Hydroxyurea Treatment for Sickle Cell Disease

An NIH Consensus Development Conference

Program and Abstracts

February 25–27, 2008

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

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The Agency for Healthcare Research and Quality provided additional support to the conference development.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available, the directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-Based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2 1/2 days. The first day and a half of the conference consist of plenary sessions in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise their draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12–16 members who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.
- May be knowledgeable in the general topic under consideration, but must not have published about or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
  - Practicing and academic health professionals
  - Biostatisticians and epidemiologists
  - Clinical trialists and researchers
  - Public representatives (ethicists, economists, attorneys, etc.)

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers; 3 present the information found in the Evidence-Based Practice Center's systematic review of the literature. The other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit their statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement was written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements have robust dissemination:

- Continuing Medical Education credits are available during and after the conference.
- A press conference is held the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at http://consensus.nih.gov.
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.

The conference statement is published in a major peer-reviewed journal.

Contact Us

For conference schedules, past statements and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

1-888-NIH-CONSENSUS (888-644-2667)
http://consensus.nih.gov

General Information

CME

The National Institutes of Health/Foundation for Advanced Education in the Sciences (NIH/FAES) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The NIH/FAES designates this educational activity for a maximum of 13.00 *AMA PRA Category 1 Credits*.™ Physicians should claim only credit that is commensurate with the extent of their participation in the activity.

Your participant packet includes a CME evaluation form, which should be completed and returned either to the conference registration desk or by mail to claim credits.

Financial Disclosure

Each speaker presenting at this conference has been asked to disclose any financial interests or other relationships pertaining to this subject area. Please refer to the material in your participant packet for details.

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at http://videocast.nih.gov. Archived videocast will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

Message Service

The telephone number for the message center at the Natcher Conference Center is 301–594–7302.

Online Content

All materials emanating from the NIH Consensus Development Program are available at http://consensus.nih.gov.

Contents

What Are the Short- and Long-Term Harms of Hydroxyurea Treatment?

What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions?

What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions? (continued)

Background

Sickle cell disease is an inherited blood disorder that affects between 50,000 and 75,000 people in the United States, and is most common among people whose ancestors come from sub-Saharan Africa, South and Central America, the Middle East, India, and the Mediterranean basin. Sickle cell disease occurs when an infant inherits the gene for sickle hemoglobin from both parents (Hb SS, or sickle cell anemia), or the gene for sickle hemoglobin from one parent and another abnormal hemoglobin gene from the other parent. Each year, approximately 2,000 babies with sickle cell disease are born in the United States. The condition is chronic and lifelong, and it is associated with a decreased lifespan. In addition, approximately 2 million Americans carry the sickle cell trait, which increases the public health burden as this disorder is passed on to future generations.

The red blood cells in people with sickle cell disease become deoxygenated (or depleted of oxygen) and crescent-shaped or "sickled." The cells become sticky and adhere to blood vessel walls, thereby blocking blood flow within limbs and organs. These changes lead to acute painful episodes, chronic pain, and chronic damage to the brain, heart, lungs, kidneys, liver, and spleen. Infections and lung disease are leading causes of death.

Pain crises are responsible for most emergency room visits and hospitalizations of people with sickle cell disease. Standard treatments for acute pain crises include painkilling medications, fluid replacement, and oxygen. In the mid-1990s, researchers began investigating the potential of hydroxyurea to reduce the number and severity of pain crises in sickle cell patients. Hydroxyurea is in a class of anti-cancer drugs, and it acts to increase the overall percentage of normally structured red blood cells in the circulation. By diluting the number of cells that "sickle," it may, if taken on a daily basis, reduce their damaging effects. Hydroxyurea was approved by the FDA for use in adults with sickle cell anemia in 1998. However, there are a number of unresolved issues about the use of hydroxyurea, including a lack of knowledgeable providers who treat sickle cell disease, and patient and practitioner questions about safety and effectiveness, including concerns regarding potential long-term carcinogenesis.

In order to take a closer look at this important topic, the National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research of the National Institutes of Health will convene a Consensus Development Conference from February 25–27, 2008, to assess the available scientific evidence related to the following questions:

- What is the efficacy (results from clinical studies) of hydroxyurea treatment for patients who have sickle cell disease in three groups: infants, preadolescents, and adolescents/adults?

- What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?

- What are the short- and long-term harms of hydroxyurea treatment?

- What are the barriers to hydroxyurea treatment for patients who have sickle cell disease, and what are the potential solutions?

- What are the future research needs?

Agenda

Monday, February 25, 2008

8:30 a.m. Opening Remarks
Charles Peterson, M.D., M.B.A.
Director
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
National Institutes of Health

8:40 a.m. Charge to the Panel
Barnett S. Kramer, M.D., M.P.H.
Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
Otis W. Brawley, M.D.
Panel and Conference Chairperson
Chief Medical Officer
American Cancer Society

9:00 a.m. Sickle Cell Anemia: Yesterday, Today, and Tomorrow
Griffin P. Rodgers, M.D., M.A.C.P.
Director
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

9:20 a.m. Sickle Cell Disease: The Consumer's Perspective
Richard Watkins

What Is the Efficacy (Results From Clinical Studies) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease in Three Groups: Infants, Preadolescents, and Adolescents/Adults?

9:40 a.m. Evidence-Based Practice Center Presentation I: The Efficacy and Effectiveness of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease
John J. Strouse, M.D.
Assistant Professor of Pediatrics
Pediatric Hematology
School of Medicine
The Johns Hopkins University

Monday, February 25, 2008 (continued)

What Is the Efficacy (Results From Clinical Studies) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease in Three Groups: Infants, Preadolescents, and Adolescents/Adults? (continued)

10:00 a.m. The Laboratory Evidence of Efficacy of Hydroxyurea in the Treatment of Sickle Cell Disease
Eugene P. Orringer, M.D.
Professor of Medicine
Executive Associate Dean, Faculty Affairs and Faculty Development
Dean's Office, School of Medicine
University of North Carolina at Chapel Hill

10:20 a.m. Summary of the Evidence Regarding Efficacy of Hydroxyurea Treatment for Sickle Cell Disease in Adults
Martin H. Steinberg, M.D.
Director
Center of Excellence in Sickle Cell Disease
Professor of Medicine and Pediatrics
Boston University School of Medicine

10:40 a.m. Summary of the Evidence Regarding Efficacy of Hydroxyurea Treatment for Sickle Cell Disease in Children and Adolescents
Russell E. Ware, M.D., Ph.D.
Chair
Department of Hematology
St. Jude Children's Research Hospital

11:00 a.m. Discussion

Noon Lunch
Panel Executive Session

What Is the Effectiveness (in Everyday Practice) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease?

1:00 p.m. Practical Treatment Considerations for Hydroxyurea in Pediatric and Adult Patients With Sickle Cell Disease, Including Maximum Tolerated Dose, Labeling of Responders Versus Nonresponders, and Adherence to Therapy
Kenneth I. Ataga, M.D.
Assistant Professor of Medicine
Division of Hematology/Oncology
Department of Medicine
School of Medicine
University of North Carolina at Chapel Hill

Monday, February 25, 2008 (continued)

What Is the Effectiveness (In Everyday Practice) of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease? (continued)

1:20 p.m. Summary of the Evidence Regarding Effectiveness of Hydroxyurea in the Treatment of Sickle Cell Disease in the Pediatric Population
Kwaku Ohene-Frempong, M.D.
Professor of Pediatrics
University of Pennsylvania School of Medicine
Director, Comprehensive Sickle Cell Center
The Children's Hospital of Philadelphia

1:40 p.m. Summary of the Evidence Regarding Effectiveness of Hydroxyurea in the Treatment of Sickle Cell Disease in the Adult Population
James R. Eckman, M.D.
Director
Georgia Sickle Cell Comprehensive Care Center
Winship Cancer Institute
Emory University

2:00 p.m. Discussion

What Are the Short- and Long-Term Harms of Hydroxyurea Treatment?

2:30 p.m. Evidence-Based Practice Center Presentation II: A Systematic Review of Safety and Harm Associated With Hydroxyurea for the Treatment of Sickle Cell Disease
Sophie Lanzkron, M.D.
Assistant Professor of Medicine and Oncology
Director, Sickle Cell Center for Adults at Johns Hopkins
School of Medicine
The Johns Hopkins University

2:50 p.m. Reproductive and Developmental Effects of Hydroxyurea
Erica L. Liebelt, M.D., FACMT, F.A.A.P.
Professor of Pediatrics and Emergency Medicine
Director, Medical Toxicology Services
University of Alabama School of Medicine
Children's Hospital and University Hospital

3:10 p.m. Adverse Effects of Hydroxyurea From Clinical Studies
Cage S. Johnson, M.D.
Director
University of Southern California Comprehensive Sickle Cell Center
Professor of Medicine
Keck School of Medicine
University of Southern California

3:30 p.m. Discussion

Monday, February 25, 2008 (continued)

What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions?

4:00 p.m. Evidence-Based Practice Center Presentation III: Appropriate Use of Therapies Among Patients With Sickle Cell Disease: A Systematic Review of Barriers and Interventions To Improve Quality
Mary Catherine Beach, M.D., M.P.H.
Assistant Professor of Medicine and Health Policy and Management
Division of General Internal Medicine
School of Medicine
The Johns Hopkins University

4:20 p.m. Barriers for Pediatric Patients: The Healthcare Providers' Perspective
Marsha J. Treadwell, Ph.D.
Director, Patient Services Core
Northern California Comprehensive Sickle Cell Center
Children's Hospital and Research Center at Oakland

4:40 p.m. Barriers for Pediatric Patients: The Consumer's Perspective
Regina Hutchins-Pullins

5:00 p.m. Discussion

5:30 p.m. Adjournment

Tuesday, February 26, 2008

What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions? (continued)

8:30 a.m. Barriers for Adult Patients: The Physician's Perspective
Wally R. Smith, M.D.
Professor of Medicine
Chairman, Division of Quality Health Care
Department of Family Medicine
Virginia Commonwealth University

8:50 a.m. Barriers for Adults: The Consumer's Perspective
Trevor K. Thompson, M.A.
Chairman, Patient Advisory Board
Diggs-Kraus Sickle Cell Center

9:10 a.m. The Medical Home Model
Thomas S. Webb, M.D., M.Sc.
Assistant Professor of Clinical Internal Medicine and Pediatrics
Principal Investigator, Cincinnati Sickle Cell Network, HRSA SCD Treatment Demonstration Program
Division of General Internal Medicine
University of Cincinnati
Cincinnati Children's Hospital
Institute for the Study of Health

Tuesday, February 26, 2008 (continued)

What Are the Barriers to Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease, and What Are the Potential Solutions? (continued)

9:30 a.m. Models of Comprehensive Care
Bruce L. Evatt, M.D.
Clinical Professor of Medicine
Emory University School of Medicine
Retired Former Director
Division of Hereditary Blood Disorders
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

9:50 a.m. Discussion

10:30 a.m. What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Pediatrician's Perspective
Michael R. DeBaun, M.D., M.P.H.
Professor of Pediatrics, Biostatistics, and Neurology
Director, Sickle Cell Medical Treatment and Education Center
Washington University School of Medicine
St. Louis Children's Hospital

10:50 a.m. What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Adult Provider's Perspective
Richard Lottenberg, M.D.
Director
University of Florida Adult Sickle Cell Disease Program
Professor
Division of Hematology/Oncology
Department of Medicine
University of Florida

11:10 a.m. What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Consumer's Perspective
Melissa S. Creary, M.P.H.
Associate Service Fellow
Division of Blood Disorders
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

11:30 a.m. Discussion

Noon Adjournment

Wednesday, February 27, 2008

9:00 a.m.	Presentation of the draft Consensus Statement
9:30 a.m.	Public Discussion
11:00 a.m.	Panel Meets in Executive Session
2:00 p.m.	Press Conference
3:00 p.m.	Adjournment

Panel

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*Otis W. Brawley, M.D., accepted a position at American Cancer Society in November 2007.

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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

The organizers would also like to thank the planning committee, the panel, The Johns Hopkins University Evidence-Based Practice Center, and the Agency for Healthcare Research and Quality, as well as the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and NIH cosponsoring Institutes and Centers. We appreciate your continued interest in both the NIH Consensus Development Program and the treatment of sickle cell disease.

Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

The abstracts for the following presentations do not appear:

Sickle Cell Disease: The Consumer's Perspective
Richard Watkins

The Laboratory Evidence of Efficacy of Hydroxyurea in the Treatment of Sickle Cell Disease
Eugene P. Orringer, M.D.

Sickle Cell Anemia: Yesterday, Today, and Tomorrow

Griffin P. Rodgers, M.D., M.A.C.P.

Sickle cell anemia is a severe hemoglobinopathy caused by a single nucleotide substitution in codon 6 of the β-globin gene. This single mutation leads to the formation of the abnormal hemoglobin, HbS ($\alpha_2\beta^S_2$), which is much less soluble than hemoglobin A (HbA, $\alpha_2\beta_2$) when deoxygenated. This insolubility results in the formation of aggregates of HbS polymer inside sickle erythrocytes as they traverse the circulation. With more extensive deoxygenation, polymer becomes so extensive that the cells become sickled in shape, yet even at high oxygen saturation values there may be sufficient quantities of HbS polymer to alter the rheological properties of the sickle erythrocyte in the absence of morphological changes. These cells can occlude end arterioles, leading to chronic hemolysis and microinfarction of diverse tissues. This process leads to vaso-occlusive crises and irreversible tissue damage.

In recent years, the role of molecular and genetic modifiers, the effects of inflammation, cellular adhesion, and endothelial damage have complemented and expanded our understanding of the pathophysiology of the disease, as has the very recent appreciation of the role of nitric oxide in sickle cell pathogenesis. This improved understanding has led to current therapies to interfere with HbS polymerization based on fetal hemoglobin (HbF) augmentation, to prevent cellular dehydration and endothelial adhesion, and to replace the defective erythroid cell population by allogeneic stem cell transplantation. The opportunity for effective intervention at different points in the pathogenetic pathway strongly suggests that the combination of two or more agents, each with a different mechanism of action, would be additive and perhaps synergistic, similar to multidrug regimens for hypertension and cancer chemotherapy.

At present, hydroxyurea (HU) is the major medical modality with proven efficacy in patients with frequent symptoms related to sickle cell disease (SCD), although there is increasing evidence that HU is prescribed to only a fraction of patients who may benefit from it. A definitive cure is not currently available for most patients. Gene therapy for SCD has proven to be the elusive therapeutic “holy grail,” due to the difficulty in transducing hematopoietic stem cells and the necessity for erythroid-specific, high-level, and balanced globin gene expression. As a result, increasing attention has been focused on the use of hematopoietic stem cell transplantation—both full intensity and, more recently, nonmyeloablative allogenic regimens. Studies of the clinical variability of the disease attributed to genetic differences in candidate genes based on single nucleotide polymorphisms and/or differences in gene expression profiles of target tissues (i.e., erythroid cells, endothelial cells, etc.) may also identify novel therapeutic targets. Current genomic studies should provide more insights on directing strategies to resolve these therapeutic challenges.

Evidence-Based Practice Center Presentation I: The Efficacy and Effectiveness of Hydroxyurea Treatment for Patients Who Have Sickle Cell Disease

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Introduction: Sickle cell disease (SCD) is a genetic disorder caused by a point mutation in the β-globin gene of hemoglobin that affects nearly 100,000 Americans.[1] In addition to reduced life expectancy of 25–30 years,[2] patients with SCD experience severe pain and reduced quality of life.[3] In February 1998, hydroxyurea (HU) was approved by the U.S. Food and Drug Administration for use in adults with SCD.

Objective: We conducted a systematic review to synthesize the published data on the efficacy and effectiveness of HU treatment for patients with SCD.

Methods: Literature inclusion criteria were tailored for each question based on the availability and applicability of trial evidence and relevance of other study designs. We addressed the efficacy and effectiveness of HU in children and adults separately. Due to limited evidence from randomized controlled trials (RCTs), we included nonrandomized trials, cohort studies with a control population, and pre-/poststudies.

Literature sources: We searched for articles published before June 30, 2007, in the MEDLINE®, EMBASE®, TOXLine, and CINAHL databases as well as hand searching reference lists and consulting experts. All searches were limited to English-language articles on treatment of humans. Review articles were excluded from the searches.

Eligibility criteria: An article was included if it addressed a key question and 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 also excluded studies with fewer than 20 patients.

