z J Med* 98;28(5):657-9
- Wirth K, Schoepf E, Mertelsmann R et al. Leg ulceration with associated thrombocytosis: healing of ulceration associated with treatment of the raised platelet count. *Br J Dermatol* 98;138(3):533-5
- Wong C C, Brown D, Howling S J et al. Hydroxyurea-induced pneumonitis in a patient with chronic idiopathic myelofibrosis after prolonged drug exposure. *Eur J Haematol.* 2003;71(5):388-90
- Woronozoff-Dashkoff K K, Litz C E. Acute lymphoblastic leukemia in a case of essential thrombocythemia. *Am J Clin Pathol* 96;106(2):206-8
- Yasuda N, Ohmori S, Usui T. Hydroxyurea-induced gangrene of the toes in a patient with chronic myelogenous leukemia. *Am J Hematol* 2000;63(2):103-4
- Yeh H, Lichtman S M. Hydroxyurea-induced cutaneous ulceration in older patients. *J Am Geriatr Soc* 2000;48(2):232
- Yokota K, Tasaka T, Iwata K et al. Huge post-operative ulcer following hydroxyurea therapy in a patient with polycythemia vera. *Haematologica.* 2003;88(12):ECR36
- Yoshida K, Saito M, Amagai M et al. Gottron-like papules induced by hydroxyurea. *Clin Exp Dermatol* 2005;30(2):191-2
- Young H S, Khan A S, Kendra J R et al. The cutaneous side-effects of hydroxyurea. *Clin Lab Haematol* 2000;22(4):229-32
- Young H S, Kirby B, Stewart E J. Aggressive, extensive, vasculitic leg ulceration associated with hydroxyurea therapy and a fatal outcome. *Clin Exp Dermatol* 2001;26(8):664-7
- Zaccaria E, Cozzani E, Parodi A. Secondary cutaneous effects of hydroxyurea: possible pathogenetic mechanisms. *J Dermatolog Treat* 2006;17(3):176-8

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	Granular membrane protein
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 β + thal	sickle β + thalassemia
S β ^o thal	sickle β ^o 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
UGT1A	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 hydra[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 hydra[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 hydra[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 hydra[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
("Anemia, Sickle Cell"[MeSH] OR "sickle cell"[tiab]) AND ("Hydroxyurea"[MeSH] OR hydroxyurea[tiab] OR hydra[tiab] OR hydroxycarbamide[tiab]) AND English[lang] NOT (animal[mh] NOT human[mh]) NOT review[pt] NOT "meta-analysis"[pt]	5009
("Hydroxyurea"[MeSH] OR hydroxyurea[tiab] OR hydra[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 hydra[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 (hydra: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 thrombocytopenia) 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 thrombocytopenia)) 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" thrombocytopenia) 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

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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
- 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?

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

Key Question 2

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

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

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?

<p>Key Question 3</p> <p><input type="radio"/> Applies to KQ3</p> <p>Clear Selection</p>	<p>This study is:</p> <p><input type="checkbox"/> Any study design, any size, describing toxicities of HU <i>alone or in combination</i> in sickle cell anemia</p> <p><input type="checkbox"/> Observational studies (> or = 20) of HU <i>alone</i> in CML/ET/PV/HIV/psoriasis/etc. including description of toxicities</p> <p><input type="checkbox"/> Case report or small case series (<20) primarily describing toxicities of HU <i>alone</i> in these other diseases (CML/ET/PV/HIV/psoriasis/etc)</p> <p><input type="checkbox"/> 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)</p> <p><input type="checkbox"/> 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)</p>
--	---

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?

<p>Key Question 4</p> <p><input type="radio"/> Applies to KQ4</p> <p>Clear Selection</p>	<p>This study is:</p> <p><input type="checkbox"/> Any study design with primary data about the <i>test of an intervention to overcome barriers to care</i> that interfere with 1) receipt of medication, 2) receipt of scheduled care, 3) adherence to medication</p> <p><input type="checkbox"/> Any study design in which <i>barriers to care</i> were investigated as affecting 1) receipt of medication, 2) receipt of scheduled care, 3) adherence to medication</p> <p><input type="checkbox"/> 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 medication</p> <p><input type="checkbox"/> Any study design with primary data about the existence of the barriers in our causal diagram*</p>
--	--

*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

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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

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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

<p>3. Nurses</p> <input type="checkbox"/> mixed or unspecified <input type="checkbox"/> inpatient <input type="checkbox"/> outpatient <input type="checkbox"/> ED <input type="checkbox"/> other	<p>4. Physicians</p> <input type="checkbox"/> unspecified or mixed <input type="checkbox"/> hematologists <input type="checkbox"/> ED doctors <input type="checkbox"/> internists <input type="checkbox"/> pediatricians <input type="checkbox"/> physicians-in-training <input type="checkbox"/> other	<p>5. Other Health Professionals</p> <input type="checkbox"/> PA <input type="checkbox"/> social worker <input type="checkbox"/> other	<p>6. Patients</p> <input type="checkbox"/> check here if this population is providing data Clear Selection	<p>7. Family/caregivers</p> <input type="checkbox"/> specify Clear Selection
--	---	--	--	---

Population characteristics of each category identified above

Population characteristics of PATIENTS only


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

<p>System</p> <input type="checkbox"/> health system organization	<p>Patient</p> <input type="checkbox"/> age	<p>Provider</p> <input type="checkbox"/> provider race/ethnicity	<p>Other</p> <input type="checkbox"/> specify <input type="checkbox"/> specify
---	---	--	---


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

For A, B, and C ONLY

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



- Attendance 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

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

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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

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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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](#)

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 instrument?

- No

- To some extent (provides a reference)
- Yes, provides 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 instrument? (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](#)

[Submit Data](#)

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Previewing at Level 8

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? Yes No Clear
- 7. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 8. Is there a reasonable response to drug withdrawal? Yes No Clear
- 9. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear
 - 18. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
 - 19. Is there a reasonable response to drug withdrawal? Yes No Clear
 - 20. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear
- 29. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 30. Is there a reasonable response to drug withdrawal? Yes No Clear
- 31. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear

40. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear

41. Is there a reasonable response to drug withdrawal? Yes No Clear

42. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear
- 51. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 52. Is there a reasonable response to drug withdrawal? Yes No Clear
- 53. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear

62. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear

63. Is there a reasonable response to drug withdrawal? Yes No Clear

64. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear
- 73. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 74. Is there a reasonable response to drug withdrawal? Yes No Clear
- 75. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No 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? Yes No Clear
- 84. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 85. Is there a reasonable response to drug withdrawal? Yes No Clear
- 86. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No Clear

87. Duration of Treatment

Enlarge Shrink

88. Time to occurrence 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? Yes No
- 95. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No
- 96. Is there a reasonable response to drug withdrawal? Yes No
- 97. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No

98. Duration of Treatment



Enlarge Shrink

99. Time to occurrence 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
- Thalassemia
- 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 occurrence 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

Thalassemia

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 occurrence 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

Thalassemia

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 occurrence 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

Thalassemia

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? Clear139. Is there an absence of concurrent diseases or other drugs that may have caused the event? Clear140. Is there a reasonable response to drug withdrawal? Clear141. 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 occurrence 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 Thalassemia 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? Yes No Clear
- 150. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 151. Is there a reasonable response to drug withdrawal? Yes No Clear
- 152. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No Clear

153. Duration of Treatment

Enlarge Shrink

154. Time to occurrence 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 occurrence 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? Yes No
- 172. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No
- 173. Is there a reasonable response to drug withdrawal? Yes No
- 174. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No

175. Duration of Treatment

Enlarge Shrink

176. Time to occurrence 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
- Thalassemia
- 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? Yes No Clear
- 183. Is there an absence of concurrent diseases or other drugs that may have caused the event? Yes No Clear
- 184. Is there a reasonable response to drug withdrawal? Yes No Clear
- 185. Is there the existence of a rechallenge in this report or a demonstrated biological/pharmacological explanation? Yes No Clear
- 186. Duration of Treatment



Enlarge Shrink

187. Time to occurene of toxicity



Enlarge Shrink

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- [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](#)

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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.

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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}**
- 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 efficacy 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:

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Previewing at Level 5

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
- Caribbean
- Middle East
- Southeast Asia
- Africa
- Other (specify) _____

4. Disease (check all that apply)

- Sickle cell anemia
- CML
- AML
- Polycythemia vera
- Essential thrombocytosis
- Psoriasis
- Solid tumors
- Thalassemia
- 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)	<input type="checkbox"/>	<input type="checkbox"/>	
8. Race (specify)	<input type="checkbox"/>	<input type="checkbox"/>	
9. Sickle Cell Anemia	<input type="checkbox"/>	<input type="checkbox"/>	_____
10. Sickle B+ thalassemia	<input type="checkbox"/>	<input type="checkbox"/>	_____
11. Sickle B* thalassemia	<input type="checkbox"/>	<input type="checkbox"/>	
12. Sickle α+ thalassemia	<input type="checkbox"/>	<input type="checkbox"/>	
13. SC genotype	<input type="checkbox"/>	<input type="checkbox"/>	
14. Splenomegaly	<input type="checkbox"/>	<input type="checkbox"/>	
15. Neutropenia	<input type="checkbox"/>	<input type="checkbox"/>	
16. Leukopenia	<input type="checkbox"/>	<input type="checkbox"/>	_____
17. Transfusion dependant	<input type="checkbox"/>	<input type="checkbox"/>	_____
18. Pregnancy	<input type="checkbox"/>	<input type="checkbox"/>	_____
19. Opioid Use	<input type="checkbox"/>	<input type="checkbox"/>	

- 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 Months _____  mean _____  <input type="checkbox"/> median	47. concomittant therapy recieved _____ 	48. duration of observation Months _____  mean _____  median _____ 	49. Indicator of adherence Please Select _____ 	50. denominator for outcomes (ITT if available) _____ 	51. frequency of monitoring labs (write in) _____ 
--	--	--	---	---	---	---	---












ARM 2

52. drugs(s) _____ 	53. # on MTD _____ 	54. Duration of therapy Months _____  mean _____  <input type="checkbox"/> median	55. concomittant therapy recieved _____ 	56. duration of observation Months _____  mean _____  median _____ 	57. Indicator of adherence Please Select _____ 	58. denominator for outcomes (ITT if available) _____ 	59. frequency of monitoring labs (write in) _____ 
--	--	--	---	---	---	---	---

ARM 3

60. drugs(s) _____ 	61. # on MTD _____ 	62. Duration of therapy Months _____  mean _____  <input type="checkbox"/> median	63. concomittant therapy recieved _____ 	64. duration of observation Months _____  mean _____  median _____ 	65. Indicator of adherence Please Select _____ 	66. denominator for outcomes (ITT if available) _____ 	67. frequency of monitoring labs (write in) _____ 
--	--	--	---	---	---	---	---

ARM 4

68. drugs(s) _____ 	69. # on MTD _____ 	70. Duration of therapy Months _____  mean _____  <input type="checkbox"/> median	71. concomittant therapy recieved _____ 	72. duration of observation Months _____  mean _____  median _____ 	73. Indicator of adherence Please Select _____ 	74. denominator for outcomes (ITT if available) _____ 	75. frequency of monitoring labs (write in) _____ 
--	--	--	---	---	---	---	---

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 (-).

Table for ARM 1 with columns: 76. Age, 77. Gender, 78. Race, 79. Genotype, 80. Haplotype, 81. Substance use, 82. Socioeconomic status, 83. Blood, 84. Crises. Each cell contains a list of variables with input fields for mean, median, and range.

ARM 2

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

Table for ARM 2 with columns: 88. Age, 89. Gender, 90. Race, 91. Genotype, 92. Haplotype, 93. Substance use, 94. Socioeconomic status, 95. Blood, 96. Crises. Each cell contains a list of variables with input fields for mean, median, and range.

ARM 3

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

Table for ARM 3 with columns: 100. Age, 101. Gender, 102. Race, 103. Genotype, 104. Haplotype, 105. Substance use, 106. Socioeconomic status, 107. Blood, 108. Crises. Each cell contains a list of variables with input fields for mean, median, and range.

ARM 4

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

Table for ARM 4 with columns: 112. Age, 113. Gender, 114. Race, 115. Genotype, 116. Haplotype, 117. Substance use, 118. Socioeconomic status, 119. Blood, 120. Crises. Each cell contains a list of variables with input fields for mean, median, and range.

		Islander, n (%) Other (specify), n (%)					(k/mm ³), mean or median Absolute neutrophil count (cells/ μ l), 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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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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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 ovbervation


















Efficacy/effectiveness	Toxicities
27 Hb F %	47 platelet count
28 % F cells	48 neutrophil count(ANC)
29 hemoglobin	49 sperm count
30 MCV	50 sperm motility
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	

43 Units (RBC) transfused	
44. other 	45. 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	Significance
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	Significance
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	Significance
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	Significance
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	Significance
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	Significance
72. ARM 1 arm identification should be identical to that in the GENERAL form	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
73. ARM 2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
74. ARM 3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
75. ARM 4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

76. Outcome (select number from list above)

Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Significance
77. ARM 1 arm identification should be identical to that in the GENERAL form	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
78. ARM 2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
79. ARM 3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
80. ARM 4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

81. Outcome (select number from list above)

Please Select

	units	mean	SD	median	range	Estimate of effect (diff, RR, HR, OR); relative to arm2	Significance
82. ARM 1 arm identification should be identical to that in the GENERAL form	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
83. ARM 2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
84. ARM 3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
85. ARM 4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

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:

Enlarge Shrink

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

- [4. TRIAGE](#)
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- [8. KQ3 TOX Case Reports](#)

[9. KO4 Barriers](#)
[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 10

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 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 (dose, 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 extent
- 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](#)

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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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 S α ⁺ thal, Pain >3/yr Exclusion: Hb S β ⁺ thal; β 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 \geq 2000, retic and platelets \geq 80,000/ul, and Hb \geq 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 S α ⁺ thal; 3/yr pain episodes, stroke; acute chest; splenic sequestration Exclusion: Hb S β ⁺ thal; Hb S β 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 S β^+ thal = sickle β^+ thalassemia; Hb S β^0 thal = Sickle β^0 thalassemia; Hb S α^+ 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	N	Recruitment start date - end date	Mean Age	% Male	Race, n	Genotype/ haplotype, n (%)	Last observation
	Intervention							
MSH								
Charache, 1995 ²¹	HU	152	Jan 1992- April 1993	30	49	Black Non-Hispanic, 149 Black Hispanic, 1 Other, 2	SS, 151; Hb Sβ ⁰ 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 Sβ ⁰ 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 Sβ ⁰ 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 Sβ ⁰ 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 S β^0 thal = Sickle β^0 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 \geq 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+, theophylline 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 \geq 3 in past year or \geq 3 pain and ACS episodes within 1 year of enrollment, ACS \geq 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	Effectiveness	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 Sβ ⁰ thal Exclusion: Splenomegaly, Preg, renal failure, CRCL<120ml/min/1.73 m ² , 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 to 20 years, SCA, Hb Sβ ⁺ thal, Hb Sβ 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-Redelsperger, 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 ^{ll}	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 assess the tolerability of HU treatment in 225 children with SCD	Jan 1992 – Dec 2003	Inclusion: Pain \geq 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	Effectiveness	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 \geq 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	Effectiveness	To assess the efficacy and safety of HU	1993-2002	Inclusion: Age, children and young adults, Pain \geq 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 S β^+ thal, Hb S β^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 S β^+ thal, Hb S β^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 Sβ 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-retrospective	Efficacy	To report on the effectiveness of HU in patients with thalassemia--a report of a physician's experiences	NR	Inclusion: Age, adults, Hb Sβ ⁺ thal, Hb Sβ 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-retrospective	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 Sβ ⁺ thal, Hb Sβ 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-retrospective	Toxicity	To evaluate the risk of cutaneous adverse reactions in SCD patients treated with HU	NR	Inclusion: adult, SCA, Hb Sβ ⁺ thal, Hb Sβ 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 Sβ ⁺ thal, Hb Sβ 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-retrospective ^{‡‡}	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 Sβ ⁺ thal, Hb Sβ 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-retrospective	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 Sβ ⁺ thal, Hb Sβ 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 Sβ ⁺ 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, 2005 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 S β^+ thal, Hb S β^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 β^+ thal, sickle β^0 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-retrospective	Effectiveness	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 sickle genotype, age, splenectomy status, and HU exposure	NR	Inclusion: < 20 years Exclusion: Hb Sβ ⁺ thal, Hb Sβ ⁰ thal	NR	NR	39
Hankins, 2007 ⁶⁵	North America	Children-prospective	Effectiveness	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 Sβ 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	Effectiveness	To evaluate the effects of long-term therapy with hydroxyurea on recovery of splenic function	NR	Inclusion: Age 3 to 22, SCA, Sβ0 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/kg, 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 Sβ⁺ thal = Sickle β⁺ thalassemia; Hb S β⁰ thal = Sickle β⁰ 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 Sβ 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; Sβ ⁰ thal 4	NR	1.3* [0.5-2.3]	57	NR	
Hankins, 2005 ⁷²	NR/NA	21	SS 95; Sβ ⁰ thal 5	NR	3.4* [2.6-4.4]	43	Black (100)	
French Cluster								
de Montalembert, 1997 ⁷⁶	NR/NA	35	SS 94; Sβ ⁰ thal 3; Sβ ⁺ 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; Sβ ⁺ thal 1; Sβ ⁰ thal 1	NR	9.8 [2-20]	55	NR	One HIV ⁺
de Montalembert, 2006 ⁴⁸	NR/NA	225	SS 94; SC 1.3; Sβthal 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; Sβ ⁰ 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; Sβ 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	Sβ ⁺ thal 42; Sβ ⁰ thal 58	NR	28.6 [19-48]	64	NR	
Scott, 1996 ⁷⁷	NR/NA	15	SS 73; Sβ ⁰ thal 13; Sα ⁺ thal 13	NR	14 [(10-17)]	40	NR	
Loukopoulos, 1998 ⁶⁹	NR/NA	44	Sβ ⁺ thal 34; Sβ 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; Sβ ⁰ thal 79	All HbS was Benin	[17-50]	58	White (100)	
Rigano, 2001 ⁷¹	NR/NA	22	Sβ ⁰ thal 76; Sβ ⁺ thal 27	Benin 100%	[29-53]	68	White (100)	Pain crises 7/yr (mean)
Chaine, 2001 ⁶⁶	NR/NA	17	SS 94; Sβ ⁰ 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; Sβ ⁰ 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; Sβ 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; Sβ ⁰ thal 5; Sβ ⁺ 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 ⁵⁰	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; Sβ ⁰ thal 1	NR	9.9* [3-17.6]	65	Black (98)	
Santos, 2002 ⁵⁹	HU	21	SS 14; Sβ 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; Sβ⁺ thal = Sickle β⁺ thalassemia; Sβ⁰ thal = Sickle β⁰ 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	Intervention	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-uloocyte 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	Intervention	N	Mean durations of drug Mean duration of followup	Deaths, n (%)	Hb F, % [±] SD	F cells, % [±] SD	Hemoglobin, g/dl	MCV, fl [±] sd	Reticulocyte count, k/ul	Weight change, kg (%)	Change in peak power, watts [±] sem	Pain crises & admissions	Transfusion
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), positively 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 admissions*	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 compared 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 Montalembert, 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-Redelsperger, 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 require d hospita lization	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 complet ed	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)		
Louko- poulos, 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)		
Louko- poulos, 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 includi ng 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 3.1/yr	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)									
		HU less than 24 months	30							4.8/yr p=0.49 relative to baseline 5.7 /yr	
		Baseline (pre-HU)									
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 admissions*	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]	
Zimmerm an, 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. RMCA 162 cm/sec
				10.3		7.8	86 (8)				
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*	Hemoglobin (g/dl)	MCV (fl)	WBC count (/ul)	Pain crises*	Hospital admissions*	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 ≤ 0.0001

