



## Complete Summary

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### GUIDELINE TITLE

National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease.

### BIBLIOGRAPHIC SOURCE(S)

Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, James AH, Laraque D, Mendez M, Montoya CJ, Pollock BH, Robinson L, Scholnik AP, Schori M. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008 Jun 17;148(12):932-8. [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

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## SCOPE

### DISEASE/CONDITION(S)

Sickle cell disease

### GUIDELINE CATEGORY

Management  
Treatment

### CLINICAL SPECIALTY

Family Practice  
Hematology  
Internal Medicine  
Pediatrics

### **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Health Care Providers  
Nurses  
Patients  
Physician Assistants  
Physicians

### **GUIDELINE OBJECTIVE(S)**

To provide researchers, health care providers, patients, and other interested members of the general public with an objective assessment of what is known about hydroxyurea as a treatment for sickle cell disease, and what questions remain

### **TARGET POPULATION**

Infants, preadolescents, adolescents, and adults with sickle cell disease

### **INTERVENTIONS AND PRACTICES CONSIDERED**

Hydroxyurea treatment

### **MAJOR OUTCOMES CONSIDERED**

- Effectiveness of hydroxyurea treatment for patients who have sickle cell disease
- Short- and long-term harms of hydroxyurea treatment
- Barriers to hydroxyurea treatment for patients who have sickle cell disease

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases  
Searches of Unpublished Data

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

**Note from the National Guideline Clearinghouse (NGC):** A systematic review of the literature was prepared by the Johns Hopkins University Evidence-based

Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) for use by the National Institutes of Health (NIH) (see the "Availability of Companion Documents" field).

### **Data Sources**

The EPC staff searched MEDLINE, EMBASE, TOXLine, and CINAHL through 30 June 2007. They 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. Efficacy trials were defined as those showing a therapeutic effect of an intervention in an ideal setting, such as a clinical trial. Effectiveness studies were defined as those showing a therapeutic effect of an intervention as demonstrated or observed in patients in their usual care setting.

### **Study Selection**

For evidence of efficacy and effectiveness of hydroxyurea in adults with sickle cell disease, EPC staff included randomized, controlled trials (RCTs), cohort studies with a control population, and before-and-after studies. For evidence of toxicity, they included RCTs; cohort studies with a control population; before-and-after studies; and case reports, a weaker form of evidence. EPC staff included studies of children with sickle cell disease only if leukemia or lymphoma was described.

The EPC knew that data on the long-term harms of hydroxyurea in individuals with sickle cell disease would be limited. Therefore, to describe all that is known about the long-term harms of hydroxyurea, they included indirect evidence from studies enrolling patients treated with hydroxyurea for other diseases (largely essential thrombocythemia, polycythemia vera, psoriasis, human immunodeficiency virus [HIV], and chronic myelogenous leukemia). The EPC staff included RCTs, cohort studies with a control population, before-and-after studies, case reports, and large case series ( $\geq 100$  patients with diseases other than chronic myelogenous leukemia).

Two reviewers independently reviewed titles and abstracts for eligibility.

### **NUMBER OF SOURCE DOCUMENTS**

A total of 246 studies were included in the review.

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Not Given)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

### **METHODS USED TO ANALYZE THE EVIDENCE**

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

**Note from the National Guideline Clearinghouse (NGC):** A systematic review of the literature was prepared by the Johns Hopkins University Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) for use by the National Institutes of Health (NIH) (see the "Availability of Companion Documents" field).

### **Data Extraction**

A single reviewer abstracted data, and a co-investigator verified accuracy. Reviewers were not masked to the articles' authors, institutions, or journal. Differences of opinion were resolved through discussion.

For all studies except case reports, reviewers extracted information on general study characteristics, participant characteristics, and efficacy and toxicity outcomes. Case reports were abstracted by using a separate form to record disease, participant age, reported adverse events, and causality according to the World Health Organization's causality assessment instrument.

### **Quality Assessment**

The quality of the included randomized controlled trials (RCTs) was assessed by using the scoring system developed by Jadad and colleagues. To assess quality of the observational studies, the EPC staff developed a form to identify key elements that should be described in reports of observational research, as advocated by leaders in the field. For the quality assessment of surveys, they adapted information from the study by Ratanawongsa and associates. The quality assessments were done independently by paired reviewers. For the RCTs, a third reviewer reconciled the findings of the first 2 reviewers. For the other study designs, the results of the 2 reviewers were averaged.