Article inclusion/exclusion: Paired reviewers excluded articles based on the title, abstract, and full text. Agreement was required to exclude an article based on title; differences in opinions at abstract and inclusion/exclusion review were resolved by consensus adjudication.

Assessment of study quality: For RCTs, we used the scoring system developed by Jadad et al.[4] For observational studies (both cohort studies and controlled clinical trials), we created a quality form, based on those previously used by our Evidence-Based Practice Center (EPC). We designed questions to evaluate the potential for selection bias (three items) and confounding (five items). Paired reviewers assessed quality independently. A third reviewer reconciled the results of the first two reviewers for the randomized trials. For the other study designs, the results of the two reviewers were averaged. We considered high-quality studies to be those with a Jadad score of 4 or 5, or receiving 80% or more of available quality points.

Data extraction: We used a sequential review process whereby the primary reviewer abstracted all relevant data into forms and a second reviewer verified the first reviewer's forms for completeness and accuracy. Differences were resolved by discussion. We created detailed evidence tables containing information extracted from eligible studies.

Grading of the evidence: We adapted the evidence-grading scheme recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group,[5] and further developed in the EPC guide,[6] to grade the quantity, quality, and consistency of the available evidence addressing the efficacy and effectiveness of HU. We considered the strength of the study designs as best for RCTs, followed by nonrandomized controlled trials and observational studies.

Results: We included 8 articles describing two RCTs and 37 articles describing observational studies (11 with overlapping participants).

- **Children.** A single, small, placebo-controlled randomized trial of HU for 6 months in Belgian children reported significantly lower rates of hospitalization and hospitalized days per year in the HU group (1.1 admissions, $p = 0.0016$ and 7.1 days hospitalized, $p = 0.0027$) compared to the placebo group (2.8 admissions and 23.4 days hospitalized). Fetal hemoglobin (HbF%) increased by an absolute 10.7% from baseline in the treated group ($p < 0.001$).[7]

  HbF% was reported as an outcome in 17 observational studies. The mean pretreatment HbF% ranged from 5 to 10%, and the on-treatment values were in the range of 15 to 20%. The percentage of HbF cells was less frequently reported, but it increased from baseline in three of the four pediatric studies. Three of these studies were retrospective; two reported increases in HbF% comparable to that in the prospective studies. Hemoglobin concentration increased modestly (roughly 1 g/dL) but significantly across studies.

  The frequency of pain crises decreased in three of five pediatric studies. In one retrospective cohort study in a resource-poor environment, with a median follow-up of 24 months, pain crises declined from three (median) per year to 0.8 per year on treatment. Importantly, these results were attained by using a fixed-dose of HU of 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 HU therapy to 1.2 per year during 18 months of therapy. Hospitalization rates decreased in all four studies describing this outcome. In the retrospective study described above, hospitalization decreased from 4 (median) per year to 0.5 per year while on treatment. In the Belgian Registry, hospitalization declined from 3.2 to 1.1 per patient-year during the third year of treatment.

  One study assessed the impact of HU on secondary stroke prevention in 35 children discontinuing chronic transfusions. The rate of recurrent stroke was 5.7 per 100 patient-years (lower than rates usually seen after stopping transfusions). One other study reported stable magnetic resonance imaging of the brain during HU treatment in 24 of 25 children.

- **Adults.** The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) randomized 299 adults with SCD. In the HU treatment arm, the median number of painful crises was 44% lower, and the time to the first painful crisis was 3 months compared to 1.5 months in the placebo arm.[8] There were fewer episodes of acute chest

syndrome and transfusions, but no significant differences in deaths, strokes, and chronic transfusion or hepatic sequestration. The significant hematological effects of HU versus placebo after 2 years were higher total hemoglobin by 0.6 g/dL and higher HbF% by 3.2%. The absolute neutrophil count and reticulocyte count were significantly lower in those receiving HU.[9] Use of HU had no significant effect on annualized costs or quality of life.

HbF% increased from a pretreatment baseline of 4–12% to 10–23% during HU treatment in six prospective and one retrospective cohort studies of adults. There was a small increase in hemoglobin in most studies. Three studies described the number of pain crises. In a study of Sicilians with hemoglobin Sβ-thalassemia, the frequency of crises decreased significantly from a median of 9 per year to 1.8 per year. In a nonrandomized study, patients receiving HU had fewer pain crises (1.4 per year, p <0.05) than those receiving cognitive behavioral therapy (4.3 per year), but this was not a strong study design for this outcome. Similarly, hospitalization rates decreased consistently for adults treated with HU. In the study of Sicilians, hospitalized days per year declined from 22.4 days to 1.2 days (p <0.0001). In a retrospective effectiveness study, the rates of hospitalization declined from baseline in the group treated for longer than 24 months (3.1 per year to 2.1 per year, p = 0.04). However, among the group treated for fewer than 24 months, there was no significant difference in hospitalization rates from baseline.

Conclusion: Based on our review, the published evidence supports with high likelihood that HU treatment (1) reduces the frequency of hospitalizations in both children and adults with SCD, (2) increases HbF% in both children and adults with SCD, and (3) reduces the frequency of transfusions and pain crises in adults (Table 1).

Table 1. Summary of Evidence About Efficacy of Hydroxyurea in Sickle Cell Disease

Pediatric Outcomes	**Evidence Grade**	**Basis for Grade**
Increase in fetal hemoglobin	High	One good RCT; consistent observational studies
Reduction in hospitalizations	High	One good RCT; consistent observational studies
Reduction in pain crises	Moderate	One good RCT; inconsistent observational studies
Reduction in neurological events	Low	Observational studies
Reduction in transfusion frequency	Insufficient	Few observational studies
Adult Outcomes		
Increase in fetal hemoglobin	High	One good RCT; consistent observational studies
Reduction in pain crises	High	One good RCT; consistent observational studies
Reduction in hospitalizations	High	One good RCT; consistent observational studies
Reduction in transfusion frequency	High	One good RCT; consistent observational studies
Mortality	Low	Inconsistent observational studies
Reduction in neurological events	Insufficient	No studies with sufficient events

RCT = randomized controlled trial

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Summary of the Evidence Regarding Efficacy of Hydroxyurea Treatment for Sickle Cell Disease in Adults

Martin H. Steinberg, M.D.

Hydroxyurea (HU), a ribonucleotide reductase inhibitor, has been used safely for many years in myeloproliferative disorders and other neoplasms. Its known effects on hematopoiesis suggested that it might lead to the induction of fetal hemoglobin (HbF) in sickle cell anemia (homozygosity for *HBB* glu6val). Following pilot studies and Phase II trials that suggested that HU could safely increase HbF in adult sickle cell anemia, a pivotal efficacy trial, the Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH), was initiated.[1–5] The MSH remains the sole placebo-controlled, double-blinded study of the efficacy of HU in adult sickle cell anemia.

In the MSH, HU reduced by nearly half the frequency of hospitalization and the incidence of pain, acute chest syndrome, and blood transfusion as well as increasing the time to a first painful episode or acute chest syndrome.[5] HbF increased from 5% to about 9% after 2 years of treatment.[6] Some aspects of quality of life and exercise performance improved.[7,8] MSH patients are likely not typical of all patients treated with this drug, as they were older symptomatic adults and were treated with maximal tolerated doses of HU. In a different study, when HU was not pushed to toxicity, HbF levels near 20% were achieved; however, this was not a controlled trial.[9]

Decreased morbidity due to HU may be associated with reduced mortality. When cumulative mortality was analyzed according to total exposure to HU in the MSH patients' follow-up, reductions in vaso-occlusive complications, HbF levels ≥0.5 g/dL, absence of acute chest syndrome, and fewer painful episodes were all associated with reduced mortality.[10] No relationship between decrements in neutrophil counts and mortality was found. Mortality was reduced 40% during 3-month intervals when patients were taking HU, from an average of 2.6 deaths per 3 months to 1.5 deaths per 3 months. Without a long-term case-control study of the effects of HU on mortality, we must rely on follow-up of MSH patients and on other uncontrolled studies to estimate this important statistic.

Observational trials of HU treatment in adults with sickle cell disease have been reported.[3,11–15] All showed an increase in HbF and a reduction in painful episodes and hospital admissions, albeit of variable size of effect.

An ability to respond to HU in adults could be dependent on the capacity of the marrow to withstand moderate myelosuppression triggering the regeneration of erythroid precursors that synthesize HbF.[6] The hematopoietic capacity of the bone marrow might be reflected by the pretreatment reticulocyte and neutrophil count. However, in children, these hematological measurements had little predictive value, whereas baseline HbF level was a reasonable predictor of the response to treatment.[16]

Unfortunately, predicting which individual patient will respond to HU treatment with an increase in HbF is still not possible. The HbS gene is associated with five major haplotypes of the β-globin gene-like cluster, and these haplotypes are associated with differential expression of the HbF. Individuals with the best HbF response to HU were less likely to have a HbS gene on a Bantu haplotype chromosome.[6] In sibling pairs with sickle cell anemia given HU, there was a

correlation between siblings in HbF level, both before and after HU treatment, and a possible HU-mediated effect on HbF.[17]

In uncontrolled studies, HU appeared to increase HbF in HbS-β^0 thalassemia and HbS-β^+ thalassemia.[13,15]

Little information is available about the efficacy of HU in HbSC disease (compound heterozygosity for *HBB* glu6val and glu6lys). In pilot studies, HU was associated with increased mean corpuscular volume and hemoglobin concentration, with variable increments in HbF.[18–20] A Phase II placebo-controlled, double-blinded clinical trial of HU in HbSC disease is ongoing.

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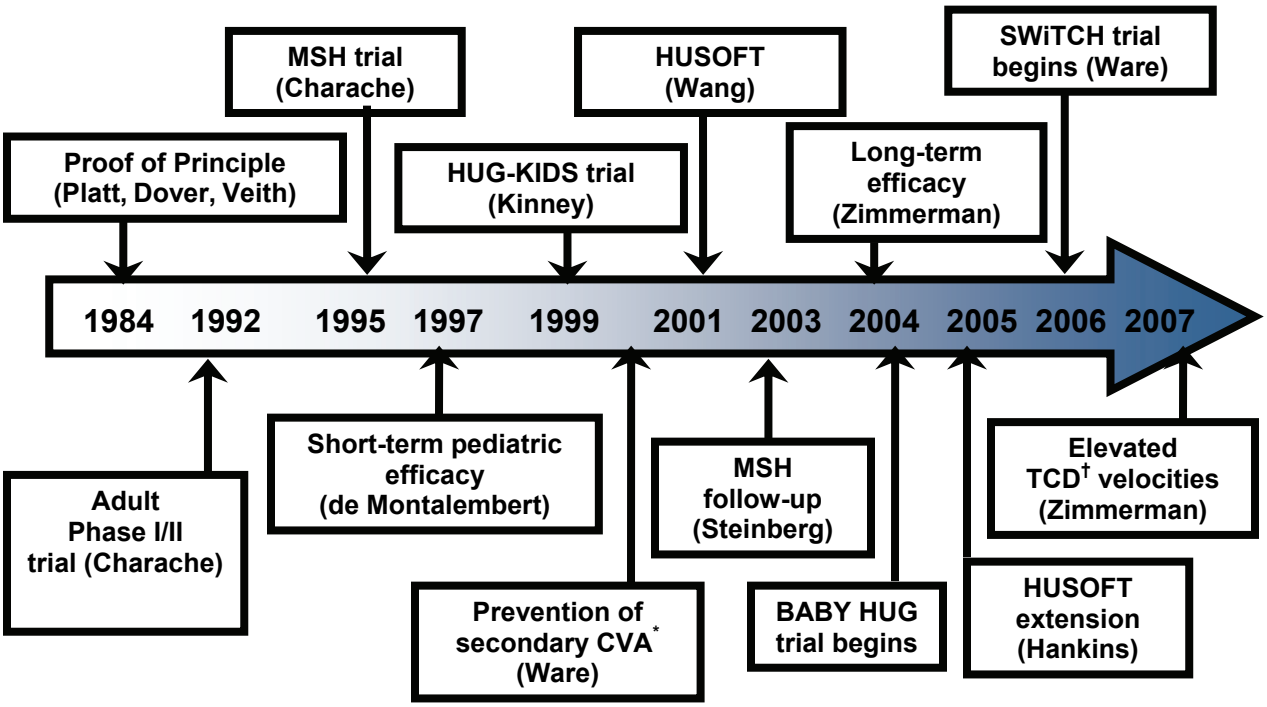
Summary of the Evidence Regarding Efficacy of Hydroxyurea Treatment for Sickle Cell Disease in Children and Adolescents

Russell E. Ware, M.D., Ph.D.

For almost 25 years, clinical experience has been accumulating regarding the safe and efficacious use of hydroxyurea (HU) therapy for patients with sickle cell disease (SCD). Figure 1 illustrates a timeline for HU treatment in this patient population, beginning with several early "proof of principle" studies in adults.[1–4] An important prospective Phase I/II study in adults treated to maximum tolerated dose (MTD)[5] was then followed by the pivotal Phase III Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) trial.[6] Subsequently, several reports described pediatric patients who received open-label HU treatment with good results.[7–10] The Phase I/II trial of the Pediatric Hydroxyurea Group (HUG-KIDS)[11] demonstrated that laboratory efficacy and toxicities were similar for children and adolescents to those previously observed for adults. The Phase I/II Hydroxyurea Safety and Organ Toxicity (HUSOFT) trial[12] then reported that infants could tolerate HU (using a liquid formulation) with laboratory and clinical efficacy.

Figure 1. Timeline of HU therapy for SCD.



Clinical experience with HU in SCD has been accumulating for almost 25 years, with many studies occurring in the past decade.

*CVA = cerebral vascular accident (stroke)

† TCD = transcranial Doppler

Long-term follow-up studies of HU for SCD have now been reported for adults,[13,14] children,[15–17] and even infants.[18] These studies showed that laboratory and clinical efficacy of HU therapy is sustained for adherent patients, with no evidence of pharmacological tolerance or resistance. More recently, the clinical efficacy of HU for cerebrovascular disease among children with SCD has been investigated. In open-label studies, HU at MTD has demonstrated efficacy for the prevention of secondary stroke[19,20] and also for lowering transcranial Doppler velocities that serve as a surrogate marker for primary stroke risk.[15,21,22] Pivotal Phase III randomized clinical trials using HU (BABY HUG and SWiTCH) are now underway.

The short-term toxicities of HU therapy are usually mild and often are none at all. Although occasional patients will describe gastrointestinal symptoms or dermatological changes (e.g., hyperpigmentation, melanonychia),[23] these are typically not severe. Dose-dependent cytopenia is a predictable and even desirable effect if the patient is escalated to MTD;[5,11,24] any exaggerated hematological changes are transient and reversible with a brief discontinuation of the drug. Table 1 illustrates the cumulative incidence of short-term laboratory toxicity associated with HU therapy at MTD for children with SCD. Even with the conservative thresholds used in the HUG-KIDS study,[11] few severe hematological toxicities were observed. Table 2 illustrates that HU at MTD has similar laboratory efficacy for children as it does for adults with SCD.

Table 1. Cumulative frequency of adverse laboratory events among children with sickle cell anemia treated to MTD of HU in HUG-KIDS.[11]

	% Patients	% Visits
Neutropenia	67	5.2
Reticulocytopenia	42	1.6
Anemia	32	1.1
ALT elevation	13	0.4
Thrombocytopenia	8	0.3
Creatinine elevation	0	0.0

Table 2. Children with sickle cell anemia have similar laboratory efficacy using HU at MTD as adults.

	Adults	Children
MTD (mg/kg/day)	21.3	25.6
Δ Hb (gm/dL)	+ 1.2	+ 1.2
Δ MCV (fL)	+ 23	+ 14
Δ HbF (%)	+ 11.2	+ 9.6
Δ Reticulocytes (10^9/L)	– 158	– 146
Δ WBC (10^9/L)	– 5.0	– 4.2
Δ ANC (10^9/L)	– 2.8	– 2.2
Δ Bilirubin (mg/dL)	– 2.0	– 1.0

Data are from published Phase I/II trials for adults[5] and children[11] with sickle cell anemia.