‡ p ≤ 0.001

§ p ≤ not significant

|| p ≤ 0.01

¶ p ≤ 0.002

p ≤ 0.005

**p = 0.0002

†† p ≤ 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: Sβ ⁰ thal, Sα ⁺ 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 β +thal; S β othal; S α +thal; SC; Age >12	HU		2 to 60 months	Hb F (%)	14.2 \pm 8.3 ^S	Hb (g/dl)	9.6 \pm 2.2 ^S		
			No HU				8.8 \pm 4.1		8.1 \pm 0.9		
Heeney, 2003 ⁹⁰	North America	Inclusion: Children; SCA; S β +thal; S β othal 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 oxyhemoglobin (%)	65	Venous reduced Hb (%)	28	Nitric Oxide Metabolites (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 = granular membrane protein; Hb = hemoglobin; HU = hydroxyurea; IR = index of rigidity; N/A = not applicable; PHT = pulmonary hypertension; S β+ thal = S β+ thalassemia; S β° thal = S β° 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]			
	NI 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	Death, n (%)	Thrombocytopenia	Netropenia, %	Absolute neutrophil count, ul +/- SD	% GI disturbance,	% Rash or Nail changes	Lower extremity ulcers	Other
			Mean follow-up duration								
MSH											
Steinberg, 2003 ⁴³	HU	152	NR	36 (23.7)							Malignancy, 1 Sepsis/Infection, 18 Hepatic Failure, 3 Renal Failure, 14
			7.7 years								
	Placebo	147	NR	39 (26.5)							
			7.4 years								
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 \pm 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)	Neutropenia	Thrombocytopenia	Leukemia	Leg ulcers	Rash or nail changes	Other
HUG-KID										
Kinney, 1999 {#2977}	HU	84	Yes		56 with ANC< 2000/ μ l	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/ μ l 6 with ANC< 500/ μ l	1 with <80,000/ μ l				
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/ μ l 3 with ANC 1000-1500/ μ l	4 with 90-100,000/ μ l	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)	Neutropenia	Thrombocytopenia	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/ μ l)
Charache, 1992 {#2991}	HU	49			17	1				No unusual infections; karyotypic 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)	Neutropenia	Thrombocytopenia	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, 2005 ⁸⁰	1/22
Myelotoxicity	Vicari, 2005 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	ddl		4
				HU (low dose) with/without ddl	HU 1000 mg/d	
				HU (high dose) with/without ddl	HU 1500 mg/d	
Havlic, 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 ddl 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 ddl d4T	HU 600 BID	2
				IDV ddl 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 ddl; 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/ ddl and HU	HU 500 mg BID	2
				ABC/EFV/ ddl		
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	ddl + HU	HU 500 mg BID	3
				ddl		
Bloch, 2006 ¹⁹¹	Australia	Jan 2000 – Feb 2002	Inclusion: acute primary HIV infection	IDV/RTV/ddl + either stavudine or lamiduvine + HU	HU 500 mg BID	2
				IDV/RTV/ddl + 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	ddl/d4T/HU [†] ddl/stavudine + placebo	HU 500 mg bid	3
Rutschmann, 1998 ¹⁹³	Europe		Inclusion: HIV+; CD4 200-500/ul; HIV RNA >1000/ml; stavudine and HU naïve Exclusion: > 6 months of ddl	ddl/stavudine/HU [§] ddl/stavudine	HU 500 mg BID	1
Rutschmann, 2000 ¹⁹⁴	Europe		Inclusion: CD4 between 2---500; HIV RNA >1000 x2 Exclusion: prior HU; prior stavudine; ddl >6 months	ddl/stavudine/HU Placebo, ddl stavudine	HU 500 mg BID	2
CML						
Hehlmann, 2003 ¹¹³	Europe	Feb 1991 - Dec 1994	Inclusion: newly diagnosed CML in chronic phase Exclusion: prior therapy	HU IFN-alpha 2a + HU	40mg/kg/d IFN 5*10 ⁶ IU/m2/d + HU added as required	2
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 IFN and HU if needed	NR 3 million units 5x/wk	2
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 IFN Busulfan	40mg/kg/d 4 million units/m ² 0.1mg/kg/d	3
Broustet, 1991 ¹¹⁶	Europe	May 1987 - Jul 1990	Inclusion: Age >18; Ph+ CML Exclusion: prior chemo; trisomy 8, isochromosome 17, double Ph+	HU IFN	4 million units/m ²	3
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 Busulfan	40 mg/kg/d 0.1 mg/kg/d	2

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	
Najejan Cluster/ PV						
Najejan, 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. 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, 1998¹⁰² 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 trial¹²³. 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}	ddl	28	NR	(79)	White (38); Black (50); White Hispanic (10)	6 months
	HU (low dose) with/without ddl	53				
	HU (high dose) with/without ddl	50				
Havlir, 2001 ¹⁸⁹	IDV, ddl, d4T + HU	68	NR	(82)	White (69); Black (16); White Hispanic (13)	
	IDV, ddl, 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, ddl + 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, ddl	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	ddl +HU	40	33.8; [26- 47]	26 (65)	NR	40 weeks
	ddl	21	31; [21- 48]	13 (62)		
Bloch, 2006 ¹⁹¹	Indinavir, ritonavir, ddl and either stavudine or lamiduvine + HU	35	Median, 36; [31-39]	NR	NR	
	Indinavir, ritonavir, ddl and either stavudine or lamiduvine	33	Median, 34; [29-40]			
Rutschmann Cluster/ HIV						
Rutschmann, 1998 ¹⁰⁹	ddl, stavudine + HU	72	NR	NR	NR	24 wks
	ddl, stavudine + placebo	72				
Rutschmann, 1998 ¹⁰²	ddl, stavudine + HU	72				48 weeks
	ddl, stavudine + placebo	72				
Rutschmann, 2000 ^{‡ 110}	ddl + stavudine + HU	72				24 months
	ddl, 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, 1984 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)		
Najejan Cluster/ PV						
Najejan, 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 (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
HIV												
Frank, 2004 ¹⁰⁴	ddl mono	28	D: 6 months		3 (11)	0	0					Grade 3 chemistry or more, 3 (11)
	HU (low dose) with/without ddl	53			10 (19)	1 (2)	0					Grade 3 chemistry or more, 7 (13)
	HU (high dose) with/without ddl	50			20 (40)*	9 (18) [†]	3 (6)					Grade 3 chemistry or more, 4 (8)
Havliir, 2001 ¹⁸⁹	IDV, ddl, d4T, + HU	68	F: 40 weeks	3								GI upset, 2 Pancreatitis, 4 Asymptomatic amylase elevation, 2
	IDV, ddl, d4T + placebo	68		0								GI upset, 1 Pancreatitis, 3
	IDV, ZDV (or d4T), 3TC	66		0								
Swindells, 2005 ¹¹¹	ABC, EFV, ddl + HU	30	F: 48 weeks								5	GI upset, 28 Neurological/psychiatric, 23 Endocrine or metabolic, 7 Arthralgia, 2 Fatigue, 6 Neuropathy, 4
	ABC, EFV, ddl	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 (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash or nail alteration, n (%)	Other n (%)
HIV												
Seminari, 1999 ¹⁰⁸	ddl + HU	40	F: 40 weeks		1	1	1					Hair loss, 2 hyperamylasemia, 1 hypertryglyceridemia, 1
	ddl	21	D: 24 weeks		0	0	0					GI upset, 1 Hyperamylasemia, 1 Hypertryglyceridemia, 1
Bloch, 2006 ¹⁹¹	Indinavir, ritonavir, ddl, and either stavudine or lamiduvine + HU	35					1					CMV esophagitis, (3) renal colic, (20) pneumonia, (3)
	Indinavir, ritonavir, ddl, and either stavudine or lamiduvine	33					0					Neuropathy, (3) rectal tear, (3) renal colic, (3)
Rutschmann Cluster/ HIV												
Rutschmann, 1998 ¹⁰⁹	ddl, stavudine + HU	72	F: 24 weeks		14 [‡]	8 [§]					5	GI upset, 16 Fatigue, 10 Neuropathy, 18 ^{††} Diarrhea, 15
	ddl, stavudine + placebo	72			3/ 25	3					4	GI upset, 11 Fatigue, 2 Neuropathy, 10 Diarrhea, 9
Rutschmann, 1998 ^{102#}	ddl, stavudine + HU	72	D: 12-48 weeks F: 48 weeks		11/ un-clear	7						Fatigue, 10 Diarrhea, 15 Paraesthesia, 29
	ddl, 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 (%)	Thrombocytopenia, 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#}	ddl, stavudine + HU	72	F: 24 months		18 ^{III}	29 ^{##}			4 Kaposi's sarcoma ^{***}		8	GI upset, 20 ^{†††} Hair loss, 1 Fatigue, 16 Neuropathy, 28 ^{††} Diarrhea, 23 Mucositis, 5
	ddl, 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 (%)	Thrombocytopenia, 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 disease/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 (%)	Thrombocytopenia, 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)
	Cyclophosphamide	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)
Najejan Cluster/ PV												
Najejan, 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 (%)	Thrombocytopenia, 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 ^{SSSS}				6				Myelofibrosis, 5
	Anagrelide + aspirin	405		3 ^{IIII}				4 ^{IIII}				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 study¹²³. 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 unclassified MPD [†]	Jan 1993 - 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 prospective 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 comparison arm	PV, ET	NR	NR	PV: HU therapy	NR	86 (range, 36-195) months	57
						ET: HU therapy			
						PV: busulfan			
						ET: alpha IFN			
PV									
Finazzi, 2005 ¹²⁴	Europe	Case series	PV	1997 - 2001	Inclusion: diagnosis of PV by PVSG	HU			63
						Any other cytoreductive drug			
						No drug or alpha IFN only			
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	30 mg/kg day x 1 week then 15 mg/kg: 5/mg/kg/d changes to keep HCT controlled		53
						HU and prior myelosuppressive therapy			

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)									
Najejan, 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 myelo-suppressive agents	HU Phlebotomy		61 (245 weeks)	44
Fruchtman, 1997 ¹²⁶	North America	Cohort with a comparison arm	PV		Inclusion: PV Exclusion: prior chemo	HU Phlebotomy		Last observation: 198.75 months	60

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			67
						Melphalan + HU			
						³² P + HU			
Bernasconi, 2002 ¹⁰⁷	Europe	Case series	ET	1985 - 1995		HU alone	15 mg/kg/d		67
						Pipobroman	1 mg/kg/d		
						None			
Gangat, 2007 ¹⁰⁶	North America	Cohort with a comparison arm	ET	Jul 1956 - Dec 2005		HU		median follow-up for the entire study population: 84 months (range, 0-424)	73
						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			
Sterkers, 1998 ¹³²	Europe	Case series	ET	1970 - Jan 1991	Inclusion: ET	HU alone	1.5 g/d	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	
						HU with other agents			
						³² P alone	0.1 mCi/kg		
						³² P with other agents			
						Busulfan alone	6 mg/d		
						Busulfan with other agents			
						Pipobroman alone	1 mg/kg/day		
						Pipobroman with other agents			
No treatment									

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.

³²P = 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 ^{117f}	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	
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.

³²P= 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 (%)	Neutropenia, n (%)	Thrombocytopenia, 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 (%)	Neutropenia, n (%)	Thrombocytopenia, 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 ^{8 136}	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°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 (%)	Neutropenia, n (%)	Thrombocytopenia, 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 ¹³⁶	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 (%)	Neutropenia, n (%)	Thrombocytopenia, n (%)	Anemia, n (%)	Leukemia, n (%)	Other neoplasm, n (%)	Leg ulcer, n (%)	Skin rash/nail alteration, n (%)	Other, n (%)
PV (continued)												
Najejan, 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 (%)	Neutropenia, n (%)	Thrombocytopenia, 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 ^{III}				
	Pipobroman	106						4 ^{III}				
	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 (%)	Neutropenia, n (%)	Thrombocytopenia, 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%

³²P = 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 than the Sickle Cell Disease*

Author/year	Source population	Inclusion criteria	Baseline characteristics	Intervention	Adherence	Quality score
Frank, 2004 ¹⁰⁴						
Havir, 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
Najejan, 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-occlusive 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-occlusive 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-occlusive 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	N	Barriers identified	Primary results
Studies on Barriers to Receipt of Appropriate Pain Medication during Vaso-occlusive 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-occlusive 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-occlusive 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-occlusive 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-occlusive 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 disagree" 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-occlusive 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 meperidine), 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-occlusive Crisis (continued)					
Cooper, 2000 ¹⁷⁵	CCT, Pre-post	Nurses, doctors Cleveland, OH	67	1) Develop individualized pain management protocols 2) Discourage the use of meperidine 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-occlusive 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 opioids 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-occlusive 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 meperidine 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-occlusive 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% (\pm 31.4%) in intervention group vs. 66.0 (\pm 20.2%) in control group ($p=0.297$). Compliance at 4-6 months was 82.0 (\pm 34.7%) in intervention group vs. 65.8 (\pm 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	<p>Inclusion: 5.0-18.9 years; HbSS; HbSβ^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 $\leq 45\%$ in the 6 months prior to study entry</p> <p>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 $3.0 \times 10^9/L$; absolute neutrophil count less than $1.5 \times 10^9/L$; platelet count less than $100 \times 10^9/L$; 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</p>	Aimed at demonstrating prevention of secondary stroke and management of iron overload.

eGFR = estimated glomerular filtration rate; Hb = hemoglobin; NR = not reported; S β^0 thal = Sickle β^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	Sauntharajah, 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, Sauntharajah, 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	Sauntharajah, 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, Koepfel 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. *TreatmentUpdate* Anti-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**
- Barbarin O A. Risk and resilience in adjustment to sickle cell disease: Integrating focus groups, case reviews, and quantitative methods. *J. HEALTH SOC. POLICY* 94;5(3-4):97-121 **Not relevant to key questions**
- Bardakdjian-Michau J, Guilloud-Bataille M, Maier-Redelsperger M et al. Decreased morbidity in homozygous sickle cell disease detected at birth. *Hemoglobin* 2002;26(3):211-7 **Not relevant to key questions**
- Barkow J M. In the matter of Cabrera. *Issues Law Med* 89;5(3):371-2 **Study size too small, No Original Data**
- Barosi G, Besses C, Birgegard G et al. A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group. *Leukemia* 2007;21(5):1136 **Not relevant to key questions, No Original Data, other**
- Barreiro P, de Mendoza C, Camino N et al. Hydroxyurea plus didanosine as maintenance therapy for HIV-infected patients on long-term successful highly active antiretroviral therapy. *HIV Clin Trials* 2003;4(6):361-71 **Not relevant to key questions, other**
- Barry M, Clarke S, Mulcahy F et al. Hydroxyurea-induced neurotoxicity in HIV disease [6]. *AIDS* 99;13(12):1592-1594 **Not relevant to key questions, other**
- Barton C, Michael M, Richmond J. Assessment of care of children with sickle cell disease. *BMJ* 90;300(6727):814 **No Original Data**
- Baucher H. Use of the new pneumococcal conjugate vaccine in the USA. *Arch. Dis. Child.* 2000;83(5):396 **Not relevant to key questions, No Original Data**

