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

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Abstract

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 (ACS) 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, $P < .0001$), median hemoglobin F +5.7% (IQR 2.5, 9.8, p=0.0001). Comparing Q-SHIP participants to non-participants, 12 weeks after ED visit, participants were more likely to have started hydroxyurea than non-participants (53% vs. 20%, p=0.0004) and to be taking hydroxyurea at last follow-up (50% versus 20%, p=0.001). 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=0.0069.

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The authors declare no conflicts of interest.

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Conclusions—Participation in a clinic to specifically address starting hydroxyurea after a SCA complication increases hydroxyurea use.

Keywords

Sickle cell disease; Hydroxyurea; Pediatrics; Patient Education

Hydroxyurea is a FDA-approved, daily oral medication that decreases SCA complications primarily by inducing fetal hemoglobin 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 phase 3, randomized, placebo-controlled trial BABY HUG.(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 the indications for drug use, explain the potential benefits of therapy, acknowledge patient and family concerns, and reduce the burden of clinic attendance or obtaining medication refills.(26–29) In a multi-center 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 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 (hemoglobin SS or $S\beta^0$-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 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 one pediatric hematologist (RSN). 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/Hydroxyurea (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 RSN 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 three months of their participation in a Q-SHIP session. Three months was chosen as the time interval rather than just one month in order to account for possible delays in starting hydroxyurea due to 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 three months of the evaluation period (April 1, 2017 - July 1, 2017). To evaluate hydroxyurea adherence, the most recent mean corpuscular volume (MCV) and hemoglobin F (%HbF) measurements were compared with baseline MCV and %HbF measurements. Q-SHIP participants who started hydroxyurea were compared to those who did not start hydroxyurea. Q-SHIP participants were also compared with eligible patients who did not participate in Q-SHIP (“non-participants”). In addition, the proportion of eligible SCA patients 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 offered hydroxyurea” if a clinic note documented that hydroxyurea was recommended or that the patient or patient’s family declined hydroxyurea. If documentation in a clinic note stated that hydroxyurea was discussed but did not explicitly indicate that therapy was offered, the participant was classified as having “no previous hydroxyurea offer.” Categorical data was analyzed with the chi-square or Fisher exact test. Continuous data was analyzed using the Wilcoxon rank-sum test or the 2-sample t-test. MCV and %HbF measures were compared using the paired Wilcoxon signed-rank test. Statistical calculations were performed with SAS 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Over 64 weeks (2/1/2016 – 4/23/2017), there were a total of 2,309 ED encounters among 739 patients with SCD (all genotypes) in the CNHS ED (FIGURE 1). Initially, 297 patients were excluded: 164 did not have SCA and 133 were not established CNHS hematology patients. Among 442 patients with SCA followed at CNHS, an additional 330 patients were excluded: 213 were already taking hydroxyurea, 62 did not have an ED encounter for pain or

ACS during the study period, 42 were receiving chronic red cell transfusions, and 13 were ineligible for hydroxyurea due to other reasons.

Among 112 patients eligible for Q-SHIP, 59% (N=66) participated in Q-SHIP a median of 6 days (IQR 2, 20 days) after ED or hospital discharge for pain (N=42), ACS (N=17), or pain and ACS (N=7). There were no significant differences in the clinical and demographic information of Q-SHIP participants compared with non-participants including markers of prior disease severity (TABLE 2; available at www.jpeds.com). Fifty-three percent of participants attended a group Q-SHIP session with other families (median 2 families, range 2-5), and 21% participated in Q-SHIP while hospitalized. Among the 46 non-participants, only three families involving 4 non-participants (9%) explicitly declined to participate in Q-SHIP. The remaining families did not participate because they could not be reached to offer participation, could not come to clinic at the time of the weekly Q-SHIP session, or had already started hydroxyurea through a routine clinic visit before participation in Q-SHIP could be offered.

Hydroxyurea offers before Q-SHIP

Pre-participation surveys from 65 of 66 participating families were analyzed (one participant did not complete a survey). Fifty-five percent (N=36) reported previously receiving an offer to start hydroxyurea. These participants reported previously declining hydroxyurea because of side-effect concerns (50%, N=18), not thinking their child's disease was severe enough to warrant treatment (31%, N=11), wanting more information (28%, N=10), and the requirement of more frequent visits for hydroxyurea monitoring (11%, N=4). Thirty-three percent (N=12) reported multiple reasons for previously refusing hydroxyurea. Among those concerned about treatment side effects (N=18), 2 families specifically cited fertility concerns, but families most commonly reported non-specific side effect concerns.

Forty-five percent of participants (N=29) reported no previous hydroxyurea offer. Fifty-nine percent (N=17/29) of these participants had documentation in their medical record that a previous hydroxyurea offer had been declined. Participants who reported no previous hydroxyurea offer were less likely to have had a regular hematology clinic visit in the last year compared with participants who reported a previous offer (69% versus 92%, p=0.019).