The documented clinical efficacy of HU for prevention of acute vaso-occlusive events has not been formally proven for children with SCD in the setting of a Phase III placebo-controlled randomized clinical trial. In open-label trials, however, there is substantial evidence that HU works similarly for children as for adults, with reductions in the number of painful events or acute chest syndrome events, compared with historical controls.[15,17,18,25] Early concerns about negative effects on growth and development have not been realized; HU actually leads to reduced energy expenditure among children,[26] as well as improved growth rates (height, weight) and development for school-aged children[11,16,27] and even infants with SCD.[18]

Critically important questions regarding the potential of HU to prevent chronic organ damage among children with SCD, or possibly to preserve existing organ function, have not yet been answered definitively. However, there is accumulating evidence that HU can have a salutary effect on preservation of organ function in children with SCD, specifically for brain,[19,22] spleen,[12,18,28,29] lung,[30] and kidney.[31] The ongoing BABY HUG trial should provide important data regarding these questions; the primary endpoint of this placebo-controlled Phase III trial is the prevention or reduction of chronic spleen and kidney damage. Finally, despite the benefits of HU for clinical efficacy related to both acute and chronic complications of SCD, its potential to be an in vivo clastogenic, teratogenic, mutagenic, and even carcinogenic agent have not been fully addressed. To date, however, studies have not documented any clinically relevant changes or increases in malignancy beyond those observed in untreated patients with SCD.[32,33]

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Practical Treatment Considerations for Hydroxyurea in Pediatric and Adult Patients With Sickle Cell Disease, Including Maximum Tolerated Dose, Labeling of Responders Versus Nonresponders, and Adherence to Therapy

Kenneth I. Ataga, M.D.

Hydroxyurea (HU) remains the only drug specifically approved for the prevention of complications related to sickle cell disease (SCD). We undertook a systematic review of the maximum tolerated dose (MTD), labeling of responders versus nonresponders, and adherence to therapy for HU. We searched MEDLINE® and the Cochrane Collaborative resources, excluding studies that: (1) were not published in English, (2) had fewer than 20 subjects, or (3) did not report information pertinent to the key clinical questions. Despite the paucity of high-quality evidence, a summary of the best available literature that evaluated these subjects was compiled.

Maximum Tolerated Dose

The data for adequate dosing of HU are limited by the number of adequately controlled clinical trials. Furthermore, there are no trials comparing the efficacy of HU in patients with SCD using the MTD to other dosing regimens. The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) reported a statistically significant decrease in the annual rate of pain crises, episodes of acute chest syndrome, and transfusions when adult patients on HU were compared with those on placebo.[1] In this study, the dose of HU was escalated to 35mg/kg/day or MTD, with only 21% of patients receiving the maximal prescribed dose. Multiple studies report on improvements in clinical and hematological parameters in patients with SCD when the dose of HU is escalated to the MTD.[2–10] However, several other studies report similar improvements using fixed doses of HU.[11–14] In one prospective, multicenter, open-label study in children that compared hematologic indices after treatment with a fixed dose of HU versus dose escalation of HU,[6] dose escalation of HU produced significantly higher levels of fetal hemoglobin (HbF), but other indices were not significantly different. Finally, as a result of increased systemic exposure and decreased urinary recovery, patients with SCD and renal insufficiency may require a lower starting dose of HU and very careful dose titration.[15]

Although escalation of the dose of HU appears to increase HbF levels, there are insufficient data to say that MTD produces more clinical benefits compared with fixed doses of HU.

Labeling of Responders Versus Nonresponders

The majority of studies of HU treatment have not assessed the factors that determine the clinical response of patients; rather, they have evaluated factors that are associated with increased HbF levels. An early study of HU suggested that the most significant factors associated with HbF level are the last plasma HU level, initial white blood cell (WBC) count, and the initial HbF concentration, but not β-globin haplotype or α-globin gene number.[16] However, plasma HU clearances are not a useful guide to MTD**,** and the ability to measure plasma levels of HU generally is not available to most physicians. In the MSH, increases in HbF level at 2 years were greatest in patients with the highest baseline reticulocyte and neutrophil counts, two or more episodes of study-defined myelotoxicity**,** and absence of a Bantu haplotype,

suggfdesting that the ability to respond to HU may depend on bone marrow reserve or the capacity of the marrow to withstand moderate doses of HU with acceptable myelotoxicity.[17,18] Surprisingly, the initial HbF level was not associated with final HbF response. In the highest quartile of HbF response, myelosuppression developed in less than 6 months, patient compliance rates with the drug regimen were highest, and final doses of HU were 15–22.5 mg/kg. Results from the Phase I–II trial of the Pediatric Hydroxyurea Group (HUG-KIDS), involving 53 children, showed that baseline HbF values, MTD of HU, and patient compliance with therapy were associated with higher HbF levels at MTD.[19] The baseline reticulocyte and WBC counts were significantly associated with higher HbF levels at MTD only after adjusting for variations in baseline HbF. In a smaller study of 29 children, HbF at maximal response was not related to HU dosage.[20] However, change in HbF was strongly correlated with change in mean corpuscular volume (MCV) but not with baseline reticulocyte or neutrophil counts.

In the MSH, it was not clear that clinical improvement was associated with an increase in HbF.[21] When patients were compared on the basis of rates of crises within 2 years, those with lower rates of crises had higher F-cell counts and MCVs as well as lower neutrophil counts. However, in multivariable analyses, only lower neutrophil counts were independently associated with lower rates of crises rates, while F-cells were associated with the rate of crises only in the first 3 months of therapy.

Adherence to Therapy

One small study reported on HU compliance by using computerized pill bottles containing cap microprocessors which monitor the frequency of bottle openings.[22] Over a period of 18.5 ± 2.1 months, compliance with HU (determined by the percent of prescribed drug actually taken) was $96 \pm 2\%$, resulting in increased levels of mean HbF. Despite the excellent compliance in this study, insufficient data remain on adherence to HU therapy in SCD.

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Summary of the Evidence Regarding Effectiveness of Hydroxyurea in the Treatment of Sickle Cell Disease in the Pediatric Population

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Sickle cell disease (SCD) is a complex disease with clinical pathology involving many organ systems. The clinical pathology of the disease can be broadly divided into three categories: hemolytic anemia, vascular occlusion and damage, and tissue and organ damage. These pathologic features are typically chronic, with superimposition of unpredictable acute exacerbations. The disease is also characterized by a wide variation in the spectrum of acute complications and chronic organ damage seen in patients. With the possible exception of the degree of anemia, no feature of SCD uniformly typifies any of its genotypes by rate or severity of occurrence. In designing clinical trials, it is customary to select the most common and easily countable clinical events to serve as the primary outcome measure. In SCD, this measure is usually pain episodes. However, some of the major complications of the disease, such as stroke and acute chest syndrome, are not related to pain in rates of occurrence.

The use of hydroxyurea (HU) therapy in children with SCD began in the early 1990s, soon after the early Phase II trials in adults were reported. There have since been several reports of clinical trials to determine the short-term efficacy and toxicity profile of HU in children with SCD.[1–4] On the basis of the Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH),[5] HU was licensed for the treatment of SCD "specifically for patients over 18 who have had at least three 'painful crises' in the previous year—to reduce the frequency of these crises and the need for blood transfusions."[6] However, HU, by increasing the level of fetal hemoglobin (HbF) in red cells and the percentage of F cells in people with SCD, can be expected to have broad effects that can ameliorate the clinical pathology of SCD. Studies of the effectiveness of HU in children may have very different outcome measures from those that may be useful in adults. Laboratory measures, composite clinical outcomes, and quality-of-life measures are all important in assessing the effectiveness of HU therapy in the long term.

Initially, pediatric trials borrowed the clinical inclusion criteria used in the adult Phase II studies.[3] Unfortunately, there has been no large-scale randomized clinical trial to determine the clinical efficacy of HU in children with SCD. The Food and Drug Administration has not approved HU specifically for use in children with SCD. Therefore, the use of HU in children with SCD is technically "off-label." Nevertheless, there is widespread use of HU in treatment of children with SCD.

The "off-label" indications for HU use in children with SCD have now gone beyond those for which the drug was licensed for use in adults and include the following: recurrent severe pain episodes, recurrent acute chest syndrome, recurrence of stroke, chronic severe anemia, abnormally high cerebral blood flow velocity (as measured by transcranial Doppler ultrasonography), and cardiac ischemia.[7]

There is no widely accepted single protocol established for the administration of HU in children with SCD. Such basic features of use of the drug in children, such as starting and maximum doses, dose escalation, dose modification for toxicity, and maximal tolerated dose have not been established. Some studies use a single dose, while most start with a low dose and

escalate to a maximal dose.[4,8] In addition, monitoring of therapy has not been standardized. The early pediatric Phase II trials used monitoring schedules similar to those used in the adult MSH trial. However, very few studies use the same protocol, making it difficult to compare effectiveness of the therapy between studies.

Although there are many indications for the use of HU in SCD, no clinical or laboratory therapeutic goals have been established for clinical practice situations. Even objective outcomes such as overall hemoglobin and HbF levels have not been applied in the clinical use of HU; moreover, those laboratory outcomes may not correlate directly with clinical outcomes. For example, the basis on which treatment can be declared a success or a failure is unclear for a given patient on HU therapy.

Compliance with HU administration is also an issue, and a fair percentage of children recruited into HU studies fail to continue the therapy for various reasons.[7] In general clinical practice, it is unknown how inconsistent compliance with the therapy affects clinical outcomes over a long period of time.

Despite these shortcomings, the few studies reporting more than 5-year use of HU in "general" clinical settings appear to demonstrate a reduced frequency of the major complications of SCD. Two of the largest reports are from Europe, where there have been attempts to maintain long-term follow-up of children treated with HU.[7,9] In the United States, where perhaps thousands of children with SCD are being treated with HU, there is no multi-institutional data collection on HU therapy in children with SCD. The failure to develop and maintain a registry of the large number of children with SCD taking HU in the United States is unfortunate, because without such a registry, it is virtually impossible to learn about the long-term effectiveness and toxicity of the drug in this population.

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Summary of the Evidence Regarding Effectiveness of Hydroxyurea in the Treatment of Sickle Cell Disease in the Adult Population

James R. Eckman, M.D.

The efficacy of hydroxyurea (HU) in adults was documented in the landmark Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH).[1] As shown in Table 1, this randomized, double-blinded, placebo-controlled trial showed that treatment with HU reduces presentation to health centers for sickle pain episodes, hospital admissions for pain episodes, episodes of acute chest syndrome, the need for transfusions, and the total units of blood transfused.[1,2] Nine-year follow-up of the original study subjects suggested a survival advantage to individuals who remained on HU and those with a higher fetal hemoglobin (HbF) response that may have been caused by fewer pain episodes and episodes of acute chest syndrome.[3]

Table 1. Multicenter Trial of Hydroxyurea[1]

Complication	HU Group	Placebo Group	p Value*
Pain episodes	2.5/year	4.5/year	p <0.001
Pain admissions	1.0/year	2.4/year	p <0.001
Acute chest syndrome	25 episodes	51 episodes	p <0.001
Transfused	48	73	p <0.001
Total units	336	586	p = 0.004

*p Values determined by a Van deWaerden Test

Subsequent publications from the MSH study showed a reduction in annual cost for the care of patients taking HU from $17,290 for those on placebo (95% CI, $13,010–$21,570) compared to $12,160 (95% CI, $9,440–$14,880) for those taking HU.[4] This finding was supported by data from Maryland reported by Lanzkron and colleagues at the recent American Society of Hematology meeting.[5] Data have also emerged from the MSH study that suggest an improved quality of life in individuals taking HU; the improvement mainly relates to reduction in pain.[6] Subsequent studies have suggested reductions in hospitalization rates,[7] while others suggest no such effect.[8]

The profile of side effects of HU treatment in sickle cell disease (SCD) has been very favorable, demonstrating similar rates of all complications except cytopenia in HU- and placebo-treated subjects.[1] Lingering concerns about increased incidence of leukemia and cancer are not presently supported by data. In the Atlanta study experience, questions about reproductive performance continue to be a major concern that prevents younger individuals from benefiting from HU therapy. The original concern was for birth defects in infants of mothers who conceived while on HU; however, this concern is still unsupported by data. Case reports and small case series reporting reduced sperm counts and morphologic abnormalities in sperm from males on HU[9,10] have been cited by many as a reason for not taking the drug. A past history of leg ulcers in individuals may be associated with an increased risk of recurrence in individuals taking HU.[11]

There are few Phase IV data in adults to guide practice in individuals with SCD. Small case series suggest that the incidence of pulmonary hypertension may be reduced by early use of HU.[12] Studies in children[13] and anecdotal experience of the author suggest that proteinuria may be reduced and renal function preserved by the use of HU in individuals with glomerular disease. Small case series and the experience of the author also suggest that the difficult complication of priapism is reduced in frequency by aggressive treatment with HU.[14,15] These areas and the impact of reduction of acute chest syndrome on chronic pulmonary disease should be major priorities in designing multicenter epidemiologic studies comparing subjects on HU with those not benefiting from such therapy.

A number of other areas deserve further investigation. There are few data on the benefits of therapy in individuals with hemoglobin SCD or sickle β-thalassemia. The true impact of HU therapy on pain and quality of life has not yet been documented. Recent studies of pain, in adults from Virginia who used daily pain diaries, suggest that pain that results in presentation to health professionals for care is the "tip of the iceberg."[16] This finding suggests that longitudinal, multicenter studies of the true impact of HU on pain and quality of life are needed. More extensive studies of the impact of HU on healthcare utilizations and costs are also warranted. Large-scale multicenter trials are clearly needed that will enroll adults with SCD to address whether HU can substitute for transfusion in individuals at risk for stroke. A randomized trial in priapism is also important because of the major impact of this complication on males' quality of life in the acute setting, the long-term occurrences of priapism and their importance, and practitioners' and patients' resistance to currently available interventions. Because pulmonary hypertension appears to be associated with a high incidence of death, use of HU to prevent this complication also should be studied.

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Evidence-Based Practice Center Presentation II: A Systematic Review of Safety and Harm Associated With Hydroxyurea for the Treatment of Sickle Cell Disease

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Introduction: Sickle cell disease (SCD) affects nearly 100,000 Americans,[1] decreases life expectancy by 25–30 years,[2] and has important morbidity.[3] Hydroxyurea (HU) is the only medication approved by the U.S. Food and Drug Administration to modify the severity of the disease.

Objective: We aimed to systematically review the literature on the efficacy, effectiveness, and harms associated with HU. We describe here our findings on the toxicities of HU.

Methods: In 2006, after a literature review and expert panel discussion, the Center for the Evaluation of Risks to Human Reproduction (CERHR) reported on the effect of HU on growth and development.[4,5] We include their results with our literature review. Their review included some animal studies, as noted below. Our assessment of the strength of evidence regarding the toxicity of HU when used in children for any diagnosis largely came from our review of the report by the panel of experts assembled by CERHR.

Literature Sources: We searched MEDLINE,® EMBASE,® TOXLine, and CINAHL through June 30, 2007. We also reviewed reference lists and discussed search results with experts. All searches were limited to English-language publications describing treatment of humans. Review articles were excluded from the searches.

Eligibility Criteria: For evidence of toxicity, we included randomized controlled trials, cohort studies with a control population, and pre- and poststudies of adults who had SCD and were treated with HU. We also included case reports, a weaker form of evidence. We included studies of children with SCD if leukemia or lymphoma was described. We also included indirect evidence from studies enrolling patients treated with HU for other diseases. Two reviewers independently reviewed titles and abstracts for eligibility.

Extraction of Data: A single reviewer abstracted data, and a coinvestigator verified accuracy. For all articles except case reports, reviewers extracted information on study and participant characteristics as well as toxicity outcomes. Case reports were abstracted using the World Health Organization (WHO) causality assessment instrument.[6]

Grading of Evidence: We graded the quantity, quality, and consistency of the evidence by adapting an evidence grading scheme recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group[7] and modified in the Evidence-Based Practice Center manual.[8] We graded the case reports according to the WHO Collaborating Center for Drug Monitoring.[6,9] For each outcome, two investigators graded the evidence, then all investigators reached consensus.

Results: Our search identified 12,555 citations potentially relevant to use of HU, in addition to the 2006 CERHR report; 64 studies and 194 case reports applied to our toxicity question.

The CERHR panel members concluded that HU treatment of children aged 5–15 years does not cause a growth delay. The panel felt there were insufficient data to evaluate the effects of HU on pubertal development. They also concluded that there were insufficient data on the effects on subsequent generations following exposure of germ cells to HU, including exposure during fetal life, infancy, childhood, and adolescence. The expert panel found no data on the effects of HU on female human or animal reproductive processes. They found sufficient data to conclude that there is developmental toxicity in rat and mice fetuses exposed to HU in utero. The expert panel concluded that HU has reproductive toxicity in male mice and felt that these experimental animal data were relevant to humans. Therefore, the expert panel had concerns about the adverse effect of HU on spermatogenesis in men receiving HU at therapeutic doses.

