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Journal Title: American Journal of Hematology
Volume: Volume 92, Number 1
Publisher: Wiley | 2017-01-01, Pages 77-81
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1002/ajh.24587
Permanent URL: https://pid.emory.edu/ark:/25593/s6zdr

Final published version: http://dx.doi.org/10.1002/ajh.24587

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Accessed March 7, 2018 1:05 PM EST
Hydroxyurea Effectiveness in Children and Adolescents with Sickle Cell Anemia: A Large Retrospective, Population-Based Cohort

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Abstract

The clinical efficacy of hydroxyurea in patients with sickle cell anemia (SCA) has been well established. However, data about its clinical effectiveness in practice is limited. We evaluated the clinical effectiveness of hydroxyurea in a large pediatric population using a retrospective cohort, pre-post treatment study design to control for disease severity selection bias. The cohort included children with SCA (SS, Sβ0-thalassemia) who received care at Children's Healthcare of Atlanta (CHOA) and who initiated hydroxyurea in 2009-2011. Children on chronic transfusions, or children with inadequate follow up data and/or children who had taken hydroxyurea in the 3 years prior were excluded. For each patient, healthcare utilization, laboratory values and clinical outcomes for the 2-year period prior to hydroxyurea initiation were compared to those 2 years after initiation. Of 211 children with SCA who initiated hydroxyurea in 2009-2011, 134 met eligibility criteria. After initiation of hydroxyurea, rates of hospitalizations, pain encounters, and emergency department visits were reduced by 47% (<0.0001), 36% (p=0.0001) and 43% (p<0.0001), respectively. Average hemoglobin levels increased by 0.7g/dl (p<0.0001). Hydroxyurea effectiveness was similar across gender, insurance types and age, although there was a slightly greater reduction in hospitalizations in younger children.

Keywords

Hydroxyurea; effectiveness; sickle cell
Introduction

Sickle cell disease (SCD) is a group of multi-system, life-threatening blood disorders which affects 100,000 people in the US and millions of people worldwide [1-3]. SCD is characterized by acute and chronic pain, chronic anemia, increased susceptibility to infections, central nervous system vasculopathy including stroke, and end organ damage affecting the kidneys, lungs, liver, reproductive organs and eyes [4]. However, there is marked inter-individual and temporal variability in the clinical severity of the disease.

Newborn screening for SCD, prophylactic penicillin treatment and comprehensive specialized care have resulted in improved outcomes for children with SCD, especially in developed countries [5-7]. Despite the improvements observed in childhood, affected patients have significant morbidity and early adult mortality [8-10].

Disease-modifying therapies currently available for SCD include hydroxyurea, blood transfusions and bone marrow transplant. Bone marrow transplantation is curative in SCD but its use has been limited by the lack of donor availability for most patients, as well as concerns about transplant-related mortality and long-term adverse effects [11-14]. Chronic red cell transfusions decrease the rate of cerebral infarction in SCD [15-17], but are associated with significant toxicities including iron overload and the risk for allo-immunization. In addition, chronic red cell transfusions are currently not a feasible therapeutic intervention in less developed countries where the large majority of patients with SCD reside and where there is persistent shortage of blood supply. Hydroxyurea, the only disease-modifying drug for SCD approved by U.S. Food and Drug Administration (FDA), has been well demonstrated in clinical trials to alter the clinical course in SCA. It improves hemoglobin levels and decreases rates of pain, dactylitis, acute chest syndrome (ACS), transfusions and hospitalizations [18, 19]. Other studies have shown that hydroxyurea improves quality of life and decreases mortality [20-23].

Thus hydroxyurea is currently the only disease modifying therapy available to the majority of children with SCA in developed countries and a minority of children in developing countries. However, its use has been limited due to concerns about unknown side effects and the need for closer monitoring whilst on the drug. Although data on the efficacy of hydroxyurea has been well demonstrated in clinical trials, data on its effectiveness in clinical practice is limited. Efficacy examines the therapeutic effect of an intervention in a controlled setting, in contrast to effectiveness, which is the therapeutic effect of an intervention in real-world situations. Previous attempts to assess the clinical effectiveness of hydroxyurea have been limited by inherent selection bias for disease severity. Hydroxyurea is more likely to be recommended to patients with severe disease manifestations than to those who have few symptoms. The benefits of hydroxyurea may therefore not be observed when such groups are compared because of the worse clinical phenotypes of the hydroxyurea group. In fact, patients on hydroxyurea may have worse outcomes compared to patients not on hydroxyurea[24].