Hydroxyurea initiation after Q-SHIP

Fifty-five percent of participants (N=36) started hydroxyurea after Q-SHIP. There were no significant differences in demographics, intervention-related variables, or markers of SCD clinical severity between participants who started hydroxyurea and those who did not (TABLE 3). Hydroxyurea initiation was not significantly influenced by the participants' previous reason for refusing hydroxyurea (p=0.41). Most patients who had wanted more information about hydroxyurea (N=8/10), had side effect concerns (N=12/18) or had multiple concerns (N=7/12) started hydroxyurea; and 45% (N=5/11) of those who had reported that their child's disease was not severe enough to warrant treatment started hydroxyurea. No patients in this cohort permanently discontinued hydroxyurea because of side effects or toxicity. After a median of 49 weeks (IQR 28, 62 weeks), 83% (N=30) of those who started hydroxyurea after Q-SHIP were still taking hydroxyurea at a recent

follow-up visit. Two patients stopped hydroxyurea because their families decided it was unnecessary. Four patients were lost to follow-up (defined as no medical encounter from 4/1/17 to 7/1/17).

Participants who started and continued hydroxyurea after Q-SHIP (N=30) had a significant increase in their MCV and %HbF. Median increase in MCV was 8.6 (IQR 5.0, 17.7, $p<0.0001$) with median follow-up of 38 weeks (IQR 21, 53 weeks). Median increase in %HbF was 5.7% (IQR 2.5, 9.8, $p=0.0001$) with median follow-up of 29 weeks (IQR 18, 45 weeks). Six participants were excluded in the %HbF comparison because they did not have a pre- or post- %HbF value. During the follow-up time period, three additional Q-SHIP participants started hydroxyurea more than 3 months after participating in Q-SHIP.

At 12 weeks after discharge from their ED encounter, Q-SHIP participants had started hydroxyurea more often than non-participants (53% vs 20%, $p=0.0004$). At the most recent follow-up visit, Q-SHIP participants were significantly more likely to be taking hydroxyurea than non-participants (50% vs. 20% $p=0.001$) after a median follow-up of one year (FIGURE 2).

Hydroxyurea Use Among ED Patients Over Time

The proportion of patients with SCA presenting to the ED who were taking hydroxyurea (assessed annually in the month of February) has steadily increased since the implementation of Q-SHIP in 2016 (FIGURE 3). Among patients otherwise eligible for Q-SHIP, the proportion on hydroxyurea increased from 32/57 (56%) in February 2016 to 44/55 (80%) in February 2018, $p=0.0069$.

DISCUSSION

After an acute SCA complication requiring ED care, follow-up in a clinic devoted to hydroxyurea education in untreated children led over half of participating families to begin and continue hydroxyurea. Most patients who started hydroxyurea shortly after a pain or ACS episode demonstrated evidence of treatment adherence. These results suggest that a clinic focused on hydroxyurea that incorporates patient and parent perspectives, and also includes time for discussion of concerns, has a positive influence on families' treatment choices.

In this study, we were surprised that 45% of families reported no prior offer of hydroxyurea, given that providers at CNHS typically offer hydroxyurea to all children with SCA as per current NHLBI guidelines. Indeed, for most families who reported no previous hydroxyurea offer there actually was documentation that they had been offered hydroxyurea. However, these families were also less likely to have had a hematology clinic visit in the last year. Inaccurate parent and patient recall of medical information is a recognized, but perhaps underappreciated, phenomenon. Our finding has two implications. First, regular hematology follow-up may help families retain essential information about SCD treatment. Second, if families do not necessarily remember discussing hydroxyurea, then revisiting indications for treatment on consecutive visits may not be futile.

How information about hydroxyurea is presented affects its use. For example, a center that "strongly recommends" hydroxyurea for all children with SCA 5 years or older recently reported that over 90% of their patients were on hydroxyurea.(13) The NHLBI guidelines state that families should be "offered" hydroxyurea; this may lead to ambiguous language from providers who offer, rather than recommend, treatment. Providers may also be communicating misgivings about hydroxyurea including concerns about carcinogenicity, teratogenicity, and adverse effects on fertility.(21,31) At some European institutions, hematologists do not universally offer hydroxyurea to patients with SCA due to concerns about late and unknown effects.(12, 24) A recent qualitative study identified two distinct patterns of communication among American pediatric hematologists when discussing hydroxyurea with patients with SCA and their families. Bakshi et al describe a "collaborative approach" involving discussion of all treatment options with families versus a "proponent approach" defined by advocating for a pre-established treatment plan.(32) In the Q-SHIP model, we adopted a "proponent approach," advocating for hydroxyurea initiation with participants.