The CERHR panel identified 21 papers relevant to use of HU in pregnancy. None was a controlled study. The CERHR report concluded that the use of HU in pregnancy does not appear to be commonly associated with adverse perinatal outcomes, and there are no data on long-term outcomes in children who were exposed in utero. However, based on minimal data from experimental studies, the CERHR was concerned that HU may increase the risk of congenital anomalies or abnormalities of fetal growth.

The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) reported few significant toxicities in adults.[10–13] The investigators described lower absolute neutrophil counts among patients on HU than on placebo, but similar numbers of patients had thrombocytopenia, thrombocytosis, malignancy, aplastic crisis, aseptic necrosis, lymphadenopathy, and bleeding. The proportion of patients reporting hair loss, fever, rash, and/or nail changes, or gastrointestinal disturbance at three or more follow-up visits was similar for the HU and placebo groups.[14] The one publication describing the long-term follow-up of the MSH participants described three malignancies, with two in the group randomized to HU.[10] In the single randomized study of children (in Belgium), white blood cell count decreased with HU treatment.[15] Three cases of leukemia (two children and one adult) were reported in observational studies. An additional three cases of leukemia were described in case reports of adults taking HU for SCD. In one study, data were collected about cancer development in 16,613 patients with SCD.[16] Cancer was diagnosed in 49 patients, including 7 cases of leukemia. Three of these 49 patients had been using HU. There were no data on the prevalence of HU use among the 16,613 people.

We reviewed 19 case reports about toxicities associated with HU use in patients with SCD. Two of these reports described a Greek child who developed Hodgkin's lymphoma.[17,18] The 18 unique case reports included 4 reports of low sperm count or decreased sperm motility, 2 cases of avascular necrosis, 2 cases of skin hyperpigmentation, and 1 case each of leg ulcer, cytopenia, splenomegaly, cryptosporidiosis, intracerebral hemorrhage, myocardial infarction, and Hodgkin's lymphoma—and the 3 leukemia cases described in the paragraph above. Each of these toxicities had only low (WHO Level 3) evidence for causality, with the exception of cytopenia which had moderate evidence (WHO Level 2).

For additional HU toxicity data, we reviewed studies of treated patients with diseases other than SCD. We identified 39 studies as well as 235 case reports in 175 publications. Among the 20 randomized controlled trials, no trial found a greater number of cases of leukemia in the group treated with HU alone. Review of 235 case reports in diseases other than SCD found WHO Level 1 evidence to support the causal role of HU in leg ulcers, interstitial pneumonitis,

hepatitis, azospermia or decrease in sperm motility, limbal stem cell deficiency (a corneal condition), pruritis, and skin neoplasms.

Conclusion: We conclude, based on our review of toxicities both in patients with SCD and in patients with other diseases, that the limited evidence suggests that HU treatment in adults with SCD does not increase the risk of leukemia. High-grade evidence supports that HU has no association with leg ulcer development in patients with SCD, although high-grade evidence supports that HU has an association with leg ulcers in patients with other conditions. The evidence is insufficient in SCD to know whether HU contributes to skin neoplasms, although high-grade evidence in other conditions supports that it does. Similarly, there is insufficient evidence to know if HU is associated with secondary malignancies in adults with SCD, and the evidence in other diseases is only low grade.

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Reproductive and Developmental Effects of Hydroxyurea

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Developmental Effects

The breadth of scientific literature documenting human developmental and reproductive effects of therapeutic hydroxyurea (HU) therapy in children is small. The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (CERHR) published its report on the Reproductive and Developmental Toxicity of Hydroxyurea in January 2007.[1] This report provides a comprehensive summary of both human and animal studies pertinent to the toxicity of HU on development and reproduction. Evidence regarding human developmental toxicity from HU includes its use during pregnancy and childhood and is summarized below.

Summary of Pregnancy Outcomes in Humans: Twenty-one papers describe pregnancy outcomes in women with sickle cell disease (SCD) and essential thrombocythemia who used HU. The largest case series of 32 pregnancies in 31 women reported 2 pregnancies marked by intrauterine growth restriction and 9 premature deliveries.[2] There were no major malformations among the offspring. Three minor malformations included pilonidal sinus, dilated ureter, and hip dysplasia. Numerous other isolated reports and small case series describe preterm deliveries, stillbirth, and intrauterine growth restriction. However, there is an inability to exclude the underlying disease as a cause for these adverse outcomes. The use of HU in pregnancy does not appear to be commonly associated with adverse perinatal outcomes. There are no data on long-term outcomes in children who were exposed in utero to HU. Evidence is insufficient to conclude that HU produces developmental toxicity with exposure during lactation.

Summary of Growth/Puberty: Nine studies report on the effects on growth and development in children with SCD who took HU. Doses of HU were 15–30 mg/kg body weight (bw)/day for most of the studies. Growth was assessed by using standardized curves or percentiles and growth velocities, depending on the study. Follow-up periods were variable. One of the largest studies—the Pediatric Hydroxyurea Safety Trial (HUGS-KIDS), a Phase I/II multicenter trial of HU in 84 children, aged 5–15, with severe sickle cell anemia—demonstrated growth velocity was ≥5th percentile in all children after 6 months, and most children after 1 year (n = 78).[3] None of the clinical studies demonstrated an adverse effect on height or weight while children were on HU therapy. A single study reported that pubertal transitions occurred at ages comparable to those reported in a historical comparison group.[4] These studies have numerous limitations: small patient numbers in most studies, lack of long-term follow-up, lack of growth assessment in other critical time periods (e.g., <5 years of age), inconsistent assessments of growth, and inconsistent assessments of pubertal development. Because of the limitations of the data, evidence is insufficient to conclude that HU treatment of children does not produce growth delay on pubertal progression in children 5–15 years of age. There are no long-term health studies on abnormal development after childhood exposure to HU.

Summary of Mutagenicity: Two studies have looked at acquired DNA mutations associated with HU treatment in children with SCD. In one study, HU was not associated with a statistically significant change in hypoxanthine phosphoribosyl transferase (HPRT) mutation frequency when children on HU therapy for 30 months were compared to children not on HU therapy.[5] Children taking HU had more Vγ-Jβ translocation events than children not on HU therapy. The study's authors suggest that this does *not* directly portend leukemia development. The other

study found no increase in Vγ-Jβ translocations in 34 children treated with HU for at least 5 years when comparisons were made with pretreatment values.[6]

Summary of Carcinogenicity: No long-term studies have assessed the risk of malignancy after childhood exposure to HU. Several observational studies have reported two cases of acute lymphoblastic leukemia in adolescents with SCD while on HU therapy and one case of acute promyelocytic leukemia in a 21-year-old female with SCD who had been on HU therapy for 8 years.[7–9]

Other: There are no studies of the developmental effects on reproductive function in individuals treated with HU during childhood or adolescence. There are no studies on subsequent generations following the exposure of developing germ cells to HU in utero or during infancy, childhood, or adolescence.

Summary of Experimental Animal Data: HU produces developmental toxicity in rat fetuses from dams exposed orally to 200 mg/kg bw/day on gestational day (GD) 7–20 or 300 mg/kg bw/day on GD 6–15, as manifested by increased malformation rate, decreased body weight, and a decrease in number of live pups.[10] At a dose of 100 mg/kg bw/day, intraperitoneal (i.p.) HU produces developmental toxicity in rat pups born to dams treated during gestation (GD 9–12); the toxicity is manifested by an increase in malformations and alterations in behavior.[11]

HU produces developmental toxicity in mouse pups born to dams treated during gestation (GD 6–17) with 200 mg/kg bw/day by gavage; the toxicity is manifested by increased malformation rate, decreased body weight, and increased resorptions and stillbirths. Numerous experimental studies using HU in pregnant animals have been conducted on various species at different dose-levels. Consistent findings in single and multiple dose-level studies demonstrate decreases in fetal growth and viability, and dose-related increases in congenital malformations. Neural tube defects, hydrocephalus, anopthalmia and micropthalmia, cleft palate, micrognathia, acrodactyly and ectrodactyly, diaphragmatic hernia, and vertebral abnormalities were the most commonly reported abnormalities in rats, all at doses of ≥200 mg/kg bw/day.[1,12]

Reproductive Effects

Summary of Human Data: There are no data on the reproductive effects of HU in humans.

Summary of Experimental Animal Data: In experimental animals, evidence is insufficient to evaluate the effect of HU on female reproductive toxicity. HU produces reproductive toxicity in male mice at 50 mg/kg bw/day i.p. given for 5 days, as manifested by decreased testis weight and sperm count.[13] HU produces reproductive toxicity in male rats at ~400–460 mg/kg bw/day in drinking water for 70–90 days; the toxicity is manifested by reduced testis weight and histologic abnormalities of seminiferous tubules.[14,15] Dose levels that caused adverse effects in the experimental animal studies are expected to produce blood concentrations that are similar to those achieved in patients on therapy. Four human case reports have described low sperm count or decreased sperm motility.[16,17] There are no data on the effects of HU on male fertility in experimental animals.

Data and Research Needs

- Additional research is needed on the potential developmental toxicity of HU to the fetus and newborn following maternal HU exposure during pregnancy and lactation.

- Ongoing studies are needed to assess the impact of HU therapy on the growth and development of children younger than 5 years of age on HU therapy.

- Studies on the potential effects of HU on growth and development in children need to be expanded to include substantially longer follow-up periods than those in current studies.

- Studies are needed to assess the potential effects on both male and female reproduction in infants, children, adolescents, and adults on HU therapy.

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Adverse Effects of Hydroxyurea From Clinical Studies

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General Effects and Uses

Hydroxyurea (HU) inhibits ribonucleotide reductase, thereby reducing the amount of deoxyribonucleotides, which are essential for DNA synthesis and repair. Consequently, cell proliferation is impeded. HU is a cytotoxic and antineoplastic agent that specifically affects S phase and interrupts the cell cycle in the G2 and S phases. HU has been used as a radiosensitizing agent in cancer treatment and has been shown to have a modest effect on human immunodeficiency virus (HIV) replication. These observations have led to its use in a variety of malignant and nonmalignant conditions characterized by cell proliferation, including:

- Myeloproliferative diseases (MPD) (e.g., chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia rubra vera (PRV), unclassified MPD)
- Solid tumors (e.g., melanoma, ovarian carcinoma, cancer of the cervix, squamous cell cancer of the head and neck)
- Psoriasis
- Secondary erythrocytosis due to congenital heart disease
- HIV-1 infection
- Hemoglobinopathies (sickle cell disease (SCD) and thalassemia intermedia)

Thus, there is considerable experience with this agent in human use. Because of its effect on rapidly replicating cell populations, toxicity affecting hematopoiesis; the skin, hair and nails; and gastrointestinal function is expected. However, unusual (idiosyncratic) adverse events have been reported.

Summary of Hematologic Toxicity

Marrow suppression is common, with neutropenia reportedly occurring most often in patients with nonhemolytic disease, followed in frequency by anemia or thrombocytopenia. Hematologic toxicity is universally reversible with discontinuation or dose reduction of HU. Patients with chronic hemolysis may have anemia more commonly than other patient groups because of early suppression of reticulocyte count.[1] A Coombs negative hemolytic anemia has been reported in three patients with positive Heinz bodies and “bite” cells which resolved within a month after discontinuation of drug. Heat stability and glucose-6-phosphate dehydrogenase (G6PD) tests were not done, but oxidant hemolysis was considered the etiology.[1,2]

Summary of Dermatologic Toxicities

Dermatologic toxicity ranges from stomatitis, xerosis (dry skin), skin hyperpigmentation, melanonychia, and alopecia to an erythema multiforme-like fixed drug eruption, leg ulcers, and a dermatomyositis-like reaction. Multiple instances of leg ulcers have been reported in patients

with various myeloproliferative diseases and with psoriasis. These ulcers are shallow and painful, with a livid border. They are located in the malleolar areas but also on the dorsum of the feet, heels, and on the distal calves. Resolution over several months after dose reduction or discontinuation of HU is the typical response. Ulcers recur with drug rechallenge.

In four patients with CML who developed leg ulcers, biopsies revealed small vessel vasculitis without immune complexes. With topical application of granulocyte-macrophage colony-stimulating factor (GM-CSF) at a dose of 5 mcg/mL given twice daily, the ulcers resolved within 4 weeks in the three treated patients.[3] Three cases of an erythematous, scaly rash over the dorsum of the hands and fingers, with prominent nail fold telangiectasias resembling the cutaneous manifestations of dermatomyositis, have been reported in MPD patients taking HU. Biopsy revealed no vasculitis, and healing occurred within weeks to months of stopping the therapy but recurred with drug re-challenge.[4–6] In 60 patients with psoriasis and treated for 2 years, a fixed drug eruption resembling erythema multiforme occurred in one. The rash recurred with drug rechallenge, and two additional patients developed palpable purpura, which demonstrated necrotizing vasculitis on biopsy.[7] The reports on two patients with CML who developed gangrene of the toes, which resolved after drug discontinuation,[8,9] are relevant to these reports of vascular toxicities.

Summary of Drug Fever/Pulmonary Alveolitis/Hepatitis Adverse Events

At least 23 cases of fever due to HU have been reported in patients with an MPD, primarily ET; fever was as high as 41.5°C, was associated with rigors, and developed from within hours of to as late as 6 weeks after initiation of HU therapy. The fever and other symptoms resolved with discontinuation of HU and recurred within hours after rechallenge with HU.[7,10–14] In some cases, the fever was accompanied by either elevated transaminases and biopsy-confirmed granulomatous hepatitis (eight instances) or a diffuse alveolitis with severe hypoxemia.[11,13,14] The etiology is believed to be a hypersensitivity reaction.

Summary of Malignant Transformation

There have been a large number of case reports of acute leukemia as well as skin cancers occurring in patients treated with HU for an MPD (reviewed by Hanft et al.[15] and IARC[16]). Of 50 patients taking HU for an MPD, 9 developed acute leukemia, with a myelodysplastic syndrome (MDS) developing in an additional patient.[17] Seven of the patients who developed leukemia were treated with HU alone. Acute myeloid leukemia (AML) or an MDS was found in 7 (3.5%) of 201 patients treated with HU alone and in 14 (5.5%) of 251 patients in whom HU was used with other agents.[18] About 40% of ET patients who developed leukemia or an MDS while taking HU had a 17p deletion. Chim and colleagues,[19] reporting their experience in Hong Kong and reviewing six other reports, estimated the incidence of leukemia or an MDS at 1.3–4.5% after HU given as the only therapy for essential thrombocythemia. Najean and co-workers[20] calculated an actuarial risk of leukemia or MDS at approximately 10% by the 13th year of therapy in patients treated with HU for polycythemia vera. The risk of other cancers was calculated as about 15% by the 14th year, or about 1.1% annually, which was only slightly greater than the age-adjusted general population rate of 0.8% annually. The cancers diagnosed in patients taking HU involved the lung, pleura, skin, thyroid, pancreas, and vagina.

The potential mutagenicity of HU in children being treated for SCD has been assessed in three studies. One study reported that 17 children with SCD, taking HU for a median of 30 months, did not have a statistically significant increase in hypoxanthine phosphoribosyltransferase 1 mutation frequency but had an increase in Vγ-Jβ translocation events compared to children not

taking HU.[15] The other study found no increase in Vγ-Jβ translocation events in 34 children with SCD treated with HU for at least 5 years when comparisons were made with pretreatment values.[21] A third study, that assessed DNA damage in the comet assay, found greater levels of damage in 28 patients with SCD treated with HU compared to normal controls.[22] Although the degree of damage correlated with dose, there was a negative correlation with duration of therapy.

There have been sporadic reports of AML, acute lymphocytic leukemia (ALL) and CML in SCD.[23–26] In a survey of sickle cell centers,[26] there were 9 cases of ALL, 2 of AML, and 1 of CML among a total of 16,613 patients; the degree of overlap between the case reports and the survey is unknown. At least four cases of AML[27–30] and one case of ALL[31] have been reported in patients with SCD treated with HU. The case reported by Rauch[28] of a 27-year-old woman with hemoglobinopathy S-O Arab, in whom acute non-lymphocytic leukemia (ANLL) arose on the background of myelodysplasia after 8 years of therapy, is especially worrisome because of the similarity to AML arising from MDS in MPD. Other data, on patients with cyanotic congenital heart disease treated with HU in excess of 5 years, found no malignant disorder occurred.[32] Furthermore, no adult patients with SCD treated in the Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia have developed secondary leukemia after up to 9 years of therapy.[33] Finally, the Belgian experience, covering 598 patient-years of HU therapy, has only one AML (the M3v type).[30] These studies do not provide adequate evidence for the carcinogenicity of HU in humans, but the drug is not classifiable as to its risk of carcinogenicity. Overall, the leukemogenic potential of HU for patients with SCD appears to be low.

