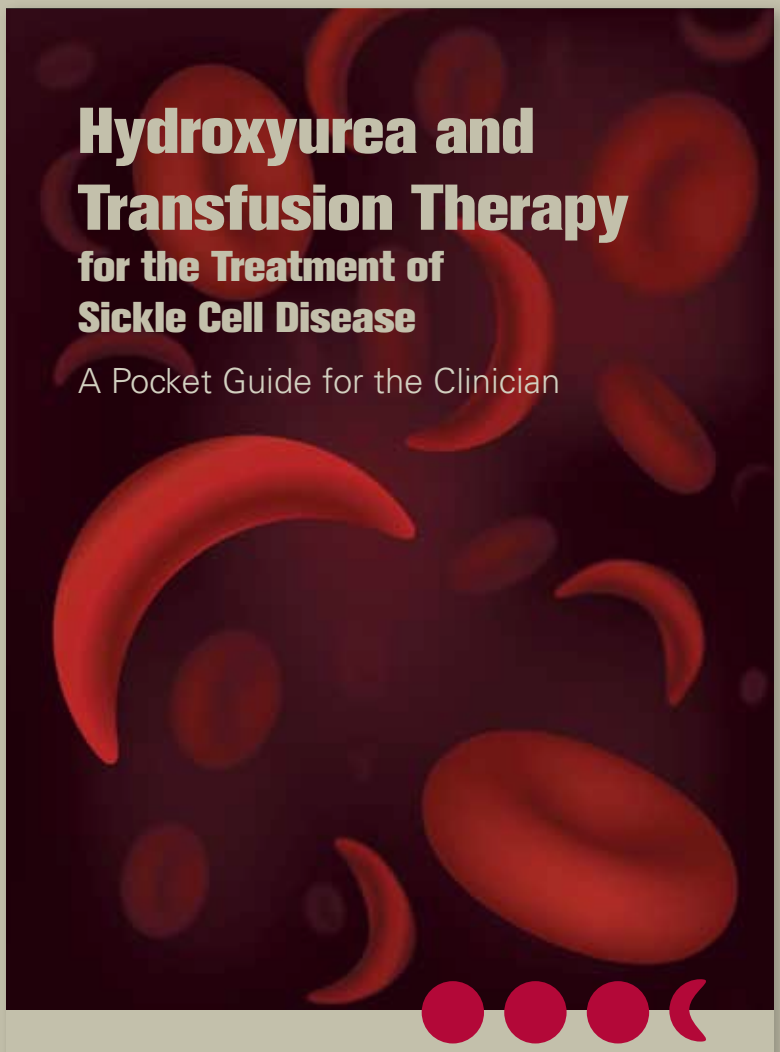

# Hydroxyurea and Transfusion Therapy

## for the Treatment of Sickle Cell Disease

A Pocket Guide for the Clinician

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## Disease Definition

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

## Hydroxyurea

Hydroxyurea was approved by the FDA in 1998 for the treatment of clinically severe SCA in adults. Its primary mechanism of action is induction of fetal hemoglobin. Treatment benefits include reduced frequency of acute sickle cell pain and acute chest syndrome, reduced need for blood transfusions and hospitalizations, and possibly improved survival.

All patients with SCA and their family members should be educated about hydroxyurea therapy *(Consensus–Expert Panel)*.

### Clinical Scenarios for Which Hydroxyurea Is Recommended for Adults With SCA

| Clinical Presentation | Strength of Recommendation | Quality of Supporting Evidence |
|---|---|---|
| Three or more sickle cell–associated moderate to severe pain crises* in a 12-month period | Strong | High |
| Sickle cell–associated pain that interferes with daily activities and quality of life | Strong | Moderate |
| History of severe and/or recurrent acute chest syndrome | Strong | Moderate |
| Severe symptomatic chronic anemia that interferes with daily activities or quality of life | Strong | Moderate |

* In the clinical trial that led to FDA approval of hydroxyurea for SCA, a pain crisis was defined as a visit to a medical facility of >4 hours requiring treatment with a parenteral opiate or NSAID.[1]

### Clinical Scenarios to Offer* Hydroxyurea for Children With SCA

| Age | Strength of Recommendation | Quality of Supporting Evidence |
|---|---|---|
| Infants and children 9–42 months | Strong | High |
| Children >42 months and adolescents | Moderate | Moderate |

* For these patients, the recommendation from the NHLBI report is to "offer" treatment, in recognition that patient values and preferences may differ, particularly considering treatment burden (eg, laboratory monitoring, office visits), availability of drug in liquid form, and cost.

