Research Reveals Avenues for Informing and Improving Sickle Cell Care

With an emphasis on real-world data, studies guide application of both longstanding and emerging therapies.

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ORLANDO — Five studies presented at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition reveal new opportunities to improve care for people living with sickle cell disease.

Sickle cell disease is the most common inherited blood disorder, affecting around 100,000 individuals in the United States and one out of every 365 Black or African American births. It is characterized by abnormal blood cells that can block blood vessels, leading to complications such as episodes of severe pain, as well as damage to tissues and organs. Despite extensive health care needs, many people living with sickle cell disease have difficulty accessing appropriate care and report feeling stigmatized or having their symptoms dismissed when they do seek care. Treatments include drugs to help prevent or relieve pain crises and reduce organ damage, as well as curative stem cell transplants and new gene therapies.

“These studies allow us to be more accountable to our patients in terms of care and pain management, and to give context about the next phase of sickle cell therapies,” said Titilope Fasipe, MD, PhD, associate professor of pediatrics at Baylor College of Medicine and co-director of the sickle cell and thalassemia program at Texas Children’s Hospital, who moderated the press briefing Sickle Cell Disease: From Discovery to Access. “In studying the good, the bad, and the ugly for both our tried-and-true therapies and emerging treatments, we can get the information that our community needs to better inform shared decision-making,” she added.

Several of the studies draw upon real-world data to understand some of the barriers to care access and how various practical factors influence clinical decision making and patient outcomes.

“In our current era, innovation has been defined by cutting-edge advances like gene therapy. However, clinically meaningful innovation also occurs when we learn new ways to care for patients with the treatments that have been available, like insights on what it means to use hydroxyurea

during pregnancy," said Dr. Fasipe.

The first study presents striking evidence of gaps in the delivery of evidence-based care, showing that two-thirds of people visiting emergency departments for sickle cell pain did not receive timely pain relief in accordance with medical guidelines.

The second study calls for a pragmatic approach to continuing or stopping hydroxyurea for pregnant women, based on findings that taking the drug during pregnancy does not appear to cause specific harms to a developing fetus.

In the third study, researchers analyzed long-term outcomes in over 1,000 patients who underwent bone marrow transplant for sickle cell disease, revealing an overall positive outlook for most patients and the best outcomes among younger patients who had a matched related donor.

The final two studies examine gene therapies, which became available over the past few years as a curative option for both sickle cell disease and beta thalassemia, another disorder affecting red blood cells. The fourth study tracks the clinical practices and timelines involved in implementation of two gene therapies, while the fifth study reports preliminary results from the first clinical trial to examine the gene therapy exagamglogene autotemcel in children younger than 12.

Emergency Departments Fall Short on Delivering Timely Treatment for Sickle Cell Pain
121: Multicenter evaluation of guideline adherence for the timeliness of pain medication for acute sickle cell disease pain

A new study finds that only one in three patients visiting emergency departments (EDs) for severe pain associated with sickle cell disease received appropriate opioid-based pain-relieving medications within the first hour as recommended by the American Society of Hematology (ASH) and National Heart, Lung, and Blood Institute (NHLBI).

Based on data from several hundred medical centers across the United States, the research represents the first large, national study to assess guideline adherence across diverse EDs. It shows substantially lower guideline adherence than has been reported in smaller studies focused on pediatric specialty EDs.

The results suggest that a majority of patients experience prolonged suffering while waiting to receive opioids as recommended for pain. Patients over age 19, female patients, and those with public health insurance were less likely to receive guideline-adherent care compared with younger patients, male patients, and those with private health insurance.

"We want to call attention to the fact that there is huge room for improvement across the board, particularly in general EDs that primarily attend to adults," said lead study author Ibrahim Gwarzo, MD, DrPH, MBBS, research scientist at Nemours Children's Health, Delaware Valley and research assistant professor Sidney Kimmel Medical College at Thomas Jefferson University. "Some strategies for improvement include greater dissemination of the guidelines, integration of the

sickle cell care protocol into general EDs, and continued advocacy for this population."

Sickle cell disease causes red blood cells to become sickle-shaped, and when these misshapen blood cells accumulate in a vessel, they can cause episodes of severe pain, known as vaso-occlusive crises. ASH and NHLBI guidelines recommend that patients experiencing vaso-occlusive crises receive opioid pain medication within 60 minutes of arrival at a hospital ED. After the initial dose, ASH guidelines recommend evaluating the patient's pain level and administering further doses as needed at intervals of 30-60 minutes, while NHLBI guidelines recommend subsequent evaluations and doses at intervals of 30 minutes.