Summary of Reports in Hemoglobinopathies

Multiple skin changes, seen in approximately 14% of children treated with HU, included atrophy, lichen planus, hyperkeratosis, hyperpigmentation, and melanonychia; these changes occurred as early as 8 weeks from onset of therapy but did not require dose adjustment. Biopsy generally showed epidermal atrophy, hyperkeratosis and degeneration of the basal cell layer, suggesting a direct cytotoxic effect.[34] In a study of 17 patients examined at regular intervals by a dermatologist and treated with HU for 6 months to 6.5 years (mean 3.04 years), ungual pigmentation developed in 8, cutaneous pigmentation in 5, xerosis in 5, palmar-plantar keratodermia in 2, and oral pigmentation in 3. Leg ulcers developed in three females and two males; all improved within 6 weeks of dose reduction or discontinuation.[35] These ulcers were related to older age and a history of prior leg ulcers. In 43 Iranian patients, aged 3–36 years, with thalassemia intermedia and treated with HU for 3–51 months, 19 developed hyperpigmentation that could have been aggravated by iron overload; xerosis developed in 8, café au lait macules in 3, nail ridging in 5, leukonychia in 4, and melanonychia in 2.[36]

A 36-year-old person with $S\beta^+$ thalassemia treated with HU for 20 months acquired a cryptosporidium infection associated with a decrease in CD4 cells but was HIV negative. Off HU, the person's CD4 count returned to normal; the infection resolved after cholecystectomy.[37]

Serum magnesium levels appear to be reduced by HU, as reported in five girls with SCD,[38] suggesting that the hypomagnesemia of SCD may be worsened by HU therapy. Azoospermia was reported in a 27-year-old man 6 months after HU was started, with at least partial recovery of sperm count 11 months later; sperm motility before therapy had been 75% and was 40% at the 11-month examination after therapy.[39]

Summary of Additional Studies/Approaches Needed

1. The data from the BABY HUG trial are eagerly awaited. Documentation of a beneficial effect of HU on the alleviation or delay of end-organ damage in children will expand the patient population appropriate for treatment.

2. HU can be used for long periods of time, and adverse effects may have long latency periods. Studies are needed to evaluate the adverse effects of long periods of exposure to HU and to assess outcomes that take many years to manifest after exposure.

3. A registry of patients with SCD that includes patients taking and not taking HU is one way of meeting the need for more accurate determination of the incidence of critical adverse events.

4. Further pharmacokinetic studies (absorption, distribution, elimination, metabolism) in patients on HU therapy are needed to determine whether twice-daily dosing is superior to once-daily dosing, and whether a twice-daily dosing strategy increases hematological toxicity.

5. Additional studies are needed to understand the beneficial and toxic effects of HU at a mechanistic level.

6. Studies of DNA before and after HU therapy are needed to assess chromosomal changes and the risk of malignant transformation; such studies should include controls with SCD who are not treated with HU.

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Evidence-Based Practice Center Presentation III: Appropriate Use of Therapies Among Patients With Sickle Cell Disease: A Systematic Review of Barriers and Interventions To Improve Quality

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Introduction

Provider provision of and patients' adherence to appropriate therapies are essential to reduce morbidity and mortality for patients with sickle cell disease (SCD).

Objective

We conducted a systematic review to synthesize studies which identified barriers to, and interventions to improve, appropriate use of therapies for patients with SCD.

Methods

Literature Sources: We searched MEDLINE®, EMBASE®, TOXLine, and CINAHL through June 30, 2007. We also reviewed reference lists and discussed search results with experts. All searches were limited to English-language publications describing treatment of humans. Review articles were excluded from the searches.

Eligibility Criteria: In our review, "use of appropriate therapies" included patients' adherence to (including decisions to initiate or discontinue) recommended therapies, as well as healthcare providers' provision of appropriate therapy, including hydroxyurea (HU), prophylactic antibiotics, iron chelation, bone marrow transplantation, and pain management during vaso-occlusive crisis (VOC). Because we were concerned that there may not be enough literature with these outcomes, we also included studies that addressed barriers to, or interventions to improve, receipt of routine, scheduled healthcare in patients with SCD.

For evidence of barriers to use of appropriate treatment among patients with SCD, we included two types of studies: descriptive studies (both qualitative and quantitative) in which patients, patients' caregivers, and/or healthcare providers reported their belief that a particular factor was a barrier; and cross-sectional studies in which a particular factor was identified as a barrier or facilitator through its association with patients' or providers' use of therapy. For evidence of the effectiveness of interventions to improve use of therapies, we included randomized controlled trials, cohort studies with a control population, and pre/post treatment studies.

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

Data Extraction: A single reviewer abstracted data, and a coinvestigator verified accuracy. Reviewers were not masked as to the articles' authors, institutions, or journal. For all articles, reviewers extracted information on general study characteristics, participant characteristics, and types of barriers identified. For example, if the study reported "Many patients felt that doctors did not have sufficient knowledge of SCD to make valid treatment decisions," this was categorized as "poor provider knowledge." Statements such as "the nurses' perceptions of their sickle cell patients were overwhelmingly negative" and "patients report negative experiences of hospital care, characterized by stigmatization" were categorized as "poor provider attitudes." Differences of opinion were resolved through discussion.

For each intervention study, we categorized the main intervention components. We also determined the extent to which the measured study outcomes were 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 stays, costs, or emergency department (ED) "treat and release rates") and descriptive comments from patients (without an explicit analysis of those comments) to be a form of indirect evidence. Most chart-abstracted measures of pain management quality (e.g., rates of patient-controlled analgesia or use of pain consults) and patients' ratings of their experience were considered to be a form of direct evidence.

For each intervention study, we also determined if there was "improvement," "potential improvement," "no improvement," or a "detrimental effect." We categorized intervention studies as demonstrating "improvement" if any direct outcome showed statistically significant improvement. We categorized intervention studies as demonstrating "potential improvement" if the authors implied that measured outcomes improved but did not provide definitive data (e.g., use of only indirect outcomes or data collected in such a way that there was substantial risk of bias). We categorized intervention studies as demonstrating "no improvement" if there was no improvement in any outcome.

Assessment of Study Quality: To assess quality of the intervention studies, cross-sectional studies employing questionnaires, and qualitative studies, we developed separate forms to identify key elements that should be described based on published methodological guidelines for that study design. The quality assessments were done independently by paired reviewers. The results of the two reviewers were averaged.

Evidence Grading: We graded the quantity, quality, and consistency of the evidence by adapting an evidence-grading scheme recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group and modified in the Evidence-Based Practice Center manual. We did not grade the evidence for the existence of barriers or facilitators that had been examined in fewer than three studies.

Results

Our search identified 48 articles that met our eligibility criteria. Of these, 35 were descriptive studies identifying barriers or facilitators to therapy, and 13 studies evaluated interventions to improve use of therapies.

Barriers to Use of Appropriate Therapy Among Patients With Sickle Cell Disease

The only types of therapies for SCD to which barriers and facilitators have been sufficiently studied (i.e., more than two studies examining a factor as a barrier or facilitator to a particular therapy) are providers' provision of pain management during VOC and patients' adherence to

prophylactic antibiotics. In regard to appropriate pain management, the two most common barriers identified by patients and providers were negative provider attitudes (*n* = 14) and lack of provider knowledge (*n* = 5). These negative provider attitudes included providers not believing that patients were genuinely in pain, providers' being suspicious of drug abuse or addiction, providers' stigmatization of patients with SCD, providers' insensitivity or lack of sympathy, and unspecified negative perceptions or attitudes. We concluded that the evidence was high and moderate that negative provider attitudes and poor provider knowledge, respectively, are barriers to use of appropriate pain medications during VOC.

In terms of prophylactic antibiotics, the only consistent association was that the sex of patients was found not to be related to use of antibiotics in any of the three studies in which it was reported. Therefore, we concluded there was moderate evidence that the sex of patients was *not* related to use of prophylactic antibiotics. Patient age, frequent hospital visits, and patient/caregiver knowledge were all studied in more than two studies, but the association of these factors to use of antibiotics was not consistent, and all were given an evidence grade of low. No factors were consistently identified as barriers or facilitators to any other therapy.

Interventions To Improve Use of Appropriate Therapies Among Patients With Sickle Cell Disease

Most intervention studies (*n* = 9) targeted providers to improve provision of pain medications to patients with VOC. Of these nine studies, all used a pre/post design, and three studies also had a concurrent control group. Three of the nine studies were focused on children with SCD, one focused on adults with SCD, and the remainder did not specify. Seven of the nine studies were conducted in the United States, and two were conducted in the United Kingdom. The majority of interventions used clinical protocols (*n* = 6), one involved audit and feedback, and two involved changing the structure of care with a Day Hospital or a fast-track admission process. Only one study also addressed providers' attitudes through sensitivity training. Five of the nine studies measured a direct outcome (e.g., pain management quality or patient ratings), while the remainder measured indirect outcomes (e.g., utilization or costs). Four studies demonstrated improvement, and five showed potential improvement. We concluded that there was moderate evidence that interventions targeted to healthcare providers can improve appropriate provision of pain medications to patients who have VOC with SCD.

Three of the remaining four intervention studies targeted patients to improve self-management, such as adherence to prophylactic antiobiotics (*n* = 1), desferoxamine (*n* = 1), and health-promoting activities (*n* = 1), and one study targeted patients to increase their utilization of routine ambulatory appointments (*n* = 1). All four patient interventions focused on children with SCD. None of the three studies targeting patients to improve self-management had any effect, and we concluded that there was low-quality evidence that interventions to affect patients' adherence can improve use of therapies. The one study which used structured telephone outreach showed a significant and strongly positive effect on receipt of routine ambulatory care, and we concluded that there was moderate-quality evidence that interventions can improve receipt of routine ambulatory care.

Conclusion

Interventions to improve the quality of pain management should be implemented and should address healthcare providers' attitudes or minimize the impact of negative attitudes of healthcare providers. One promising telephone outreach intervention to improve receipt of ambulatory care should be replicated, and more studies are needed to identify effective interventions to improve receipt of all other therapies for SCD.

Barriers for Pediatric Patients: The Healthcare Provider's Perspective

Elliott Vichinsky, M.D., Marsha J. Treadwell, Ph.D.

In clinical trials, hydroxyurea (HU) has significantly decreased complications of sickle cell disease (SCD).[1–3] The results of these trials led to the U.S. Food and Drug Administration's approval of HU for the selective treatment of SCD. HU may be more efficacious in pediatric than in adult patients. The possibility of treating infants who have SCD to inhibit the development of organ impairment—such as functional asplenia, central nervous system ischemia, and pulmonary injury—may be the most important future use of HU.[4] In pediatrics, HU use decreases hospitalizations, painful events, and acute chest syndrome; HU also may prevent primary and secondary stroke.[2,3,5,6] Over 10 years of widespread use of HU in pediatrics has not uncovered any unknown significant toxicity. However, several major barriers most likely will prevent its use in the pediatric SCD community.

The perception of risk and benefit by parents and physicians is a strong determinant in the acceptance of HU therapy. In an environment in which detailed counseling and follow-up do not occur, families are cautious and often refuse therapy or are passively noncompliant. Education of families demonstrates that those who perceive their child as severely affected by SCD are likely to choose HU therapy. The determination of SCD severity by families is not derived solely from hospitalization rates but includes the burden of the child's illness on the family as a whole. Therapy utilization and compliance increases with increasing education of the extended family and the child. However, 25%–50% of families refuse therapy because of the potential side effects, e.g., fears of birth defects and cancer risk, regardless of actual likelihood of occurrence.[7] Preliminary studies on families' perceptions of the balance of risks and benefits of therapy are limited and suggest that complex interactions with the health provider and their extended family are important variables.

As increasing data demonstrate a lower than expected risk from HU treatment in pediatrics, acceptance and compliance would be expected to increase. However, the pediatric community and healthcare system have had limited success in implementing the most basic therapies necessary for pediatrics and an even lower success rate for children with chronic genetic disorders. Nationwide, less than half of children receive indicated therapies necessary to avoid serious adverse health outcomes.[8] For example, only 50% of children who reach 2 years of age are fully immunized. Less than 45% of children with asthma are given basic necessary treatment. Although it is known that screening, early detection, and treatment of *Chlamydia* decreases serious complications in teenage girls by two-thirds, only one-third of adolescent girls are screened.[8]

In treating genetic diseases, implementation of standard-of-care guidelines is worse than in the general pediatric population.[4,8,9] This is most apparent in the provision of pneumococcal prophylaxis for publicly insured children with SCD. Penicillin prophylaxis in children with SCD reduces the incidence of serious infection by 84%. The American Academy of Pediatrics recommends that all such children under age 5 receive daily penicillin. In a longitudinal study of prescriptions written in the Tennessee and Washington State Medicaid programs, only 21% of patients received 270 days of medication coverage.[10] In contrast to often-held beliefs, parent compliance regarding prophylactic penicillin is high when associated with education and reinforcement. Despite frequent interactions with the healthcare system, children requiring

prophylactic penicillin were not prescribed the drug. This fact indicates widespread, infrastructural problems in pediatric healthcare for SCD.

Education and counseling, necessary and key components to prescribing and monitoring HU, do not appear to be a priority for pediatric providers. Many of the States in the national newborn-screening program for SCD rely on pediatricians to provide initial counseling and education. In a national survey of pediatricians and family physicians, one-half of the physicians preferred not to be part of the initial evaluation and counseling sessions. Many felt that families with a child with sickle cell trait did not require formal genetic counseling, or they were not trained to provide such counseling.[11] The low level of training and interest of graduating pediatric residents for counseling sickle cell trait suggests that improvement in the communities' involvement is unlikely. Three-quarters of graduating pediatricians missed key information required for patient and family understanding during counseling sessions.[12]

Standard-of-care recommendations issued from the American Academy of Pediatrics and recommendations from the National Institutes of Health (NIH) regarding care for pediatric patients with SCD often are not followed. In addition to penicillin prophylaxis and newborn counseling as mentioned, preventative care and early detection regimens outlined for kidneys, bone, anesthesia, brain, psychological, and heart are not routinely followed. While extended phenotypically matched red cells are recommended for transfusion in SCD, the majority of national blood banks do not follow this policy. Red cell pheresis has been demonstrated to maintain safe sickle cell hemoglobin-S levels without iron burden in chronically transfused children. However, these programs are largely unavailable. Day hospital management of pain events decreases hospitalizations by over 80% and improves quality of life but is not implemented.[13] The lack of standardized care for SCD is responsible for the marked geographic differences in mortality among children. Some States have a ninefold greater risk than other regions of pediatric deaths from SCD.[14]

SCD is a genetic disease that affects the life span of the patient. Optimal care requires communication between pediatric and adult healthcare providers as well as a successful transfer process for young adults. HU is commonly prescribed in pediatric care and requires a seamless transition of its management to the adult provider. Unfortunately, pediatric/adult transition programs for genetic diseases are uncommon and rarely successful in SCD. The majority of patients transferred, or leaving a pediatric facility, are not successfully integrated into an adult care program. Many factors are responsible for this lack, but it results in a dramatic decrease in quality of care and high preventable morbidity.[15]

Several fundamental health, social, and economic factors prevent implementation of effective therapy for SCD in general and with HU in pediatrics specifically.[10,16,17] The major obstacle to optimal use of HU in pediatrics is the existing healthcare infrastructure for SCD.[18–20] No coordinated process translates research findings into clinical practice and monitors their effectiveness. Resources required, even if cost-effective, are unavailable or denied. Prophylactic penicillin, phenotypically matched red cells, transcranial Doppler screening, genetic counseling, day hospital care, and pheresis services are other examples of effective therapy that have not been implemented successfully into clinical practice.[10,12,13]

When a coordinated multidisciplinary approach is available for patients, compliance and utilization are high.[3] In clinical trials utilizing the comprehensive care structure, including pill-count monitoring, compliance varied from 88% to 96%. However, in the community setting, where there are limited resources and lack of uniform standards, healthcare providers with limited information and personal bias invest little time in educating and monitoring patients.[16]

Insurance costs, out-of-pocket expenses, and lack of education about the relative risks and benefits of therapy further lower acceptance and compliance with therapy.