### Other Treatment Recommendations

In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to the treatment regimen to improve anemia *(Weak recommendation, low-quality evidence)*.

In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy *(Moderate recommendation, very low quality evidence)*.

In patients with HbS$\beta^+$-thalassemia or HbSC who have recurrent sickle cell–associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy *(Moderate recommendation, low-quality evidence)*.

In patients not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert *(Moderate recommendation, very low quality evidence)*.

### Consensus Treatment Protocol for Hydroxyurea

An established prescribing and monitoring protocol is recommended to maximize benefits and safety *(Strong recommendation, high-quality evidence)*. Studies have not compared different protocols. The following is based on protocols used in published studies, basic science and pharmacokinetics of the drug, and consensus of the expert panel that developed the NHLBI report:

#### Pre-Treatment Laboratory Tests

- CBC with WBC differential, reticulocyte count, platelet count, and RBC mean corpuscular volume (MCV)
- Quantitative measurement of HbF if available (eg, hemoglobin electrophoresis, high-performance liquid chromatography)
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

#### Pre-Treatment Considerations

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy.
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea.

#### Initial Dosing

- For adults: 15 mg/kg/day (round up to the nearest 500 mg if using 500 mg capsules); 5–10 mg/kg/day if patient has chronic kidney disease (may use 200, 300, or 400 mg capsules if available)
- For infants and children: 20 mg/kg/day (compounded hydroxyurea solution 100 mg/ml)

### Monitoring and Dosage Modification

- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for a target absolute neutrophil count ≥2,000/µL; however, younger patients with lower baseline neutrophils may safely tolerate absolute neutrophil counts down to 1,250/µL.
- Maintain platelet count ≥80,000/µL.
- If neutropenia or thrombocytopenia occurs:
  - Hold hydroxyurea dosing.
  - Monitor CBC with WBC differential weekly.
  - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias.
- If dose escalation is warranted based on clinical and laboratory findings, proceed as follows:
  - Increase by 5 mg/kg/day increments every 8 weeks.
  - Give until mild myelosuppression (absolute neutrophil count 2,000/µL to 4,000/µL) is achieved, up to a maximum of 35 mg/kg/day.
- Once a stable dose is established, laboratory safety monitoring should include CBC with WBC differential, reticulocyte count, and platelet count every 2–3 months.

### Ongoing Considerations

- Patients should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up doses if a dose is missed.
- Monitor RBC MCV and HbF levels for evidence of consistent or progressive laboratory response. A clinical response to treatment with hydroxyurea may take 3–6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy.
- For the patient who has a clinical response, long-term hydroxyurea therapy is indicated.
- Hydroxyurea therapy should be continued during hospitalizations or illness.

## Red Cell Transfusion

Transfusion may be used to treat acute complications of SCD and to prevent chronic complications. Transfusion may also be used in the perioperative period in patients with SCD to prevent vaso-occlusive crises, stroke, or acute chest syndrome after surgery.