- Baudo F, Cattaneo N, Cipriani D et al. Clinical trial of hydroxyurea in chronic myelocytic leukemia. *Haematol Lat* 67;10(4):359-62 **Study size too small**
- Beckloff G L, Lerner H J, Cole D R et al. Hydroxyurea in bladder carcinoma. *Invest Urol* 66;3(5):530-4 **Study size too small**
- Beelen D W, Graeven U, Elmaagacli A H et al. Prolonged administration of interferon-alpha in patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia before allogeneic bone marrow transplantation may adversely affect transplant outcome. *Blood* 95;85(10):2981-90 **Not relevant to key questions**
- Belgrave F Z, Gilbert S K. Health care adherence of persons with sickle cell disease. The role of social support. *Ann. New York Acad. Sci.* 89;565(-):369-370 **No Original Data**
- Bemis E L. Sickle cell safari. *Blood* 73;42(1):147-9 **Not relevant to key questions**
- Benito-Leon J, Martin E, Vincent A et al. Neuromyotonia in association with essential thrombocythemia. *J. Neurol. Sci.* 2000;173(1):78-79 **Not relevant to key questions**
- Benkerrou M, Delarche C, Brahimi L et al. Hydroxyurea corrects the dysregulated L-selectin expression and increased H(2)O(2) production of polymorphonuclear neutrophils from patients with sickle cell anemia. *Blood* 2002;99(7):2297-303 **Study size too small**
- Bergman R, Friedman-Birnbaum R, Carter A. Acquired ichthyosis in a patient with polycythemia rubra vera. *CUTIS* 85;36(2):157-158 **Not relevant to key questions**
- Bernardini K, Lanthaler A J, Buratti T et al. Monolateral renal infarction and erythromelalgia in a case of chronic myelogenous leukemia. *Am J Hematol* 2006;81(3):224-5 **Not relevant to key questions**
- Bernaudin F, Verlhac S, Coic L et al. Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. *Pediatr Radiol* 2005;35(3):242-8 **Study size too small**
- Bezwoda W R, Nissenbaum M, Derman D P. Treatment of metastatic and recurrent cervix cancer with chemotherapy: a randomised trial comparing hydroxyurea with cisdiaminedichloro-platinum plus methotrexate. *Med Pediatr Oncol* 86;14(1):17-9 **Study size too small**
- Billings F T, 3rd. Treatment of sickle cell anemia with bone marrow transplantation-pros and cons. *Trans Am Clin Climatol Assoc* 89;1018-19; discussion 19-20 **No Original Data**
- Binder W D, Brown D F, Nadel E S. Blurred vision, epistaxis, and fever in a young man. *J Emerg Med* 2002;23(3):275-8 **Not relevant to key questions**
- Bird S T, Earp J A, Drezner S M et al. Patient education for sickle cell disease: a national survey of health care professionals. *Health Educ Res* 94;9(2):235-42 **Not relevant to key questions, other**
- Biron F, Lucht F, Peyramond D et al. Pilot clinical trial of the combination of hydroxyurea and didanosine in HIV-1 infected individuals. *Antiviral Res* **Study size too small**
- Blanckenberg D H, Wood R, Horban A et al. Evaluation of nevirapine and/or hydroxyurea with nucleoside reverse transcriptase inhibitors in treatment-naive HIV-1-infected subjects. *AIDS* 2004;18(4):631-40 **Not relevant to key questions**
- Blau C A. Therapy for globin-chain disorders [7]. *NEW ENGL. J. MED.* 93;329(5):364 **No Original Data**
- Bleyer W A, Danielson M G. Oral cancer chemotherapy in paediatric patients: Obstacles and potential for development and utilisation. *Drugs* 99;58(SUPPL. 3):133-140 **No Original Data**
- Blumenreich M S, Kellihan M J, Joseph U G et al. Long-term intravenous hydroxyurea infusions in patients with advanced cancer. A phase I trial. *Cancer* 93;71(9):2828-32 **Not relevant to key questions, study size too small**
- Bobo L, Miller S T, Smith W R et al. Health perceptions and medical care opinions of inner-city adults with sickle cell disease or asthma compared with those of their siblings. *South Med J* 89;82(1):9-12 **Not relevant to key questions**
- Boga C, Ozdogu H, Sezgin N et al. Serum cancer antigen 15-3 concentrations in patients with sickle cell disease [2]. *Br. J. Haematol.* 2006;134(5):546-547 **Not relevant to key questions**
- Bojanowski C. Use of protocols for ED patients with sickle cell anemia. *J Emerg Nurs* 89;15(2(Pt 1)):83-7 **Not relevant to key questions**
- Bolanos-Meade J, Lopez-Arvizu C, Cobos E. Acute myeloid leukaemia arising from a patient with untreated essential thrombocythaemia. *Eur J Haematol* 2002;68(6):397-9 **Not relevant to key questions**
- Bolin R W, Robinson W A, Sutherland J et al. Busulfan versus hydroxyurea in long-term therapy of chronic myelogenous leukemia. *Cancer* 82;50(9):1683-6 **Study size too small**
- BOLTON B H, KAUNG D T, LAWTON R L Et Al. HYDROXYUREA (NSC-32065)--A PHASE I STUDY. *Cancer Chemother Rep* **Other**
- Borba R, Lima C S, Grotto H Z. Reticulocyte parameters and hemoglobin F production in sickle cell disease patients undergoing hydroxyurea therapy. *J Clin Lab Anal* 2003;17(2):66-72 **Study size too small**
- Bourantas K L, Syrou M, Tsiara S et al. Combination therapy with interferon alfa-2b and hydroxyurea during the accelerated phase of chronic myelogenous leukemia. *Acta Haematol* 96;95(2):117-21 **Study size too small**

- Bowers M. Hydroxyurea. *BETA* 97;9-11 **No Original Data**
- Bowman J E. Minority health issues and genetics. *Community Genet* 98;1(3):142-4 **No Original Data**
- Bowman J E. Social implications of sickle cell programs. *Urban Health* 74;3(4):16-17+ **No Original Data**
- Britto M T, DeVellis R F, Hornung R W et al. Health care preferences and priorities of adolescents with chronic illnesses. *Pediatrics* 2004;114(5):1272-80 **Not relevant to key questions**
- Britto M T, Garrett J M, Dugliss M A et al. Preventive services received by adolescents with cystic fibrosis and sickle cell disease. *Arch Pediatr Adolesc Med* 99;153(1):27-32 **Not relevant to key questions**
- Britto M T, Garrett J M, Dugliss M A et al. Risky behavior in teens with cystic fibrosis or sickle cell disease: a multicenter study. *Pediatrics* 98;101(2):250-6 **Not relevant to key questions**
- Britto M T, Slap G B, DeVellis R F et al. Specialists understanding of the health care preferences of chronically ill adolescents. *J Adolesc Health* 2007;40(4):334-41 **Not relevant to key questions**
- Brodie J L. Sickle cell anemia--the disease of challenge. *J Am Med Womens Assoc* 72;27(8):411-5 **passim No Original Data**
- Brooks B J, Hanson D S, Cryer P A et al. Erythropoietin therapy for sickle cell anemia in Jehovah's Witnesses. *South Med J* 91;84(11):1416-7 **Not relevant to key questions, study size too small**
- Brower V. The squeaky wheel gets the grease. *EMBO Rep.* 2005;6(11):1014-1017 **No Original Data**
- Brown A K, Miller S T, Agatista P. Care of infants with sickle cell disease. *Pediatrics* 89;83(5 SUPPL.):897-900 **Not relevant to key questions**
- Brown R T, Connelly M, Rittle C et al. A longitudinal examination predicting emergency room use in children with sickle cell disease and their caregivers. *J Pediatr Psychol* 2006;31(2):163-73 **Not relevant to key questions**
- Brown R T, Lambert R. Family functioning and children's adjustment in the presence of a chronic illness: Concordance between children with sickle cell disease and caretakers. *Fam. Syst. Health* 99;17(2):165-179 **Not relevant to key questions**
- Brugnara C, Zelmanovic D, Sorette M et al. Reticulocyte hemoglobin: an integrated parameter for evaluation of erythropoietic activity. *Am J Clin Pathol* 97;108(2):133-42 **Study size too small**
- Brunning R D. The effects of leukemia and lymphoma chemotherapy on hematopoietic cells. *Am J Med Technol* 73;39(5):165-74 **Not relevant to key questions, No Original Data**
- Bunn H F. Induction of fetal hemoglobin in sickle cell disease. *Blood* 99;93(6):1787-1789 **No Original Data**
- Burke S M. Hydroxyurea in sickle cell disease. *MCN Am J Matern Child Nurs* 96;21(4):210 **No Original Data**
- Burns E R, Reed L J, Wenz B. Volumetric erythrocyte macrocytosis induced by hydroxyurea. *Am. J. Clin. Pathol.* 86;85(3):337-341 **Not relevant to key questions, study size too small**
- Caccialanza P, Finzi A F. Clinical and experimental investigations on the effect of cytostatic drugs in psoriasis. *Ital Gen Rev Dermatol* **Not relevant to key questions**
- Campbell P J, Green A R. The long-term outlook for essential thrombocythemia. *Mayo Clin. Proc.* 2006;81(2):157-158 **No Original Data**
- Candoni A, Tiribelli M, Fanin R. Plasma cell leukemia occurring in a patient with thrombocythemia treated with hydroxyurea and busulphan. *Leuk. Lymphoma* 2004;45(4):821-824 **Not relevant to key questions**
- Candoni A, Tiribelli M, Fanin R. Plasma cell leukemia occurring in a patient with thrombocythemia treated with hydroxyurea and busulphan. *Leuk Lymphoma* **Not relevant to key questions, other**
- Carella A M, Frassoni F. ICE, mini-ICE or high-dose hydroxyurea to mobilize Philadelphia (Ph1)-negative PBPC in chronic myelogenous leukaemia. *Br J Haematol* 96;95(1):213-5 **Not relevant to key questions, No Original Data**
- Carella A M. Mini-ICE protocol is better than high-dose hydroxyurea to mobilize Ph-negative cells in earlier phases of chronic myelogenous leukemia [1]. *Leuk. Lymphoma* 98;31(3-4):437-438 **Not relevant to key questions, study size too small, No Original Data**
- Carr A, Hudson J, Chuah J et al. HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study. *AIDS* 2001;15(14):1811-22 **Other**
- Cassileth P A, Hyman G A. Treatment of malignant melanoma with hydroxyurea. *Cancer Res* 67;27(10):1843-5 **Study size too small**
- Cassileth P A. Intensive therapy in elderly patients with acute myeloid leukemia. *J Clin Oncol* 90;8(5):937-8 **Not relevant to key questions, No Original Data**
- Catlin A. The dilemma of Jehovah's Witness children who need blood to survive. *HEC Forum* 96;8(4):195-207; discussion 208-11 **Not relevant to key questions**
- Cepeda J A, Wilks D. Excess peripheral neuropathy in patients treated with hydroxyurea plus didanosine and stavudine for HIV infection. *AIDS* **Not relevant to key questions, other**
- Chang Y H, Lu M Y, Jou S T et al. Forty-seven children suffering from chronic myeloid leukemia at a center over a 25-year period. *Pediatr Hematol Oncol* 2003;20(7):505-15 **Not relevant to key questions**
- Charache S. Experimental therapy of sickle cell disease. Use of hydroxyurea. *Am J Pediatr Hematol Oncol* 94;16(1):62-6 **No Original Data**

- Charche S. Sickle-cell anemia: the known and the unknown. *Ann Intern Med* 72;77(1):148-9 **No Original Data**
- Chernoff R G, Ireys H T, DeVet K A et al. A randomized, controlled trial of a community-based support program for families of children with chronic illness: pediatric outcomes. *Arch Pediatr Adolesc Med* 2002;156(6):533-9 **Not relevant to key questions**
- Cheung A Y C, Browne B, Capen C. Hydroxyurea-induced fever in cervical carcinoma: Case report and review of the literature. *Cancer Invest.* 99;17(4):245-248 **Not relevant to key questions**
- Cheung M C, Hicks L K, Pendergrast J. Thrombocytosis. *N Engl J Med* **No Original Data**
- Chistolini A, Gabriella Muzzucconi M, Ferrari A et al. Essential thrombocythemia: A retrospective study on the clinical course of 100 patients. *Haematologica* 90;75(6):537-540 **Not relevant to key questions**
- Choo D, McHenry P. Combination therapy with acitretin and hydroxyurea for severe psoriasis [1]. *J. Dermatol. Treat.* 99;10(1):71-72 **Not relevant to key questions**
- Clare N. Management of sickle cell disease. Management would improve if doctors listened more to patients. *BMJ* 98;316(7135):935 **No Original Data**
- Clarke P C, Clare N R. Sickle cell anaemia: a challenge for health education. *Health Educ J* 81;40(2):50-2 **Not relevant to key questions, No Original Data**
- Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 96;88(6):1951-3 **Study size too small**
- Cobo F, Cervantes F, Martinez C et al. Multiple myeloma following essential thrombocythemia. *LEUK. LYMPHOMA* 95;20(1-2):177-179 **Not relevant to key questions**
- Cole D R, Beckloff G L, Rousselot L M. Clinical Results With Hydroxyurea In Cancer Chemotherapy; Preliminary Report. *N Y State J Med* 65;652132-6 **Study size too small**
- Collier A C, Schwartz M A. Strategies for second-line antiretroviral therapy in adults with HIV infection. *Adv. Exp. Med. Biol.* 99;458(-):239-266 **No Original Data**
- Combinations studied for sickle cell disease. *AM. PHARM.* 93;33(6):15-16 **No Original Data**
- Comer E W. Integrating the health and mental health needs of the chronically ill: a group for individuals with depression and sickle cell disease. *Soc Work Health Care* 2004;38(4):57-76 **Not relevant to key questions**
- Conkle C. Patient allegedly abandoned by physicians and hospital. *J Ark Med Soc* 93;89(11):547-51 **Not relevant to key questions**
- Connelly M, Wagner J L, Brown R T et al. Informant discrepancy in perceptions of sickle cell disease severity. *J Pediatr Psychol* 2005;30(5):443-8 **Not relevant to key questions**
- Conran N, Fattori A, Saad S T et al. Increased levels of soluble ICAM-1 in the plasma of sickle cell patients are reversed by hydroxyurea. *Am J Hematol* 2004;76(4):343-7 **Study size too small**
- Conran N, Oresco-Santos C, Acosta H C et al. Increased soluble guanylate cyclase activity in the red blood cells of sickle cell patients. *Br J Haematol* 2004;124(4):547-54 **Study size too small, other**
- Conyard S, Krishnamurthy M, Dosik H. Psychosocial aspects of sickle-cell anemia in adolescents. *Health Soc Work* 80;5(1):20-6 **No Original Data**
- Conyard S, Krishnamurthy M, Dosik H. Psychosocial aspects of sickle-cell anemia in adolescents. *Health Soc Work* 80;5(1):20-6 **Not relevant to key questions, No Original Data**
- Cortes J, Kantarjian H, O'Brien S et al. Result of interferon-alpha therapy in patients with chronic myelogenous leukemia 60 years of age and older. *Am J Med* 96;100(4):452-5 **Not relevant to key questions, study size too small**
- Covas D T, de Lucena, Angulo I et al. Effects of hydroxyurea on the membrane of erythrocytes and platelets in sickle cell anemia. *Haematologica* 2004;89(3):273-80 **Study size too small**
- Crawford M. The multicultural society. Sickle cell disease in children. *Nursing (Lond)* 91;4(31):23-5 **No Original Data**
- Crawford S. Hydroxyurea information for children and parents. *Paediatric Nursing* 2003;15(2):40 **No Original Data**
- Creasey W A, Capizzi R L, DeConti R C. Clinical and biochemical studies of high-dose intermittent therapy of solid tumors with hydroxyurea (NSC-32065). *Cancer Chemother Rep* 70;54(3):191-4 **Study size too small**
- Curtin N J, Campbell P J, Green A R. The Philadelphia translocation and pre-existing myeloproliferative disorders +AFs-3+AF0-. *Br. J. Haematol.* 2005;128(5):734-736 **Not relevant to key questions**
- Curtin N J, Campbell P J, Green A R. The Philadelphia translocation and pre-existing myeloproliferative disorders. *Br J Haematol* 2005;128(5):734-6 **Study size too small**
- Cusimano M D. Hydroxyurea for treatment of meningioma. *J Neurosurg* 98;88(5):938-9 **Not relevant to key questions, No Original Data**
- Dahl M G, Comaish J S. Long-term effects of hydroxyurea in psoriasis. *Br Med* **Study size too small**
- Dalton R N, Turner C, Dick M et al. The measurement of urinary hydroxyurea in sickle cell anaemia. *Br J Haematol* 2005;130(1):138-44 **Study size too small, Not relevant to key questions**

- Dames-Fincher G. A patient's perspective on sickle cell disease treatment. *J Natl Med Assoc* 92;84(9):739, 741 **No Original Data**
- Dampier C, Ely E, Brodecki D et al. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. *J Pediatr Hematol Oncol* 2002;24(8):643-7 **Not relevant to key questions**
- Davey R J. Lead poisoning and sickle cell anemia programs at neighborhood health centers: a survey. *Med Care* 74;12(9):788-94 **Not relevant to key questions**
- Davidoff A, Kenney G, Dubay L. Effects of the State Children's Health Insurance Program Expansions on children with chronic health conditions. *Pediatrics* 2005;116(1):e34-42 **Not relevant to key questions**
- Davies S C, Bevan D H. Sickle cell pain crisis. *Lancet* 96;347(8996):263 **No Original Data**, other
- Davies S C, Roberts I A. Bone marrow transplant for sickle cell disease--an update. *Arch Dis Child* 96;75(1):3-6 **Not relevant to key questions, No Original Data**, other
- Davies S. Bone marrow transplantation for sickle cell anaemia. *Br J Hosp Med* 93;49(4):229 **Not relevant to key questions, No Original Data**
- Davis H, Gergen P J, Moore R M. Geographic differences in mortality of young children with sickle cell disease in the United States. *Public Health Rep* 97;112(1):52-8 **Not relevant to key questions**
- Day S W. Development and evaluation of a sickle cell assessment instrument. *Pediatr Nurs* 2004;30(6):451-8 **Not relevant to key questions**
- De Bergsagel, De Frenkel E P, Alfrey C P Et Al. Megaloblastic Erythropoiesis Induced By Hydroxyurea (NSC-32065). *Cancer* **No Original Data**, other
- de Montalembert M, Bachir D, Hulin A et al. Pharmacokinetics of hydroxyurea 1,000 mg coated breakable tablets and 500 mg capsules in pediatric and adult patients with sickle cell disease. *Haematologica* 2006;91(12):1685-8 **Not relevant to key questions**
- de Montalembert M, Davies S C. Is hydroxyurea leukemogenic in children with sickle cell disease?. *Blood* 2001;98(9):2878-9 **No Original Data**
- De Oliveira F M, Scrideli C A, Tone L G. A case of near-triploid with t(2;14)(p12;q32) in blast crisis of chronic myeloid leukemia detected by spectral karyotyping (SKY) [2]. *J. Pediatr. Hematol. Oncol.* 2007;29(4):274-276 **Not relevant to key questions**
- de Paula E V, Lima C S, Arruda V R et al. Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003;70(3):151-5 **Study size too small**
- Desimone J. Introduction: The evolving role of DNA demethylating agents in the treatment of sickle cell disease and thalassemia. *Semin. Hematol.* 2004;41(SUPPL. 6):1-2 **No Original Data**
- DeVet K A, Ireys H T. Psychometric properties of the maternal worry scale for children with chronic illness. *J Pediatr Psychol* 98;23(4):257-66 **Not relevant to key questions**
- Diggs L W, Flowers E. Sickle cell anemia in the home environment. Observations on the natural history of the disease in Tennessee children. *Clin Pediatr (Phila)* 71;10(12):697-700 **Not relevant to key questions**
- Dive C, Evans C A, Owen P J et al. Abelson tyrosine kinase activation suppresses apoptosis in haemopoietic cells deprived of interleukin 3 (IL-3) or treated with hydroxyurea. *LEUKEMIA* 93;7(5):775 **Not relevant to key questions, Invitro only**
- Dohrenwend A, Sehgal R. Lost between the cracks: pain patients denied inpatient treatment for illicit drug addiction. *Psychosom Med* 2005;67(4):677-8 **No Original Data**
- Donovan P B, Berk P D, Goldberg J D. Hydroxyurea, an effective agent for the treatment of polycythemia vera. *CLIN. RES.* 82;30(2):315A **Not relevant to key questions**, other
- Dorsey C J, Murdaugh C L. The theory of self-care management for vulnerable populations. *Journal of Theory Construction & Testing* 2003;7(2):43 **Not relevant to key questions, No Original Data**
- Doswell W M. Sickle cell anemia: you can do something to help. *Nursing* 78;8(4):65, 67-8, 70 **No Original Data**
- Dover G J, Charache S, Boyer S H. Increasing fetal hemoglobin in sickle cell disease: comparisons of 5-azacytidine (subcutaneous or oral) with hydroxyurea. *Trans Assoc Am Physicians* 84;97140-5 **Not relevant to key questions, other, study size too small**
- Dover G J, Charache S, Nora R et al. Progress toward increasing fetal hemoglobin production in man: experience with 5-azacytidine and hydroxyurea. *Ann N Y Acad Sci* 85;445218-24 **No Original Data**
- Dover G J, Charache S. The effect of increased fetal hemoglobin production on the frequency of vaso-occlusive crisis in sickle cell disease. *Prog Clin Biol Res* 87;240277-85 **Study size too small**
- Dover G J, Humphries R K, Moore J G et al. Hydroxyurea induction of hemoglobin F production in sickle cell disease: relationship between cytotoxicity and F cell production. *Blood* 86;67(3):735-8 **Study size too small**
- Dowling M D, Haghbin M, Gee T S et al. Comparative results obtained in the treatment of acute leukemia. *Recent Results Cancer Res* 73;43133-44 **Not relevant to key questions**
- Driscoll M C, Lerner N, Anyane-Yeboah K. Prenatal diagnosis of sickle hemoglobinopathies: The experience of the Columbia University Comprehensive Center for Sickle Cell Diseases. *AM. J. HUM. GENET.* 87;40(6):548-558 **Not relevant to key questions**