Concrete actions will result in improved utilization and efficacy of HU. Medicare and Medicaid programs and other State and Federal health agencies should require documentation of standard-of-care practices needed for SCD. Pediatric standard-of-care guidelines for SCD should be promoted and monitored by the American Academy of Pediatrics. Federal funding should be used to encourage compliance with adequate education, counseling, and monitoring of HU therapy. Multidisciplinary care for SCD should be modeled after comprehensive cancer services. Community health centers should be fiscally encouraged to link with comprehensive SCD programs.

To continue to receive Federal funding, programs funded by the NIH should be required to adopt treatment guidelines for SCD that are monitored for effectiveness. A coordination of Federal agencies must occur, with a common goal of implementing and monitoring clinical and research advances. The development of detailed, effective educational materials that are widely incorporated into the lay and medical community should complement clinical research.

An increased diversity in the healthcare community, with improved ethnic competence among healthcare providers, is required. Empowerment of patients and education of community advocacy groups to work with healthcare providers will increase patient trust and decrease healthcare discrimination.

Healthcare costs for the use and monitoring of HU are often prohibitive. Out-of-pocket expenses and copayments for medications and laboratory tests often discourage or prevent utilization of and compliance with HU therapy. The cost of time and resources needed for transportation to a multidisciplinary sickle cell program can be improved by better linkage of community programs with centers and outreach center satellites.

In summary, the benefit of HU therapy will not be achieved in pediatric patients with SCD unless major changes occur in healthcare policy and health services delivery. The first step to improving this problem is the recognition of responsibility by the research community, healthcare providers, and insurers. This step is followed by concrete actions designed to standardize care and monitor its implementation.

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Barriers for Pediatric Patients: The Consumer's Perspective

Regina Hutchins-Pullins (Parent); Lori E. Crosby, Psy.D., Janelle Hines, M.S.

Hydroxyurea (HU) can be a beneficial medication for many patients with sickle cell disease (SCD); however, this treatment requires that the patient take medication each day and have routine blood draws. HU also has serious side effects and takes several months to produce noticeable health changes. This presentation will discuss barriers to HU use from the parents' perspective and provide recommendations to improve access to and families' comfort level with HU.

Many parents are uncomfortable with the side effects of HU. Parents are particularly concerned about the risk for cancer and infertility. Parents may also be very reluctant to consider giving HU to babies and young children because they may be worried about the effect this medication will have on the child's growth and development. The fear and uncertainty about the safety of this treatment, and concerns about its effects on the child's future health, are important factors in parents' decisionmaking about HU. Young adults who may be in intimate relationships may be hesitant to begin taking HU due to the risks to offspring. Healthcare providers need to partner with parents and young adult patients in the decisionmaking process and have open and frank discussions with parents about their feelings.

In an effort to better understand the benefits and risks of HU, parents may turn to family members, others with the disease, and/or conduct their own research. In the current system, it is often difficult for families to access and understand research about the use of HU in the treatment of SCD, particularly its use in children and adolescents. It is essential, however, that families receive accurate information about the benefits and risks of HU so that they can make informed decisions about their child's healthcare. Parents and adult consumers would benefit from the development of a centralized resource center for HU and SCD. A center of this type, whether in the form of a building or Web page, would equip families with the information they need and could be used as a forum for children (and their parents) and adult consumers being treated with HU to share their experiences.

Health insurance may be a significant barrier to the use of HU for some families. Parents employed in small companies or with inadequate healthcare may need to pay large deductibles or frequent copays for the medication and required lab work. Additional support from the Federal level and from pharmaceutical companies in the form of samples and discount programs would serve as a first step toward improving access to HU for many families.

Parents report that forgetting to take the medication is one of the most frequent problems or barriers. Because parents understand the importance of consistently taking the medication to realize health benefits, they typically provide reminders to their children. These reminders are helpful in improving adherence with the medication, but daily reminders can have a negative impact on the parent–child relationship. Children may become frustrated with having to take a medication each day or with parental reminders. It is important that the healthcare team provide parents with adequate support and help them generate strategies to use when children become frustrated. Related to this is the burden of having to keep track of when the medication is running out and ensuring that the prescription is refilled. This requires planning and organization

and may be tough for families who are already juggling multiple schedules and medical appointments. Healthcare providers should encourage parents to use pharmacies that offer automated or electronic prescription services that will remind parents when it is time to get the prescription refilled.

Another significant barrier to HU treatment is the burden and frequency of lab work. Initially, children are required to get monthly lab work and clinic visits. It is very difficult for families to fit these activities into their already busy schedules. Also, many times children get tired of going to frequent clinic visits. This may result in parents having difficulty getting children to attend clinic appointments for parents. Parents may also have a difficult time getting their children to continue taking HU past the first month. When children do not see immediate results, they begin to doubt that the medication is working and may decide that the burden of taking the medication daily is not worth it. Families would benefit from additional support from the medical team in the form of weekly or biweekly phone calls. These phone calls would provide parents with the opportunity to discuss any problems and ask questions. They could also serve as another opportunity for members of the medical team to reinforce the importance of taking the medication consistently and having routine blood work.

Many parents have worked with their children and healthcare providers to overcome these barriers. These parents feel strongly that the long-term benefits of HU have been positive and outweigh the side effects. It is crucial that Federal agencies, pharmaceutical companies, and healthcare providers keep the dialogue open with consumers about HU. It takes a village to raise a thriving child, and it will take legislators, agency directors, providers, parents, and consumers working together if the goal is to improve access to, acceptance of, and families' comfort level with HU.

Barriers for Adult Patients: The Physician's Perspective

**Wally R. Smith, M.D.; Marshall Scherer, B.S.;
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Three primary topics are summarized in the following abstract: general barriers to care in sickle cell disease (SCD); major barriers to the use of hydroxyurea (HU) in SCD; and solutions to barriers to HU use in patients with SCD. Background data for understanding barriers to care in SCD include reviews of selected articles and analysis of a national hospital discharge database to compare demographic trends, hospital utilization, and costs of care in SCD versus other diseases. Data to understand better the major barriers to HU use in patients with SCD include data from the National Hospital Discharge database; primary data on HU use from HU trials, and a study of unselected SCD patients; and data and conclusions from articles obtained through a formal literature search on barriers to use of HU in SCD. Data and recommendations for solutions to barriers to HU in patients with SCD come from the above formal literature search; a separate formal literature search conducted by the authors on transitions to adult care in SCD; and expert opinion.

General Barriers to Care in Sickle Cell Disease

Financial barriers to care in SCD appear to be significant. Woods and colleagues[1] abstracted administrative data from 8,403 admissions among 1,189 Illinois adults with SCD from 1992 to 1993. Total hospitalization charges were more than $59 million, and the median cost per crisis was $5,197 (interquartile range (IQR) $3,122–$8,386) and per surgical admission, $18,980 (IQR $9,734–$34,339). Numerous studies, including those by Powars et al.,[2] Platt et al.,[3,4] Yang et al.,[5] and Davis et al.,[6] are consistent with extensive analyses of financial charge summaries we abstracted from the Agency for Healthcare Research and Quality's Healthcare Costs and Utilization Project Nationwide Inpatient Sample (NIS), 1988–2005.[7] Based on the higher percentage of and higher average expense of adult versus pediatric hospital charges in SCD, we conclude that the burden of care for SCD has shifted from predominantly pediatric to predominantly adult care. Furthermore, as SCD patients are being disproportionately admitted from the emergency department (ED), we conclude that SCD is an ambulatory care-sensitive condition, like asthma,[8] and that major barriers exist to ambulatory care for SCD.

Specific Barriers and Solutions to Barriers to Hydroxyurea Use in Sickle Cell Disease

Barrier 1: Low Income and Underinsurance

We identified lack of income and underinsurance as one of four barriers to the appropriate utilization of HU in SCD patients. The NIS linked the ZIP code of each discharged patient to income data by ZIP code to determine the median income of households in the patient's ZIP code. NIS also profiled insurance coverage for each discharged patient. We compared median incomes of discharged patients with SCD in 2005 to those of all discharged patients. We found that people living in ZIP codes of SCD discharges in 2005 were, on average, poorer than those living in ZIP codes of all discharges: 45.11% of discharges for SCD were from ZIP codes in the low annual income stratum ($0–$35,999), compared to 27.23% of all discharges.

We compared insurance coverage of discharges for SCD versus all 2005 discharges. Compared with all discharges combined, discharges for SCD were covered less often by Medicare (20.41% vs. 37.17%) and more often by Medicaid (52.51% vs. 19.51%). Discharges for SCD were also covered by private insurance far less often than all discharges combined (19.86% vs. 34.24%).

Based on knowledge of medication and visit coverage provided by various Federal insurance programs, we suggest one of two solutions to remove the income and insurance barriers to both ambulatory care and use of HU in patients with SCD. First, Medicare coverage could be extended to all adult SCD patients (age >17 years), including the recently added Part D prescription drug benefit. Alternatively, since Medicaid already covers prescription drug costs and care visits, the age of qualification for Medicaid for SCD patients could be extended to age 64.

Barrier 2: Sickle Cell Disease Physician Workforce and Reluctance To Prescribe Hydroxyurea

We identified a second barrier to the use of HU in treating SCD: a lack of a SCD physician workforce and physician reluctance to prescribe HU. To explore the literature for articles describing this barrier, we performed an exhaustive MEDLINE™ search. The most relevant article we identified, by Zumberg et al.,[9] surveyed adult healthcare providers about their HU practice patterns. The majority of community hematologist/oncologist respondents saw less than three patients per month with SCD. Reluctance to prescribe HU was evident, as it was prescribed by only 55% of community hematologists/oncologists to at least 10% of their patients. Barriers to wider use of HU cited in this article include physicians' concerns about carcinogenic potential, doubts of its effectiveness, perceived patient apprehension about adverse effects, concern about lack of contraceptive use, and patient compliance.

Evidence for this barrier is also presented in data from the Pain in Sickle Cell Epidemiology Study (PiSCES), one of the most comprehensive studies of pain in SCD.[10] When eligibility for receiving HU therapy was defined as three or more hospital or ED utilizations per year, only 36 of 99 eligible patients reported receiving HU either in the previous year or for 1 or more days during PiSCES.

To extinguish physicians' reluctance to prescribe HU, further resources could focus on updating physicians on recently published material supporting the effectiveness of HU in symptomatic SCD, as recommended by Zumberg and colleagues.[9]

To address physician workforce issues as well as reluctance to prescribe HU, current Centers of Excellence in SCD, usually managed by State departments of health, could refer the children they are already following to designated adult physicians for HU screening and prescription.

To investigate whether such transition programs exist, and the overall effectiveness of such programs, we performed another exhaustive literature search using MEDLINE. The relevant four articles were primarily written by a single working group on transitions in SCD care and did not test the efficacy of a transition program.[11–14]

Barrier 3: Undermeasurement of Pain in Sickle Cell Disease

We identified a third barrier to use of HU in SCD: the undermeasurement of both SCD pain episodes and full-blown crises. To investigate this barrier, we analyzed data from PiSCES. Data

on insurance claims for admissions from January 2002 through December 2004 for PiSCES patients were matched with PiSCES data by Social Security Numbers. The percentage of PiSCES patients eligible for HU ranged from 11% to 16%, not 10% as was assumed in the Zumberg study.[9] Furthermore, we found in our analysis of home-treated versus hospital-treated pain crises in PiSCES that as many as 39% of patients eligible for HU may be unrecognized if home-treated crises are excluded as ineligible.

We conclude that pain in SCD is highly undermeasured, both in frequency and intensity. In light of this undermeasurement and the preponderance of daily pain in SCD, one solution to this barrier is to loosen criteria of eligibility for HU treatment to include more patients who may also benefit.

Barrier 4: Patients' Adherence to Hydroxyurea

The fourth barrier to HU utilization we identified is patients' adherence. To obtain published data on HU adherence, we conducted a MEDLINE search using the terms patient AND compliance AND hydroxyurea; the search yielded 19 relevant articles. A trial by Olivieri and Vichinsky reported compliance rates of 96 ± 2% in SCD patients taking HU,[15] and the HUG-KIDS Trial for HU therapy[16] reported noncompliance rates of 5.6 ±4.0% of participants.

In adults, data on HU compliance comes primarily from the Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH).[17] Capsule counts suggested that about 75% of patients took more than 80% of their capsules. Accurate assessment of compliance during the MSH nonrandomized follow-up phase was difficult, occurring by annual survey. HU was taken voluntarily. Ninety-six patients (32%) never received HU during the initial study or follow-up, 48 (16%) received it for <1 year, and 156 (52%) received it for ≥1 year.[18]

Data obtained from PiSCES patients (n = 62) patients who indicated any HU use at all revealed widely varied adherence. Almost 10% of patients who were prescribed HU used it <10% of days during PiSCES; and about 35% of the patients used HU between 90% and 100% of PiSCES days.

Solutions to adherence problems recommended by Zumberg and colleagues included alleviating patients' apprehensions about the adverse effects of HU. We conclude from the above data that close monitoring and pill counts will increase adherence, but other ways to improve HU compliance have not been demonstrated in the literature. Solutions to improve HU compliance could include State-supervised efforts to reduce physicians' reluctance to prescribe the drug as well as education and monitoring of patients. Recent studies have recommended testing urinary[19] and plasma[20] HU levels to measure compliance and response.

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Barriers for Adults: The Consumer's Perspective

Trevor K. Thompson, M.A.

History

Trevor is a 38-year-old African-American male with a life-long history of sickle cell anemia (hemoglobin (Hgb) SC). His mother carried the sickle cell gene commonly known as the sickle cell trait (Hgb AS), and his father carried the sickle cell gene commonly known as the sickle cell trait (Hgb C). Trevor was diagnosed with sickle cell disease (SCD) at age 18, while he was in the military.

Medications

Currently, he takes folic acid, methylsulfonyl methane, and hydroxyurea (HU). Additionally, he takes opioid pain pills as needed.

Past Medical History

As a child, Trevor was told that he only had the sickle cell trait. However, he suffered from numerous occurrences of sickle cell pain crisis. The medical community was unfamiliar with sickle cell treatments and the various forms of the disease, and sometimes they chalked up his crises as growing pains or, even worse, that he was faking. Not until Trevor was in the military was he accurately diagnosed with SCD.

Surgical History

In his late twenties, Trevor began experiencing complications with his hip and was diagnosed with bone infarctions; these could have led to aseptic necrosis. Trevor did research and consulted with a physician at a national sickle cell conference about his condition. The physician advised him to exercise. With exercise, he was able to avoid hip replacement surgery. However, at age 32, Trevor had to have eye surgery due to sickle cell retinopathy. A total of four surgeries were performed before he eventually lost use of his right eye. On February 16, 2004, at age 36, Trevor had his first blood transfusion, which saved his life. Trevor had his gallbladder removed as a proactive procedure to avoid future complications.

Current Status

Currently, Trevor has not been hospitalized in 18 months. He has experienced numerous episodes of intense pain crisis; however, he treats himself with pain pills and hydration at home.

Trevor is happily married to Cherry Whitehead-Thompson and has a beautiful daughter, Alexandria E. S. Thompson, who has the sickle cell trait.

He is a graduate of Xavier University in New Orleans, Louisiana, and received his Masters of Arts from the University of Mississippi in Oxford, Mississippi. He is currently a Doctoral Education candidate at the University of Memphis. His concentration is leadership and policy. Trevor Thompson is the Coordinator for Parental Involvement in the Memphis City Schools System.

Trevor is committed to living out his dreams and continues to give back to his community. The Memphis City Council has recognized Thompson twice for Outstanding Commitment to the Community. In 1999, Thompson was recognized as a recipient of the Outstanding Christian Educator for the Millennium Award sponsored by Alpha Kappa Alpha Sorority Inc., Beta Epsilon Omega Chapter. Thompson was awarded the 2002 Outstanding Civic Leader in Education by the National Pan-Hellenic Council, Inc. of the Memphis Metropolitan Area, and he was selected as the 2002 Brother of the Year for the Association of Tennessee Alphamen for Alpha Phi Alpha Fraternity Inc. The Association of Tennessee Alphamen has awarded him the 2003 August M. Witherspoon Leadership Award and the 2003 & 2005 Charles A. Green Service Award for Alpha Phi Alpha Fraternity Inc. Recently, he was named the 2007 United Negro College Fund Alumnus of the Year for Xavier University of Louisiana.