To circumvent this problem, we designed a pre-post, retrospective cohort study, which compared each individual patient's outcomes for specified periods prior to and after the
initiation of hydroxyurea. The goal of this study was to evaluate the effectiveness of hydroxyurea in a large pediatric SCA population. The hypothesis was that hydroxyurea is effective in modifying the clinical course of children with SCA: specifically that in a 2 year period after its initiation, compared with the preceding 2 years, hydroxyurea decreases the frequency of hospitalizations, total inpatient days and other SCA associated complications. We also assessed if the effect of hydroxyurea was modified by age, gender or insurance status.

Methods

Study Population

Children with a confirmed sickle cell anemia (SCA) diagnosis (HbSS or HbS β⁰ thalassemia) who received care at the Children’s Healthcare of Atlanta (CHOA) SCD Program and who initiated hydroxyurea during 2009 through 2011 were eligible for inclusion in this study. The pediatric sickle cell program at CHOA provides comprehensive sickle cell care to >1,700 active patients with sickle cell disease. About 70% of patients with SCD at CHOA have SCA (HbSS or HbS β⁰ thalassemia). During the study period (2009 – 2013), 41% of patients ≥1 year of age with SCA, who were not on chronic transfusions, received hydroxyurea. According to data from the Georgia Hospital Association, during the years 2009 – 2014, CHOA accounted for 95% of all inpatient discharges in children with SCD less than 18 years of age in the 28-county Atlanta metropolitan area (2010 population ~ 5.3 million). Thus the study likely incorporates a population-based sample. Our standardized clinical guidelines for dosing hydroxyurea recommend initial dosage of 20mg/kg/day, followed by dose escalation every 2 months to 25-30mg/kg or maximum tolerated dose if lower.

The cohort consisted of patients who were newly treated with hydroxyurea for at least 3 months and had at least 3 months of clinical information recorded preceding hydroxyurea initiation and at least 3 months available after initiation. Patients were excluded from the study if they had concurrent chronic transfusion therapy (which for study purposes was defined as monthly transfusions for at least three months), bone marrow transplant, or had ever taken hydroxyurea in the 3 years preceding the identified hydroxyurea initiation date. The use of transfusions for acute complications during the study period was not an exclusion criterion, and in fact was one of the endpoints. For each patient, demographic information, laboratory values, health services utilization frequency and SCA-related events were ascertained for up to two-years prior to and after hydroxyurea initiation. The CHOA Institutional Review Board approved this study with a waiver of consent from participants.

Study Variables and Data Sources

Patient date of birth, sex, and SCD genotype were abstracted from the medical record. Each patient’s SCD genotype was confirmed by a pediatric hematologist’s review of laboratory and clinical records. CHOA records were used to determine the number of times each patient visited a CHOA emergency department for a SCD-related reason, number of inpatient admissions and the length of stay in days for each admission. The rate of hospitalizations for the study period was defined as the number of hospitalizations among
the cohort divided by the period of observation, both pre- and post-hydroxyurea initiation. The diagnosis of acute chest syndrome during the study period was adjudicated by two hematologists who reviewed chest x-rays and clinical symptoms associated with the episode. Laboratory values reported (i.e. hemoglobin, hemoglobin F and mean corpuscular volume (MCV) were an average of all the values recorded in each time period (pre- and post-hydroxyurea initiation). Each patient’s transfusion history was obtained from blood bank records. Each unit of blood received was counted as one transfusion. Receipt of more than one aliquot of blood from a single unit was recorded as a single transfusion. Medical records were also reviewed to determine the hydroxyurea dose (mg/kg/d) for each subject at their last clinical encounter prior to study exit.

