ASH Draft Recommendations for Dosing and Monitoring of Hydroxyurea for Sickle Cell Disease (SCD)

Introduction

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgments about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please email **guidelines@hematology.org**. Evidence Profiles and Evidence to Decision Frameworks are available via links below. If you are unable to access these links, please email Natalie Martin at nmartin@hematology.org.

The public comment period for these draft recommendations is open until **January 20th, 2026.**

Recommendations

Monitoring

- **Question 1A:** *Should minimal lab monitoring vs. extensive lab monitoring be used in people with SCD on a specific phase of dosing of hydroxyurea?*
  - **Recommendation 1A.** The ASH guideline panel recommends conducting research to evaluate the effectiveness and safety of minimal lab monitoring compared to extensive lab monitoring for monitoring toxicity in people with sickle cell disease on a stable dose of hydroxyurea. (ungraded research recommendation)
  - **Remarks:**
    - The panel did not make a practice recommendation about extensive vs minimal laboratory monitoring during any phase of hydroxyurea use due to a lack of evidence regarding desirable or undesirable effects of various monitoring practices. The panel recommended research be conducted, such as registry-based studies that identify patients who had dose changes or adverse events detected based on the lab tests used. The panel agreed that despite limited data on the optimal monitoring scheme, laboratory monitoring should not be an impediment to the use of hydroxyurea. In choosing the type of testing for the purpose of monitoring hydroxyurea toxicity during stable dose, and after baseline testing (e.g. renal, liver function tests), the panel outlined the following considerations:
      - Minimum lab monitoring was defined by the panel as complete blood count (CBC) with reticulocyte count. In settings where reticulocyte count is not available, CBC alone is probably sufficient, though not preferred by the panel. Absence of reticulocyte measurement should not be a barrier to hydroxyurea use.
      - Among the studies reviewed by the panel, one study included CBC only, three studies included CBC and reticulocyte, and 13 studies included more extensive laboratory monitoring. Other tests included in the monitoring for those studies included: total bilirubin, transaminase, and serum creatinine concentration.
      - At initiation of hydroxyurea, consider renal and liver function tests.
      - Additional tests may be warranted in certain clinical situations (e.g. concern for acute illness) or for purposes other than routine monitoring for toxicity. For example, fetal hemoglobin (HbF) percent and mean corpuscular volume (MCV) may be useful for tracking adherence.

- Frequency of monitoring is highly relevant to this question, but is addressed in Q1B.
- The extent of laboratory monitoring may be limited by cost and/or insurance coverage, and as such, minimum laboratory monitoring may be necessary and/or preferred in those situations.

- Evidence Profile
- Evidence to Decision Framework

- **Question 1B:** *Should less frequent monitoring (every 3-6 months) vs. more frequent monitoring (every 1-2 months) be used for people with SCD on a specific phase of dosing of hydroxyurea?*
  - **Recommendation 1B.** The ASH guideline panel recommends conducting research to evaluate the effectiveness and safety of less frequent lab monitoring compared to more frequent lab monitoring for monitoring toxicity in people with sickle cell disease on a stable dose of hydroxyurea. (ungraded research recommendation)
  - **Remarks**:
    - The panel did not make a practice recommendation about more frequent vs. less frequent laboratory monitoring during any phase of hydroxyurea use due to a lack of evidence regarding desirable or undesirable effects of various monitoring practices. The panel recommended research be conducted, such as registry-based studies that identify patients who had dose changes or adverse events detected based on the frequency of lab tests used. The panel agreed that despite limited data on the optimal monitoring scheme, laboratory monitoring should not be an impediment to the use of hydroxyurea. In choosing the frequency of testing for the purpose of monitoring hydroxyurea toxicity during stable dose, the panel outlined the following considerations:
      - For the purpose of systematic review of data, more frequent laboratory monitoring was defined by the panel every 1-2 months (or more often) and less frequent monitoring was defined as not more frequent than every 3-6 months, specifically for checking for toxicity when on a stable dose.
      - Among the studies reviewed by the panel, monitoring strategies ranged from every 1-3 months. Studies included all phases of dosing (initiation, dose titration/adjustment, and stable dose).
      - The panel highlighted appropriateness of monitoring frequency every 6 months when evaluating for toxicity, and a frequency of 3 months if concerned about adherence.
      - The panel did not address the appropriate frequency of laboratory monitoring at initiation of treatment.

- In patients with high adherence, monitoring frequency of every 6 months was considered appropriate.
- In settings where there are barriers to laboratory monitoring, monitoring frequency of every 6 months was considered appropriate.
- The tests included in monitoring are highly relevant to this question, but are addressed in Q1A.