Trevor holds memberships in the National Coalition of Title I for Parents (life member), Xavier University of Louisiana Memphis Alumni chapter (president), Alpha Phi Alpha Fraternity Inc. (life member), Parent Teacher Association (PTA), Delta Fine Arts Foundation (board member), and Diggs-Kraus Sickle Cell Advisory Council (chairman).

Summary

Trevor has been taking HU for approximately 7 years. The medication has improved his quality of life. Before taking HU, Trevor would have four to six sickle cell crises a year. He literally feared the changes of the seasons, because he knew that he would go into a crisis. During the formative years of taking the medication, his crises were reduced to approximately two per year. SCD has never interrupted his career; however, HU has improved his quality of life. HU treatment has given him confidence, self-esteem, and the motivation to marry, to travel, and to further his education.

God and faith have been his salvation, and when he is in crisis, prayer and meditation bring him peace. Additionally, he has a great support system. He is blessed to have a wonderful wife, daughter, and family members who care for him and provide him comfort.

The Medical Home Model

Thomas S. Webb, M.D., M.Sc.

The Medical Home Model is an approach to providing comprehensive, patient- and family-centered medical care that emphasizes accessibility, care coordination, and collaboration among patients and all of their healthcare team members. The concept of a Medical Home originated in pediatrics in 1967, initially addressing the need to maintain a centralized medical record for children with chronic diseases or disabling conditions,[1] but the concept was expanded in 1992 and 2002 to address the chronic, longitudinal medical care needs of children with "special health care needs."[2] More recently, the American Academy of Family Physicians,[3] American College of Physicians (ACP),[4] and American Osteopathic Association[5] have also adopted and adapted the Medical Home Model as the optimal goal for providing longitudinal care to all patients, particularly those with chronic conditions.

What Is a Medical Home?

The American Academy of Pediatrics (AAP) describes the Medical Home as a *process* of providing medical care that is "accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective."[2] The Medical Home is typically associated with the patient's primary care practice, but for some complicated, chronic conditions, it may reside with the subspecialty provider.

The key characteristics of a Medical Home include:[2,6,7]

Accessible: The ideal location for care is within the patient's community. This concept emphasizes that care and coordination are preferably provided within the primary care practice rather than at the tertiary care center. The practice should accept all types of insurance and accommodate all types of disabilities and transportation needs.

Continuous: The patient develops a long-term relationship with a stable group of familiar Medical Home providers who participate in all aspects of care, including all healthcare transitions from home to hospital, hospital to home, and from pediatric to adult care, if applicable.

Comprehensive: Care addresses the primary, preventive, and subspecialty needs of the patients, which includes their medical, developmental, vocational-educational, psychosocial, and financial issues. The principal provider of care is able to manage or direct all aspects of care, and access to the Medical Home team is available both day and night, on weekdays and weekends.

Family-centered: The family is recognized as an essential and continuous system of support for the patient. The patient and family are principal agents in medical decisionmaking and care coordination; therefore, they require complete and unbiased information from medical professionals about treatment options, community resources, and family networks. Care is provided in an atmosphere of collaborative decisionmaking, shared responsibility, and mutual trust.

Coordinated: The Medical Home is the centralized source of information about the patient, facilitates communication and collaboration among providers, links families to support services, assists patients in preparing for specialty visits and reviews recommendations with families after such encounters, advocates for patients, and coordinates their medical needs in school, work, and community living settings.

Compassionate: The Medical Home team demonstrates concern for the patient and family, supports difficult decisions in a nonjudgmental manner, respects the roles and competencies of other healthcare providers, identifies useful support services, and recognizes the needs and concerns of other family members (e.g., siblings, grandparents, and children of adult patients).

Culturally effective: The patient's and family's cultural beliefs, rituals, and customs are recognized and incorporated into the care plan. The primary language of the family is identified, and both interpreters and translated written materials are provided at clinical encounters.

What Are the Key Components of the Medical Home Model?

The ACP has adapted the AAP Medical Home and incorporated the principles of the Wagner Chronic Care Model into a patient-centered, physician-guided Advanced Medical Home.[4] The Chronic Care Model organizes medical systems to promote patient self-management skills, evidence-based medical care, patient–physician and primary care–specialist collaboration, and optimal sharing of clinical information.[8] Similar to the pediatric model, the Advanced Medical Home results in an informed, empowered patient receiving timely, efficient, safe, coordinated care from a proactive medical care team. This model acknowledges that, for some patients with complex conditions, the principal provider of care may be a subspecialist rather than a primary care provider.

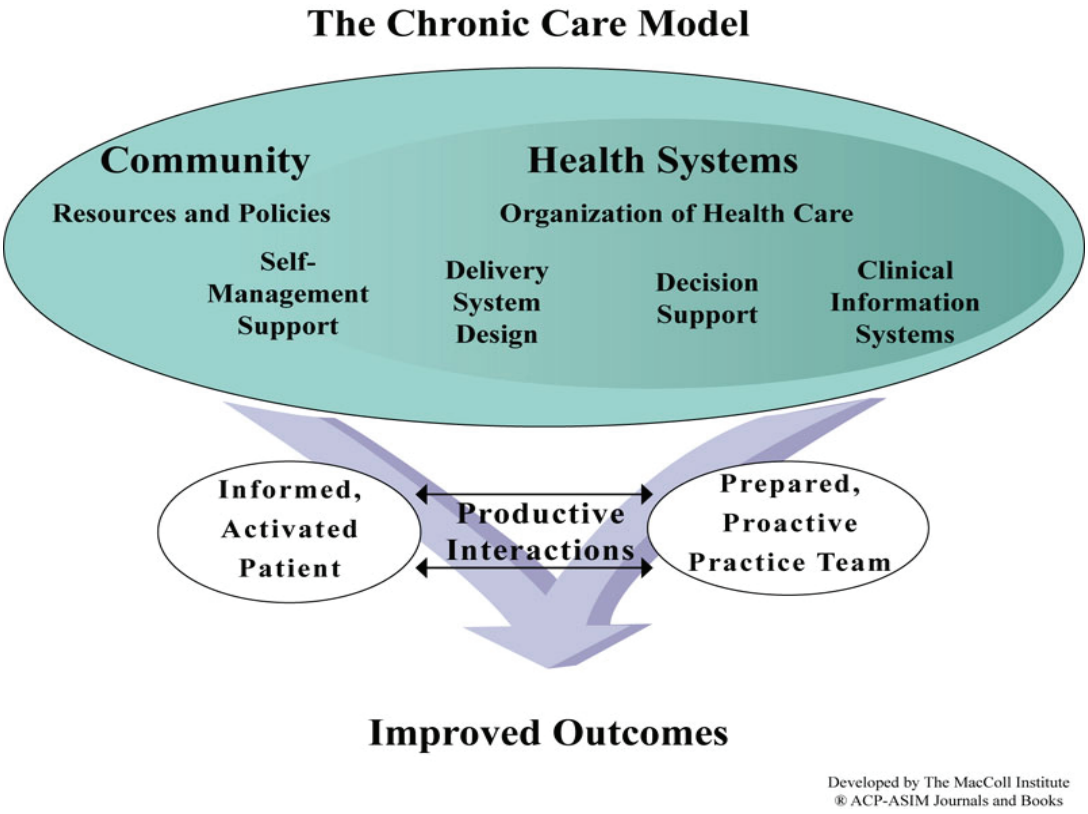
The key components of an Advanced Medical Home, based on the Chronic Care Model, are (see Figure 1):[4,8]

Self-management support: Patients are encouraged to develop the knowledge and skills to optimally manage their own care, including understanding their medical condition, maximizing their current health, preventing secondary complications, and utilizing all available resources.

Delivery system design: Advanced Medical Homes have enhanced, same-day services; multiple communication modalities, including telephone and e-mail consultation; coordination of care among service providers; and defined roles and tasks for all team members to maximize the efficiency of the medical visit.

Decision support: Both medical providers and patients have access to the highest quality of evidence-based medical care available. Information for both primary care providers and patients is presented in the most appropriate and efficient format for the clinical encounter. Decision support tools, such as clinical guidelines, professionally prepared patient education materials, and disease management software (if available), are included in the medical visit.

Figure 1. The Chronic Care Model[10]



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Clinical information systems: Ideally, the Advanced Medical Home has access to information technology which facilitates comprehensive, secure recordkeeping, care coordination features, monitoring of key quality care indicators and performance feedback, and patient safety functions such as medication reconciliation software.

What Are the Perceived Benefits of the Medical Home?

Starfield and Shi[9] note there is good evidence that an identified Medical Home is associated with better problem-and-needs recognition, more accurate and earlier diagnosis, increased patient satisfaction, fewer emergency room visits and hospitalizations, fewer missed appointments, fewer overall drug prescriptions, and lower costs.

How Could the Medical Home Model Improve Treatment With Hydroxyurea?

Using the concepts of the Medical Home, hydroxyurea treatment could be improved by:

- More frequent recommendations, due to more *informed, proactive* primary or principal care providers using *evidenced-based* guidelines and *decision support* tools.

- More frequent acceptance by patients, due to greater trust in an *identified, longstanding principal provider* and access to *patient education* materials written at the appropriate cultural and health-literacy level.

- Fewer complications, due to *clinical information systems* that identify when blood monitoring is due and alert when abnormal results are present.

- Greater adherence to treatment because patients have *self-management* training to remember medication schedules, know how to ask questions and raise concerns with the healthcare team, and identify and solve problems when side effects occur.

- Fewer problems with nonadherence due to medication costs and fewer problems with insurance coverage due to *comprehensive care-coordination* services that include financial counseling.

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Models of Comprehensive Care

Bruce L. Evatt, M.D.

A substantial number of Americans are affected by hereditary defects that produce diseases of the blood system. Some of these conditions—for example, sickle cell anemia, hemophilia, thalassemia, and thrombophilia—are associated with significant chronic morbidity, disability, and increased mortality. Besides being hereditary blood disorders, these conditions have common management and outcome issues: (1) complications, disability, and mortality can often be prevented; (2) the success of their prevention depends on access to specialized medical care; (3) preventive services require substantial resources; and (4) substantial educational and social service resources are required to achieve optimal management success.

Because these conditions are similar, the management experiences of the other conditions should be considered, in the design of a healthcare model, for possible adaptation to the particular clinical requirements for a specific disease. In addition, particular requirements render management models for such conditions especially attractive for the application of public health principles in the design:

- First, because care of these conditions is very specialized, it is best met through a multidisciplinary team approach. Thus, appropriately trained and experienced medical staff members are needed to avoid poor therapeutic decisions that can lead to severe disability and mortality.

- Second, maintaining such trained and experienced healthcare providers can often be achieved only by concentrating care of patients in specialized centers.

- Third, premium emphasis should be placed on preventive medicine, because complications resulting from these conditions are often severe and extremely difficult and expensive to treat.

- Fourth, maintaining a coordinated network of specialty centers enables patients to have access to clinical research and evaluation.

- Finally, careful structure of the specialty centers provides optimal care based on allocation of limited resources.

To illustrate this point, since 1970, a preventive health approach to care has been developed for patients with hemophilia. The evolution of this health model was driven by lessons learned from well-documented outcome studies. This model could serve as a possible care model for sickle cell disease, thalassemia, and thrombophilia.

At least 20,000–25,000 persons are affected by hemophilia in the United States. When untreated, these defects lead to abnormal and sometimes life-threatening bleeding episodes. Before the 1960s, when no comprehensive care was available, individuals with hemophilia suffered from severe joint disabilities that appeared in the early teens, and most patients died before the age of 20. Cryoprecipitate was discovered in 1964, and subsequent development of clotting factor concentrates dramatically increased clinical management options.[1] Because concentrates could be stored easily, administered at home, and carried with patients during

travel, patients began to adopt the practice of home therapy. Early treatment of bleeding episodes and home therapy quickly evolved as the primary management options. Training and education of patients about disease management became necessary with the increasing popularity of home therapy. Specialized centers soon delivered services to meet these needs.[2,3] These approaches to patient care produced significant effects on general patient health and survival; as a result, the hemophilia community requested support from the Federal Government for networks of hemophilia treatment centers (HTCs).[4,5]

To meet these demands, in 1975, Congress initiated Federal funding to specialized HTCs across the country to provide comprehensive care to persons with bleeding disorders.[6] This support initially came from the Health Resources and Services Administration (HRSA). The Centers for Disease Control and Prevention (CDC) began to provide additional funds to HTCs in the 1980s, in response to the high rates of human immunodeficiency virus infection occurring in hemophilia patients and the need to include prevention services in the clinical care setting. As a result, since 1983, CDC and HRSA have coordinated activities and support for care and risk-reduction efforts aimed at preventing the complications of hemophilia.

In 1991, the National Hemophilia Foundation requested that CDC further expand its activities within the bleeding disorders community. Meetings conducted in 1992 between patients and hemophilia care providers outlined a national strategy for preventing the complications of hemophilia and related bleeding and clotting disorders. As a result of this initiative, Congress instructed CDC to develop a national program aimed at preventing the complications of bleeding and clotting disorders: specifically, to reduce the human suffering and financial burden associated with these diseases. In response, CDC has provided funding to HTCs for prevention activities related to organization, education, training, and counseling services for patients with hemophilia as well as evaluation and intervention studies to improve existing programs.

Currently, the Federal HTC system comprises 134 centers in 50 States and U.S. territories. These centers provide comprehensive services, including diagnosis, clinical management, orthopedic and dental care, and counseling for patients with hemophilia and von Willebrand's disease. Of the approximately 20,000–25,000 persons with hemophilia in the United States, 67% visit a local HTC at least once annually for preventive care.[7]

These activities have been highly successful in reducing morbidity associated with hemophilia. Studies indicate that, compared to patients receiving care within an HTC, those not receiving HTC care have a 60% higher mortality rate, and their hospitalization rates are 30% higher despite having milder clinical symptoms.[8,9]

Today, comprehensive care using an integrated public health approach is vital for patients with hemophilia to prevent early death and to free patients from the complications that inhibit them in living their lives. Experience has shown that, once introduced, there is a progressive restoration of normal, healthy lives to the hemophilia community.[10,11] Accompanying this progress is a gradual decreased dependency on the HTC—except during brief periods when the expertise within the comprehensive center is mandatory for life-saving clinical management or to prevent severe morbidity. This model is now being adapted to persons with thrombophilia and with thalassemia.

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What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Pediatrician's Perspective

Michael R. DeBaun, M.D., M.P.H.

Pain and acute chest syndrome are the most common morbidities experienced by children with sickle cell anemia. Most children with sickle cell anemia visit a physician once a year for management of their pain. When outpatient pain management strategies fail, two-thirds of these children will ultimately require inpatient admission. Acute chest syndrome is the second most common cause of hospitalization for children with sickle cell disease (SCD). Hydroxyurea (HU) has been used to prevent pain and acute chest syndrome in adults with sickle cell anemia and decreases the incidence of both complications by approximately 50% in this population. However, limited evidence exists to guide pediatric clinicians as to the benefits and risks of HU treatment for children with sickle cell anemia. Furthermore, even less evidence is available to address factors that may influence adherence to and ultimately effectiveness of HU treatment among children with SCD.

Small clinical studies provide some evidence for the benefit of using HU to prevent multiple pain episodes. These studies were not designed to determine the long-term toxicity of HU or SCD-related complications that may be attributable to the use of HU, such as splenic sequestration or avascular necrosis of the long bones. Splenic sequestration may occur more often in children treated with HU because of improvement in spleen function after receiving HU. Avascular necrosis is associated with higher steady-state hemoglobin level, a common occurrence after the start of HU therapy.

A reasonable approximation of the risk–benefit profile for the use of HU in pediatrics has not been established and requires formal evaluation. Extrapolating the benefit of HU from adult studies to children has significant limitations. Multiple examples exist where the benefits in the adult population were well established; however, when a formal trial was completed among children, there was no significant clinical utility. Additionally, extrapolating clinical experience in children who have sickle cell anemia to children who have hemoglobin SC and Sβ-thalassemia to support the use of HU has even less foundation, as the incidence rate for SCD-related complications significantly differs between these sickle cell phenotypes.

The use of HU to prevent painful episodes is the only established indication in children. The common pediatric practice of prescribing HU for children with repetitive acute chest syndrome episodes has not been based on rigorous clinical studies. Outside a formal trial setting, less evidence is available to justify the use of HU for primary or secondary prevention of an overt stroke, silent stroke, or recurrent priaprism.

