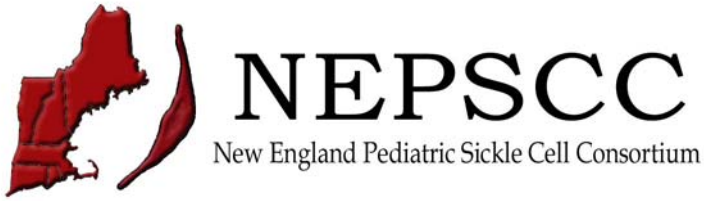
New England Pediatric Sickle Cell Consortium



Use of Hydroxyurea in Pediatric Patients with Sickle Cell Disease

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Disclaimer Statement:

- Hospital clinical pathways are designed to assist clinicians by providing an analytical framework for the diagnosis and treatment of specific medical problems. They may be used for patient education and to assist in planning future care. They are not intended to replace a physician's judgment or to establish a protocol for all patients with a particular condition. The ultimate decision regarding the care of any patient should be made in respect to the individual circumstances presented by the patient.
- Any specific medications and dosing must always be reviewed carefully for each patient in view of any history of drug allergy or adverse reactions.
- This document was based on available research and clinical experience at time of its compilation.
- The following protocol is a regional guideline, and may be adapted by individual institutions as needed.

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Inclusions:
Children and adolescents with sickle cell disease (HbSS, HbSβ^0 Thalassemia, or other severe sickle genotype/phenotype).

Patients must be under the supervision of a physician experienced with the dosing and monitoring of hydroxyurea in pediatric patients.

I. Introduction[1]

- Hydroxyurea has become an accepted therapeutic option for many patients with sickle cell anemia (SCA). For adult patients, hydroxyurea has dose-related hematological efficacy and an acceptable short-term toxicity profile [2].
- Clinical efficacy has also been proven; in a double-blinded placebo-controlled randomized trial involving severely affected adults with SCA, hydroxyurea significantly reduced the number of painful vaso-occlusive events, blood transfusions, episodes of acute chest syndrome, and hospitalizations [3].
- Most recently, long-term hydroxyurea use has been shown to decrease mortality in adults with SCA [4].
- For pediatric patients, hydroxyurea has a similar toxicity profile with only mild, transient, and reversible myelosuppression [5, 6].
- The multicenter Phase I/II safety trial of hydroxyurea therapy for severely affected school-aged children with SCA (HUG KIDS) demonstrated significant increases in hemoglobin concentration, mean corpuscular volume, and the percentage of both fetal hemoglobin and F cells [7].
- Subsequently, hydroxyurea has been shown to aid the growth and development of children with SCA [8] and to help prevent stroke recurrence in children with previous cerebrovascular accident [9].
- Despite this documented laboratory and clinical efficacy for persons with SCA, there are important unresolved issues regarding hydroxyurea in the pediatric population, particularly with regard to the appropriate age to initiate therapy. In one small group of pre-school children, hydroxyurea was well-tolerated with both hematological and clinical efficacy [10]. For infants with SCA, a prospective multicenter open-label Phase I/II pilot trial (HUSOFT) demonstrated hematological benefits with only modest toxicity [11], suggesting that hydroxyurea might be considered for very young patients before the onset of acute and chronic organ damage. An upcoming NIH-sponsored Phase III double-blinded, placebo-controlled randomized clinical trial (BABY HUG) will test formally the hypothesis that hydroxyurea can prevent chronic organ damage in infants with SCA [12].

II. Indications

A. Standard indications (any of of the following)
- Frequent pain crises.
- Acute chest syndrome.
- Severe or symptomatic anemia (Hb < 7g/dL).
- Hemolytic alloantibodies / autoantibodies.
- Severe complications without benefit from standard therapy (priapism, leg ulceration).

B. Scenarios to be considered (Not proven efficacious)
- Chronic transfusion therapy precluded by presence of multiple allo-antibodies.
- Abnormal Transcranial Doppler refusing transfusion therapy.
- History of stroke refusing / non-compliant with transfusion / chelation therapy.

III. Exclusions:

- Pregnancy or sexually active and unwillingness to use contraception.
- Active liver disease (HBV or HCV infection).
- History of severe HU toxicity or hypersensitivity.
- History of significant non-compliance with recommended medical care.

- Micromedex indicates live virus vaccines should not be used while on hydroxyurea, although some clinicians do not follow this.

IV. Starting Hydroxyurea

A. Documentation:

- Document informed consent with patient and/or parent/guardian of minor patients. Should include discussion of required monitoring, potential toxicity, potential teratogenicity/carcinogenicity, and need for contraception/abstinence.
- Signed written consent not required as hydroxyurea is FDA approved in adults with sickle cell anemia and Phase II safety studies have been performed on children > age 5 years.
- Additional information to be given to parents of younger children re: availability of data on their age group and potential concerns.