Q-SHIP creates time dedicated to hydroxyurea education. Some pediatric hematologists report that they lack the time to explain the risks and benefits of hydroxyurea.(21) Like general pediatricians,(33) pediatric hematologists have more topics to cover during a routine SCA clinic visit than time allows. Due to these other priorities and time constraints, implementing a shared decision making model for initiating hydroxyurea therapy in children with SCA is difficult.(27) Q-SHIP's focus on hydroxyurea allows time for this discussion, and signifies to families that our clinical team believes this treatment is worth additional effort to discuss.(34)

The video shown during Q-SHIP includes portions of videos that were produced by outside academic centers and patient advocacy groups. This helps incorporate patient perspectives and also reinforces that other centers make similar recommendations about hydroxyurea. At the University of Florida, a video featuring patients with SCA speaking positively about hydroxyurea inspired viewers' interest in starting therapy.(35) Collaboration and resource sharing among centers may provide reinforcement for a single center's practices and help providers at centers nationally and internationally meet evidence-based care for children with SCD. Videos may especially benefit patients with limited health literacy, a measure of a person's ability to understand health information and make health decisions. Written materials about SCD for patients and families often exceed the average literacy level of adults in the United States and may not be appropriate for all parents of children with SCA.(36,37) Finally, videos on the internet may be helpful to families as parents can review these videos with other decision-makers outside of clinic.

Similar hydroxyurea initiation rates were observed regardless of whether Q-SHIP was conducted with groups of different families together or when a single family participated. The benefits of group clinic visits, especially for underserved populations, include opportunities for increased provider time and intensive education.(38,39) A randomized trial comparing group medical appointments to individual medical appointments for patients with SCD is ongoing,(40) and novel SCD clinic structures designed to improve care and distribute knowledge are being explored in both resource-rich and resource-poor settings.

(41) This kind of research may help centers with limited resources lead thorough and thoughtful hydroxyurea initiation decision making sessions for families.

Although the majority of families who participated in Q-SHIP started hydroxyurea, a significant number did not initiate treatment even with this intensive education. This failure to start hydroxyurea was not associated with any particular prior rationale for refusing hydroxyurea. We had hypothesized that patients who had experienced fewer acute SCD complications would be less likely to accept hydroxyurea, but indicators of disease severity were not associated with hydroxyurea initiation after Q-SHIP. This observation is consistent with other studies that found patients' and parents' desire to pursue hematopoietic stem cell transplant for SCD is not associated with the patient's disease severity.(42–44) Research is needed to better understand whether these families' rejection of therapy rests on surmountable objections to treatment. At the end of this study, Q-SHIP participants were significantly more likely to be on hydroxyurea compared with non-participants. The non-participants in this study are an imperfect control group because, although they did not differ in demographic or clinical characteristics from participants, their lack of participation was non-random. Compared with participating families, this population may have distinct barriers to hydroxyurea initiation that were not explored by this study. These patients may require more resources or be especially reluctant to start treatment.

Our finding that the proportion of patients presenting to the ED with complications of SCA who were taking hydroxyurea increased after the implementation of Q-SHIP provides additional evidence that this initiative helped increase overall hydroxyurea use at our institution. Although it is possible this increased hydroxyurea use over time was unrelated to Q-SHIP, no increase in hydroxyurea use was observed in the year immediately before the start of Q-SHIP (FIGURE 3). This data also suggests that Q-SHIP's benefits are sustainable. The program did require considerable effort (~5 hours/week) to identify all eligible patients and refer them to the education session during the study period, but currently the program continues without this intensive screening of all ED patients. Although we have observed a decreased number of referrals to the weekly Q-SHIP session without this screening, this trend also reflects the fact that, due to increased hydroxyurea use, fewer Q-SHIP eligible patients are presenting to the ED. Q-SHIP has likely also helped change the culture of our institution such that hydroxyurea is more likely to be offered to eligible patients at every opportunity.

The current study has several limitations. We cannot evaluate if the success of Q-SHIP was more influenced by the proximity to a recent acute SCA complication, the dedicated clinic time to hydroxyurea education, or an inclination of participants towards initiating hydroxyurea even before attending Q-SHIP. We now accept referrals to Q-SHIP for any patient who is eligible for hydroxyurea but not receiving therapy; a recent hospitalization or ED encounter is no longer a pre-requisite for participation. This project was not a randomized clinical trial and we thus lack an ideal control group to measure the effect of Q-SHIP on hydroxyurea initiation. Nonetheless, our study design reflects real-world implementation of an intervention. This is a single center study where specific clinic time is reserved for a weekly Q-SHIP session. This kind of protected clinic time may not be feasible at centers with fewer patients with SCA, but Q-SHIP can be adapted to the context of the

implementing site. For example, the interval between ED or hospital discharge and Q-SHIP session was not significantly associated with hydroxyurea initiation, suggesting that timing Q-SHIP within one week of the acute SCA complication is not critical. A center might choose to offer monthly rather than weekly sessions. We did not measure parental education, household income, or family size, variables that may have influenced participation in Q-SHIP and initiation of hydroxyurea. Finally, Q-SHIP sessions were led by a single physician and participants may have been uniquely influenced by this person.