Reliable indicators of adherence to HU use have not been well established, although therapeutic efficacy of HU requires sustained use for several months. Given the paucity of data demonstrating the range of potential indications coupled with the toxicity profile of HU, prudent start of HU therapy must be assessed on a case by case basis. Initiating HU must be done in consultation with a pediatric hematologist or primary care physician in conjunction with a pediatric hematologist. In the event that the patient is not taking HU regularly, careful evaluation is required to identify potential modifiable barriers for adherence to therapy. Assessment of the

barriers to adherence will require ongoing vigilance that must include the patient and parents in creative problem solving.

Formal multicenter clinical trials, sponsored by the National Institutes of Health, using HU in children with SCD should be conducted to assess the magnitude of the risk–benefit profiles of this chemotherapeutic agent. The highest priority should be given to the clinical conditions that have the greatest patient and family burden, such as acute chest syndrome. A clinical trial for prevention of acute chest syndrome in children is mandated, given the paucity of evidence describing its efficacy despite the common use of HU in clinical practice, the high incidence of acute chest syndrome in children, the high morbidity and risk of death, and the significant differences in clinical and natural history between acute chest syndromes in children compared to those in adults with SCD. Additional research is required to better understand the factors that influence adherence to HU treatment among children and adolescents. Otherwise, the true benefit of this therapy will be greatly limited.

What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Adult Provider's Perspective

Richard Lottenberg, M.D.

Introduction

For the last decade, compelling evidence has supported recommendations to use hydroxyurea (HU) to decrease morbidity, mortality, and medical costs for certain adult patients with sickle cell disease (SCD). Uptake of this evidence-based intervention is still less than optimal.

History of Hydroxyurea Recommendations and Availability

The Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) provided efficacy data to support the use of HU in symptomatic adult patients with sickle cell anemia.[1] In 1995, following early termination of the trial, the National Heart, Lung, and Blood Institute (NHLBI) issued a clinical alert announcing the results and that HU could be prescribed for this population. By 1998, the U.S. Food and Drug Administration (FDA) had approved HU for treatment of adult patients who had at least three painful crises in the previous year. In 2002, the 4th edition of the NHLBI monograph addressing the management of SCD provided clinical indications and recommendations for HU treatment based on the findings of the MSH.[2] The following year, results of a 9-year observational follow-up study of patients enrolled in MSH demonstrated reduced mortality for patients receiving HU.[3] Resource utilization analysis of MSH data showed that the cost of HU therapy is more than offset by the substantial reduction in hospitalizations of those patients for whom it is appropriately prescribed.[4] Thus, most Medicaid programs and other third-party payers have adopted coverage for HU. A pharmaceutical assistance program provides the drug to patients who lack health insurance.

Diffusion of Hydroxyurea Use Into Clinical Practice

Adoption of HU therapy in the treatment of adults with SCD has not been optimal despite the compelling results of the MSH and evidence of cost-effectiveness. Analysis of data on hospitalizations for sickle cell anemia in Maryland for fiscal years 1995 through 2003 revealed an increase in the number and costs of hospitalizations following FDA approval of HU treatment.[5] In one hospital, 70% of patients who would meet accepted criteria were not receiving HU. A retrospective study, using medical claim data for Florida Medicaid recipients from 2001 through 2005, identified a low prevalence of HU use and, in agreement with the Maryland data, a substantial number of patients who met criteria for HU therapy were not receiving it.[6] Furthermore, only a small subset of patients consistently received prescriptions for HU.

Barriers to Implementation of an Evidence-Based Intervention

First, HU is available as a generic product; there is little incentive for pharmaceutical companies to market the drug to physicians. Second, there are physician-based barriers to implementation. A 2002 survey of Florida and North Carolina hematologists/oncologists provided some insights into physicians' prescribing practices.[7] Both community-based and academic physicians were

able to list clinical indications consistent with the recommendations of the National Institutes of Health (NIH) monograph. However, the survey revealed that most community-based physicians saw fewer than three patients who had SCD per month. Patient volume has previously been implicated as a factor contributing to quality of healthcare.[8,9] Additional barriers identified included concerns about potential carcinogenicity, concerns about contraceptive use with the drug, and the doubts of a significant number of physicians about the effectiveness of HU treatment. The last identified barrier speaks to the lack of decision support systems for physicians. Furthermore, a review of current medical and hematology textbooks revealed that only 50% of the texts provided clinical indications or initial dose recommendations for HU treatment.[10] Even fewer texts include guidance for dose modification. The NIH monograph on Management of Sickle Cell Disease provides a treatment protocol for HU therapy; however, two recent surveys revealed that only a minority of hematologists/oncologists in Florida adult practices used the publication on a regular basis.[7,11]

Recommendations for Increasing Hydroxyurea Use

Several recommendations can be made to enhance the appropriate use of HU. HU therapy consultative services are needed for physicians practicing outside major medical centers specializing in SCD. Research initiatives are needed to identify effective educational programs and materials. Development of clinical practice tools should focus on assisting with identification of patients as well as requirements for initiation and monitoring of the treatment. Tools are also needed for the decisionmaking process for starting treatment, continuing treatment, and assessing clinical response. Instruments are needed to assist physicians in informing the patient about the benefits and risks of HU therapy tailored to the individual's clinical condition. Patient education materials should focus on facilitating physician–patient concordance on the risk/benefit ratio for HU treatment. Once these materials are established, information on their availability should be widely disseminated among healthcare providers and patients.

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What Do Physicians, Insurers, and Consumers Need To Know About Hydroxyurea for Appropriate Utilization? The Consumer's Perspective

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Hydroxyurea (HU) is an effective and important therapy for patients with sickle cell disease (SCD).[1,2] Efficacy of HU has been proven and demonstrated in the Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia (MSH) as well as several other trials. Despite positive results of reducing painful events, acute chest syndrome incidence, and frequency of blood transfusion, only a small percentage of the eligible sickle cell population participates in HU therapy.[3,4] HU is prescribed to those who cite frequent painful crises, acute chest syndrome, and symptomatic anemia.[5] Since the U.S. Food and Drug Administration approval of HU and its incorporation into clinical practice, little is known about the perceptions of HU by patients who have SCD. Recent literature suggests that healthcare providers who are not specialists in SCD are reluctant to administer HU as a clinical therapy, but this does not account for the patients who are exposed to the option and reject it. Reasons why healthcare providers may not prescribe HU include concerns about compliance, reproduction, and side effects.[5] Presumably, these same concerns are important to the patient population who may consider HU as a therapeutic option. Other concerns may involve fear of long-term effects with continued use. Although HU has been used as a cancer treatment for many years, its use for SCD therapy has existed for less than 10 years.

A very important component of HU usage is the relay of appropriate information to the persons considering it for themselves or their children. Information is a common tool for health education and is often an essential foundation for health decisions. The Consumer Information Processing (CIP) model reflects a combination of rational and motivational ideas. The use of information is an intellectual process; however, motivation drives the search for information and how much attention people pay to it. Information Search and Information Environment are two constructs within the CIP model that can help elucidate the model as it relates to HU use and perceived barriers. Information Search is the process of acquiring and evaluating information. It is affected by motivation, attention, and perception of the consumer (e.g., patients who have SCD). Information Search involves the provision of information so it takes little effort to obtain, draws the consumer's attention, and is clear. Information Environment is the amount, location, format, readability, and the ability to process relevant information. It involves tailoring specific information to the audience and ensuring that information is in an accessible location or venue.[6,7]

Within these constructs are important components that include the patient/provider relationship, knowledge and attitude of the patient and provider, perceptions of the patient and provider, consumer education outside of the clinical setting (e.g., social network, media, and Internet), transition issues, and behavioral beliefs and attitudes.[7] Each of these components works individually and together to help influence decisionmaking.

More information is needed about perceptions of HU among patients who have SCD. A community assessment, using a cross-sectional design with qualitative and quantitative research methods, should be conducted to assess the real and perceived barriers to HU usage

by persons who have SCD. Focus groups with consumers, questionnaire dissemination, and individual provider interviews should be used to capture more information about HU use.

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The Laboratory Evidence of Efficacy of Hydroxyurea in the Treatment of Sickle Cell Disease

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Since its approval by the FDA in 1996, hydroxyurea (HU), a ribonucleotide reductase inhibitor, has had a major impact on the clinical expression of sickle cell disease (SCD). As the first agent clearly demonstrated to reduce the frequency of such sickle cell-related complications as vaso-occlusive crises and episodes of acute chest syndrome, HU has now been given to many patients, particularly those who are severely affected by SCD. Because of concerns regarding its side effects following long-term exposure as well as its potential as a carcinogen, a mutagen, and/or a teratogen, the initial experience with HU in patients with SCD was limited to adults. Over time, however, when it became apparent that with careful administration and follow-up, HU could be given safely to adult patients with SCD, children also began to receive this agent. Initially, they were given HU as participants in clinical trials, but soon thereafter it also became part of standard therapy for children with SCD. In most cases, children, like adults, have shown substantial benefit following treatment with HU.

Because data from the Cooperative Study of Sickle Cell Disease (CSSCD) indicated that the percentage of fetal hemoglobin (HbF) could influence such manifestations of SCD as the frequency of painful events (1), the occurrence of episodes of acute chest syndrome (2), and overall life expectancy (3), and since HU (and other cytotoxic agents) have been found to enhance HbF production (4-5), it was initially presumed that the beneficial effect of HU was a direct consequence of its ability to increase the percentage of HbF. In the initial multicenter trial in which HU was given to a total of 32 adult patients with SCD who received the drug for a period of at least 16 weeks, a highly significant increase in the mean circulating level of HbF (from 4% to 15%) was observed (6). Similar increases in F-cells, F-reticulocytes, and the amount of HbF per F-cell were also noted in these study subjects. Although not designed nor sufficiently powered to demonstrate HU's clinical benefit in terms of vaso-occlusive episodes, many of the participants in this NIH-funded Phase I safety trial clearly appeared to receive clinical benefit from HU. In addition to the increase in HbF, these study subjects exhibited a number of highly significant changes in a variety of other hematological parameters including increases in total Hgb and MCV and decreases in total WBC, neutrophils, reticulocytes, and platelets. The laboratory results from this Phase I study and the favorable safety profile that was observed in these patients served as the basis for the Phase III Multicenter Study of Hydroxyurea (MSH) (7). While the MSH also showed an HU-induced increase in the various HbF measurements, the most prominent increment in these HbF parameters in the HU-treated patients was seen during the initial three months of therapy. Thereafter, the overall increases in the various HbF measurements trended downward such that by the end of year two, the various HbF parameters

achieved by the HU-treated patients in the MSH were substantially less than the HbF levels that were noted at the end of the earlier, 16 week Phase I study. Two subsequent analyses, in which the results of the 299 participants the MSH were subdivided into quartiles according to their response to HU, found that those patients with the best clinical response in terms of vaso-occlusive crises also had the most robust and sustained increases in both HbF and MCV (8-9). However, these same two analyses also found that those patients in the quartile with the fewest vaso-occlusive events also had the lowest numbers of circulating neutrophils, monocytes, reticulocytes, and platelets. Therefore, it was difficult to be certain which of these various changes (or perhaps what combination of changes) was actually responsible for the clinical efficacy of HU observed in this clinical setting.

In children, the response to HU was first examined in the Pediatric Hydroxyurea Safety Trial, often referred to as HUG-KIDS (10). Much like the initial Phase I adult trial described above, the NIH-funded HUG-KIDS study was not designed to analyze the clinical efficacy of HU in terms of vaso-occlusive crises. Rather, this Phase I/II safety study showed that HU was safe and well-tolerated in children with SCD. In addition, just like the original Phase I study conducted in adults, the children who participated in HUG-KIDS showed a substantial increase in the mean circulating level of HbF (7.3% to 17.8%) during the 12 months of this study. These investigators also found that those children who achieved the highest HbF responses after 12 months of HU therapy: a) had the highest levels of HbF at baseline; and b) were able to tolerate the highest dosages of HU throughout the course of the study. Finally, when the peak HbF response was broken down into quartiles (i.e., maximal to minimal HbF responders), highly significant correlations were observed between the magnitude of the increase in HbF and the extent of: a) the increase in total hemoglobin and MCV; and b) the decrease in total WBC and reticulocytes. In a second pediatric Phase I Safety Study that was conducted at a single institution, virtually identical hematologic results were observed (11). While neither of these two pediatric studies looked at the frequency of painful events and/or hospitalizations, a few other studies did. While these were not randomized, placebo-controlled trials, they did obtain baseline data such that the HU-treated patients served as their own controls. Jayabose et al. (12) treated 14 SCD children with HU and found a highly significant decrease in the number of vaso-occlusive events (both painful crises and episodes of acute chest syndrome) when compared to the experience of these same children prior to HU therapy (i.e., 2.5 events per year before HU to 0.87 events per year on HU). Ferster et al. (13) also reported that after initiation of HU therapy, the 93 children in their study experienced significant decreases in both the number and duration of hospitalizations when compared to what had been observed in these same children during the 12 months prior to the initiation of HU therapy. Furthermore, an analysis of the subset of 22 children who had received HU for at least 5 years confirmed a significant difference in hospitalizations ($P = 0.0002$) as well as days in the hospital ($p < 0.01$). In addition to these clinical responses, both studies observed hematologic findings that were similar to those observed in the other adult and pediatric studies (i.e., increases in total Hb, % HbF and MCV and decreases

in circulating neutrophils, evidence of red cell destruction, etc). Therefore, just as in the adult studies, it remains unclear as to which of these various changes (or what combination of these changes) is responsible for the observed reduction in vaso-occlusive events.

With the increased understanding of the pathophysiology of SCD that we have gained over the past 10-15 years, it has become readily apparent that it is not simply the polymerization of hemoglobin S (HbS) and the formation of rigid, sickle erythrocytes (RBC) that leads to the impairment of blood flow and the resulting vaso-occlusion that is experienced by patients with SCD. We have learned, for example, that HbS-containing RBC (especially reticulocytes) are sticky and tend to adhere to one another, to the endothelium, and to the various proteins that comprise the subendothelial matrix. In addition, leukocytes, neutrophils, monocytes, inflammation, and blood clotting all appear to make important contributions to the process of vaso-occlusion. As emphasized above, HU can produce significant changes in many of these parameters. Furthermore, virtually all of the HU-induced changes tend to occur in the direction that would be of benefit in this clinical setting. As one example, Drs. Charache et al, in their extensive evaluation of the MSH (8), employed a multivariable analysis to provide convincing evidence of an independent association between lower neutrophil counts and lower crisis rates. By contrast, the increase in F-cell levels was associated with lower crisis rates, but only during the initial 3 months of HU therapy.

One final factor that is of critical importance to all of these studies relates to the issue of compliance. No matter how efficacious a therapy might be, it will only be effective if it is taken by the patient. In the original adult Phase I Study, for example, while those patients with the poorest HbF responses might have been refractory to the drug, it is important to emphasize that many of them were strongly suspected of noncompliance. Evidence of such noncompliance was suggested by the absence of HU in most of the random plasma samples from these “poor responders” (6). Similarly, in the HUG-KIDS Study, the extent of the increase in HbF level was inversely correlated with compliance with the treatment regimen as determined by pill counts (10). It is worth noting that Drs. Olivieri and Vischinsky conducted a study in children with SCD that was specifically designed to evaluate compliance with HU (14). By using the MEMS cap monitoring system, they found compliance to be remarkably high (96%) in their patient population. Perhaps because of parental supervision, it is quite possible that children with SCD may be substantially more compliant with the prescribed HU than are their adult counterparts. In any event, compliance is a vitally important factor in this setting, as we have all seen “HU-treated” patients with SCD whose hematological parameters (HbF, MCV, neutrophils, reticulocytes, etc) fail to change despite “taking” dosages of HU that often exceed 30 mg/kg/day.

In summary, it is readily apparent that when HU is administered to patients with SCD, it has a significant effect not just on the clinical expression of the disease, but also on a wide variety of laboratory parameters. Furthermore, in most cases these changes in

laboratory values tend to occur together (i.e., those patients who achieve the highest HbF levels also tend to have the most prominent increases in parameters such as total hemoglobin and MCV as well as the most striking declines in parameters such as total WBC, neutrophils, reticulocytes, and other markers of red cell destruction). Virtually all of these HU-induced changes in laboratory parameters occur in a direction that one would expect to be beneficial in the setting of SCD. It is therefore difficult to be certain whether one specific change (e.g., the increase in HbF) is responsible for the bulk of the observed clinical benefit and everything else is a secondary manifestation this primary effect, or alternatively whether the observed clinical benefit results from a combination of some or all of the various changes that occur in this clinical setting.

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