To study the implementation of these guidelines in practice, researchers analyzed electronic health records on 398,895 ED visits for vaso-occlusive crises between 2019 and 2024 in which at least one opioid pain medication was administered. These visits occurred among 41,547 unique patients at 233 medical centers.

The results showed that the first opioid dose was given within 60 minutes of arrival in just 32.5% of visits. Among the approximately three-quarters of visits in which multiple doses of opioid medications were administered, the timing of the second dose also failed to meet guideline recommendations in most instances. In these cases, the second dose was administered within 60 minutes after the first dose (in accordance with ASH guidelines) 36% of the time, while the second dose was administered within 30 minutes after the first dose (in accordance with NHLBI guidelines) just 9% of the time.

Researchers found that patients younger than 19 received guideline-adherent care far more often – in 52% of cases – compared with older patients, who received timely treatment in just 30% of cases. They suggested that clinicians' familiarity with sickle cell treatment protocols may play a role in this disparity.

"Generally, pediatric EDs might be more familiar with sickle cell disease because those are typically near more academic sites and may have more specialized care, as opposed to freestanding adult or general EDs in more remote locations where the exposure to sickle cell disease is pretty limited," said Dr. Gwarzo.

As a result of the ongoing epidemic of opioid dependence, ED clinicians sometimes encounter patients who request opioid medications as a result of their dependence but are not actually experiencing severe pain. Given this context, researchers suggested that some clinicians may be concerned about giving opioid medications to people they suspect of opioid dependence.

"One of the challenges of identifying sickle cell disease pain is that there is no biomarker for it, and as a provider, you rely on what the patient tells you about how severe the pain is," said Dr. Gwarzo. "Providers are more likely to be hesitant to administer opioids for the adult population than for little kids." He added that implicit bias may also influence a clinician's decision on whether to give opioids when a patient visits the ED for pain.

The study found that guideline adherence was higher when patients were male, with 37% of male patients receiving their first dose within 60 minutes compared with 29% of female patients. Adherence was also higher among the one-quarter of patients who were privately insured compared with those on public insurance. Arriving at the ED overnight was also associated with higher adherence, perhaps because patient volumes are generally lower at night.

Opiate medications can be administered orally, injected, or infused. The study showed no difference in guideline adherence by route of administration for the first dose, but adherence was significantly higher for the second dose when medications were given orally (which showed guideline adherence in 24% of cases) compared with injection or infusion (less than 8%).

Overall, researchers said that the findings underscore the importance of improving clinician training and awareness to ensure people living with sickle cell disease receive recommended treatments in a timely manner, wherever they receive treatment. Dr. Gwarzo added that further studies could assess interventions to improve guideline adherence and elucidate the benefits of compliance, such as potential reductions in hospitalization.

Dr. Ibrahim Gwarzo, of Nemours Children's Health, Delaware Valley and Sidney Kimmel Medical College at Thomas Jefferson University, will present this study on Saturday, December 6, 2025, at 9:30 a.m. Eastern time in W311E-H of the Orange County Convention Center.

Study Shows No Clear Evidence of Harm from Hydroxyurea Use During Pregnancy
2: Outcomes of pregnancies in sickle cell patients treated with hydroxyurea: Findings from the escort-HU cohort studies

Taking the sickle cell drug hydroxyurea during or shortly before pregnancy does not appear to cause specific issues in newborns, according to the first prospective study of pregnancies involving hydroxyurea exposure.

Since there may yet be undocumented effects, the authors still recommend discontinuing the drug before pregnancy, if possible. However, the findings offer reassurance that hydroxyurea exposure may not cause harm when unplanned pregnancies occur or when the drug is the only or best option for managing sickle cell complications during pregnancy. Blood transfusions can offer an alternative treatment for some, but they are not available in all countries and not safe for all patients.

"Overall, the rate of live births was better than that seen in previous studies, and we had no maternal mortality, even though these patients were highly symptomatic," said lead study author Anoosha Habibi, MD, associate professor in the sickle cell referral center of Hôpitaux Universitaires Henri Mondor in Créteil, France. "Based on these findings, we call for a pragmatic approach. We have to decide case by case and evaluate the risk from transfusion and stopping hydroxyurea."

