Targeted Hydroxyurea Education after an Emergency Department Visit Increases Hydroxyurea Use in Children with Sickle Cell Anemia

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Objective To evaluate the impact of an initiative to increase hydroxyurea use among children with sickle cell anemia (SCA) who presented to the emergency department (ED).

Study design This observational cohort study included children with SCA not taking hydroxyurea who presented to the ED with pain or acute chest syndrome and then attended a Quick-Start Hydroxyurea Initiation Project (Q-SHIP) session. A Q-SHIP session includes a hematologist-led discussion on hydroxyurea, a video of patients talking about hydroxyurea, and a direct offer to start hydroxyurea.

Results Over 64 weeks, 112 eligible patients presented to the ED and 59% (n = 66) participated in a Q-SHIP session a median of 6 days (IQR 2, 20 days) after ED or hospital discharge; 55% of participants (n = 36) started hydroxyurea. After a median follow-up of 49 weeks, 83% (n = 30) of these participants continued hydroxyurea. Laboratory markers of hydroxyurea adherence were significantly increased from baseline: median mean corpuscular volume +8.6 fL (IQR 5.0, 17.7, $P < .0001$) and median hemoglobin F +5.7% (IQR 2.5, 9.8, $P = .0001$). Comparing Q-SHIP participants to nonparticipants, 12 weeks after ED visit, participants were more likely to have started hydroxyurea than nonparticipants (53% vs 20%, $P = .0004$) and to be taking hydroxyurea at last follow-up (50% vs 20%, $P = .001$). Two years after the implementation of Q-SHIP the overall proportion of eligible patients on hydroxyurea presenting to our ED increased from 56% to 80%, $P = .0069$.

Conclusions Participation in a clinic to specifically address starting hydroxyurea after a SCA complication increases hydroxyurea use. *(J Pediatr 2018;■■:■■-■■).*

Hydroxyurea is a Food and Drug Administration-approved, daily oral medication that decreases sickle cell anemia (SCA) complications primarily by inducing fetal hemoglobin (Hb) production.[1] Hydroxyurea treatment decreases pain and acute chest syndrome (ACS) events in children with SCA[2,3] and is associated with improved cerebrovascular health, growth, health-related quality of life, and survival.[4-15] In 2002, the National Heart, Lung, and Blood Institute (NHLBI) recommended hydroxyurea for children with severe disease. In 2014, the NHLBI guidelines expanded the pediatric indication for hydroxyurea and now state that treatment with hydroxyurea should be offered to all children with SCA starting at 9 months of age.[16,17] The new recommendation was based primarily on evidence from the randomized, placebo-controlled Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG; clinicaltrials.gov: NCT00006400).[3] Despite evidence of clinical benefit, low cost, and few other available treatments, hydroxyurea remains underused among children and adults with SCA.[18-21]

Barriers to hydroxyurea treatment include patient, parent, provider, and systems-level challenges. Physicians report not initiating hydroxyurea because of concerns about patient adherence.[21-24] Patients and families worry about side effects, often lack understanding of how hydroxyurea works, and cite insufficient discussion of their concerns as barriers to hydroxyurea initiation.[25,26] However, treatment acceptance could be improved by discussing hydroxyurea with parents and patients in ways that define its indications, explain its potential benefits, acknowledge patient and family concerns, and reduce the burden of clinic attendance.[26-29] In a multicenter survey study, hydroxyurea use in children with SCA was significantly associated with parents' level of knowledge about the medication.[25] In a single-center study, most parents of children with SCA who received education about hydroxyurea concluded that hydroxyurea was safe, beneficial, and preferable to treatment with chronic

ACS	Acute chest syndrome
CNHS	Children's National Health System
ED	Emergency department
Hb	Hemoglobin
MCV	Mean corpuscular volume
NHLBI	National Heart, Lung, and Blood Institute
Q-SHIP	Quick-Start Hydroxyurea Initiation Project
SCA	Sickle cell anemia
SCD	Sickle cell disease

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transfusions or hematopoietic stem cell transplant.[30] Clinical events may also prompt initiation of therapy. Parents of children with SCA who never initiated hydroxyurea reported that acute events requiring emergency care or hospitalization would cause them to request a hydroxyurea prescription.[25]

Strategies for overcoming hydroxyurea treatment barriers are needed.[26] We hypothesized that providing intensive hydroxyurea education and the opportunity to initiate hydroxyurea to parents and their children with SCA shortly after an emergency department (ED) visit for pain or ACS would lead to increased treatment acceptance. Given this background, we implemented the Quick-Start Hydroxyurea Initiation Project (Q-SHIP) in February 2016 with a goal of increasing hydroxyurea use in children at our institution who are eligible for this treatment.