**Statistical Analysis**

Cohort demographic, clinical, and socioeconomic related characteristics were described using means (and 95% confidence intervals) and medians (with interquartile range or ranges). The primary statistical analysis consisted of comparing the overall number of hospitalizations, emergency room visits, and other events before and after hydroxyurea initiation. Rate ratios were computed using unadjusted Poisson regression models. Because each patient served as their own “control” in a pre-post study, confounding by disease severity was not a key concern. However, because we were interested in whether any effect of hydroxyurea on hospitalizations and inpatient days varied by age, gender, or insurance status, we assessed relevant interactions and reported stratified results for any of the characteristics with significant interactions. For interaction analyses involving age, we considered age categorically: as age ≤ 7 years at HU initiation and age > 7 years, as 7.5 was the median cohort age. Differences in medians were compared using the Wilcoxon Signed Rank Test and means using the Student’s T test. Statistical inferences were made based on \( \alpha = 0.05 \). SAS Enterprise guide 6.1 was used for data analysis.

**Results**

One hundred and thirty four (64%) of 211 patients with SCA (HbSS and HbS \( \beta^0 \) thalassemia) who started hydroxyurea in 2009 – 2011 met eligibility criteria. Fifty-two patients were excluded from the study because they had concurrent chronic transfusion and hydroxyurea therapy, 22 patients had limited or no follow up data pre and/or post hydroxyurea initiation, two patients underwent bone marrow transplant and the exact hydroxyurea start date in one patient was unknown. Overall, 77 (36%) of 211 patients with sickle cell anemia who started hydroxyurea in 2009 – 2011 were ineligible for the study.

78% of the study population (105 patients) had data for a full 2 years pre- and post-hydroxyurea initiation. The median age of the study population was 7.5 years at time of hydroxyurea initiation; 39% of the population was ≤5 years, 33% was 6 - ≤10 years old, 20% was 11 - ≤15 years old, and 8% was >15 years old. Fifty-five percent of the population was female. Total number of person-years pre- and post-hydroxyurea was 252 and 257 respectively among the 134 children. There were a total of 636 emergency department visits pre-hydroxyurea and 376 visits post-hydroxyurea. There were 312 total hospitalizations in
the study group pre-hydroxyurea and 175 hospitalizations post-hydroxyurea. The average dose of hydroxyurea in the study cohort at study exit was 24.9mg/kg/d (s.d. 5.6 mg/kg/d).

There was a significant reduction in acute healthcare utilization after hydroxyurea initiation. After initiation of hydroxyurea, the rate of hospitalization was 0.53 the rate before and the number of inpatient days was 0.5 the rate before, reflecting 47% and 50% reductions in these outcomes, respectively (p value <0.0001). Similarly, emergency department visits, pain encounters, episodes of acute chest syndrome and blood transfusions also decreased by 43%, 36%, 43% and 57% respectively (Table I). The hemoglobin level (median and IQR), pre- and post-hydroxyurea initiation was 8.05g/dl (7.40 – 8.60) and 8.90g/dl (8.04 – 9.51) respectively, with a median increase of 0.69 g/dl (0 – 1.29), p<0.0001. Mean corpuscular volume (MCV) increased from 83.73fl (78.15 – 87.73) pre-hydroxyurea to 96.42fl (88.36 – 103.37), a median increase of 12.32, p <0.0001. As would be expected, there were also significant decreases in total white cell and absolute neutrophil counts. Total white cell and absolute neutrophil counts decreased by median values of −4.4 (−6.1 – −2.1), p <0.0001) and −2.2 (−3.9 – −0.5, p < 0.0001) respectively. The median absolute increase in hemoglobin F levels (Hb F) in the whole cohort was only 1.77 % (−6.74 – 6.02; p = 0.90), which was not statistically significant (Table II), however when this was examined by age, children who were five years of age or younger, showed a median decrease of −5.4% (−18.2 – 4.6, p 0.001), whereas children who were older than five, showed a median increase in HbF of 3.2% (−1.2 – 8.7, p 0.0008).