Hydroxyurea is an oral medication that helps blood cells maintain a healthy shape, aiding in the

prevention of sickle cell complications like painful vaso-occlusive crises and tissue damage. Since the drug has never been tested in pregnant women, its effects during pregnancy are unknown, and as a precaution, women are advised to stop taking the drug three to six months before they plan to conceive.

“Women are usually advised to stop hydroxyurea several months before pregnancy, but this is extremely difficult because these patients are often highly symptomatic and no one knows exactly when pregnancy will occur,” said Dr. Habibi. “So, many women remain without treatment for months, during which some develop severe vaso-occlusive crises and complications.”

“In higher-resourced settings, we can manage treatment interruption and provide safe transfusions for most patients, but in many regions in Africa, India, and the Caribbean, the safety of transfusion is limited, or the access is simply unavailable,” said Dr. Habibi. “In those contexts, asking women to stop hydroxyurea may actually put them in danger of vaso-occlusive crises, and both maternal and fetal outcomes can worsen.”

Drawing from a collection of prospective cohort studies involving 77 medical centers in Europe, the study included data from 245 pregnancies that occurred in 183 women taking hydroxyurea between 2009 to 2025. Most of the women had been taking hydroxyurea for many years before conceiving. In 84% of cases, the women were taking hydroxyurea when they became pregnant, suggesting that many of the pregnancies may have been unplanned.

Researchers analyzed outcomes from a subset of 178 pregnancies after excluding pregnancies that were voluntarily aborted, ongoing at the time of analysis, and those in which hydroxyurea was discontinued before conception. Of these 178 pregnancies, three-quarters resulted in live births. No maternal deaths and no hydroxyurea-related newborn malformations were reported.

The rate of miscarriage (17%) was similar to that seen in the general population, and the rate of premature birth (17%) was similar to that seen in previous studies of people living with sickle cell disease. Two pregnancies were discontinued in the hydroxyurea-exposed group for maternal medical reasons, and two fetal deaths occurred, one a late-term miscarriage before 21 weeks and one a stillbirth at 34 weeks, with neither death deemed to be related to hydroxyurea exposure.

Overall, the results provide no evidence of specific harms related to hydroxyurea exposure during pregnancy. This suggests that continuing hydroxyurea during pregnancy could be a reasonable choice when transfusion is not an option and a woman is at high risk of complications of untreated sickle cell disease, according to researchers.

While the data were collected prospectively, the researchers pointed out that the cohort study was not designed to monitor pregnancies, so the data regarding pregnancy outcomes are limited and the data on the percentage of transfusions performed may not be exhaustive. Dr. Habibi said that more studies are needed to confirm the research findings and assess long-term outcomes in children who were exposed to hydroxyurea in the womb.

The study was requested by the European Medicines Agency and funded by AddMedica.

Anoosha Habibi, MD, of Hôpitaux Universitaires Henri Mondor, will present this study on Sunday, December 7, 2025, at 2:25 p.m. Eastern time during the plenary scientific session in West Hall D2 of the Orange County Convention Center.

Long-Term Outlook Is Positive for Most After Hematopoietic Cell Transplant for Sickle Cell Disease
1051: Longterm survival and late effects following hematopoietic cell transplantation for sickle cell disease into a modern era: A center for international blood and marrow transplant research (CIBMTR) analysis

Patients who underwent hematopoietic cell transplantation for sickle cell disease saw high rates of survival without disease symptoms and low rates of severe side effects or complications years after their procedure, according to a new study. The study included over 1,000 patients, representing the largest and most comprehensive analysis of long-term transplant outcomes to date in people living with sickle cell disease.

“A majority of patients in this cohort are alive; the transplant worked so they no longer show symptoms of their sickle cell disease, and most have had no late effects post-transplant,” said lead study author Elizabeth Stenger, MD, associate professor in the department of pediatrics at Emory University School of Medicine and pediatric hematologist/oncologist at the Aflac Cancer and Blood Disorders Center of Children’s Healthcare of Atlanta in Georgia. “There are families that really want to know the data, and this will be among the largest and most statistically well-powered studies that can provide this information to patients we are counseling about transplant.”

Hematopoietic cell transplantation can eliminate symptoms of sickle cell disease by giving patients the ability to make healthy blood cells instead of ones prone to sickling. For the procedure, patients first undergo a chemotherapy-based conditioning regimen to clear the bone marrow of their own stem cells. Stem cells from a healthy donor are then infused and migrate to the bone marrow, where they begin producing healthy blood cells.