Methods

We evaluated the effectiveness of our clinical program Q-SHIP, which was designed to increase hydroxyurea use by patients with SCA, among eligible patients who presented to the Children's National Health System (CNHS) ED between February 1, 2016 and April 23, 2017. We attempted to reach all patients who met eligibility criteria (see below) to participate in Q-SHIP. This was not a controlled trial, but rather compares results for those who voluntarily participated in the program and those who did not.

Eligible patients had laboratory-confirmed SCA (Hb SS or Sβ^0-thalassemia), presented with SCA-related pain or ACS during the study period, and were not already taking hydroxyurea. Patients were deemed ineligible if they were less than 9 months old, receiving chronic red cell transfusions, or pregnant, as hydroxyurea is not currently indicated for these patients. Patients who were not primarily followed at our center (pediatric hematology providers unaffiliated with CNHS refer patients to our ED) were also excluded because they could not follow up at CNHS for the required monitoring of hydroxyurea treatment.

Patients eligible for Q-SHIP were identified through a weekly chart review of all patients with sickle cell disease (SCD) evaluated in the CNHS ED, using an electronic ED clinical registry that includes all ED patient encounters. Clinical providers or a Q-SHIP team member attempted to contact all eligible patients to invite them to participate in a Q-SHIP session.

Participants attended a Q-SHIP session in the outpatient hematology clinic after ED discharge or during a hospitalization (if approved by the inpatient service attending). This session is held weekly and led by 1 pediatric hematologist. It is held separate from a routine clinic visit so that it focuses on hydroxyurea. Participants complete a brief survey (**Appendix 1**; available at www.jpeds.com) and spend approximately 45 minutes reviewing "Hydroxyurea for Sickle Cell Disease: A Guide for Starting Treatment," a handbook for families developed by the interdisciplinary SCD team at CNHS, which is available at https://www.childrensnational.org/HydroxyureaApp (**Appendix 2**; available at www.jpeds.com). Participants then watch a 15-minute video (https://www.youtube.com/watch?v=2a7FXibkubQ&feature=youtu.be) about hydroxyurea that merges publicly available footage from academic medical centers and patient advocacy group videos (**Table I**; available at www.jpeds.com). These videos feature patients and parents of children with SCA discussing their experiences with hydroxyurea. At the conclusion of the session, parents who are ready to start their child on hydroxyurea receive a prescription contingent on laboratory confirmation that their child meets institutional guidelines for treatment (**Appendix 3**; available at www.jpeds.com). Follow-up with the participant's primary hematologist is arranged 2-4 weeks after starting therapy. Parents who are not interested in starting their child on hydroxyurea, or who want more time to review the presented information, are encouraged to contact the hematologist who leads Q-SHIP or their primary hematologist if they later decide to start hydroxyurea. Q-SHIP participants receive no additional special follow-up.

Per institution hydroxyurea treatment guidelines (**Appendix 3**), SCD providers at CNHS routinely offer hydroxyurea treatment to all patients with SCA older than 9 months if there is no contraindication to its use. Eligible patients who do not participate in Q-SHIP all receive standard care that would typically include a discussion of hydroxyurea as a component of routine SCA care. The educational booklet (**Appendix 2**) developed for Q-SHIP is available for all providers for use outside of a formal Q-SHIP session.

The CNHS Institutional Review Board approved this study. A waiver of written informed consent was granted.

Statistical Analyses

For this analysis, patients were classified as "started hydroxyurea after Q-SHIP" if they had a clinic visit for hydroxyurea monitoring within 3 months of their participation in a Q-SHIP session. Three months was chosen as the time interval rather than just 1 month to account for possible delays in starting hydroxyurea because of the insurance authorization process, as well as to allow for additional time that some families may need to review the material discussed during a Q-SHIP session before making a decision to start hydroxyurea. Patients were classified as "taking hydroxyurea at recent follow-up" if hydroxyurea use was documented in a clinical encounter within the last 3 months of the evaluation period (April 1, 2017-July 1, 2017). To evaluate hydroxyurea adherence, the most recent mean corpuscular volume (MCV) and %HbF measurements were compared with baseline MCV and %HbF measurements. Q-SHIP participants who started hydroxyurea were compared with those who did not start hydroxyurea. Q-SHIP participants were also compared with eligible patients who did not participate in Q-SHIP ("nonparticipants"). In addition, the proportion of eligible patients with SCA who were actually taking hydroxyurea was measured among those who presented to the ED for pain or ACS in the month of February in 2015, 2016, 2017, and 2018.

Clinical and demographic information was obtained by retrospective chart review. Patients were classified as "previously

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