Table III shows the effect of hydroxyurea in children ≤7 years old compared to children >7 years. While hydroxyurea was effective in both groups, children ≤7 years of age had greater reductions in hospitalizations after initiation of hydroxyurea than older children and adolescents (p value 0.03 for interaction with age). There was no interaction between age and the effect of hydroxyurea on the total inpatient days (interaction p value 0.3097). Given that with increasing age, children with SCD are less likely to be hospitalized for febrile illnesses and to explore the greater reduction in hospitalization noted in the younger age groups, we compared the rate of hospitalization in our cohort by age group, for the pre-hydroxyurea period. There was no significant difference in the rates of hospitalization prior to hydroxyurea initiation across age groups in our cohort (F value 2.13, p 0.099), thus establishing that the greater reduction in hospitalization rate noted in children ≤7 years, after initiation of hydroxyurea was not due to age alone. To further explore this age difference in the effect on hospitalizations, we stratified the patients based on three other measures of response to hydroxyurea, the change in MCV, hemoglobin and hemoglobin F levels (Table IV), acknowledging that differences in any of these parameters could be related to differences in either adherence to the medication or biological variation in response. For both age groups, ≤7 years of age and > 7 years of age, we examined the effect on hospitalizations using the median change in MCV (12fL), Hb (0.69g/dl) and HbF (1.77%) (Table IV). In the combined sample and in both age groups, patients with changes in either MCV, Hb or HbF above the median changes, had greater reductions in hospitalizations than those with smaller changes in MCV, Hb or HbF. Among the children with lower changes in MCV, Hb or HbF, only those ≤7 years of age showed a statistically significant improvement in hospitalizations, and in those with larger changes in MCV, Hb or HbF, older children also benefited, though the reduction in hospitalizations was greater in younger children. Thus,
regardless of the response to HU reflected in these laboratory parameters, younger children had a greater reduction in hospitalizations than older children. It is also interesting to note that even though a greater proportion of younger children had changes in HbF that were less than the median change, that cohort still demonstrated greater reduction in hospitalizations than their older counterparts.

Finally, we explored the interaction between the effect of hydroxyurea, gender, and insurance. Hydroxyurea effectiveness did not vary by gender (interaction p value >0.05) nor insurance type (interaction p-values >0.05).

**Discussion**

This study demonstrates that hydroxyurea was clinically effective in pediatric patients with sickle cell anemia. The two-year rates of hospitalization and inpatient days after initiation of hydroxyurea were about half the rate prior to initiation of hydroxyurea. Similarly, the number of pain encounters, ER visits, episodes of acute chest syndrome and transfusion all decreased. Hemoglobin levels improved by 0.69g/dl.

These results are remarkably similar to published effects of hydroxyurea in efficacy trials. In the Baby Hug and adult MSH trials, the landmark efficacy trials of hydroxyurea in SCA, patients on hydroxyurea had mean increases in hemoglobin levels 0.9g/dl and 0.6g/dl respectively, compared to patients on placebo. The median number of pain events in adult patients on hydroxyurea in the MSH trial, was 44% lower compared with placebo (2.5 vs. 4.5 pain events/yr., p<0.001). Similarly, pediatric patients on the Baby Hug study had nearly 40% reduction in pain events (Hazard ratio 0.59, 95% CI 0.42-0.83, p value 0.002). Both studies also showed decreases in hospitalization rates [18, 19, 25]. While the change in Hb F levels was rather low in our study, published changes in Hb F levels after initiation of hydroxyurea in clinical practice have been quite variable [19, 20, 23]. Voskaridou et al reported a median increase in Hb F levels from 6.8% to 20.4% after a year in adult patients on hydroxyurea [23]. However, Lobo et al reported a mean change in hydroxyurea of only 3.2% in pediatric patients after a year on hydroxyurea [20]. In the Baby Hug study, Hb F levels fell at study exit compared to study entry; patients on hydroxyurea had 13% decline in Hb F levels, compared to a 37% decline in patients on placebo [19]. This observation could be explained in part by the fact that Hb F levels fall during the first few years of life, and hydroxyurea may thus lessen this rate of decline. About 40% of patients on this hydroxyurea effectiveness study were less than 5 years of age at hydroxyurea initiation, some of whom were in the phase of life with declining Hb F levels. Thus, it is not surprising that the change in Hb F noted in this study is not comparable to changes in Hb F noted in some adult studies. Additionally, post-hydroxyurea Hb F levels in this study represent the averages of values taken at various times over the two-year follow-up period, and thus may not be representative of Hb F levels at the end of 2 years treatment.

Our results are important as they demonstrate that hydroxyurea improves clinical outcomes in ‘real life settings’, even without incentives for adherence typically associated with clinical trials, such as free supply of drugs, reminders for clinic visits, pill counting to measure compliance, and financial incentives for follow up visits. While the number of effectiveness
studies, examining outcomes after initiation of hydroxyurea are limited, it is important to note that Nottage et al also noted reductions in hospitalization rates and blood transfusions comparing hydroxyurea exposed and non-exposed patients in another large sickle cell cohort[26].