- D'Sa S, Parker N, Ware M A et al. Fast track admission for children with sickle cell crises. Opiates other than pethidine are better (multiple letters) +AFs-2+AF0-. Br. Med. J. 98;316(7135):+AFs-d+AF0-934, 935 **No Original Data**
- Duckett C L. Caring for children with sickle cell anemia. Children 71;18(6):227-31 **No Original Data**
- Dukes-Hamilton C S. Antiretroviral Activity Of Hydroxyurea Alone And In Combination With Ddi. **Not relevant to key questions**
- Dula A. African American suspicion of the healthcare system is justified: what do we do about it?. Camb Q Healthc Ethics 94;3(3):347-57 **Not relevant to key questions, No Original Data**
- Dumaplin C A. Pediatric pharmacology. Avoiding admission for afebrile pediatric sickle cell pain: pain management methods. Journal of Pediatric Healthcare 2006;20(2):115 **No Original Data**
- Elander J, Lusher J, Bevan D et al. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesic dependence. J Pain Symptom Manage 2004;27(2):156-69 **Not relevant to key questions**
- Embury S H. New treatments of sickle cell disease. West J Med 96;164(5):444 **No Original Data**
- Feldman L, Allen S, Westerman M et al. Long-term use of hydroxyurea for sickle cell anemia. JAMA 2003;290(6):752-3; author reply 754 **No Original Data**
- Fielding J, Batalden P, Tolbert G et al. A coordinated sickle cell program for economically disadvantaged adolescents. Am J Public Health 74;64(5):427-32 **Not relevant to key questions**
- Finazzi G, Ruggeri M, Rodeghiero F et al. Efficacy and safety of long-term use of hydroxyurea in young patients with essential thrombocythemia and a high risk of thrombosis [1]. Blood 2003;101(9):3749 **Not relevant to key questions, No Original Data**
- Finch S C. Sickle cell survey. Conn Med 73;37(9):460-1 **Not relevant to key questions, No Original Data**
- First reports of adverse drug reactions (ADRs) in recent weeks. Drugs Ther. Perspect. 2001;17(4):15 **Not relevant to key questions, No Original Data**
- Fithian J H. Sickle cell disease education at the Children's Hospital of Philadelphia. J Sch Health 92;62(8):388-91 **Not relevant to key questions**
- Flanagan C. Home management of sickle cell anemia.. Pediatr Nurs 80;6(2):A-D **Not relevant to key questions, No Original Data**
- Fletcher C. Appraisal and coping with vaso-occlusive crisis in adolescents with sickle cell disease. Pediatr Nurs 2000;26(3):319-24 **Not relevant to key questions**
- Flexner C W. Trial Of Hydroxyurea In Combo With Antivirals In Hiv. **Not relevant to key questions**
- Flexner C, Bartlett J G. Complications of HIV therapy. Hopkins HIV **No Original Data**
- Flores F, Eaglstein W A, Kirsner R S. Hydroxyurea-induced leg ulcers treated with Apligraf [4]. Ann. Intern. Med. 2000;132(5):417 **Not relevant to key questions**
- 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**
- Foli A, Lori F, Maserati R et al. Hydroxyurea and didanosine is a more potent combination than hydroxyurea and zidovudine. Antivir Ther 97;2(1):31-8 **Study size too small, other**
- Forbes K, Forbes B, Lee A. Re: Sickle cell-related pain: Perceptions of medical practitioners +AFs-2+AF0-. J. Pain Symptom Manage. 98;15(6):333 **No Original Data**
- Fost N. Ethical problems in pediatrics. Curr Probl Pediatr 76;6(12):1-31 **Not relevant to key questions, No Original Data**
- Fowler M G, Whitt J K, Lallinger R R et al. Neuropsychologic and academic functioning of children with sickle cell anemia. J. Dev. Behav. Pediatr. 88;9(4):213-220 **Not relevant to key questions**
- France-Dawson M. Sickle cell conditions and health knowledge. Nurs Stand 90;4(35):30-4 **No Original Data**
- Fred H L. Cause or coincidence?. South Med J 92;85(9):923 **Not relevant to key questions**
- Frenkel E P, Skinner W N, Smiley J D. Studies On A Metabolic Defect Induced By Hydroxyurea (Nsc-32065). Cancer Chemother Rep **In vitro only**
- Frequency of sickle cell crises cut by hydroxyurea use. Am J Health Syst Pharm 95;52(8):778 **No Original Data**
- Friedman S A. The diagnosis and medical management of vascular ulcers. Clin. Dermatol. 90;8(3-4):30-39 **No Original Data**
- Fucharoen S, Siritanaratkul N, Winichagoon P et al. Hydroxyurea increases hemoglobin F levels and improves the effectiveness of erythropoiesis in beta-thalassemia/hemoglobin E disease. Blood 96;87(3):887-92 **Not relevant to key questions**
- Fuggle P, Shand P A, Gill L J et al. Pain, quality of life, and coping in sickle cell disease. Arch Dis Child 96;75(3):199-203 **Not relevant to key questions**

- Fuller J, Davis P, Dancer J et al. Comparison of attitudes about communication in children and adolescents with sickle cell disease. *Percept Mot Skills* 98;87(2):634 **Not relevant to key questions**
- Gale R P, Hehlmann R, Zhang M J et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. The German CML Study Group. *Blood* 98;91(5):1810-9 **Not relevant to key questions**
- Galesic K, Bozic B, Racic I et al. Thrombotic microangiopathy associated with alpha-interferon therapy for chronic myeloid leukaemia. *Nephrology (Carlton)* 2006;11(1):49-52 **Not relevant to key questions**
- Galton D A. Chemotherapy of chronic myelocytic leukemia. *Semin Hematol* **No Original Data**
- Gamberini M R, Fortini M, De Sanctis V. Healing of leg ulcers with hydroxyurea in thalassaemia intermedia patients with associated endocrine complications. *Pediatr Endocrinol Rev* 2004;2 Suppl 2319-22 **Not relevant to key questions**
- Gambero S, Canalli A A, Traina F et al. Therapy with hydroxyurea is associated with reduced adhesion molecule gene and protein expression in sickle red cells with a concomitant reduction in adhesive properties. *Eur J Haematol* 2007;78(2):144-51 **Study size too small**
- Gandhi V, Plunkett W, Kantarjian H et al. Cellular pharmacodynamics and plasma pharmacokinetics of parenterally infused hydroxyurea during a phase I clinical trial in chronic myelogenous leukemia. *J Clin Oncol* 98;16(7):2321-31 **Not relevant to key questions**
- García a F, Plana M, Arnedo M et al. A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* **Study size too small**
- Gartstein M A, Short A D, Vannatta K et al. Psychosocial adjustment of children with chronic illness: an evaluation of three models. *J Dev Behav Pediatr* 99;20(3):157-63 **Not relevant to key questions**
- Gary L E. The sickle cell controversy. *Soc Work* 74;19(3):263-72 **No Original Data**
- Geddes E W, Falkson G. Malignant hepatoma in the Bantu. *Cancer* 70;25(6):1271-8 **Study size too small**
- Gentry B F, Dancer J. Public school speech-language pathologists' knowledge of sickle cell disease. *Percept Mot Skills* 98;86(3 Pt 1):1034 **Not relevant to key questions**
- Gentry B, Goodwin A, Dancer J. Knowledge of sickle cell disease among specialists in communicative disorders in medical settings. *Percept Mot Skills* 97;85(3 Pt 2):1394 **Not relevant to key questions**
- Gil K M, Anthony K K, Carson J W et al. Daily coping practice predicts treatment effects in children with sickle cell disease. *J Pediatr Psychol* 2001;26(3):163-73 **Not relevant to key questions**
- Gil K M, Carson J W, Porter L S et al. Daily stress and mood and their association with pain, health-care use, and school activity in adolescents with sickle cell disease. *J Pediatr Psychol* 2003;28(5):363-73 **Not relevant to key questions**
- Gil K M, Phillips G, Abrams M R et al. Pain drawings and sickle cell disease pain. *Clin J Pain* 90;6(2):105-9 **Not relevant to key questions**
- Gil K M, Thompson R J, Keith B R et al. Sickle cell disease pain in children and adolescents: change in pain frequency and coping strategies over time. *J Pediatr Psychol* 93;18(5):621-37 **Not relevant to key questions**
- Gil K M, Wilson J J, Edens J L et al. Effects of cognitive coping skills training on coping strategies and experimental pain sensitivity in African American adults with sickle cell disease. *Health Psychol* 96;15(1):3-10 **Not relevant to key questions**
- Gill F M, Brown A, Gallagher D et al. Newborn experience in the Cooperative Study of Sickle Cell Disease. *Pediatrics* 89;83(5 Pt 2):827-9 **Not relevant to key questions**
- Gill L J, Shand P A X, Fuggle P et al. Pain assessment for children with sickle cell disease: Improved validity of diary keeping versus interview ratings. *BR. J. HEALTH PSYCHOL.* 97;2(2):131-140 **Not relevant to key questions**
- Giordano P C, Bouva M J, Hartevelde C L. A confidential inquiry estimating the number of patients affected with sickle cell disease and thalassemia major confirms the need for a prevention strategy in the Netherlands. *Hemoglobin* 2004;28(4):287-96 **Not relevant to key questions**
- Gladwin M T, Rodgers G P. Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia. *Lancet* 2000;355(9214):1476-8 **No Original Data**
- Gladwin M T, Shelhamer J H, Ognibene F P et al. Nitric oxide donor properties of hydroxyurea in patients with sickle cell disease. *Br J Haematol* 2002;116(2):436-44 **Study size too small**
- Glover R E, Ivy E D, Orringer E P et al. Detection of nitrosyl hemoglobin in venous blood in the treatment of sickle cell anemia with hydroxyurea. *Mol Pharmacol* 99;55(6):1006-10 **Study size too small**
- Golden W E, Moore G. Sickle cell syndromes: misdiagnosis can affect treatment. *J Ark Med Soc* 2004;101(5):144-5 **Not relevant to key questions**
- Goldin A, Venditti J M, Mead J A Et Al. Antileukemic Activity Of Hydroxyurea (Nsc-32065) And Other Urea Derivatives. *Cancer* **Other**

- Gortner C. Hydroxyurea. BETA 98;7 **No Original Data**
- Gottlieb J A, Frei E, 3rd Luce J K. Dose-schedule studies with hydroxyurea (NSC-32065) in malignant melanoma. *Cancer Chemother Rep* 71;55(3):277-80 **Study size too small, Not relevant to key questions**
- Gramvussakis S, George S A. Chronic actinic dermatitis (photosensitivity dermatitis/actinic reticuloid syndrome): Beneficial effect from hydroxyurea [17]. *Br. J. Dermatol.* 2000;143(6):1340 **Not relevant to key questions**
- Granel B, Serratrice J, Bouabdallah R et al. Atypical porphyria cutanea tarda in a patient with chronic myelogenous leukemia [2]. *Dermatology* 2001;203(1):82-83 **Not relevant to key questions**
- Green B T, Branch M S. Ischemic colitis in a young adult during sickle cell crisis: Case report and review. *Gastrointest. Endosc.* 2003;57(4):605-607 **Study size too small, Not relevant to key questions**
- Griesshammer M, Arnold R, Bangerter M et al. Chronic myeloid leukemia in accelerated phase: treatment results with conventional chemotherapy and allogeneic bone marrow transplantation in 96 patients. *Eur J Haematol* 98;61(1):7-13 **Not relevant to key questions**
- Griffith K M. Hydroxyurea (Nsc-32065): Results Of A Phase I Study. *Cancer Chemother* **Not relevant to key questions, other**
- Grund F M, Armitage J O, Burns P. Hydroxyurea in the prevention of the effects of leukostasis in acute leukemia. *Arch Intern Med* 77;137(9):1246-7 **Not relevant to key questions, study size too small**
- Grunke M, Dechant C, Lö w P et al. Hydroxyurea as part of a salvage regimen for heavily pretreated patients with advanced HIV infection. *J Acquir Immune Defic Syndr* **Not relevant to key questions, study size too small**
- Guarini L, Piomelli S, Poh-Fitzpatrick M B. Hydroxyurea in congenital erythropoietic porphyria [7]. *NEW Engl. J. Med.* 94;330(15):1091-1092 **Not relevant to key questions**
- Guilhot F, Lamagnere J P, Harousseau J L et al. A multicentre study of a randomized therapeutic protocol in previously untreated patients with Ph-positive chronic myelogenous leukaemia: interferon alfa-2b and hydroxyurea with or without cytosine arabinoside , preliminary results. *Eur J Cancer* 91;27 Suppl 4S26 **Not relevant to key questions**
- Gulati S C, Vega R, Gee T. Growth and development of children born to patients after cancer therapy. *Cancer Invest.* 86;4(3):197-205 **Not relevant to key questions**
- Gullattee A C. Medico-legal insurance implications of sickle cell anemia. *J Natl Med Assoc* 73;65(5):415-9 **No Original Data**
- Gupta P. Bone marrow transplantation for sickle cell anemia: is it the right choice?. *Indian Pediatr* 97;34(5):460-2 **Not relevant to key questions**
- Guthrie T. Hydroxyurea for sickle cell. *P T* 95;20(7):497-498 **No Original Data**
- Hagar W. Long-term use of hydroxyurea for sickle cell anemia. *JAMA* 2003;290(6):753; author reply 754 **No Original Data**
- Hampton M L, Anderson J, Lavizzo B S et al. Sickle cell "nondisease". A potentially serious public health problem. *Am J Dis Child* 74;128(1):58-61 **Not relevant to key questions**
- Handa H, Akiba T, Yoshida Y et al. Development of bilateral malleolus skin ulcers during hydroxyurea treatment in an elderly patient with chronic myelogenous leukemia. *Kitakanto Med. J.* 98;48(2):167-169 **Other**
- Harrington P, Clarke S, Ryan M et al. Efficacy and tolerability of didanosine-hydroxyurea containing regimens in a cohort of heavily antiretroviral experienced patients. **Not relevant to key questions**
- Harris M S. Genetic disease programs and the black community. *Urban Health* 79;8(8):40, 42-3, 54 **No Original Data**
- Harrison P V. Drugs and side-effects. *Clin. Exp. Dermatol.* 90;15(1):77-78 **Not relevant to key questions, other**
- Hassan A, Jam'a A, Al Dabbous I A. Hydroxyurea in the treatment of sickle cell associated priapism. *J. Urol.* 98;159(5):1642 **Study size too small**
- Hassan H T, Zyada L E. Treatment with recombinant human interferon alpha plus low dose cytarabine with or without hydroxyurea for acute monoblastic leukaemia. *Hematol. Rev. Commun.* 93;7(3):125-131 **Not relevant to key questions, study size too small**
- Hawkins M R, Diehl-Svrjcek B, Dunbar L J. Caring for children with special healthcare needs in the managed care environment. *Lippincotts Case Manag* 2006;11(4):216-23 **Not relevant to key questions**
- Hazzard A, Celano M, Collins M et al. Effects of STARBRIGHT World on knowledge, social support, and coping in hospitalized children with sickle cell disease and asthma. *Child. Health Care* 2002;31(1):69-86 **Not relevant to key questions**
- Hehlmann R, Anger B, Messerer D et al. Randomized study on the treatment of chronic myeloid leukemia (CML) in chronic phase with busulfan versus hydroxyurea versus interferon-alpha. *Blut* 88;56(2):87-91 **Not relevant to key questions**
- Hehlmann R, Berger U, Pfirrmann M et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. *Blood* 2007;109(11):4686-4692 **Not relevant to key questions**