### Do Not Transfuse: Recommendations *Against* Transfusion

| Complication | Strength of Recommendation Against | Quality of Supporting Evidence |
|---|---|---|
| **Acute** | | |
| Anemia, asymptomatic | Consensus–Expert Panel | |
| Kidney injury, unless multisystem organ failure | Consensus–Expert Panel | |
| Pain crisis, uncomplicated | Moderate | Low |
| Priapism | Moderate | Low |
| **Chronic** | | |
| Splenic sequestration, recurrent | Weak | Low |

### Transfusion for Acute and Chronic Complications

| Complication | How to Transfuse | Strength of Recommendation | Quality of Supporting Evidence |
|---|---|---|---|
| **Acute** | | | |
| Acute chest syndrome: symptomatic, severe (ie, oxygen saturation <90% despite supplemental oxygen) | Exchange | Strong | Low |
| Acute chest syndrome: symptomatic, with decreased Hb of 1 g/dL below baseline | Simple | Weak | Low |
| Anemia, symptomatic | Simple | Consensus–Expert Panel | |
| Aplastic crisis | Simple | Consensus–Expert Panel | |
| Hepatic sequestration | Exchange or simple | Consensus–Expert Panel | |
| Intrahepatic cholestasis | Exchange or simple | Consensus–Expert Panel | |
| Multisystem organ failure | Exchange or simple | Consensus–Expert Panel | |
| Splenic sequestration plus severe anemia | Simple | Strong | Low |
| Stroke, acute | Simple or exchange | Moderate | Low |
| **Chronic** | | | |
| Stroke risk, in children with transcranial Doppler (TCD) reading* >200 cm/sec | Chronic program, exchange or simple | Strong | High |
| Stroke risk, in adults and children with previous clinically overt stroke | Chronic program, exchange or simple | Moderate | Low |

* TCD reading is the time averaged mean maximal cerebral blood flow velocity.

### Transfusion Prior to Surgical Procedures With General Anesthesia

| Population | Recommendation | Strength of Recommendation | Quality of Supporting Evidence |
|---|---|---|---|
| SCA with Hb level ≤8.5 g/dL | Transfuse RBCs to bring the Hb concentration to 10 g/dl. | Strong | Moderate |
| SCA with Hb level already >8.5 g/dL without transfusion | Consult a sickle cell expert for guidance as to the appropriate transfusion method. | Strong | Low |
| SCA and receiving hydroxyurea therapy | | | |
| SCA and requires high-risk surgery (eg, neurosurgery, prolonged anesthesia, cardiac bypass) | | | |
| HbSC or HbS$\beta^+$-thalassemia | Consult a sickle cell expert to determine if full or partial exchange transfusion is indicated. | Moderate | Low |

## Minimizing Adverse Effects of Transfusion

Transfusions can be lifesaving but carry a risk of severe adverse effects including death. Many hazards, such as risk of alloimmunization, are amplified in SCD. Many best practices to minimize adverse effects remain under investigation.

### Common Adverse Effects

| Adverse Effect | Signs and Symptoms |
|---|---|
| Alloimmunization | Alloimmunization presents as an immunological response by the recipient against "foreign" non-self-antigens that may follow an erythrocyte transfusion and result in destruction of transfused erythrocytes. |
| Autoimmunization | Autoimmunization presents as the development of an immune response to an individual's own erythrocytes, which may result in the destruction of erythrocytes. |
| Acute hemolytic transfusion reaction | Rare; usually occurs because of ABO incompatibility. Occurs during or within hours of transfusion. Signs and symptoms include fever and chills, chest pain, dyspnea, hypotension, and flank/abdominal pain. |
| Delayed hemolytic transfusion reaction (DHTR) | Acute anemia, pain (resembling acute vaso-occlusive crisis), or jaundice within 3 weeks after a blood transfusion. |

### Recommendations

RBC units should include matching for C, E, and K antigens ***(Moderate recommendation, low-quality evidence).*** More extensive matching may be done when RBC alloantibodies are present.