Our study found that younger children had an even greater reduction in hospitalizations after hydroxyurea initiation compared to older children. We initially suspected that this difference was due to a higher rate of non-adherence in the older age group since older children typically have less parental supervision in medication administration. However, the changes in MCV were similar in the older and younger age groups. We also examined the trend in hospitalization rate by age in this population using the data prior to initiation of hydroxyurea. The slight reduction in median hospitalization rates after age 5 among children not on hydroxyurea was not statistically significant and could not account for either the pre/post hydroxyurea reduction in hospitalization rates over the four year observation period in the larger population, or the age differential in the effect of hydroxyurea on hospitalization rate. We cannot explain this effect biologically and are not suggesting that this is always the case. We have not found a similar trend in the literature. It will be interesting to see if future studies show a similar trend.

The strengths of this study include the relatively large sample size, representing a population-based sample of pediatric patients with sickle cell disease in a large metropolitan area. The use of a pre/post analysis which allows for control of variables that do not change with time and extraction of data from symmetrical time periods pre- and post-initiation of hydroxyurea allowed for control of varied patterns of hospitalization for SCA that may occur with changing seasons.

A number of limitations are also acknowledged. Indications for use of hydroxyurea have been evolving rapidly. During the period of the study, hydroxyurea was indicated for patients with more severe clinical phenotypes. Current NIH guidelines for the management of sickle cell disease recommend offering hydroxyurea to children with SCA, even those who are asymptomatic [27]. The degree of benefit seen in this study might be different when compared to children started on hydroxyurea with less severe phenotypes. Secondly, the study excluded patients for whom hydroxyurea was initially prescribed, but then discontinued before 3 months. Thus the study may have selected for patients who were more likely to be compliant. Thirdly, it is possible that the decision to initiate HU therapy for a given patient might have been prompted by a period of relatively frequent acute events for that individual, and that the subsequent period might have been “less severe” even if HU had not been initiated. There is no way to control for such an effect of regression to the mean, short of randomization, which is not an option for an effectiveness study. Nevertheless, it seems unlikely that such a statistical effect is responsible for the reduction in utilization observed in this study, given that our findings mirrored quite faithfully the results of the efficacy trials (MSH, baby HUG), and that long term use of HU has been shown to improve longevity in SCD[20, 21, 23, 28]. Further, almost every patient had 2 years of data pre-initiation and another 2 years post-initiation which would decrease the likelihood of results being due to regression to the mean. It is also possible that closer follow up and observation that is inherent in hydroxyurea treatment may have its own therapeutic benefit and may have
contributed to the improved health outcomes observed, but this does not invalidate our results. Additionally, neither individual patient adherence nor provider adherence to dose escalation guidelines was measured in this study so it is not known how either of these parameters could have affected patient outcomes.

In conclusion, our data demonstrates that hydroxyurea is *clinically effective* in pediatric patients with SCA. Hydroxyurea decreased hospitalizations, emergency department visits, pain encounters, ACS, use of transfusions and improved hemoglobin levels. Hydroxyurea effectiveness was similar across gender, insurance types and age, although there was a somewhat greater reduction in hospitalizations in younger patients. These results are important as they parallel results obtained from hydroxyurea efficacy studies, thus demonstrating that in ‘real life’ settings, even without the additional monitoring and adherence incentives of clinical trials, hydroxyurea improves short-term outcomes in pediatric sickle cell anemia.

**Acknowledgements**

Supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent official view of the National Institutes of Health. This work was also supported by a grant from the Abraham J. & Phyllis Katz Foundation.

The authors thank Erin Meyer MD, Cassandra Josephson and Anne Winkler MD for providing transfusion data and Brad Kloth, Karl Ellis, Bruce Rhodes, Matthew Miller, Greg Rocks, Yurtizi Jones and Chris Perry for assistance with collection of clinical and utilization data.