- Hehlmann R, Heimpel H, Griesshammer M et al. Chronic myelogenous leukemia: recent developments in prognostic evaluation and chemotherapy. The German CML Study Group. *Leukemia* 92;6 Suppl 3110S-114S **Not relevant to key questions, No Original Data**
- 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**
- Hehlmann R, Heimpel H, Hasford J. Randomized comparison of interferon-(alpha), hydroxyurea, and busulfan in chronic myeloid leukemia: Response to Kantarjian and Talpaz and to Tura and Baccarani [7]. *BLOOD* 95;85(10):3000-3002 **Not relevant to key questions, No Original Data**
- Hehlmann R, Heimpel H, Hossfeld D K et al. Randomized study of the combination of hydroxyurea and interferon alpha versus hydroxyurea monotherapy during the chronic phase of chronic myelogenous leukemia (CML Study II). *Bone Marrow Transplant.* 96;17(SUPPL. 3):S21-S24 **Not relevant to key questions, other**
- Hehlmann R, Heimpel H, Kolb H J et al. The German CML study, comparison of busulfan vs. hydroxyurea vs. interferon alpha and establishment of prognostic score 1. *Leuk Lymphoma* 93;11 Suppl 1159-68 **Other**
- Heimler A, Chabot A. Sick cell counseling in a children and youth project. *Am J Public Health* 74;64(10):995-7 **Not relevant to key questions**
- Heller P, Kombliht L I, Cuello M T et al. BCR-ABL transcripts may be detected in essential thrombocythemia but lack clinical significance [5]. *Blood* 2001;98(6):1990 **Not relevant to key questions**
- Hellmann K. Investigational drugs for the treatment of malignant melanoma. *Proc R Soc Med* 74;67(2):100-1 **Not relevant to key questions**
- Helton K J, Wang W C, Wynn L W et al. The effect of hydroxyurea on vasculopathy in a child with sickle cell disease. *AJNR Am J Neuroradiol* 2002;23(10):1692-6 **Study size too small**
- Hendrickse R G, Barnes P M. Sick cell anaemia: report of a therapeutic trial. *West Afr Med J* 66;15(2):55-64 **Not relevant to key questions**
- 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**
- Hernandez J M, Orfao A, Gonzalez M et al. Immunophenotypic characterisation of acute leukaemia after polycythemia vera. *J Clin Pathol* 93;46(7):668-71 **Not relevant to key questions**
- Herron S, Bacak S J, King A et al. Inadequate recognition of education resources required for high-risk students with sickle cell disease. *Arch Pediatr Adolesc Med* 2003;157(1):104 **Not relevant to key questions**
- Hilbe W, Apfelbeck U, Fridrik M et al. Interferon-alpha for the treatment of elderly patients with chronic myeloid leukaemia. *Leuk Res* 98;22(10):881-6 **Not relevant to key questions, No Original Data**
- Ho P T C, Murgo A J, Silver R T et al. Hydroxyurea and sickle cell crisis [2]. *NEW ENGL. J. MED.* 95;333(15):1008-1009 **Not Original Data**
- Ho P T, Murgo A J. Hydroxyurea and sickle cell crisis. *N Engl J Med* 95;333(15):1008; author reply 1009 **No Original Data**
- Hobbs J R, Obaro S K. Bone marrow transplantation in sickle cell disease. *Lancet* 93;342(8883):1362-3 **No Original Data**
- Hofmann M, de Montalembert M, Beauquier-Maccotta B et al. Posttraumatic stress disorder in children affected by sickle-cell disease and their parents. *Am J Hematol* 2007;82(2):171-2 **Not relevant to key questions**
- Holtzman N A. The impact of the federal cutback on genetic services. *Am J Med Genet* 83;15(2):353-71 **Not relevant to key questions, No Original Data**
- Horan J, Lerner N. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med* 2000;342(21):1612-3 **No Original Data**
- How safe is hydroxyurea in the treatment of polycythemia vera?. *Haematologica* 99;84(8):673-674 **Not relevant to key questions, No Original Data**
- Hsiao E, Charles R, Magid C et al. An unusual development. *Am J Med* 2005;118(6):609-11 **Not relevant to key questions**
- Hu Y H, Ruckenstein E. Tunable Delocalization of Unpaired Electrons of Nitroxide Radicals for Sickle-Cell Disease Drug Improvements. *J Phys Chem B* 2007; **Not relevant to key questions**
- Hubbard R. Transparent women, visible genes, and new conceptions of disease. *Camb Q Healthc Ethics* 95;4(3):291-5 **No Original Data**
- Huguley C M. Chronic myelocytic and chronic lymphocytic leukemia. *Cancer* 72;30(6):1583-7 **No Original Data, other**
- Hurtig A L, Koepke D, Park K B. Relation between severity of chronic illness and adjustment in children and adolescents with sickle cell disease.. *J Pediatr Psychol* 89;14(1):117-132 **Not relevant to key questions**
- Huynh T H, Johnson M W, Hackel R E. Bilateral proliferative retinopathy in chronic myelogenous leukemia. *Retina* 2007;27(1):124-125 **Not relevant to key questions**
- 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**

- Hydroxyurea (Droxia/Hydrea/Mylocel). *Clinical Journal of Oncology Nursing* 2003;7(6):57 **No Original Data**
- Hydroxyurea 100 mg/mL. *Int. J. Pharm. Compd.* 2006;10(5):384 **Not relevant to key questions, No Original Data**
- Hydroxyurea combinations. *AIDS Patient Care* 95;9(2):87 **No Original Data**
- Hydroxyurea in HIV therapy. *HIV Hotline* **No Original Data**
- Hydroxyurea marketed for sickle cell anemia. *Am J Health Syst Pharm* 98;55(9):875 **No Original Data**
- Hydroxyurea under study. *Posit Aware* 95;5 **No Original Data**
- Hydroxyurea vs anagrelide. *Pharm. J.* 2005;275(7357):38 **No Original Data**
- Hydroxyurea: what it is. *New Mexico AIDS InfoNet. Newline People AIDS Coalit N Y* 98;15 **No Original Data**
- In re Cabrera. *Atl Report* 89;5521114-21 **Not relevant to key questions**
- Jackson R E, Short B J. Frequency and prognosis of coexisting sickle cell disease and acute leukemia in children. *Clin Pediatr (Phila)* 72;11(3):183-5 **Not relevant to key questions**
- Jacobs P, le Roux I, Jacobs L. Megakaryoblastic transformation in myeloproliferative disorders. *Cancer* 84;54(2):297-302 **Not relevant to key questions**
- 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**
- Johnson C S. An Alternative Approach To Hydroxyurea Therapy In Sickle Cell Disease. **Not relevant to key questions**
- 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, Yarbrow 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**
- Kirby B, Rogers S, Pittelkow M R et al. Hydroxyurea-induced dermatopathy: A unique lichenoid eruption complicating long-term therapy with hydroxyurea [2] (multiple letters). *J. Am. Acad. Dermatol.* 98;38(5 1):781-782 **Not relevant to key questions, No Original Data**
- Kirby B, Rogers S. Hydroxyurea-induced dermatopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 98;38(5 Pt 1):781-2 **No Original Data**
- 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 (Biosuppressin-BIOGAL) for the treatment of chronic myelogenous leukaemia. *Ther Hung* 81;29(1):38-41 **Study size too small**
- Kliwer 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**
- Kluin-Nelemans J C, Delannoy A, Louwagie A et al. Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-(alpha)2b for chronic myeloid leukemia. *Blood* 98;91(8):2713-2721 **Not relevant to key questions**
- 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, Yarbrow 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**
- Konotey-Ahulu F I D. Sickle-cell disease and the patient [3]. *Lancet* 2005;365(9457):382-383 **No Original Data**
- Konotey-Ahulu F I. Management of patients with sickle-cell disease. *Lancet* 72;2(7780):772 **No Original Data**
- Koontz K, Short A D, Kalinyak K et al. A randomized, controlled pilot trial of a school intervention for children with sickle cell anemia. *J Pediatr Psychol* 2004;29(1):7-17 **Not relevant to key questions**
- Koren A, Segal-Kupershmit D, Zalman L et al. Effect of hydroxyurea in sickle cell anemia: a clinical trial in children and teenagers with severe sickle cell anemia and sickle cell beta-thalassemia. *Pediatr Hematol Oncol* 99;16(3):221-32 **Study size too small**
- 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**
- Kramer K D, Nash K B. The sickle cell mutual assistance movement. *J Health Soc Policy* 94;5(3-4):203-14 **Not relevant to key questions**
- 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**
- Kunitz S J. Some notes on physiologic conditions as social problems. *Soc Sci Med* 74;8(4):207-11 **No Original Data**
- 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**
- Lee D A, Mueller B U. Long-term use of hydroxyurea for sickle cell anemia. *JAMA* 2003;290(6):753-4; author reply 754 **No Original Data**
- Lee E J, Phoenix D, Brown W et al. Sickle cell disease: problem solving/coping methods among affected children and their non-affected siblings. *J Sch Nurs* 98;14(5):24-8 **Not relevant to key questions**
- Lee E J, Phoenix D, Jackson B S et al. The role of family: perceptions of children with sickle cell. *J Natl Black Nurses Assoc* 99;10(2):37-45 **Not relevant to key questions**
- Lee M T, Piomelli S, Granger S et al. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. *Blood* 2006;108(3):847-52 **Not relevant to key questions**
- Leonardi V, Meli M, Palmeri S. Hydroxyurea as a modulator of multidrug resistance in resistant solid tumor: A pilot study. *Oncol. Rep.* 97;4(4):723-727 **Not relevant to key questions**
- Lerner H J, Beckloff G L, Godwin M C. Hydroxyurea (NSC-32065) intermittent therapy in malignant diseases. *Cancer Chemother Rep* 69;53(6):385-95 **Study size too small**
- Lerner H J, Beckloff G L, Godwin M C. Phase II study of hydroxyurea administered intermittently in malignant melanoma. *Am Surg* 70;36(8):505-8 **Study size too small**
- Levantine A, Almeyda J. Drug reactions. XXIV. Cutaneous reactions to cytostatic agents. *Br J Dermatol* **No Original Data**
- Levy J C, Strong R M, Browne C et al. An integrated system for health supervision. *Pediatr Clin North Am* 74;21(2):291-305 **Not relevant to key questions**
- Lima C S, Arruda V R, Costa F F et al. Minimal doses of hydroxyurea for sickle cell disease. *Braz J Med Biol Res* 97;30(8):933-40 **Study size too small**
- Lipshutz H, Lerner H J, Beckloff G L. Hydroxyurea in the management of head and neck cancer. II. Surgical aspects. *Plast Reconstr Surg* 67;40(3):240-2 **Not relevant to key questions**
- Listernick R. An 11-year-old boy with sickle cell disease and abdominal pain. *Pediatr. Ann.* 2005;34(9):673+677-679 **No Original Data**
- Little J A, McGowan V R, Kato G J et al. Combination erythropoietin-hydroxyurea therapy in sickle cell disease: experience from the National Institutes of Health and a literature review. *Haematologica* 2006;91(8):1076-83 **Not relevant to key questions, study size too small**
- Liu J, Al-Hothari M A, Mahboob F A. Non surgical treatment of recurrent or stuttering priapism in sickle cell children. *Saudi Med. J.* 2003;24(10):1143-1145 **No Original Data, study size too small**

- Lofvenberg E, Wahlin A, Roos G et al. Reversal of myelofibrosis by hydroxyurea. *EUR. J. HAEMATOL.* 90;44(1):33-38 **Not relevant to key questions**
- Lomen P L, Khilanani P, Kessel D. Phase I study using combination of hydroxyurea and 5-azacytidine (NSC-102816). *Neoplasma* 80;27(1):101-6 **Not relevant to key questions, study size too small**
- Long D L, Pierre R V. Autosomal monosomy mosaicism in human bone marrow aspirate. Report of a case. *Am J Clin Pathol* 68;50(4):482-4 **Not relevant to key questions**
- Longhurst H J, Pinching A J. Drug Points: pancreatitis associated with hydroxyurea in combination with didanosine. *BMJ* **Not relevant to key questions, other**
- Lori F, Foli A, Groff A et al. Optimal suppression of HIV replication by low-dose hydroxyurea through the combination of antiviral and cytostatic ('virostatic') mechanisms. *AIDS* 2005;19(11):1173-81 **Invitro only, No Original Data, other**
- Lori F, Pollard R B, Whitman L et al. Lowering the dose of hydroxyurea minimizes toxicity and maximizes anti-HIV potency. *AIDS Res Hum Retroviruses* 2005;21(4):263-72 **Not relevant to key questions, other**
- Losada R, Bravo I, Capildeo K et al. Is the group of older sickle cell disease patients from Trinidad and Tobago different? [3]. *Am. J. Hematol.* 2006;81(3):219-220 **Not relevant to key questions**
- Losada R, Bravo I, Capildeo K et al. Is the group of older sickle cell disease patients from Trinidad and Tobago different?. *Am J Hematol* 2006;81(3):219-20 **Not relevant to key questions**
- Louwagie A, Delannoy A, Kluin-Nelemans J C. Low-dose interferon-alpha 2b combined with hydroxyurea versus hydroxyurea alone for chronic myelogenous leukemia. *Bone Marrow Transplant.* 96;17(SUPPL. 3):S19-S20 **Not relevant to key questions**
- Loven D, Hardoff R, Sever Z B et al. Non-resectable slow-growing meningiomas treated by hydroxyurea. *J Neurooncol* 2004;67(1-2):221-6 **Study size too small**
- Low-dose interferon-alpha 2b combined with hydroxyurea versus hydroxyurea alone for chronic myelogenous leukemia. The Benelux CML Study Group. *Bone Marrow Transplant* 96;17 Suppl 3S19-20 **Not relevant to key questions**
- Lu C M, Wang E, Lawrence H J. Simultaneous presence of major secondary chromosomal abnormalities in blast crisis of chronic myeloid leukemia. *Cancer Genet. Cytogenet.* 2007;172(2):174-175 **Not relevant to key questions**
- Lucas G J, Lehrnbecher W. Hydroxyurea in nasopharyngeal cancer. *JAMA* 69;210(13):2397 **Not relevant to key questions**
- Luce J K. Chemotherapy of melanoma. *Semin Oncol* 75;2(2):179-85 **No Original Data**
- Lusher J M, Sarnalk S. Hematology. *J. Am. Med. Assoc.* 96;275(23):1814-1815 **No Original Data**
- Lusher J, Elander J, Bevan D et al. Analgesic addiction and pseudoaddiction in painful chronic illness. *Clin J Pain* 2006;22(3):316-24 **Not relevant to key questions**
- Lutz M J, Barakat L P, Smith-Whitley K et al. Psychological adjustment of children with sickle cell disease: Family functioning and coping. *Rehabil. Psychol.* 2004;49(3):224-232 **Not relevant to key questions**
- Luzzati R, Di Perri G, Fendt D et al. Pharmacokinetics, safety and anti-human immunodeficiency virus (HIV) activity of hydroxyurea in combination with didanosine [11]. *J. Antimicrob. Chemother.* 98;42(4):565-566 **Not relevant to key questions, study size too small**
- Luzzati R, Di Perri G, Fendt D et al. Pharmacokinetics, safety and anti-human immunodeficiency virus (HIV) activity of hydroxyurea in combination with didanosine. *J Antimicrob Chemother* 98;42(4):565-6 **Not relevant to key questions, study size too small**
- Luzzato L. Services for people with haemoglobinopathy [20]. *BR. MED. J.* 94;308(6945):1714 **No Original Data**
- Magee C C, Abraham K, Farrell J et al. Renal thrombotic microangiopathy associated with interferon-alpha treatment of chronic myeloid leukemia. *Am J Kidney Dis* 2000;36(1):E5 **Not relevant to key questions**
- Maggio A, Rigano P, D'Amico G et al. Treatment with hydroxyurea and iron chelation therapy in patients with hemoglobinopathies. *Eur. J. Haematol.* 2005;75(3):267-269 **Not relevant to key questions, study size too small**
- Makis A C, Hatzimichael E C, Kolios G et al. Circulating endothelin-3 levels in patients with sickle cell disease during hydroxyurea treatment. *Haematologica* 2004;89(3):360-1 **Not relevant to key questions, study size too small**
- Malhotra U, Bosch R J, Wang R et al. Effect of adjunct hydroxyurea on helper T cell immunity in HIV type 1-infected patients with virological suppression. *AIDS Res Hum Retroviruses* 2004;20(8):807-12 **Not relevant to key questions, study size too small**
- Maloisel F, Uettwiller F, Laplace A et al. Emergence of unusual cytogenetic abnormalities under interferon-alpha therapy in patients with chronic myelogenous leukemia. *Cancer Genet Cytogenet* 99;113(2):172-6 **Not relevant to key questions, study size too small**
- Mammen E F. Part 2: Essential thrombocythemia and polycythemia vera. *Semin. Thromb. Hemost.* 2006;32(4):305-306 **No Original Data**
- Manley A F. Legislation and funding for sickle cell services, 1972-1982. *Am J Pediatr Hematol Oncol* 84;6(1):67-71 **Not relevant to key questions, No Original Data**