  - Evidence Profile
  - Evidence to Decision Framework

Dosing

- **Question 2:** *Should dose escalation vs. a fixed dose be used for hydroxyurea in people with SCD?*
  - **Recommendation 2.** The ASH guideline panel recommends dose escalation over fixed dosing for hydroxyurea dosing in people with SCD (strong recommendation based on moderate certainty in the evidence ⊕⊕⊕◯)
  - **Remark:**
    - There are feasibility concerns for use of dose escalation in some settings, where fixed dosing would be more feasible to use.
  - Evidence Profile
  - Evidence to Decision Framework
- **Question 3:** *Should hydroxyurea at a higher fixed dose (e.g. 20 mg/kg/day) vs. a lower fixed dose (e.g. 10 mg/kg/day) be used in people with SCD?*
  - **Recommendation 3.** The ASH guideline panel suggests using a higher fixed dose over a lower fixed dose of hydroxyurea when using fixed dosing for people with sickle cell anemia (conditional recommendation, based on very low certainty in the evidence about effects ⊕◯◯◯).
  - **Remarks:**
    - The panel reviewed 3 RCTs comparing higher fixed doses of hydroxyurea with lower fixed doses of hydroxyurea. All studies included patients with sickle cell anemia (HbSS and Hb S/b^0-thalassemia) and did not include adults. Studies were performed in low- and middle-income countries (LMICs).
    - For the purpose of the systematic review, higher fixed dose was defined by the panel as 20 mg/kg/day and lower fixed dose as 10 mg/kg/day as these were what were used in the included studies. However, in practice a high fixed dose used may be higher than 20 mg/kg/day, given that this is not universally accepted as a high fixed dose. The panel also acknowledges that in clinical practice, the dose range is far broader, from < 10 mg/kg/day up to 35 mg/kg/day (or a max of 2000 mg daily).

- The typical setting for this recommendation is one where fixed dosing would be used because other options such as dose escalation or algorithm-guided dosing are not feasible.

  - Evidence Profile
  - Evidence to Decision Framework

- **Question 4:** *Should algorithm/tool guided dosing vs. no algorithm/tool guided dosing be used for selection of a starting hydroxyurea dose in people with SCD?*
  - **Recommendation 4.** The ASH guideline panel suggests using algorithm-guided dosing for selecting a starting dose of hydroxyurea in people with SCD (conditional recommendation, based on very low certainty in the evidence ⊕◯◯◯).
  - **Remarks:**
    - The panel reviewed 2 RCTs and 1 comparative non-randomized study (NRS) comparing algorithm/tool guided dosing with no algorithm/tool guided dosing for hydroxyurea. All studies included patients with sickle cell anemia (HbSS and Hb S/b-0-thalassemia) and one included young adults. Studies were performed in high-income settings.
    - Simple equation-based algorithms may be more feasible than new software (i.e., PK-based) for dosing calculation
    - The research evidence for this recommendation was from studies conducted in children.
  - Evidence Profile
  - Evidence to Decision Framework

Timing of Starting Hydroxyurea

- **Question 5:** *Should starting hydroxyurea based on diagnosis vs. based on symptoms or a milestone be used in people with SCD not currently taking hydroxyurea?*
  - **Recommendation 5.** The ASH guideline panel recommends starting hydroxyurea in all patients with HbSS and HbS/beta-0-thalassemia based on diagnosis versus starting based on symptoms (strong recommendation, based on moderate certainty of evidence ⊕⊕⊕◯).
  - **Remark:**
    - The panel reviewed 3 studies, including 1 retrospective cohort study and 2 RCTs. One study included children with sickle cell anemia (HbSS and Hb S/b-0-thalassemia) and one study included children and adults with HbSC. Studies were performed in high-income countries (HICs) and LMICs.
  - Evidence Profile
  - Evidence to Decision Framework