### **Data Synthesis**

Detailed evidence tables with information extracted from eligible studies were created. The data were not quantitatively pooled for any of the outcomes because there were few RCTs. The substantial qualitative heterogeneity among the observational studies made pooling these studies problematic. EPC staff explored graphically the relationship across studies between potential predictors of response (age, mean corpuscular volume, sample size, change in leukocyte count) and the change in fetal hemoglobin. They considered the evidence about efficacy and effectiveness together because the observational studies were not easily categorized as efficacy or effectiveness studies.

### **Grading of Evidence**

The quantity, quality, and consistency of the evidence were graded 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. In this system, the grade of evidence depends on the required domains and not on the number of studies; consistency, directness, and precision are considered to be more informative than number of studies. If an outcome was evaluated in 1 or no RCTs, EPC staff also based their evidence grade on the best available nonrandomized trials or observational studies. They assessed the quality and consistency of the evidence by evaluating the risk for bias in the studies (as indicated by the study quality scores), the directness with which the data addressed the study question, and the precision and strength of the findings within individual studies. For each outcome of interest, 2 investigators graded the strength of the evidence for each question and all investigators then reached consensus.

The results from case reports were used as additional evidence of directness in the grading of toxicity. The case reports were graded according to the World Health Organization's Collaborating Center for Drug Monitoring. This method uses 4 criteria to evaluate the case reports and determines from these criteria how strong the causal relationship is between the drug and the described toxicity. The EPC staff determined from the body of case reports a level of causality based on the number of case reports and the strength of the causal relationships.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus (Consensus Development Conference)

### **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference from 25 to 27 February 2008 to assess the available scientific evidence related to the following questions:

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

At the conference, invited speakers presented information pertinent to these questions, and a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ) ([www.ahrq.gov/clinic/tp/hydscdtp.htm](http://www.ahrq.gov/clinic/tp/hydscdtp.htm)) was summarized. Conference attendees provided both oral and written statements in response to the key questions. The panel members weighed all of this evidence as they addressed the conference questions.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

The guideline developers reviewed published cost analyses.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Not stated

# **RECOMMENDATIONS**

## **MAJOR RECOMMENDATIONS**

The burden of suffering is tremendous among many patients with sickle cell disease. These patients experience disease-related pain on many days of their lives and usually do not seek medical attention until their symptoms are overwhelming. They often attempt to treat themselves and thus do not always come to the attention of the health care system. Obtaining optimal care for patients with sickle cell disease is challenging. Many patients are not in a coordinated program aimed at prevention of long-term complications and acute pain crises. They rely heavily on emergency and short-term care facilities for pain control.

Obtaining specialty care can be a substantial challenge because the number of health professionals trained to treat the disease is limited and the number of professionals specializing in the treatment of this disease is decreasing. The likelihood that patients with sickle cell disease have a principal physician is low. Transitioning from pediatric care to adult care poses particular challenges. Many children rely on public insurance for their care. Gaps in coverage occur, leading to gaps in care.

No population-based registries exist that provide good estimates of the number of people with sickle cell disease. Surveys indicate that a large proportion of patients who have sickle cell disease are poor and from underserved communities. Most U.S. patients with sickle cell disease are ethnic minorities. For many, the limited resources and lack of culturally competent care by experienced clinicians set the stage for suboptimal care.

Hydroxyurea is an important major advance in the treatment of sickle cell disease. Strong evidence supports the efficacy of hydroxyurea in adults to decrease severe painful episodes, hospitalizations, number of blood transfusions, and the acute chest syndrome. Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are encouraging. The current data on the risks of both short- and long-term harms of hydroxyurea

therapy are reassuring, and the risks of hydroxyurea use in adults are acceptable compared with the risks of untreated sickle cell disease.

It is difficult to draw conclusions about the effectiveness of hydroxyurea in everyday practice because we lack precise estimates of the number of people with sickle cell disease in the United States and the number of people receiving hydroxyurea. Furthermore, although barriers to the use of hydroxyurea in persons with sickle cell disease seem to be extensive, little research exists on the barriers at the patient-, parent/family/caregiver, provider, and system levels. More studies are required to address these issues.

The best way to achieve optimal care for patients with sickle cell disease, including preventive care, is for patients to be treated in clinics specializing in the care of this disease. All patients with sickle cell disease should have a principal health care provider, and that provider, if not a hematologist, should be in frequent consultation with one. The National Institutes of Health funds sickle cell research centers, and several states currently support sickle cell specialty clinics. Increased funding for basic, clinical, and social research on this disease is critically needed. There is an urgent need for centers specializing in the treatment of sickle cell disease to organize and network together to improve patient access to quality care.