B. Baseline Investigation:

- Documented complete physical exam (all vital signs including weight, height, and pulse oximetry).
- Hb electrophoresis with quantitative HbF%
- CBC with Differential and reticulocyte count.
- Chemistry profile (Electrolytes, LDH, Total protein, Albumin, Total bilirubin).
- Liver function tests (AST, ALT).
- Renal Function (BUN, Cr).
- Serum B-12 and Folate (to ensure HU-related macrocytosis does not mask deficiency)
- Serum Iron, TIBC, Ferritin (to ensure HU related-macrocytosis does not mask Fe-deficiency).
- Hepatitis B, Hepatitis C, Parvovirus B19 and HIV serology.
- Pregnancy test for post-menarchal females.

C. Dosing

- Initial dose 15-20 mg/kg/day given as a single daily dose. Divided dosing unnecessary and may decrease compliance.
- Dose escalation by 5 mg/kg every 4-6 weeks.
- Increase dose until one of the following:
  - Evidence of hematological toxicity (see below) and thus "maximal tolerated dose" (MTD)
  - Goal ANC 2000-3000 achieved
  - 35 mg/kg/day dose achieved
- If clear positive clinical and/or hematological effect is observed before MTD can consider stopping escalation, although there is some evidence of dose response that would suggest continuing to MTD may enhance clinical effect further.
- Re-evaluation of dosage (mg/kg) will occur with each monitoring visit.
- How Supplied: 200, 300, 400, 500 mg capsules
- Liquid formulation can be prepared by compounding pharmacy using published guideline [13]. Alternatively, capsules may be opened and dissolved into a glass of water with vigorous stirring.

D. Monitoring Visits*:

1. Dose Escalation
   - Laboratory evaluation every 2-4 weeks:
     - CBC, Differential, Reticulocyte count.
     - Bilirubin, ALT, BUN, Cr every dose escalation
     - Inquiry regarding side-effects, sexual activity and birth control.
   - Clinical examination visits every 4 weeks (more frequently if education or compliance needs reinforcement)
     - Weight, BP, vitial signs and Pulse Sa02.

- Hematological system and toxicity focused physical exam each visit.
- Quantitative HbF Q 3-6 months

- Record all lab values and evidence of toxicity and side effects on flow sheet. A brief clinical note to be completed for each visit.
- Continue until patient has been at stable or maximal tolerated dose for 8 weeks without toxicity

2. Stable/Maximal Tolerated Dose

- Clinical and laboratory examination visits every 4 - 8 weeks
  - CBC with differential and reticulocyte count every 4 - 8 weeks
  - Quantitative HbF every 6-12 months
  - ALT, AST, BUN, Cr every 6 months.
- Weight, BP, vitial signs and Pulse Sa02.
- Hematological system and toxicity focused physical exam each visit.
- Inquiry regarding side-effects, sexual activity and birth control.

*Variations from guideline will be noted and checked with the patient's primary hematologist. Laboratory data and/or brief clinical notes must be recorded for each visit.

II. Toxicity

A. Toxicity:

- Bone Marrow:
  - Absolute neutrophil counts < 1000-1500/mm^3
  - Absolute reticulocyte count < 80,000/mm^3 associated with Hb<9 g/dL
  - Platelet count < 80,000/mm^3
  - Fall of $\geq$ 20% Hb concentration
- Renal
  - $\geq$ 50% or more increase in serum creatinine or an increase of > 0.5 mg/dL
- Hepatic/Gastrointestinal
  - $\geq$ 100% increase in ALT
- Other
  - Unexplained rash or hair loss.

B. Toxicity Management:

- In the event of bone marrow, hepatic or renal toxicity, HU may be held for 4-7 days and lab values repeated.
  - If values remain abnormal, HU continue to hold until values return to baseline.
  - If values have returned to baseline, the drug may be restarted at the same dose at which the toxicity occurred.
- Other potential toxicity will be carefully evaluated to determine if holding the drug is necessary.

III. Contraception and Pregnancy

A. Counseling and Teaching

- Counsel that SCD does not impair fertility.
- Counsel patients and parents of minor patient re: possible teratogenic effects.
- Given the minimal data available regarding pregnancy outcomes for persons on hydroxyurea, counsel both male and female patients to use effective methods of contraception if sexually active.
- Counsel male and female patients to discontinue treatment before planned pregnancy.
- Counsel female patients that if pregnancy is suspected to discontinue medication immediately and until tested for pregnancy.

- Many hematologists require use of hormonal contraception for female patients of reproductive age on hydroxyurea.

IV. Cessation of Therapy:

- Compliance: If the patient is unable to come for monitoring visits as scheduled and/or it is apparent that HU is not being taken consistently, and then therapy should be discontinued.
- If toxicity is a recurring problem such that the dose has to be reduced on multiple occasions and no clinical or biochemical benefit is observed, therapy should be discontinued.
- If any of the exclusion criteria are met then therapy should be discontinued.

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