Pregnancy

- **Question 6A:** *Should continuing hydroxyurea vs. holding hydroxyurea be used in females with SCD who are taking hydroxyurea and intending to conceive?*
  - **Recommendation 6A.** The ASH guideline panel suggests either continuing hydroxyurea or discontinuing hydroxyurea on a case-by-case basis with shared decision making with individual female patients who are taking hydroxyurea and intending to conceive (conditional recommendation, very low certainty of evidence ⊕◯◯◯).
  - **Remarks:**
    - The panel reviewed 4 retrospective cohort studies, 4 prospective cohort studies, and 1 cross-sectional study comparing the use of hydroxyurea vs. no hydroxyurea in females with SCD. The panel determined that these studies did not have sufficient direct data to inform the judgement about desirable and undesirable effects of hydroxyurea continuation vs. discontinuation, and additional research evidence is needed.
    - The panel delineated several considerations that patients and providers may weigh when making this decision:
      - Baseline severity of SCD Prior pregnancy: the course of the pregnancy and the maternal and fetal outcomes
      - Availability of transfusion support
  - Evidence Profile
  - Evidence to Decision Framework
- **Question 6B:** *Should continuing hydroxyurea vs. holding hydroxyurea be used in males with SCD who are taking hydroxyurea and intending to conceive?*
  - **Recommendation 6B.** The ASH guideline panel suggests against holding hydroxyurea in males with SCD who are intending to conceive (conditional recommendation, based on low certainty of evidence ⊕⊕◯◯).
  - **Remarks:**
    - The panel reviewed 1 retrospective cohort study and 4 prospective cohort studies comparing the use of hydroxyurea vs. no hydroxyurea in males with SCD who are intending to conceive. The panel reviewed indirect evidence from one additional RCT. Studies included all SCD genotypes and were performed in LMICs and HICs.
    - The panel highlighted the need for providers to engage with individual patients to consider the balance of risks for symptomatic sickle cell disease vs. the desire to conceive. The panel outlined several considerations that patients and providers could weigh when making this decision:
      - The duration of time that hydroxyurea will be held

- The duration of time spent trying to conceive while on hydroxyurea
- Previous efforts to conceive and conception history
- Sickle cell disease status, measured clinically and with laboratory evaluation
- Baseline sperm assessment

- Evidence Profile
- Evidence to Decision Framework

- **Question 7:** *Should continuing hydroxyurea vs. holding hydroxyurea be used in females with SCD who are taking hydroxyurea and become pregnant?*
  - **Recommendation 7.** The ASH guideline panel suggests either continuing hydroxyurea or discontinuing hydroxyurea on a case-by-case basis with shared decision making with individual patients with SCD (conditional recommendation, very low certainty of evidence ⊕◯◯◯).
  - **Remarks:**
    - The panel reviewed 2 retrospective cohort studies and 2 prospective cohort studies comparing continuing hydroxyurea vs. discontinuing hydroxyurea in pregnant women with SCD. The studies included patients with all genotypes. Studies were performed in both LMICS and HICs. The panel determined that these studies did not have sufficient direct data to inform the judgement about desirable and undesirable consequences of hydroxyurea continuation vs. discontinuation, and additional research evidence is needed.
    - This question was intended to address concerns about the balance of effects between hydroxyurea on maternal and fetal pregnancy outcomes. Concerns about the balance of effects of hydroxyurea use on fertility (pre-conception) are addressed in Q6A.
    - The panel highlighted the need for providers to engage with individual patients to consider the balance of potential risks to the pregnancy/newborn due to increased symptomatic sickle cell disease vs any potential additional risk to the pregnancy/newborn conferred by post-conception, in utero exposure to hydroxyurea. The panel outlined several considerations that patients and providers could weigh when making this decision:
      - Current and past history of Sickle cell disease severity, measured clinically and with laboratory evaluation
      - Prior pregnancy experience: the course of the prior pregnancy and the maternal and fetal outcomes of that prior pregnancy on or off hydroxyurea
      - Ability and availability of transfusion support to replace hydroxyurea as a disease modifying treatment during pregnancy
  - Evidence Profile
  - Evidence to Decision Framework

Holding Hydroxyurea

- **Question 8:** *Should holding hydroxyurea vs. continuing hydroxyurea be used in people with SCD who are taking hydroxyurea and have a specific condition or are undergoing a procedure?*
  - **Recommendation 8.** The ASH guideline panel suggests against holding hydroxyurea in people with SCD who are taking hydroxyurea and have a non-critical condition or are undergoing a procedure (conditional recommendation, low certainty of evidence ⊕⊕◯◯).
  - **Remarks:**
    - The panel reviewed one before-and-after study comparing the incidence of clinical outcomes before, during and after holding hydroxyurea.
    - Although there was no evidence to support specific reasons for holding hydroxyurea, the panel determined that holding hydroxyurea may be warranted during certain critical illnesses, such as sepsis, ICU admission, life-threatening cytopenias, or during a secondary condition that increases the risk of severe cytopenia.
    - The panel noted that any hold should be temporary and initiated with a plan to resume the medication that is clearly communicated to the patient and to the referring hematologist.
    - The panel noted that there were no studies that addressed the onset or worsening of renal or hepatic disease.
  - Evidence Profile
  - Evidence to Decision Framework

Adherence

- **Question 9:** Should any intervention aimed at improving adherence to hydroxyurea vs. no intervention be used in people with SCD currently taking hydroxyurea?
  - **Recommendation 9.** The ASH guideline panel suggests using interventions aimed at improving adherence to hydroxyurea for people with SCD (conditional recommendation, low certainty of evidence ⊕⊕◯◯).
  - Evidence Profile
  - Evidence to Decision Framework