This study demonstrated that Q-SHIP helps overcome barriers to hydroxyurea prescription and acceptance. By providing adequate time and mixed-media resources for a thoughtful exchange of information between a clinician and family at a time when the family may be more receptive to this information, questions and concerns about hydroxyurea can be more fully explored and addressed. This study also identified a gap in provider-patient communication about hydroxyurea, and provides support for a solution: targeted education focused on hydroxyurea after an SCA complication. Modifications to this intervention and other novel interventions should be studied in order to continue to improve hydroxyurea treatment use among patients with SCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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APPENDIX 1

Q-SHIP Questionnaire

Survey administered to parents or patient (if >18 years) prior to Q-SHIP participation.

Have you / your child been previously offered treatment with hydroxyurea?

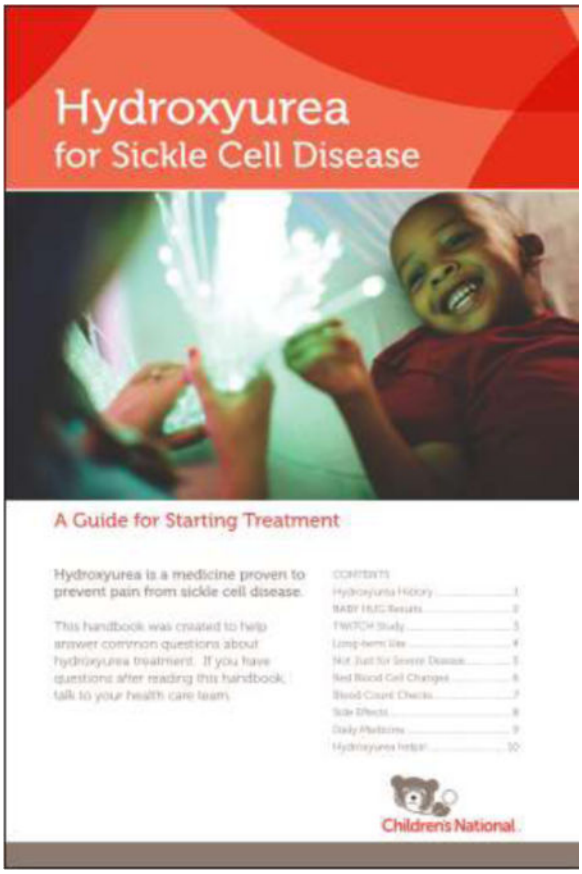
YES NO

If YES, what are the reasons you / your child has not started treatment with hydroxyurea? Please list all reasons and circle the most important reason.

APPENDIX 2

Hydroxyurea for Sickle Cell Disease: A Guide for Starting Treatment

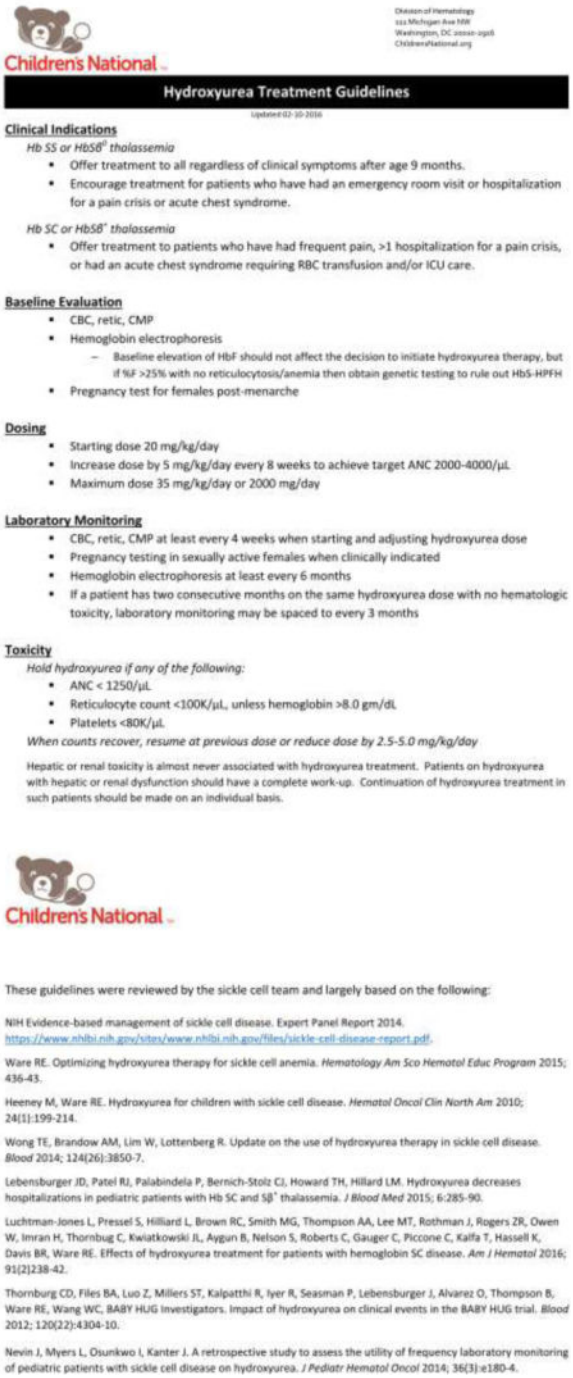
A handbook for families developed by the interdisciplinary SCD team at CNHS. The topics of this handbook are covered during a Q-SHIP session.