#### **CLINICAL ALGORITHM(S)**

None provided

### **EVIDENCE SUPPORTING THE RECOMMENDATIONS**

#### **TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

The type of supporting evidence is not specifically stated for each recommendation.

### **BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

#### **POTENTIAL BENEFITS**

Appropriate use of hydroxyurea for the treatment of sickle cell disease

#### **POTENTIAL HARMS**

##### **Short-term Side Effects of Hydroxyurea**

- Decreased leukocyte count (leukopenia)
- Decreased platelet count (thrombocytopenia)
- Decreased erythrocyte count (anemia)
- Decreased reticulocyte count (fewer newly formed erythrocytes)
- Nausea (usually mild)\*
- Skin rash
- Pneumonitis (lung inflammation)

- Temporarily decreased sperm count or sperm abnormalities\*

### **Long-term Side Effects of Hydroxyurea**

- Increased risk for superficial skin cancer\*
- Skin and nail darkening (hyperpigmentation)
- Permanently decreased sperm count\*
- Reproductive\* (hydroxyurea can in theory increase the risk for miscarriage, birth defects, restricted fetal growth, or postnatal development; sexually active couples should avoid pregnancy if either person is receiving hydroxyurea.)

\*Evidence is insufficient or low that this side effect is associated with hydroxyurea.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health or the U.S. government. The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

The following solutions were proposed to remove barriers to hydroxyurea treatment for patients with sickle cell disease.

1. Promote models of care (such as comprehensive care, medical home, family-centered) across the lifespan that support quality of care and improved access to evidence-based treatment, including hydroxyurea.
2. Provide multidisciplinary care (for example, from health educators, social workers, case managers, physicians, and nurses) to improve the physical and mental health of patients with sickle cell disease and the financing structures to support such care.
3. Provide support for community health worker models (such as patient navigators, patient advocates, and peer advocates).
4. Provide support for coordination and comanagement of patients with the use of telemedicine.
5. Ensure better translation of findings to the patient and caregiver populations by using culturally or language-appropriate written and visual materials.
6. Implement health promotion models in educational interventions for adherence to therapies.
7. Engage and support community-based efforts to improve knowledge of the benefits and risks of hydroxyurea.
8. Improve federal, state, and local coordination of activities regarding sickle cell disease.

9. Provide support for cultural competency training across the interdisciplinary team regarding care for sickle cell disease.
10. Improve insurance coverage of sickle cell disease (for example, extend Medicare coverage to adults with sickle cell disease who are younger than 65 years).
11. Eliminate barriers that restrict access to public insurance.
12. Support ongoing training of health professionals to achieve and maintain competence in the care of patients with sickle cell disease, including hydroxyurea treatment.
13. Increase funding by government, industry, and philanthropic organizations for patients with sickle cell disease.
14. Encourage partnership and support of advocacy groups for sickle cell disease.
15. Develop enhanced information systems to better coordinate delivery of care in the health care system.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, James AH, Laraque D, Mendez M, Montoya CJ, Pollock BH, Robinson L, Scholnik AP, Schori M. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008 Jun 17;148(12):932-8. [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2008 Jun 17

### GUIDELINE DEVELOPER(S)

National Institutes of Health (NIH) Consensus Development Panel on Sickle Cell Disease - Independent Expert Panel  
Office of Medical Applications of Research (NIH) - Federal Government Agency [U.S.]

## **SOURCE(S) OF FUNDING**

United States Government

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National Institutes of Health (NIH) Consensus Development Panel

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

None disclosed

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available from the [National Institutes of Health \(NIH\) Consensus Development Conference Program Web site](#).

Print copies: Available from the NIH Consensus Development Program Information Center, PO Box 2577, Kensington, MD 20891; Toll free phone (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); autofax (in U.S.), 1-888-NIH-CONSENSUS (1-888-644-2667); e-mail: [consensus\\_statements@mail.nih.gov](mailto:consensus_statements@mail.nih.gov).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med 2008 Jun 17;148(12):939-56. Available in Portable Document Format (PDF) from the [Annals of Internal Medicine Website](#).
- Hydroxyurea for the treatment of sickle cell disease evidence report. Rockville (MD): Agency for Healthcare Research and Quality. Available in Portable Document Format (PDF) from the [National Institutes of Health \(NIH\) Consensus Development Conference Program Web site](#).

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI Institute on January 15, 2009. The information was verified by the guideline developer on January 29, 2009.

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