**References**


*Am J Hematol. Author manuscript; available in PMC 2018 January 01.*
Table I
Effect of hydroxyurea initiation on clinical outcomes using Poisson Regression

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio (Confidence Limits)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>0.53 (0.43 – 0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inpatient Days</td>
<td>0.50 (0.40 – 0.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.57 (0.49 – 0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain Encounters</td>
<td>0.64 (0.51 – 0.81)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACS</td>
<td>0.57 (0.39 – 0.83)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Blood Exposure</td>
<td>0.43 (0.29 – 0.64)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### Table II
Change in laboratory values pre- and post-hydroxyurea

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre - Hydroxyurea Median (IQR)</th>
<th>Post-Hydroxyurea Median (IQR)</th>
<th>Change Median (IQR)</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>8.05 (7.40 – 8.60)</td>
<td>8.90 (8.04 – 9.51)</td>
<td>0.69 (0 – 1.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MCV (Fl)</td>
<td>83.73 (78.15 – 87.73)</td>
<td>96.42 (88.36 – 103.37)</td>
<td>12.32 (8.23 – 17.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbF (%)</td>
<td>15.45 (8.13 – 26.40)</td>
<td>17.62 (10.88 – 23.30)</td>
<td>1.77 (–6.74 – 6.02)</td>
<td>0.90</td>
</tr>
<tr>
<td>WBC count (×10^3/uL)</td>
<td>14.3 (12 – 16.5)</td>
<td>10 (8.2 – 11.7)</td>
<td>– 4.2 (– 6.1 – – 2.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ANC (×10^3/uL)</td>
<td>7.6 (5.7 – 9.4)</td>
<td>5.23 (4 – 6.5)</td>
<td>– 2.2 (– 3.9 – – 0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>1430 (1069 – 1718)</td>
<td>1018 (774 – 1318)</td>
<td>– 244 (– 496 – – 61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl)</td>
<td>2.64 (1.6 – 3.5)</td>
<td>2.2 (1.5 – 3.4)</td>
<td>– 0.08 (– 0.82 – 0.38)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

P values based on signed rank test

*ANC – Absolute neutrophil count

§Change in HbF is calculated as follows: (Post-Hydroxyurea HbF level – Pre-Hydroxyurea HbF level).
Table III

Effects of Hydroxyurea on Hospitalizations and Inpatient Days Stratified by Age.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Rate Ratio (Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 7</td>
<td>67</td>
<td>0.42 (0.31-0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>67</td>
<td>0.67 (0.49-0.92)</td>
<td>0.0125</td>
</tr>
<tr>
<td>Inpatient Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 7</td>
<td>67</td>
<td>0.45 (0.32-0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>67</td>
<td>0.55 (0.40-0.75)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

* Interaction p value with age for the effect of hydroxyurea on hospitalizations = 0.0349

* Interaction p value with age for effect of hydroxyurea on inpatient days = 0.3097
### Table IV

Effect of Hydroxyurea on Hospitalizations (Rate Ratios Pre/Post HU) Stratified by Change in MCV, HbF and Hb.

<table>
<thead>
<tr>
<th>Change in MCV</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
<th>Change in MCV</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤12 fl</td>
<td>67</td>
<td>0.73 (0.56 – 0.94)</td>
<td>0.01</td>
<td>67</td>
<td>0.36 (0.25 – 0.53)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 fl</td>
<td>31</td>
<td>0.64 (0.43 – 0.94)</td>
<td>0.03</td>
<td>36</td>
<td>0.23 (0.17 – 0.47)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in HbF</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
<th>Change in HbF</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.77%</td>
<td>56</td>
<td>0.63 (0.49 – 0.81)</td>
<td>0.0003</td>
<td>55</td>
<td>0.40 (0.26 – 0.61)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>&gt;1.77%</td>
<td>36</td>
<td>0.51 (0.37 – 0.72)</td>
<td>&lt;0.0001</td>
<td>21</td>
<td>0.26 (0.13 – 0.52)</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change in Hb</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
<th>Change in Hb</th>
<th>N</th>
<th>Rate Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.69 g/dl</td>
<td>67</td>
<td>0.81 (0.64 – 1.02)</td>
<td>0.08</td>
<td>67</td>
<td>0.34 (0.23 – 0.49)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>&gt;0.69 g/dl</td>
<td>33</td>
<td>0.66 (0.47 – 0.93)</td>
<td>0.02</td>
<td>34</td>
<td>0.27 (0.16 – 0.45)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Median change in MCV = 12.32 fl Median change in HbF = 1.77% Median change in Hb = 0.69 g/dl Rate ratios are indicated with 95% confidence intervals. P values reflect pre/post stratum comparison for each stratum.