APPENDIX 3

Children's National Hydroxyurea Treatment Guidelines

Guidelines created by the sickle cell team at CNHS that outline standard of care clinical practices regarding hydroxyurea for SCD.



Children's National

Division of Hematology
111 Michigan Ave NW
Washington, DC 20010-2916
ChildrensNational.org

Hydroxyurea Treatment Guidelines

Updated 02-10-2016

Clinical Indications

Hb SS or HbSβ^0 thalassemia

- Offer treatment to all regardless of clinical symptoms after age 9 months.
- Encourage treatment for patients who have had an emergency room visit or hospitalization for a pain crisis or acute chest syndrome.

Hb SC or HbSβ^+ thalassemia

- Offer treatment to patients who have had frequent pain, >1 hospitalization for a pain crisis, or had an acute chest syndrome requiring RBC transfusion and/or ICU care.

Baseline Evaluation

- CBC, retic, CMP
- Hemoglobin electrophoresis
  - Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy, but if %F >25% with no reticulocytosis/anemia then obtain genetic testing to rule out HbS-HPFH
- Pregnancy test for females post-menarche

Dosing

- Starting dose 20 mg/kg/day
- Increase dose by 5 mg/kg/day every 8 weeks to achieve target ANC 2000-4000/μL
- Maximum dose 35 mg/kg/day or 2000 mg/day

Laboratory Monitoring

- CBC, retic, CMP at least every 4 weeks when starting and adjusting hydroxyurea dose
- Pregnancy testing in sexually active females when clinically indicated
- Hemoglobin electrophoresis at least every 6 months
- If a patient has two consecutive months on the same hydroxyurea dose with no hematologic toxicity, laboratory monitoring may be spaced to every 3 months

Toxicity

Hold hydroxyurea if any of the following:

- ANC < 1250/μL
- Reticulocyte count <100K/μL, unless hemoglobin >8.0 gm/dL
- Platelets <80K/μL

When counts recover, resume at previous dose or reduce dose by 2.5-5.0 mg/kg/day

Hepatic or renal toxicity is almost never associated with hydroxyurea treatment. Patients on hydroxyurea with hepatic or renal dysfunction should have a complete work-up. Continuation of hydroxyurea treatment in such patients should be made on an individual basis.

Children's National

These guidelines were reviewed by the sickle cell team and largely based on the following:

NIH Evidence-based management of sickle cell disease. Expert Panel Report 2014. https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf.

