

# Increasing hydroxyurea dose helps to keep young sickle cell patients out of the hospital

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Jeremie Estep, MD, said the papers' findings underscore the need to improve and expand access to hydroxyurea in the US and internationally. Credit: Seth Dixon / St. Jude Children's Research Hospital

St. Jude Children's Research Hospital investigators have shown that

using the drug hydroxyurea to boost average fetal hemoglobin levels above 20 percent in children and teenagers with sickle cell anemia was associated with at least a two-fold reduction in hospitalization for any reason.

Results of the federally funded HUSTLE study—Hydroxyurea Study of Long-Term Effects—appeared online this week in the *American Journal of Hematology*.

The findings should help settle the debate about how to optimize [hydroxyurea](#) for treatment of [sickle cell disease](#) in young people. Rather than calculating a standard dose of hydroxyurea based on patients' weight, researchers used a dose-escalation approach to determine the maximum tolerated dose for each of the 230 St. Jude patients enrolled in the study.

"Our analysis showed that using this approach, hospitalizations for the average patient fell to less than one every couple of years rather than four to six annually," said lead author Jeremie Estep, M.D., an assistant member of the St. Jude Department of Hematology. "This frees children from the fevers, pain and other symptoms of this disease and gives them and their families more chances to enjoy childhood and adolescence."

Sickle cell anemia is the most common inherited blood disorder. The disease affects about 100,000 U.S. residents and occurs most often in African-American and Hispanic individuals. They inherit a mutation that affects the hemoglobin protein that red [blood cells](#) use to ferry oxygen throughout the body. Rather than soft, pliable [red blood cells](#) that travel easily through blood vessels, the [sickle cell mutation](#) leaves patients with red blood [cells](#) that can become brittle and banana-shaped. The sickled cells clog blood vessels and lead to pain, organ damage, strokes and other symptoms and also leave patients at risk for premature death in middle age.

St. Jude pioneered the use of hydroxyurea to treat sickle cells in children. The drug is now offered to all sickle cell patients who are 9 months or older. The drug increases production of fetal hemoglobin, which functions normally in individuals with [sickle cell anemia](#). Previously published data from HUSTLE and other studies reported that hydroxyurea was safe, reduced stroke risk and improved spleen and kidney function.

Despite hydroxyurea's proven benefits, the optimal dosing strategy for the drug has remained controversial. Also lacking has been evidence of overall improved patient outcomes if hydroxyurea is used to increase blood levels of fetal hemoglobin to more than 20 percent.

For this study, patients received a starting dose of hydroxyurea that was escalated in a stepwise manner until patients reached a predetermined maximum dose (either 35 milligrams per kilogram daily or 2,000 milligrams daily) or experienced mild neutropenia. About 2 percent of patients in this study developed transitory neutropenia, or a low level of disease-fighting white blood cells called neutrophils. More than 75 percent of patients had completed the dose escalation when study data were analyzed.

More than half the patients received a hydroxyurea starting dose of 20 milligrams per kilogram. The average dose was 27 milligrams per kilogram daily when the dose escalation process ended and ranged among patients from 13 to 35 milligrams per kilogram daily.

Pharmaceutical records suggest that patient compliance was good. Throughout the four-year study, almost 94 percent of patients had possession of their medication, which exceeded the national average. "St. Jude has invested in the clinical infrastructure, including case managers and other staff to support and follow up with families to make sure they receive recommended care, including medication," Estepp said. "These

results show how patients and families benefit."

Average fetal hemoglobin levels in patients rose from 9.7 percent prior to treatment to 21.7 percent, a level that was sustained for the four years covered in this analysis. Overall, 60 percent of study patients attained fetal hemoglobin levels of more than 20 percent.

The odds of being hospitalized for pain or any reason were about doubled for sickle cell [patients](#) with fetal hemoglobin levels of 20 percent or less. The lower level was also associated with 2.6-times greater odds of hospitalization for the respiratory illness acute chest syndrome and about four-time greater odds of being hospitalized for fever.

"These results support a hydroxyurea dosing strategy designed to produce fetal hemoglobin levels that exceed 20 percent in an effort to decrease hospitalization of children with sickle cell disease," Estep said. St. Jude researchers are now leading a multi-center trial to determine if toddlers with sickle cell disease would benefit from a similar dosing strategy or would respond better to a standard dose.

Estep said the findings also underscore the need to improve and expand access to hydroxyurea in the U.S. and internationally.

**More information:** Jeremie H. Estep et al, A clinically meaningful fetal hemoglobin threshold for children with sickle cell anemia during hydroxyurea therapy, *American Journal of Hematology* (2017). [DOI: 10.1002/ajh.24906](https://doi.org/10.1002/ajh.24906)

Provided by St. Jude Children's Research Hospital

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