- Marsh J C W, Bevan D H. Haematological care of the Jehovah's witness patient. *Br. J. Haematol.* 2002;119(1):25-37 **No Original Data**
- Martel-Pelletier J, Pelletier J-P. Degradative changes in human articular cartilage induced by chemotherapeutic agents. *J. RHEUMATOL.* 86;13(1):164-174 **Not relevant to key questions**
- Marwick C. Sickle cell problems continue to challenge medical science, but some progress is noted. *JAMA* 90;263(4):490, 493 **No Original Data**
- Maserati R. Hydroxyurea in the treatment of HIV-1 infection: Toxicity and side effects. *J. Biol. Regul. Homeostatic Agents* 99;13(3):181-185 **No Original Data**
- Maunoury C, Acar P, De Montalembert M et al. Myocardial perfusion in children with sickle cell disease. *Am. J. Cardiol.* 2003;91(3):374-376 **Not relevant to key questions**
- Maxwell K, Streetly A, Oni L. Fair shares for London. *Mod Midwife* 97;7(11):15-9 **Not relevant to key questions**
- Maxwell K, Streetly A. Living with sickle cell pain. *Nurs Stand* 98;13(9):33 **No Original Data**
- Mayer M L, Konrad T R, Dvorak C C. Hospital resource utilization among patients with sickle cell disease. *J Health Care Poor Underserved* 2003;14(1):122-35 **Not relevant to key questions**
- McCabe E R B, Patterson P J, Botsonis H et al. Genetic services for underserved populations. C. Finance/insurance issues: A study of medical costs associated with selected genetic disorders in Texas. *Birth Defects Orig. Artic. Ser.* 90;26(2):132-138 **Not relevant to key questions**
- McCabe M G, Broadbent V, Williams D M. Unusual cause of extradural haemorrhage. *Med. Pediatr. Oncol.* 2001;36(6):654-656 **Not relevant to key questions**
- McClain B C, Kain Z N. Pediatric palliative care: a novel approach to children with sickle cell disease. *Pediatrics* 2007;119(3):612-4 **No Original Data**
- McDonald C J. Chemotherapy of psoriasis. *Int J Dermatol* **No Original Data**
- McDonald C J. The uses of systemic chemotherapeutic agents in psoriasis. *Pharmacol* **No Original Data**
- McMahon C, Callaghan C O, O'Brien D et al. The increasing prevalence of childhood sickle-cell disease in Ireland. *Ir J Med Sci* 2001;170(3):183-5 **Not relevant to key questions**
- McMeekin T O, Moschella S L. Iatrogenic complications of dermatologic therapy. *Primum non nocere. Med Clin North Am* **No Original Data**
- McMullin M F, Bareford D, Campbell P et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br. J. Haematol.* 2005;130(2):174-195 **No Original Data**
- McNamara J J. Planning for the economic and career impact of a sickle cell anemia program. *Health Serv Rep* 74;89(3):283-5 **Not relevant to key questions, No Original Data**
- Mehta J, Powles R, Singhal S et al. High-dose hydroxyurea and G-CSF to collect Philadelphia-negative cells in chronic myeloid leukemia: preliminary results. *Leuk Lymphoma* 96;23(1-2):107-11 **Study size too small**
- Mehta J, Singhal S, Mehta B C. Prognosis and therapy in chronic myeloid leukaemia. *J Assoc Physicians India* 92;40(2):130-1 **No Original Data**
- Merlat A, Lai J L, Sterkers Y et al. Therapy-related myelodysplastic syndrome and acute myeloid leukemia with 17p deletion. A report on 25 cases. *Leukemia* 99;13(2):250-7 **Not relevant to key questions, study size too small**
- Merz B. Promising drug combination for sickle cell anemia. *JAMA* 89;261(21):3069 **No Original Data**
- Midence K, McManus C, Fuggle P et al. Psychological adjustment and family functioning in a group of British children with sickle cell disease: preliminary empirical findings and a meta-analysis. *Br J Clin Psychol* 96;35 (Pt 3)439-50 **Not relevant to key questions**
- Mitka M. Seeking a way to alleviate sickle cell disease. *JAMA* 2002;288(16):1970 **No Original Data**
- Moertel C G, Reitemeier R J, Hahn R G. Evaluation of hydroxyurea (NSC-32065) by parenteral infusion. *Cancer Chemother Rep* 65;4927-9 **Not relevant to key questions**
- Morgan M T. Don't blame the patients. *West J Med* 99;171(5-6):313-4 **No Original Data**
- Morison W L. Anti-viral treatment of warts. *Br J Dermatol* 75;92(1):97-9 **Not relevant to key questions**
- Morra E, Alimena G, Lazzarino M et al. Evolving modalities of treatment with interferon alfa-2b for Ph1-positive chronic myelogenous leukaemia. *Eur J Cancer* 91;27 Suppl 4S14-7 **Not relevant to key questions**
- Morris C R, Vichinsky E P, van Warmerdam J et al. Hydroxyurea and arginine therapy: impact on nitric oxide production in sickle cell disease. *J Pediatr Hematol Oncol* 2003;25(8):629-34 **Study size too small**
- Morris K. Addressing the crisis of care for sickle-cell disease. *Lancet* 99;353(9163):1504 **No Original Data**
- Moskowitz J T, Butensky E, Harmatz P et al. Caregiving time in sickle cell disease: psychological effects in maternal caregivers. *Pediatr Blood Cancer* 2007;48(1):64-71 **Not relevant to key questions**

- Munoz A, Bureo E, Ortega J J et al. Treatment of Ph1-positive chronic myelogenous leukemia in children: comparison between allogeneic bone marrow transplantation and conventional chemotherapy. Spanish Working Party for BMT in Children (GETMON). *Haematologica* 98;83(11):981-4 **Not relevant to key questions, study size too small**
- Murphy M J. Hydroxyurea may enhance effectiveness of anti-HIV regimens presently in use. *Fac Notes (New Orleans La)* 98;10(2):1-2 **No Original Data**
- Murphy M L, Chaube S. Preliminary Survey Of Hydroxyurea (Nsc-32065) As A Teratogen. *Cancer Chemother Rep* **Invitro only, other**
- Naclerio A L, Gardner J W, Pollack M M. Socioeconomic factors and emergency pediatric ICU admissions. *Ann. New York Acad. Sci.* 99;896(-):379-382 **Not relevant to key questions**
- Nadel C, Portadin G. Sick cell crises: psychological factors associated with onset. *N Y State J Med* 77;77(7):1075-8 **Not relevant to key questions**
- Nagel R L. The dilemma of marrow transplantation in sickle cell anemia. *Semin Hematol* 91;28(3):233-4 **Not relevant to key questions, No Original Data**
- Nahavandi M, Wyche M Q, Perlin E et al. Nitric Oxide Metabolites in Sick Cell Anemia Patients after Oral Administration of Hydroxyurea; Hemoglobinopathy. *Hematol* 2000;5(4):335-339 **Study size too small**
- Najean Y, Dresch C, Rain J D. Chronic myelogenous leukemia and myeloproliferative syndromes: Intermediary analysis of a French protocol of treatment of polycythemia (1980-1990): 253 patients. *Nouv. Rev. Fr. Hematol.* 91;33(2):201-203 **Not relevant to key questions**
- Najean Y, Rain J-D. Treatment of polycythemia vera: Use of 32P alone or in combination with maintenance therapy using hydroxyurea in 461 patients greater than 65 years of age. *BLOOD* 97;89(7):2319-2327 **Not relevant to key questions**
- Nand S, Messmore H, Fisher S G et al. Leukemic transformation in polycythemia vera: analysis of risk factors. *Am J Hematol* 90;34(1):32-6 **Study size too small**
- Nanjangud G, Kadam P R, Saikia T et al. Karyotypic findings as an independent prognostic marker in chronic myeloid leukaemia blast crisis. *Leuk Res* 94;18(5):385-92 **Study size too small**
- Napolez A. Narcotic dependency in the sickle cell population [12]. *Am. J. Emerg. Med.* 2001;19(4):329 **No Original Data**
- Natarajan S, Williamson D, Grey J et al. Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. *J Dermatolog Treat* 2001;12(1):33-6 **Not relevant to key questions**
- Nathan D G. Regulation of fetal hemoglobin synthesis in the hemoglobinopathies. *Ann N Y Acad Sci* 85;445177-87 **No Original Data**
- Neinstein Ls, Katz B. Patients with hematologic disorders need careful birth control counseling. *Contracept Technol Update* 85;6(3):43-6 **No Original Data**
- Nevinny H B, Hall T C. Chemotherapy with hydroxyurea (NSC-32065) in renal cell carcinoma. *J Clin Pharmacol J New Drugs* 68;8(6):352-9 **Study size too small**
- Newman E M, Carroll M, Akman S A et al. Pharmacokinetics and toxicity of 120-hour continuous-infusion hydroxyurea in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 97;39(3):254-8 **Not relevant to key questions, study size too small**
- Newton H B, Slivka M A, Stevens C. Hydroxyurea chemotherapy for unresectable or residual meningioma. *J Neurooncol* 2000;49(2):165-70 **Study size too small**
- Nienhuis A W, Ley T J, Humphries R K. Pharmacological manipulation of fetal hemoglobin synthesis in patients with severe (beta)-thalassemia. *Ann. New York Acad. Sci.* 85;VOL. 445(-):198-211 **Not relevant to key questions**
- Nocentini G, Barzi A. Implications and problems in analysing cytotoxic activity of hydroxyurea in combination with a potential inhibitor of ribonucleotide reductase. *Pharmacol Res* **Invitro only**
- Noll R B, McKellop J M, Vannatta K et al. Child-rearing practices of primary caregivers of children with sickle cell disease: the perspective of professionals and caregivers. *J Pediatr Psychol* 98;23(2):131-40 **Not relevant to key questions**
- Noll R B, Ris M D, Davies W H et al. Social interactions between children with cancer or sickle cell disease and their peers: teacher ratings.. *J Dev Behav Pediatr* 92;13(3):187-193 **Not relevant to key questions**
- Nzewi E. Malevolent ogbanje: recurrent reincarnation or sickle cell disease?. *Soc Sci Med* 2001;52(9):1403-16 **Not relevant to key questions**
- Ohaeri J U, Shokunbi W A, Akinlade K S et al. The psychosocial problems of sickle cell disease sufferers and their methods of coping. *Soc Sci Med* 95;40(7):955-60 **Not relevant to key questions**
- Ohashi N, Yonemura K, Sugiura T et al. Withdrawal of interferon-alpha results in prompt resolution of thrombocytopenia and hemolysis but not renal failure in hemolytic uremic syndrome caused by interferon-alpha. *Am J Kidney Dis* 2003;41(3):E10 **Not relevant to key questions**
- Okpala I, Daniel Y, Haynes R et al. Relationship between the clinical manifestations of sickle cell disease and the expression of adhesion molecules on white blood cells. *Eur J Haematol* 2002;69(3):135-44 **Study size too small**
- Oliver T G, Glenn L, Anthony J L et al. The establishment of a sickle cell program in the college and community health setting. *J Am Coll Health* 86;34(6):290-1 **Not relevant to key questions, No Original Data**

- Olshaker J S, Barish R A, Naradzay J F X et al. Prescription noncompliance: Contribution to Emergency Department visits and cost. *J. Emerg. Med.* 99;17(5):909-912 **Study size too small**
- Olson V, Coyne P, Smith V et al. Critical pathway improves outcomes for patients with sickle-cell disease. *Oncol Nurs Forum* 97;24(10):1682 **Not relevant to key questions**, other
- Olujuhunge A, Cinkotai K I, Yardumian A. Hydroxyurea therapy for sickle cell disease in Britain. Disappointing recruitment despite promising results. *BMJ* 98;316(7146):1689 **No Original Data, Not relevant to key questions**
- O'Neil J A. Sharing care, grief, and next time. *J Pediatr Oncol Nurs* 95;12(3):146 **No Original Data**
- Orringer E. Efficacy Of Hydroxyurea As A Prophylactic Therapy For Sickle Cell. **Not relevant to key questions**
- Orringer E. Safety And Efficacy Of Hydroxyurea As A Prophylactic Therapy For Sickle Cell. **Not relevant to key questions**
- Othieno-Abinya N A, Nyabola L O, Kiarie G W et al. Chronic myeloid leukaemia at the Kenyatta National Hospital, Nairobi. *East Afr Med J* 2002;79(11):593-7 **Not relevant to key questions**, other
- Oyedeji G A. The effects of sickle cell disease on the families of affected children. *Cent Afr J Med* 95;41(10):333-4 **Not relevant to key questions**
- Palejwala A A, Hong L Y, King D. Managing patients with an absent or dysfunctional spleen. Under half of doctors know that antibiotic prophylaxis should be life long. *BMJ* 96;312(7042):1360; author reply 1361 **Not relevant to key questions, No Original Data**
- Palermo T M, Schwartz L, Drotar D et al. Parental report of health-related quality of life in children with sickle cell disease. *J Behav Med* 2002;25(3):269-83 **Not relevant to key questions**
- Papassotiriou I, Voskaridou E, Stamoulakatou A et al. Increased erythropoietin level induced by hydroxyurea treatment of sickle cell patients. *Hematol J* 2000;1(5):295-300 **Study size too small**
- Papineschi F, Carulli G, Petrini M. Pllicamycin-hydroxyurea association in chronic granulocytic leukemia and multidrug resistance. *Haematologica* 91;76(4):349 **Not relevant to key questions**
- Parker R, Lanvin D, Gilks B et al. Spontaneous regression of stage IV clear cell carcinoma of the endometrium in a patient with essential thrombocytosis. *Gynecol Oncol* 2001;82(2):395-9 **Not relevant to key questions**
- Parodi A, Alibrandi B, Rebora A. Dermatomyositis-like cutaneous lesions due to hydroxyurea. *G. ITAL. Dermatol. Venereol.* 92;127(7-8):361-362 **Not relevant to key questions**
- Parra Ruiz J, Callejas Rubio J L, Munoz Medina L et al. Dermatitis in a patient with chronic myeloid leukemia. *Rev. Clin. Esp.* 2002;202(4):235-236 **Other**
- Passamonti F, Pietra D, Rumi E et al. PRV-1 and its correlation with treatments and disease status in 210 patients with polycythemia vera and essential thrombocythemia +AFs-9+AF0-. *Leukemia* 2005;19(5):888-889 **Not relevant to key questions**
- Patel A B, Athavale A M. Sickle cell disease in central India. *Indian J Pediatr* 2004;71(9):789-93 **Not relevant to key questions**
- Patel A B, Pathan H G. Quality of life in children with sickle cell hemoglobinopathy. *Indian J Pediatr* 2005;72(7):567-71 **Not relevant to key questions**
- Pathophysiology and management of sickle cell pain crisis. Report of a Meeting of Physicians and Scientists, University of Texas Health Science Center at Houston, Texas. *Lancet* 95;346(8987):1408-11 **Study size too small**
- Paton N I, Aboulhab J. Hydroxychloroquine, hydroxyurea and didanosine as initial therapy for HIV-infected patients with low viral load: safety, efficacy and resistance profile after 144 weeks. *HIV Med* 2005;6(1):13-20 **Not relevant to key questions**
- Pavlidis N A. Cancer and pregnancy. *Ann. Oncol.* 2000;11(SUPPL. 3):247-253 **No Original Data**
- Paydas S, Zorludemir S, Sahin B. Vasculitis and leukemia. *Leuk Lymphoma* 2000;40(1-2):105-12 **Not relevant to key questions**
- Pearson H A, O'Brien R T, McIntosh S et al. Routine screening of umbilical cord blood for sickle cell diseases. *JAMA* 74;227(4):420-1 **Not relevant to key questions**
- Pearson T C, Green A R, Reilly J T et al. Leukemic transformation in polycythemia vera [1] (multiple letters). *Blood* 98;92(5):1837-1338 **No Original Data**
- Pearson T C, Green A R, Reilly J T et al. Leukemic transformation in polycythemia Vera. MPD(UK) Study Group. *Blood* 98;92(5):1837-8 **No Original Data**
- Pegelow C H, Armstrong F D, Light S et al. Experience with the use of prophylactic penicillin in children with sickle cell anemia. *J Pediatr* 91;118(5):736-8 **Not relevant to key questions**
- Perry D F, Ireys H T. Maternal perceptions of pediatric providers for children with chronic illnesses. *Matern Child Health J* 2001;5(1):15-20 **Not relevant to key questions**
- Perry V. Myths and facts...about sickle-cell disease. *Nursing* 2005;35(12):27 **No Original Data**
- Perutz M F, Rosa J, Schechter A. Therapeutic agents for sickle cell disease. *Nature* 78;275(5679):369-70 **No Original Data**
- Petrakis N L. Sickle-cell disease. *Lancet* 74;2(7893):1368-9 **No Original Data**

- Petti M C, Tafuri A, Latagliata R et al. High-dose hydroxyurea in the treatment of poor-risk myeloid leukemias. *Ann Hematol* 2003;82(8):476-80 **Study size too small**
- Piver M S. Standard administration of hydroxyurea recommended. *Am J Obstet Gynecol* 89;161(5):1425-6 **Not relevant to key questions, No Original Data**
- Platt A, Beasley J, Miller G et al. Managing sickle-cell pain... and all that goes with it: learn the complex problems this disease triggers and how to support your patient during a crisis. *Nursing* 2002;32(12):32hn1 **No Original Data**
- Platt O S, Guinan E C. Bone marrow transplantation in sickle cell anemia - The dilemma of choice. *NEW ENGL. J. MED.* 96;335(6):426-428 **No Original Data**
- Platt O S, Orkin S H, Dover G et al. Hydroxyurea increases fetal hemoglobin production in sickle cell anemia. *Trans Assoc Am Physicians* 84;97268-74 **No Original Data**
- Platt O S. Sickle cell paths converge on hydroxyurea. *Nat Med* 95;1(4):307-8 **No Original Data**
- Podos S M, Canellos G P. Lens changes in chronic granulocytic leukemia. Possible relationship to chemotherapy. *Am J Ophthalmol* 69;68(3):500-4 **Study size too small, Not relevant to key questions**
- Porter L S, Gil K M, Sedway J A et al. Pain and stress in sickle cell disease: An analysis of daily pain records. *Int. J. Behav. Med.* 98;5(3):185-203 **Not relevant to key questions**
- Potrykus C. Sickle cell. Black counsellors under pressure. *Health Visit* 93;66(7):239-40 **No Original Data**
- Powars D R. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001;139(6):763-4 **No Original Data**
- Powers S W, Mitchell M J, Graumlich S E et al. Longitudinal assessment of pain, coping, and daily functioning in children with sickle cell disease receiving pain management skills training. *J. Clin. Psychol. Med. Settings* 2002;9(2):109-119 **Not relevant to key questions**
- Prasad R, Hasan S, Castro O et al. Long-term outcomes in patients with sickle cell disease and frequent vaso-occlusive crises. *Am J Med Sci* 2003;325(3):107-9 **Not relevant to key questions**
- Price C L, Boyd J H, Watkins A R et al. Mailing of a sickle cell disease educational packet increases blood donors within an African American community. *Transfusion* 2006;46(8):1388-93 **Not relevant to key questions**
- Prielipp R C, Butterworth J F. Clinical guidelines. *Anesth Analg* 2000;90(2):503 **Not relevant to key questions, No Original Data**
- Psychosocial aspects of sickle cell disease: past, present, and future directions of research. *J Health Soc Policy* 94;5(3-4):1-269 **No Original Data**
- Puffer E, Schatz J, Roberts C W. The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. *Child Neuropsychol* 2007;13(2):142-54 **Study size too small**
- Quaglino D, Torelli U, Emilia G. A preliminary clinical evaluation of the therapeutic effects of hydroxyurea in patients with myelogenous leukaemia. *Eur J Cancer* 66;2(1):69-74 **Study size too small**
- Rahimi-Levene N, Hagay Z, Elchalal U et al. Essential thrombocytopenia and pregnancy +AFs-4+AF0-. *AM. J. HEMATOL.* 94;45(4):348-349 **Not relevant to key questions, No Original Data**
- Randall V R. Slavery, segregation and racism: trusting the health care system ain't always easy! An African American perspective on bioethics. *St Louis Univ Public Law Rev* 96;15(2):191-235 **No Original Data**
- Randi M L, Fabris F, Girolami A. Leukemia and myelodysplasia effect of multiple cytotoxic therapy in essential thrombocytopenia. *Leuk Lymphoma* 2000;37(3-4):379-85 **Not relevant to key questions**
- Randi M L, Fabris F, Girolami A. Leukemia and myelodysplasia in patients with essential thrombocytopenia treated with cytotoxic agents [2]. *Haematologica* 99;84(11):1049-1050 **Study size too small, other**
- Randi M L, Fabris F, Girolami A. Leukemia and myelodysplasia in patients with essential thrombocytopenia treated with cytotoxic agents. *Haematologica* 99;84(11):1049-50 **No Original Data**
- Randi M L, Fabris F, Girolami A. Second malignancies in patients with essential thrombocytopenia [1]. *Br. J. Haematol.* 2002;116(4):923 **No Original Data**
- Randi M L, Fabris F, Girolami A. Second malignancies in patients with essential thrombocytopenia. *Br J Haematol* 2002;116(4):923-4 **No Original Data**
- Recent prescription approvals, changes, and recalls. *Oncol. Spectr.* 2001;2(8):576 **No Original Data, other**
- Reichman R C. Actg A5025: S&E Of Hydroxyurea In Subjects On Potent Antiretroviral T. **Not relevant to key questions**
- Reynolds N, Smith C H. Hydroxyurea in psoriasis [1] (multiple letters). *Clin. Exp. Dermatol.* 99;24(6):496-497 **No Original Data**
- Rivers R, Williamson N. Sickle cell anemia: complex disease, nursing challenge (continuing education credit). *RN* 90;53(6):24-9 **No Original Data**
- Roberts L. One worked; the other didn't. *Science* 90;247(4938):18 **Not relevant to key questions, No Original Data**
- Robertson L E, Estey E, Kantarjian H et al. Therapy-related leukemia and myelodysplastic syndrome in chronic lymphocytic leukemia. *LEUKEMIA* 94;8(12):2047-2051 **Not relevant to key questions**