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Abbreviations

ACS
Acute chest syndrome

CNHS
Children's National Health System

ED
Emergency Department

Hb
Hemoglobin

IQR
Interquartile Range

Lung and Blood Institute, NHLBI
National Heart

PICU
Pediatric Intensive Care Unit

Q-SHIP
Quick-Start Hydroxyurea Initiation Project

SCA
Sickle cell anemia

SCD
Sickle cell disease

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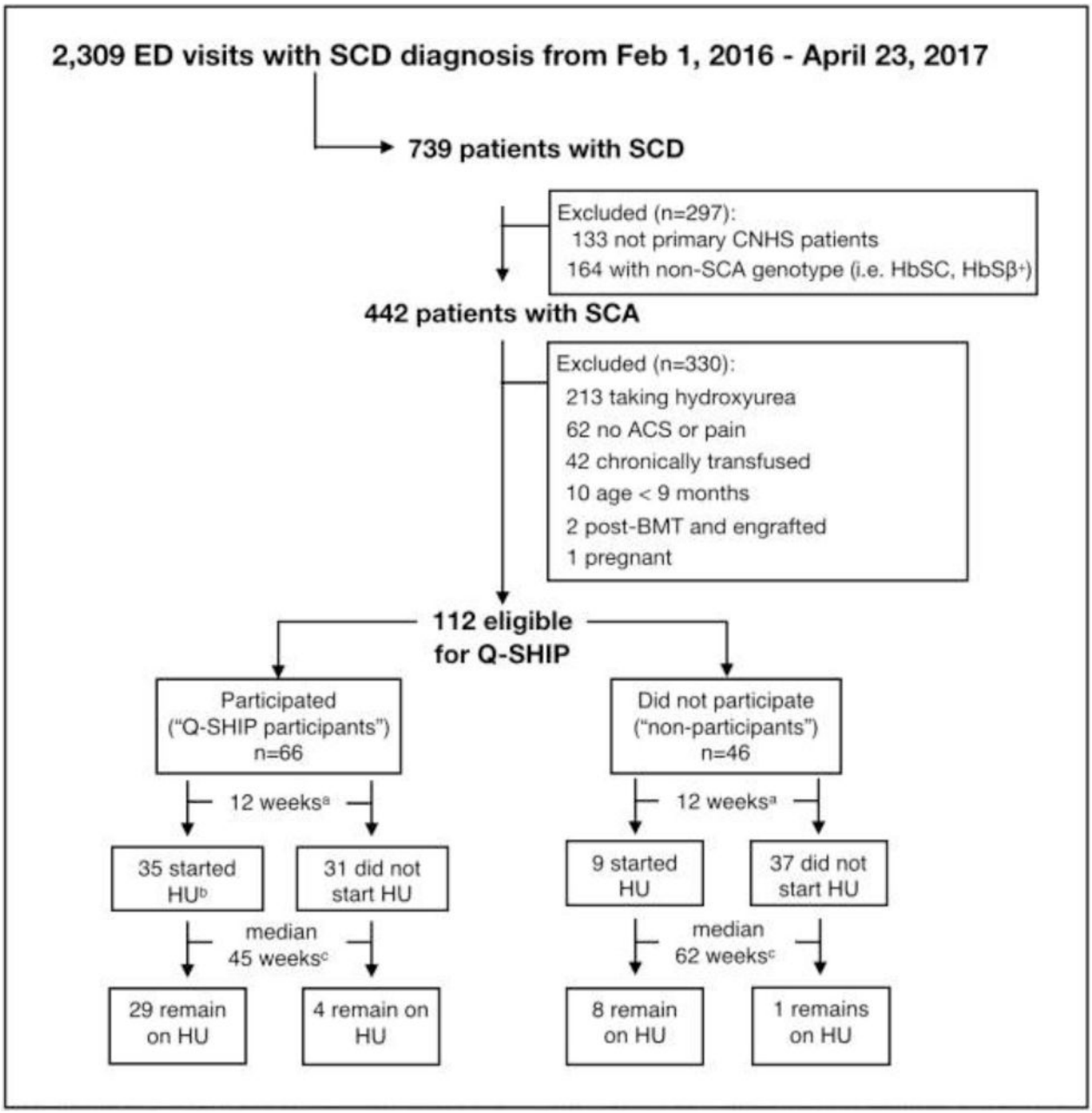

FIGURE 1. Flow diagram of Q-SHIP participants and differences in hydroxyurea initiation between Q-SHIP participants and non-participants at 12-weeks and at long-term follow-up

"Started hydroxyurea" is defined as clinic documentation of treatment initiation during the 12-week period and hydroxyurea use at the subsequent clinic visit. "Taking hydroxyurea at recent encounter" is defined as a medical encounter from 4/1/17-7/1/17 documenting hydroxyurea use. [a]12 weeks from ED encounter discharge. [b]One participant started hydroxyurea 12 weeks after the ED encounter discharge but less than 12 weeks after the Q-SHIP session. [c]Total follow-up time from ED encounter discharge to 7/1/2017.