Consult the blood bank for evaluation of a possible DHTR if acute anemia, pain, or jaundice occur within 3 weeks after a blood transfusion ***(Strong recommendation, moderate-quality evidence).***

In patients with SCA who are not chronically transfused and who are therefore at risk for hyperviscosity due to high percentages of circulating HbS-containing erythrocytes, avoid transfusing to a target Hb >10 g/dL ***(Moderate recommendation, low-quality evidence).***

In patients who receive chronic transfusion therapy, perform serial assessment of iron overload by methods such as liver biopsy or MRI techniques ***(Strong recommendation, moderate-quality evidence).***

Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload ***(Moderate recommendation, moderate-quality evidence).***

## Consensus Protocol for Monitoring Individuals on Chronic Transfusion Therapy

An established monitoring protocol is recommended ***(Moderate recommendation, low-quality evidence).*** Studies have not compared different protocols. The following is based on protocols used in published studies, indirect evidence from basic science, and consensus of the expert panel that developed the NHLBI report:

### At Initiation

- Obtain patient treatment history to include locations of prior transfusions and adverse effects.
- Notify the blood bank that the patient being initiated on chronic transfusion therapy has SCD. Ask the blood bank to contact hospitals where the patient reports receiving previous transfusions to obtain transfusion information.
- Obtain a RBC phenotype, type and screen, quantitative measurement of percent HbA and percent HbS, CBC, and reticulocyte count.
- Inform the patient if he or she is alloimmunized, so that this information can be communicated as part of the patient's past medical history.

### Suggested Evaluation Before Each Transfusion

- CBC and reticulocyte count: Helps guide the frequency and volume of transfusions. It is expected that with effective chronic transfusion therapy, the patient's bone marrow will be suppressed and the reticulocyte count should decrease, but the value may rise by the time of the next transfusion.
- Quantitative measurement of percent HbA and percent HbS: Confirms the success of chronic transfusion therapy with achieving the target percent of HbS.
- Type and screen: Used to assess whether the patient has developed any new RBC antibodies from the prior transfusion.

### Suggested Periodic Evaluations

- Liver function tests annually or semiannually: Used to assess liver function in individuals with iron overload.
- Serum ferritin quarterly: Used to assess iron stores in individuals with iron overload; can be helpful in evaluating compliance with chelation.
- Screening for hepatitis C, hepatitis B, and HIV annually.
- Evaluation for iron overload every 1–2 years by validated liver iron quantification methods such as liver biopsy, MRI R2 or MRI T2* or R2* techniques.

## Rating System and Implications of Recommendations

As indicated in parentheses in this guide, evidence-based recommendations from the NHLBI report are separately rated according to the strength of the recommendation ***(strong, moderate, or weak)*** and the quality of the supporting evidence ***(high, moderate, low, or very low)***. These ratings are intended to have the following implications (adapted from GRADE[2]):

| | High-quality evidence ←···→ | Low-quality evidence |
|---|---|---|
| Strong recommendation | Recommendation can apply to most patients in most circumstances. | Recommendation may change when higher quality evidence becomes available. |
| ↕ | | |
| Weak recommendation | The best action may differ depending on circumstances or patient or societal values. | Other alternatives may be equally reasonable. |

Consensus statements represent opinion of the expert panel that authored the NHLBI report. Wherever indicated, these statements are based on minimal or no supporting evidence or very indirect evidence ***(Consensus–Expert Panel)*** or were adapted from existing guidelines ***(Consensus–Adapted)***.

## References


1 Charache S et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med.* 1995;332(20):1317–22.

2 Schünemann HJ et al. An official ATS statement: grading the quality of evidence and strength of recommendation in ATS guidelines and recommendations. *Am J Respir Crit Care Med.* 2006;174(5):605–14.


This pocket guide is adapted from the National Heart, Lung, and Blood Institute's *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014*, available at *www.nhlbi.nih.gov/guidelines*. Two companion pocket guides adapted from the same report are available: "Management of Acute Complications of Sickle Cell Disease" and "Health Maintenance and Management of Chronic Complications of Sickle Cell Disease."

This guide is not intended to be construed as a standard of care or to preempt clinical judgment. Recommendations based on expert opinion or less than high-quality evidence should inform shared decisionmaking with the patient about diagnostic and treatment alternatives. Even recommendations based on high-quality evidence may be inappropriate for some patients depending on clinical circumstances including individual patient preferences.

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