- Rochester-Peart C. Specialist nurse support for clients with blood disorders. *Nurs Times* 97;93(41):52-4 **Not relevant to key questions, No Original Data**
- Rodgers G P, Dover G J, Noguchi C T et al. Hematologic responses of patients with sickle cell disease to treatment with hydroxyurea. *N Engl J Med* 90;322(15):1037-45 **Study size too small**
- Rodgers G P, Dover G J, Noguchi C T et al. Induction of fetal hemoglobin in sickle cell patients by hydroxyurea: the N.I.H. experience. *Prog Clin Biol Res* 89;316B281-93 **Study size too small**
- Rodgers G P. Hydroxyurea and new agents for the treatment of sickle cell disease. *Clin Adv Hematol Oncol* 2004;2(11):713-5 **No Original Data**
- Rodgers G P. Recent approaches to the treatment of sickle cell anemia. *JAMA* 91;265(16):2097-101 **Study size too small, No Original Data**
- Rodgers G P. Spectrum of fetal hemoglobin responses in sickle cell patients treated with hydroxyurea: the National Institutes of Health experience. *Semin Oncol* 92;19(3 Suppl 9):67-73 **Study size too small**
- Rodriguez G. Phase I-II Trial Of Hydroxyurea In Treatment Of Squamous Carcinoma. **Not relevant to key questions**
- Rodriguez-Gomez F, Cuevas O, Anguita J et al. Clinical microbiological case: Penile ulcer and lung infiltrates in a leukemic patient. *Clin. Microbiol. Infect.* 2001;7(12):695-696+713 **Not relevant to key questions**
- Rogers Z R, Buchanan G R. Expanding the role of hydroxyurea in children with sickle cell disease. *J Pediatr* 2004;145(3):287-8 **No Original Data**
- Rogers Z R. Hydroxyurea therapy for diverse pediatric populations with sickle cell disease. *Semin Hematol* 97;34(3 Suppl 3):42-7 **Study size too small**
- Rosenthal M A, Ashley D L, Cher L. Treatment of high risk or recurrent meningiomas with hydroxyurea. *J Clin Neurosci* 2002;9(2):156-8 **Study size too small**
- Ruiz-Genao D P, Sanz-Sanchez T, Bartolome-Gonzalez B et al. Dermatomyositis-like reaction induced by chemotherapeutic agents. *Int. J. Dermatol.* 2002;41(12):885-887 **Not relevant to key questions**
- Rustin G J S, Rustin F P, Dent J. Second tumour incidence not increased following cytotoxic chemotherapy for gestational trophoblastic tumours. *PROC. AM. SOC. CLIN. ONCOL.* 82;Vol. 1(-):C-405 **Not relevant to key questions, other**
- Rutkow I M, Lipton J M. Some negative aspects of sickle cell anemia screening programs (negative aspects of sickle cell screening). *Conn Med* 74;38(5):257-62 **Not relevant to key questions**
- Rutkow I M, Lipton J M. Some negative aspects of state health departments' policies related to screening for sickle cell anemia. *Am J Public Health* 74;64(3):217-21 **Not relevant to key questions**
- Sadovsky R. Hydroxyurea in children with sickle cell disease. *Am. Fam. Phys.* 97;55(3):963-964 **No Original Data**
- Saleh A W, Velvis H J, Gu L H et al. Hydroxyurea therapy in sickle cell anemia patients in Curacao, The Netherlands Antilles. *Acta Haematol* 97;98(3):125-9 **Study size too small, other**
- Santiago L G. More information on hydroxyurea. *GMHC Treat Issues* 96;10(8):10 **No Original Data**
- Santiago L. Hydroxyurea continues to show promise. *GMHC Treat Issues* 96;10(2):9-11 **No Original Data**
- Sauer G C. Combined methotrexate and hydroxyurea therapy for psoriasis.. *Arch Dermatol* 73;107(3):369-370 **Not relevant to key questions**
- Savitt T L. The invisible malady: sickle cell anemia in America, 1910-1970. *J Natl Med Assoc* 81;73(8):739-46 **No Original Data**
- Schechter A N, Rodgers G P, Adams-Graves P et al. Hydroxyurea in sickle cell disease [4]. *New Engl. J. Med.* 96;334(5):333-334 **No Original Data**
- Schechter A N, Rodgers G P, Strasser B J. Sickle cell anemia therapy: Progress since Pauling [3] (multiple letters). *Science* 2000;287(5453):592-593 **No Original Data**
- Schechter A N, Rodgers G P. Hydroxyurea in sickle cell disease. *N Engl J Med* 96;334(5):333 **No Original Data**
- Schechter A N, Rodgers G P. Hydroxyurea in sickle cell disease. *N Engl J Med* 96;334(5):333 **Not relevant to key questions**
- Schechter A N, Rodgers G P. Sickle cell anemia--basic research reaches the clinic. *N Engl J Med* 95;332(20):1372-4 **No Original Data**
- Schechter A N. Sickle cell disease expenditures and outcomes.. *Public Health Rep* 97;112(1):38-39 **No Original Data**
- Scheer A C, Wilson R F. Cancer of the lung and its response to non-surgical treatment. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol* 75;83(1):1-6 **Not relevant to key questions, study size too small**
- Schmugge M, Frischknecht H, Yonekawa Y et al. Stroke in hemoglobin (SD) sickle cell disease with moyamoya: successful hydroxyurea treatment after cerebrovascular bypass surgery. *Blood* 2001;97(7):2165-7 **Study size too small**
- Schrag D, Xu F, Hanger M et al. Fragmentation of care for frequently hospitalized urban residents. *Med Care* 2006;44(6):560-7 **Not relevant to key questions**
- Schreibman S M, Gee T S, Grabstald H. Management of priapism in patients with chronic granulocytic leukemia. *J Urol* 74;111(6):786-8 **Not relevant to key questions**

- Schrell U M, Rittig M G, Koch U et al. Hydroxyurea for treatment of unresectable meningiomas. *Lancet* 96;348(9031):888-9 **Study size too small**
- Schwarzenberg L, Mathe G, Pouillart P et al. Chemotherapy with hydroxyurea, leucopheresis and splenectomy in the treatment of chronic myeloid leukemia at the problastic phase. *Haematologica* 72;57(11):601-11 **Not relevant to key questions**
- Schwarzenberg L, Mathe G, Pouillart P et al. Hydroxyurea, leucopheresis, and splenectomy in chronic myeloid leukaemia at the problastic phase. *Br Med J* 73;1(5855):700-3 **Not relevant to key questions**
- Schwerner H, Mellody T, Goldstein A B et al. Evaluating the impact of a disease management program for chronic complex conditions at two large northeast health plans using a control group methodology. *Dis Manage.* 2006;9(1):34-44 **Not relevant to key questions**
- Scott J P. Hydroxyurea On Adhesion Of Sickle Cells To Vascular Endothelium. **Not relevant to key questions**
- Scott R B. Health care priority and sickle cell anemia. *JAMA* 70;214(4):731-4 **Not relevant to key questions, No Original Data**
- Scott R B. Sickle-cell anemia--high prevalence and low priority. *N Engl J Med* 70;282(3):164-5 **No Original Data**
- Secundy M G. Psychosocial issues: Unanswered questions in the use of bone marrow transplantation for treatment of hemoglobinopathies. *AM. J. PEDIATR. HEMATOL. ONCOL.* 94;16(1):76-79 **No Original Data**
- Selby R, Nisbet-Brown E, Basran R K et al. Valproic acid and augmentation of fetal hemoglobin in individuals with and without sickle cell disease [4]. *BLOOD* 97;90(2):891-893 **Not relevant to key questions**
- Selby R, Nisbet-Brown E, Basran R K et al. Valproic acid and augmentation of fetal hemoglobin in individuals with and without sickle cell disease. *Blood* 97;90(2):891-3 **Not relevant to key questions**
- Selleri C, Alfinito F, Del Vecchio L et al. Cytoplasmic GpIIb-IIIa and cytokine secretion by blasts in a case of megakaryoblastic transformation of essential thrombocythemia. *Leuk. Lymphoma* 93;10(6):497-500 **Not relevant to key questions**
- Serjeant B E, Forbes M, Williams L L et al. Screening cord bloods for detection of sickle cell disease in Jamaica. *Clin Chem* 74;20(6):666-9 **Not relevant to key questions**
- Serjeant G R, Hutson C. Patterns of attendance at Jamaican sickle cell clinics 1952 to 1981. *Trans R Soc Trop Med Hyg* 84;78(5):648-52 **Not relevant to key questions**
- Serjeant G R. The case for dedicated sickle cell centres. *Indian J. Hum. Genet.* 2006;12(3):148-151 **No Original Data**
- Sharpe J N, Brown R T, Thompson N J et al. Predictors of coping with pain in mothers and their children with sickle cell syndrome. *J Am Acad Child Adolesc Psychiatry* 94;33(9):1246-55 **Not relevant to key questions**
- Shatin D, Levin R, Ireys H T et al. Health care utilization by children with chronic illnesses: a comparison of medicaid and employer-insured managed care. *Pediatrics* 98;102(4):E44 **Not relevant to key questions, study size too small**
- Shepherd P C, Richards S M, Allan N C. Progress with interferon in CML--results of the MRC UK CML III study. *Bone Marrow Transplant* 96;17 Suppl 3S15-8 **Not relevant to key questions**
- Sherman D S, Fish D N. Hydroxyurea in the treatment of HIV infection. *AIDS Reader* 99;9(1):18-19+23 **No Original Data**
- Shilalukey K, Kaufman M, Bradley S et al. Counseling sexually active teenagers treated with potential human teratogens. *J Adolesc Health* 97;21(3):143-6 **Not relevant to key questions**
- Shullenberger C C. Phase Ii Studies Of Hydroxyurea (Nsc-32065) In Adults: Leukemia. *Cancer Chemother Rep* 64;4049-50 **Study size too small**
- Shuster J. Hydroxyurea and hepatitis. *Nursing* **No Original Data**
- Shuster J. Shock-like sensations associated with antidepressant withdrawal; Acute tumor lysis syndrome caused by hydroxyurea; Zolpidem-induced visual hallucinations; Tooth discoloration with linezolid; Sleepwalking caused by SSRI; ADR-related reports from the Archives of Internal Medicine. *Hosp. Pharm.* 2003;38(7):631-633 **No Original Data**
- Silbergleit R, Jancis M O, McNamara R M. Management of sickle cell pain crisis in the emergency department at teaching hospitals. *J Emerg Med* 99;17(4):625-30 **Not relevant to key questions**
- Silver R T. Hydroxyurea and sickle cell crisis. *N Engl J Med* 95;333(15):1008-9 **No Original Data**
- Simonelli C, Comar M, Zanussi S et al. No therapeutic advantage from didanosine (ddI) and hydroxyurea versus ddI alone in patients with HIV infection. *AIDS* **Study size too small**
- Simonelli C, Comar M, Zanussi S et al. No therapeutic advantage from didanosine (ddI) and hydroxyurea versus ddI alone in patients with HIV infection [6]. *AIDS* 97;11(10):1299-1300 **Study size too small**
- Simonsson B, Oberg G, Bjoreman M et al. Intensive treatment in order to minimize the Ph-positive clone in chronic myelogenous leukemia. *Leuk Lymphoma* 92;7 Suppl55-7 **Not relevant to key questions**
- Simonsson B, Oberg G, Killander A et al. Intensive treatment in order to minimize the Ph-positive clone in chronic myelogenous leukemia (CML). *Swedish CML-*

- group. Bone Marrow Transplant 94;14 Suppl 3S55-6
Not relevant to key questions
- Smith D C, Vaughan W P, Gwilt P R et al. A phase I trial of high-dose continuous-infusion hydroxyurea. Cancer Chemother Pharmacol 93;33(2):139-43 **Not relevant to key questions**
- Smith H D, McIntire M S, Grant R S. Health for the public: sickle cell program. Nebr Med J 74;59(3):68-72 **Not relevant to key questions, No Original Data**
- Smith J P, Rutledge F, Burns B C et al. Systemic chemotherapy for carcinoma of the cervix. Am J Obstet Gynecol 67;97(6):800-7 **Not relevant to key questions, study size too small**
- Smith L A, Wise P H, Wampler N S. Knowledge of welfare reform program provisions among families of children with chronic conditions. Am J Public Health 2002;92(2):228-30 **Not relevant to key questions**
- Smith W R, Bovbjerg V E, Penberthy L T et al. Understanding pain and improving management of sickle cell disease: the PiSCES study. J Natl Med Assoc 2005;97(2):183-93 **Not relevant to key questions**
- Smith W. Multicenter Study Of Hydroxyurea 5 Years Follow-Up Study. **Not relevant to key questions**
- Smith-Wynter L O. Research study. The feasibility of nursing patients with sickle cell crisis at home. British Journal of Community Nursing 99;4(10):531 **Not relevant to key questions**
- Snyder A B, Barone J G, DiGiacomo J C et al. Postoperative pulmonary leukostasis. Crit Care Med 90;18(1):116-7 **Not relevant to key questions**
- Solimando DA. Hydroxyurea and pentostatin. Hosp. Pharm. 98;33(6):629-635 **No Original Data**
- Somlo P, Revesz T. Chemotherapy-induced fatal pulmonary fibrosis. NEOPLASMA 84;31(6):739-744 **Not relevant to key questions**
- Souza R, Jardim C, Carvalho C. The need for national registries in rare diseases. Am J Respir Crit Care Med 2006;174(2):228; author reply 228 **No Original Data**
- Sox C. Health supervision for children with sickle cell disease. Pediatrics 2003;111(3):710-1; author reply 710-1 **No Original Data**
- Spell D W, Feldman L, Allen S et al. Long-term Use of Hydroxyurea for Sickle Cell Anemia [2] (multiple letters). J. Am. Med. Assoc. 2003;290(6):752-754 **No Original Data**
- Spell D W, Feldman L, Allen S et al. Long-term use of hydroxyurea for sickle cell anemia... Steinberg MH, Barton F, Castro O et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 2003;290(6):752 **No Original Data**
- Spell D W. Long-term use of hydroxyurea for sickle cell anemia. JAMA 2003;290(6):752; author reply 754 **No Original Data**
- Spier S, Solomon L M, Esterly N B et al. Hydroxyurea and macrocytosis. Br J Dermatol **Not relevant to key questions, study size too small**
- Squibb hydroxyurea (Hydrea). Clin Pharmacol Ther 69;10(1):142-6 **No Original Data, Not relevant to key questions**
- Stagno F, Guglielmo P, Consoli U et al. Successful healing of hydroxyurea-related leg ulcers with topical granulocyte-macrophage colony-stimulating factor [2]. Blood 99;94(4):1479-1480 **Not relevant to key questions**
- Stavroyianni N, Stamatopoulos K, Viniou N et al. Autoimmune hemolytic anemia during (alpha)-interferon treatment in a patient with chronic myelogenous leukemia. Leuk. Res. 2001;25(12):1097-1098 **Not relevant to key questions, No Original Data**
- Steensma D P, Harrison C N, Tefferi A. Hydroxyurea-associated platelet count oscillations in polycythemia vera: a report of four new cases and a review. Leuk Lymphoma **Not relevant to key questions**
- Steinberg M H. Pneumococcus and sickle cell disease: The beginning of the end?. Clin. Infect. Dis. 2007;44(11):1434-1435 **No Original Data**
- Stolbach L L, Begg C B, Hall T et al. Treatment of renal carcinoma: a phase III randomized trial of oral medroxyprogesterone (Provera), hydroxyurea, and nafoxidine. Cancer Treat Rep 81;65(7-8):689-92 **Study size too small**
- Strauss R G. Sickle cell patients deserve controlled recommendations. Transfusion 2002;42(5):658-9; author reply 659-60 **No Original Data**
- Streetly A, Dick M, Layton M. Sickle cell disease: the case for coordinated information. BMJ 93;306(6891):1491-2 **No Original Data**
- Stuart A, Jones S M, Walker L J. Insights into elevated distortion product otoacoustic emissions in sickle cell disease: comparisons of hydroxyurea-treated and non-treated young children. Hear Res 2006;212(1-2):83-9 **Not relevant to key questions, study size too small**
- Sualdea Montes M, Pedraza Cezon L, Martinez Nieto C et al. Compassionate use of hydroxyurea in the treatment of meningioma. **Other**
- Suttorp M, Rister M, Schmitz N. Interferon-alpha-2 (IFN) plus hydroxyurea for treatment of juvenile chronic myelogenous leukemia. Med Pediatr Oncol 94;22(5):358-9 **Study size too small, No Original Data**