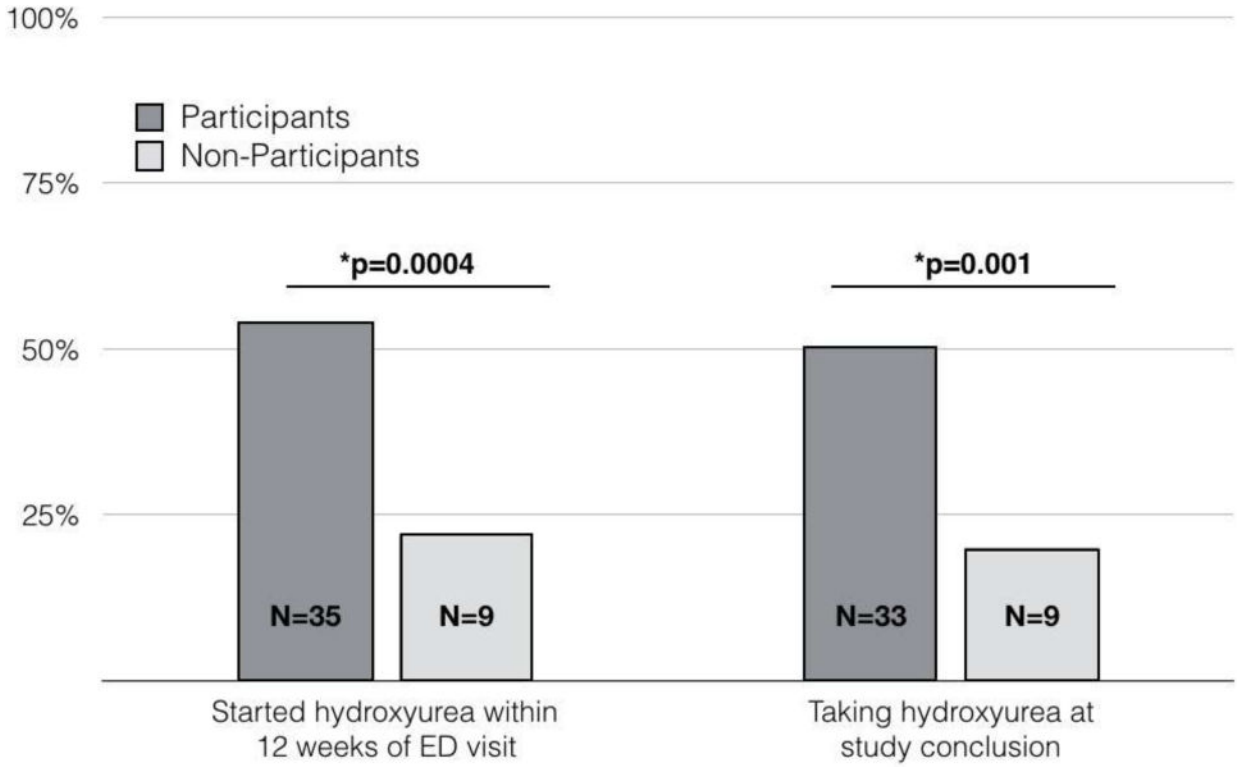

FIGURE 2. Interval Hydroxyurea Use in Q-SHIP Participants and Non-Participants During Follow-Up

Hydroxyurea initiation in Q-SHIP participants and non-participants over time. Twelve weeks from ED presentation, Q-SHIP participants were significantly more likely to start hydroxyurea than non-participants (35/66 participants versus 9/46 non-participants, p=0.0004). At the study's conclusion, significantly more Q-SHIP participants were taking hydroxyurea than non-participants (33/66 participants versus 9/46 non-participants, p=0.001).

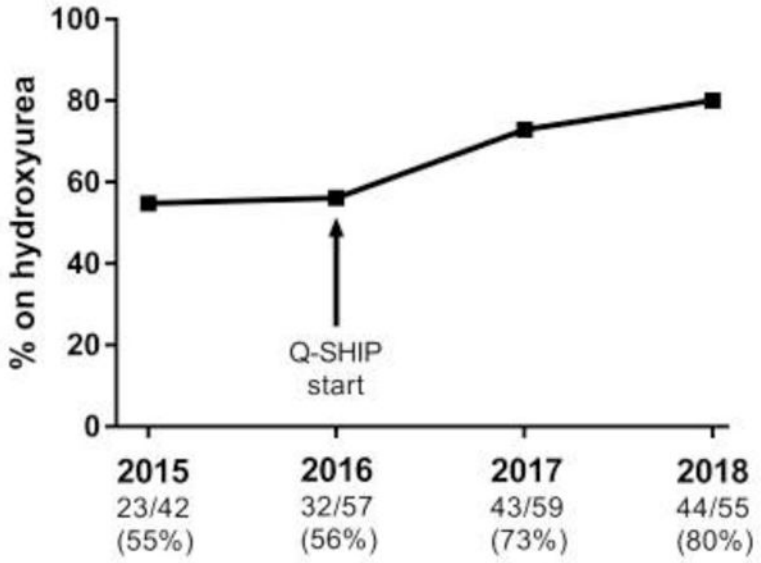

FIGURE 3. Steady Increase in the Proportion of Patients in the ED taking Hydroxyurea Since Start of Q-SHIP

Among patients with SCA followed at CNHS, aged >9 months, not on chronic transfusion who presented to the ED for pain and/or ACS during the month of February, the number of patients on hydroxyurea is shown for 2015, 2016, 2017, and 2018. There was no significant increase in this proportion when comparing the year before Q-SHIP was started (February 2015) to the baseline proportion at the start of Q-SHIP (February 2016): 55% vs. 56%, p=0.89. In contrast, there was a significant increase in this proportion when comparing this baseline proportion (February 2016) to two years after the start of Q-SHIP (February 2018): 56% vs. 80%, p=0.0069.

TABLE 1

online-only, Q-SHIP Video Citations

The Q-SHIP video incorporates videos from these freely available sources listed here.

Institution/Organization	Video Title	URL
Children's Medical Center Dallas, University of Texas Southwestern	Hydroxyurea: The Patient Experience	https://www.youtube.com/watch?v=BhCrB3cKAAQ
Monroe Carell Jr Children's Hospital at Vanderbilt	Hydroxyurea Treatment for Children with Sickle Cell Disease	https://www.youtube.com/watch?v=nx7MvMjeNJ0
Sickle Cell Disease Association of America Philadelphia/Delaware Valley Chapter	Hydroxyurea "Ask Me Why"	https://www.youtube.com/watch?v=mgp5PI-DsDI
National Heart Lung and Blood Institute, National Institutes of Health	My Story: Living with Sickle Cell Disease	https://www.youtube.com/watch?v=qe59ar-GZmg
University of Florida	You Don't Know Until You ASK! Is Hydroxyurea Your Hope for Better Days?	Division of Hematology/Oncology, Department of Medicine, University of Florida courtesy of Dr.Richard Lottenberg (lottenr@medicine.ufl.edu)
Central-Northern New Jersey Sickle Cell Network, Newark Beth Israel Medical Center and the Children's Hospital of New Jersey	Hydroxyurea: The Best Hope for Sickle Cell Anemia Patients	https://www.youtube.com/watch?v=L_xSgQWjO7A

TABLE 2

online-only, Characteristics of Q-SHIP Participants Compared to Non-Participants

There were no differences in age, sex, insurance type, frequency of hematology clinic follow-up, baseline hemoglobin and %HbF, ED visits in the past 2 years, previous pediatric intensive care unit (PICU) admission, and previous transfusions.

	Participated in Q-SHIP N=66	Not participated in Q-SHIP N=46	p-value
Age, median year (IQR)	8.5 (4.4, 16.0)	9.0 (5.1, 16.5)	0.38
Male	34 (52%)	22 (48%)	0.70
Medicaid insurance	49 (74%)	32 (70%)	0.59
Hematology clinic visit in the last year	54 (82%)	35 (76%)	0.46
Baseline hemoglobin, mean g/dl (SD)[a]	8.4 (1.1)	8.7 (1.2)	0.23
Baseline %HbF, mean % (SD)[b]	15.9 (9.4)	15.7 (10.4)	0.93
Number of ED visits or hospitalizations for ACS or pain in prior 2 years, median (IQR)	3 (2, 5)	2 (1, 4)	0.42
Prior PICU admission or transfer	17 (26%)	14 (30%)	0.59
Number of prior transfusions, median (IQR)	2 (0, 4)	1 (0, 4)	0.72

[a] defined as hemoglobin at last regular hematology clinic visit, >3 months from any transfusion;

[b] n=102, ten patients were excluded as they either did not have a %HbF after age 3 years or no %HbF in the last 6 months if age < 3 years.

TABLE 3
Comparison of Q-SHIP Participants Who Did and Did Not Start Hydroxyurea

There were no differences between those who did and did not start hydroxyurea according to previous hydroxyurea offer, participation in a group session or while hospitalized, or clinical variables including baseline hemoglobin and %HbF, ED visits, or intensive care unit admission.

	Started HU after Q-SHIP N=36	**Did not start HU after Q-SHIP N=30**	**p-value**
Age, median years (IQR)	7.5 (5.0, 15.3)	9.3 (3.1, 16.3)	0.94
Reported previous HU offer[a]	22/35 (63%)	14/30 (47%)	0.19
Group Q-SHIP session with other patient families	20 (56%)	15 (50%)	0.66
Attended Q-SHIP… …after only an ED visit …during a hospitalization …after a hospitalization	13 (36%) 8 (22%) 15 (42%)	10 (33%) 6 (20%) 14 (47%)	0.81 0.83 0.68
Days from ED or hospital discharge to Q-SHIP participation, median (IQR)	5 (2, 20)	8 (3, 28)	0.59
Baseline hemoglobin, mean g/dl (SD)	8.3 (1.2)	8.6 (1.0)	0.29
Baseline %HbF, mean % (SD)[b]	15.0 (9.5)	16.9 (9.3)	0.43
Number of ED visits or hospitalizations for pain or ACS in prior 2 years, median (IQR)	3 (2, 5)	2 (2, 4)	0.29
Prior PICU admission or transfer	12 (33%)	5 (17%)	0.12
Number of prior transfusions, median (IQR)	2 (1, 5)	1 (0, 4)	0.12

[a] n=65, one patient did not compete pre-session questionnaire;

[b] n=63, three patients did not have baseline %HbF.