- Swaim M W, Agarwal S, Rosse W F. Successful treatment of hepatitis C in sickle-cell disease. *Ann Intern Med* 2000;133(9):750-1 **Study size too small**
- Taking management of sickle cell disease to a new level. *Dis Manag Advis* 2001;7(1):1-5 **No Original Data**
- Tavakkoli F, Nahavandi M, Wyche M Q et al. Effects of hydroxyurea treatment on cerebral oxygenation in adult patients with sickle cell disease: an open-label pilot study. *Clin Ther* 2005;27(7):1083-8 **Study size too small**
- Taveira L M, Goncalves C, Paiva A et al. Efficacy of hydroxyurea in the treatment of a patient with erythrodermic psoriasis and chronic myelogenous leukaemia. *J. Eur. Acad. Dermatol. Venereol.* 97;9(3):266-268 **Not relevant to key questions**
- Tefferi A, Fenaux P, Preudhomme C et al. Is hydroxyurea leukemogenic in essential thrombocythemia? [5] (multiple letters). *Blood* 98;92(4):1459-1461 **No Original Data**
- Tefferi A. Is hydroxyurea leukemogenic in essential thrombocythemia?. *Blood* 98;92(4):1459-60; author reply 1460-1 **No Original Data**
- Tefferi A. Pregnancy and thrombocythemia +AFs-5+AF0-. *Am. J. Hematol.* 98;57(2):181-182 **No Original Data**
- Telen M J, Harris G, Whitworth E. Caring for patients with sickle cell disease in North Carolina. *N C Med J* 99;60(1):14-7 **Not relevant to key questions, No Original Data**
- Telfair J, Gardner M M. Adolescents with sickle cell disease: determinants of support group attendance and satisfaction. *Health Soc Work* 2000;25(1):43-50 **Not relevant to key questions**
- Teo R Y L, Tan E. A case of hydroxyurea-induced transverse melanonychia. *Int. J. Dermatol.* 2006;45(11):1329-1330 **Not relevant to key questions**
- Terrin M L. Multicenter Study Of Hydroxyurea Follow-Up. **Not relevant to key questions**
- Tessier J, Emmons W, Newton J et al. Age and hydroxyurea increase the risk of drug-associated peripheral neuropathy in HIV-infected patients. *Infect. Dis. Clin. Pract.* 2002;11(5):276-278 **Other**
- Thiele J, Kvasnicka H M, Ollig S et al. Anagrelide does not exert a myelodysplastic effect on megakaryopoiesis: A comparative immunohistochemical and morphometric study with hydroxyurea. *Histol. Histopathol.* 2005;20(4):1071-1076 **Invitro only, study size too small**
- Thomas V J, Cohn T. Communication skills and cultural awareness courses for healthcare professionals who care for patients with sickle cell disease. *J Adv Nurs* 2006;53(4):480-8 **Not relevant to key questions**
- Thomas V J, Dixon A L, Milligan P. Cognitive-behaviour therapy for the management of sickle cell disease pain: An evaluation of a community-based intervention. *Br. J. Health Psychol.* 99;4(3):209-229 **Not relevant to key questions**
- Thomas V J, Gruen R, Shu S. Cognitive-behavioural therapy for the management of sickle cell disease pain: identification and assessment of costs. *Ethn Health* 2001;6(1):59-67 **Not relevant to key questions**
- Thomas V. Cognitive behavioural therapy in pain management for sickle cell disease. *Int J Palliat Nurs* 2000;6(9):434-42 **Not relevant to key questions**
- Thompson R J, Gil K M, Burbach D J et al. Role of child and maternal processes in the psychological adjustment of children with sickle cell disease. *J. CONSULT. CLIN. PSYCHOL.* 93;61(3):468-474 **Not relevant to key questions**
- Thompson R J, Gil K M, Keith B R et al. Psychological adjustment of children with sickle cell disease: stability and change over a 10-month period. *J Consult Clin Psychol* 94;62(4):856-6 **Not relevant to key questions**
- Todd K H, Green C, Bonham V L et al. Sickle Cell Disease Related Pain: Crisis and Conflict. *J. Pain* 2006;7(7):453-458 **No Original Data**
- Torres G. Hydroxyurea, a potential new anti-HIV agent. *GMHC Treat Issues* 95;9(1):7-9 **No Original Data**
- Torrey E, Simpson K, Wilbur S et al. Malignant mastocytosis with circulating mast cells. *Am. J. Hematol.* 90;34(4):283-286 **Not relevant to key questions**
- Treatment of Ph-positive chronic myeloid leukemia with alpha-interferon (ROFERON-A). The Italian Cooperative Study Group experience. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *Leuk Lymphoma* 93;11 Suppl 1153-7 **Not relevant to key questions**
- Triadou P, Maier-Redelsperger M, Krishnamoorthy R et al. Fetal haemoglobin variations following hydroxyurea treatment in patients with cyanotic congenital heart disease. *Nouv Rev Fr Hematol* 94;36(5):367-72 **Not relevant to key questions, other**
- Tubiana M, Frindel E, Vassort F. Critical survey of experimental data on in vivo synchronization by hydroxyurea. *Recent Results Cancer Res* 75;(52):187-205 **Not relevant to key questions**
- Tunde-Ayinmode M F, Adelekan M L. Psychosocial impact of sickle cell disease in children seen at University of Ilorin Teaching Hospital, Ilorin, Nigeria. *East Afr Med J* 2005;82(2):73-8 **Not relevant to key questions**
- Tura S, Baccarani M, Zuffa E et al. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *NEW ENGL. J. MED.* 94;330(12):820-825 **Not relevant to key questions**

- Tura S, Baccarani M. Alpha-interferon in the treatment of chronic myeloid leukemia. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. *Blood* 95;85(10):2999-3002 **Not relevant to key questions, No Original Data**
- Uozumi K, Ohno N, Shimotakahara S et al. Trisomy 8 in essential thrombocythemia in leukemic transformation. *Cancer Genet. Cytogenet.* 2000;116(1):84-86 **Not relevant to key questions**
- Use of penicillin prophylaxis in sickle cell disease. *AM. FAM. PHYS.* 96;53(5):1828-1829 **No Original Data**
- Van Genderen P J J, Michiels J J, Ring T et al. Hydroxyurea in essential thrombocytosis [6]. *NEW ENGL. J. MED.* 95;333(12):802-803 **No Original Data**
- Van Genderen P J J, Michiels J J, Ring T et al. Hydroxyurea in essential thrombocytosis [6]. *NEW ENGL. J. MED.* 95;333(12):802-803 **Not relevant to key questions**
- Varma S, Lanigan S W. Leg ulceration with associated thrombocytosis: Healing of ulceration associated with treatment of the raised platelet count [16]. *Br. J. Dermatol.* 99;140(1):188-189 **No Original Data**
- Varma S, Lanigan S W. Leg ulceration with associated thrombocytosis: healing of ulceration associated with treatment of the raised platelet count. *Br J Dermatol* 99;140(1):188-9 **No Original Data**
- Vassallo C, Brazzelli V, Ardigo M et al. Nails changes in once-hematologic patients [12]. *Haematologica* 2001;86(3):334-336 **No Original Data**
- Vavasseur J W. Psychosocial aspects of chronic disease: cultural and ethnic implications.. *Birth Defects Orig Artic Ser* 87;23(6):144-153 **No Original Data**
- Vavasseur J. A comprehensive program for meeting psychosocial needs of sickle cell anemia patients. *J Natl Med Assoc* 77;69(5):335-9 **Not relevant to key questions, No Original Data**
- Verschraegen C F, Kudelka A P, Loyer E et al. A phase II trial of high-dose hydroxyurea administered parenterally in patients with epithelial ovarian carcinoma refractory to platinum. *Int. J. Gynecol. Cancer* 98;8(6):494-498 **Not relevant to key questions**
- Vichinsky E P, Serjeant G R, Davies S C. Understating the morbidity of sickle cell disease [1] (multiple letters). *Br. J. Haematol.* 97;99(4):974-978 **No Original Data**
- Vines G. An unsuitable case for treatment. *New Sci* 95;147(1994):37-9 **No Original Data**
- Vines G. Gene tests: the parents" dilemma. *New Sci* 94;144(1951):40-4 **No Original Data**
- Voelker R. Cancer drug may join the AIDS arsenal. *JAMA* 95;274(7):523 **No Original Data**
- Vokes E E, Ratain M J, Janisch L et al. A phase I study of cisplatin, 5-fluorouracil and leucovorin with escalating doses of hydroxyurea in chemotherapy naive patients [3]. *EUR. J. CANCER* 91;27(2):217-218 **Not relevant to key questions**
- Wailoo K. Stigma, race, and disease in 20th century America. *Lancet* 2006;367(9509):531-533 **No Original Data**
- Walco G A, Dampier C D. Chronic pain in adolescent patients. *J Pediatr Psychol* 87;12(2):215-25 **No Original Data**
- Walker J E. Sickle cell anemia services: do physicians and laymen agree?. *IMJ Ill Med J* 75;147(6):535-7, 541 **Not relevant to key questions**
- Walters M C, Patience M, Leisenring W et al. Bone marrow transplantation for sickle cell disease. *N Engl J Med* 96;335(6):369-76 **Not relevant to key questions**
- Wan T S, Ma S K, Chan L C. Acquired pericentric inversion of chromosome 9 in essential thrombocythemia. *Hum Genet* 2000;106(6):669-70 **Not relevant to key questions**
- Wang W C. Pain at home in sickle cell disease: an underrecognized problem. *J Pediatr Hematol Oncol* 2002;24(8):610-2 **Not relevant to key questions, No Original Data**
- Ware M A, Hambleton I, Ochaya I et al. Day-care management of sickle cell painful crisis in Jamaica: a model applicable elsewhere?. *Br J Haematol* 99;104(1):93-6 **Not relevant to key questions**
- Ware R E, Steinberg M H, Kinney T R. Hydroxyurea: an alternative to transfusion therapy for stroke in sickle cell anemia. *Am J Hematol* 95;50(2):140-3 **Study size too small**
- Ware R E, Zimmerman S A, Schultz W H. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 99;94(9):3022-6 **Study size too small**
- Weiner D L, Brugnara C. Hydroxyurea and sickle cell disease: a chance for every patient. *JAMA* 2003;289(13):1692-4 **No Original Data**
- Weinlich G, Fritsch P. Leg ulcers in patients treated with hydroxyurea for myeloproliferative disorders: What is the trigger? [13]. *Br. J. Dermatol.* 99;141(1):171-172 **No Original Data**
- Weinlich G, Fritsch P. Leg ulcers in patients treated with hydroxyurea for myeloproliferative disorders: what is the trigger?. *Br J Dermatol* 99;141(1):171-2 **No Original Data**
- Weissman S B, Sinclair G I, Green C L et al. Hydroxyurea-induced hepatitis in human immunodeficiency virus-positive patients. *Clin. Infect. Dis.* 99;29(1):223-224 **Not relevant to key questions**
- Weston G J, Martin A J, Mufti G J et al. Hydroxyurea treatment of meningiomas: a pilot study. *Skull Base* 2006;16(3):157-60 **Study size too small**

- Whelan C T, Jin L, Meltzer D. Pain and satisfaction with pain control in hospitalized medical patients: no such thing as low risk. *Arch Intern Med* 2004;164(2):175-80 **Not relevant to key questions**
- While A E, Mullen J. Living with sickle cell disease: the perspective of young people. *Br J Nurs* 2004;13(6):320-5 **Not relevant to key questions, study size too small**
- Wierenga K J, Hambleton I R. Comment on: Loureiro & Rozenfeld "Epidemiology of sickle cell disease hospital admissions in Brazil". *Rev Saude Publica* 2006;40(4):740-1; author reply 741 **Not relevant to key questions, No Original Data**
- Wilkinson D Y. For whose benefit? Politics and sickle cell. *Black Scholar* 74;5(8):26-31 **Not relevant to key questions, No Original Data**
- Windrum P, Hull D R, Morris T C M. Herb-drug interactions. *Lancet* 2000;355(9208):1019-1020 **Not relevant to key questions, No Original Data**
- Wisdom E. Genetic services for underresourced populations. B. Project funding on local and regional levels: Local funding: The Ohio experience. *BIRTH DEFECTS ORIG. ARTIC. SER.* 90;26(2):212-214 **Not relevant to key questions, No Original Data**
- Wong K F, Kwong Y L. Isochromosome 8q is a marker of secondary acute myeloid leukemia [1]. *Cancer Genet. Cytogenet.* 2000;120(2):171-173 **Not relevant to key questions**
- Wong K F. A novel interstitial deletion of 3p in essential thrombocythemia +AFs-2+AF0-. *Cancer Genet. Cytogenet.* 2004;153(1):84-85 **Not relevant to key questions, No Original Data**
- Wonkam A, Angwafo F F. Prenatal diagnosis may represent a point of entry of genetic science in sub-Saharan Africa: A survey on the attitudes of medical students and physicians from Cameroon [8]. *Prenat. Diagn.* 2006;26(8):760-761 **Not relevant to key questions**
- Wood B L. Disentangling pathways of effect in family intervention for chronic illness. *Fam. Syst. Health* 2000;18(4):419-422 **Not relevant to key questions, No Original Data**
- Woods K F, Kutlar A, Johnson J A et al. Sickle cell telemedicine and standard clinical encounters: a comparison of patient satisfaction. *Telemed J* 99;5(4):349-56 **Not relevant to key questions**
- Woofter J C, Anderson P C. Megaloblastic anemia in the management of severe psoriasis. *W V Med* **Not relevant to key questions**
- Wright J, Bareford D, Wright C et al. Day case management of sickle pain: 3 years experience in a UK sickle cell unit. *Br J Haematol* 2004;126(6):878-80 **Not relevant to key questions**
- Wyatt H V. Improving care for people with sickle cell disease. *Health Educ J* 88;47(2-3):70 **No Original Data**
- Yang Y M, Shah A K, Watson M et al. Comparison of costs to the health sector of comprehensive and episodic health care for sickle cell disease patients. *Public Health Rep* 95;110(1):80-6 **Not relevant to key questions**
- Yasuda N, Ohmori S-I, Usui T. Hydroxyurea-induced gangrene of the toes in a patient with chronic myelogenous leukemia [3]. *Am. J. Hematol.* 2000;63(2):103-104 **Not relevant to key questions**
- Yen A, Freeman L, Fishbaugh J. Hydroxyurea induces precommitment during retinoic induced HL-60 terminal myeloid differentiation: Possible involvement of gene amplification. *LEUK. RES.* 87;11(1):63-71 **Not relevant to key questions**
- Yesley M S. Genetic privacy, discrimination, and social policy: challenges and dilemmas. *Microb Comp Genomics* 97;2(1):19-35 **Not relevant to key questions, No Original Data**
- Yoon S L, Black S. Comprehensive, integrative management of pain for patients with sickle-cell disease. *J Altern Complement Med* 2006;12(10):995-1001 **Not relevant to key questions**
- Young G A R. Drug-induced haematological disorders. *Curr. Ther.* 84;25(8):61-69 **No Original Data**
- Young W I, Peters J, Houser H B et al. Awareness of sickle cell abnormalities. A medical and lay community problem. *Ohio State Med J* 74;70(1):27-30 **Not relevant to key questions**
- Yuregir G, Kilinc M, Ekerbicer H et al. Screening of hemoglobinopathies in Kahramanmaraş province (Turkey) situated in a high prevalence area [6]. *J. Trop. Pediatr.* 2001;47(2):124-125 **Not relevant to key questions**
- Zala C, Salomon H, Cahn P. Treatment of primary HIV infection: a pilot study of stavudine and didanosine plus nevirapine with or without hydroxyurea. *Antivir Ther* 99;4 Suppl 395-9 **No Original Data**
- Zelson J H, O'Brien R T, Pearson H A. A community program for education, testing and counseling for abnormal hemoglobins. *Conn Med* 73;37(9):435-9 **Not relevant to key questions**
- Zemlickis D, Lishner M, Degendorfer P et al. Fetal outcome after in utero exposure to cancer chemotherapy. *ARCH. INTERN. MED.* 92;152(3):573-576 **Not relevant to key questions**
- Zielinski W T, Mosher C L. Updating, expanding outpatient facilities. *Hospitals* 73;47(3):91-4 **passim Not relevant to key questions**
- Zuazu J, Julia A, Sierra J et al. Pregnancy outcome in hematologic malignancies. *CANCER* 91;67(3):703-709 **Not relevant to key questions**
- Zuniga G, Torres-Bugarin O, Ramirez-Munoz M P et al. Micronucleated erythrocytes in splenectomized patients with and without chemotherapy. *Mutat Res* 96;361(2-3):107-12 **Other, Not relevant to key questions**

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) (<i>insufficient</i> 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) (<i>insufficient</i> 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 abnormalities	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) (<i>insufficient</i> 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) (<i>insufficient</i> 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/Cytogen etic 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) (<i>insufficient</i> 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 if 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

Kofi Anie, PhD
Clinical Health Psychologist
Central Middlesex Hospital
Honorary Senior Lecturer
Imperial College London
London, England

Wylie Burke, MD, PhD
Professor and Chair
Department of Medical History and Ethics
University of Washington
Seattle, WA

Christine Corbin
Program Coordinator
Sickle Cell Disease Association of America,
Inc
Baltimore, MD

Peter Fagan, PhD
Johns Hopkins HealthCare LLC
Glen Burnie, MD

Jeffery Keefer, MD, PhD
Division of Pediatric Hematology
Johns Hopkins University School of
Medicine
Baltimore, MD

Erica Liebelt, MD, PhD
National Toxicology Program
Associate Professor of Pediatrics and
Emergency Medicine
Director, Medical Toxicology Services
UAB School of Medicine
Birmingham, AL

Heidi Malm, PhD
Associate Professor
Loyola University Chicago
Chicago, IL

Martin H. Steinberg, MD
Professor of Medicine, Pediatrics, Pathology
and Laboratory Medicine,
Boston University School of Medicine
Director,
Center of Excellence in Sickle Cell Disease
Boston Medical Center
Boston, MA

Internal Technical Experts

Samuel Charache, MD, PhD
Emeritus Professor of
Medicine and Pathology
John Hopkins School of Medicine
Baltimore, MD

James F. Casella, MD
Rainey Professor of Pediatric Hematology
Department of Pediatrics
Johns Hopkins University
School of Medicine
Baltimore, MD

Cynthia S. Rand, PhD
Professor of Medicine
Division of Pulmonary and
Critical Care Medicine
Johns Hopkins University
School of Medicine
Baltimore, MD