This procedure has been in use for several decades, but strategies for donor matching and conditioning have evolved over time. Long-term outcomes from hematopoietic cell transplantation, as it is currently practiced, have not been well studied in people living with sickle cell disease. In particular, it is unknown whether patients may face unique long-term effects of chemotherapy conditioning due to sickle cell disease-related organ damage.

Researchers analyzed data from 1,013 patients who received a hematopoietic cell transplant at 112 medical centers in the United States and internationally between 1996 to 2022. About half were female and just over half had a matched related donor. Procedures that resulted in primary graft failure (meaning that the donor stem cells did not persist early after transplant) were excluded from the data set.

At seven years post-transplant, 90% of transplant recipients remained alive, 83% were alive and

had experienced no issues with transplant rejection, and 63% were alive without having experienced any late rejection or severe graft-versus-host disease (GVHD), a condition in which the transplanted donor cells attack the recipient's body.

Sickle cell disease outcomes, which were assessed at a median of five years post-transplant, were also largely positive. Most patients (86%) remained free from sickle cell disease symptoms with hemoglobin S levels at or below 50%, and most (74%) had no sickle cell disease-related complications reported at any time point post-transplant.

Excluding infections, the most common late effects of transplant were those affecting the liver (seen in 10% of patients at seven years post-transplant), lungs (8%), reproductive organs (6%), and pancreas (i.e., diabetes; 6%). Of the 9% of patients who died, the most common causes of death were organ failure, infection, and GVHD.

Factors associated with better outcomes included being younger at the time of transplant, having a matched related donor instead of a genetically mismatched or unrelated donor, and having bone marrow instead of peripheral blood as the source of donated cells.

Remaining free of GVHD was also significantly associated with better long-term outcomes. At a median of five years, 26% of patients had experienced chronic GVHD and 30% had experienced acute GVHD, both of any severity.

Given its uniquely large sample with heterogenous transplant characteristics, researchers said that the study findings can help families and doctors make informed decisions about whether – and when – to pursue a transplant. "This study can provide more concrete data about [the risks and benefits] if transplant is undertaken early versus waiting," said Dr. Stenger. "Right now, allogeneic hematopoietic cell transplantation is the only known and available option for this population capable of eliminating the full spectrum of disease symptoms. Especially if we do it while patients are young or before the onset of organ damage, these patients can go on to live much more normal lives."

The study also underscores the importance of ongoing health monitoring following a transplant. "From a clinical standpoint, [it reinforces] the need to make sure these patients are having the recommended annual follow-up to screen and monitor for late effects so that if they are happening, we can catch them early and hopefully prevent them from becoming symptomatic and more clinically significant," said Dr. Stenger.

Since the study relied on data provided to a registry, researchers noted that the level of detail is somewhat limited for some factors.

Researchers are now working to compare survival outcomes among people living with sickle cell disease who received a hematopoietic cell transplant versus those who did not receive a transplant including those who received disease-modifying treatment. Dr. Stenger said that additional insights on potential late effects could be gained through future studies with a longer

follow-up period.

Elizabeth Stenger, MD, of Emory University School of Medicine and the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, will present this study on Monday, December 8, 2025, at 4:30 p.m. Eastern time in W331 of the Orange County Convention Center.

Study Offers Real-World Data on Commercial Implementation of Gene Therapies for Sickle Cell Disease and Beta Thalassemia
948: Accelerating access to gene therapy: Lessons from commercial implementation in sickle cell disease and transfusion-dependent thalassemia

The first study assessing the real-world commercial roll-out of gene therapies for sickle cell disease and beta thalassemia offers lessons learned to inform best practices as manufacturers and medical centers prepare to meet growing demand for gene therapies in the coming years.

"Gene therapy requires system-level coordination and close collaboration across patients, treatment centers, payers, and manufacturers," said study author Joanne Lager, MD, chief medical officer at Genetix Biotherapeutics Inc. "The demand for these one-time durable gene therapies is growing, and we're learning how to deliver treatment more efficiently as we gain more experience."

Sickle cell disease and beta thalassemia are both inherited disorders that affect the hemoglobin in red blood cells. In beta thalassemia, not enough functional hemoglobin is produced, which impacts the ability of red blood cells to carry oxygen, leading to debilitating symptoms and cumulative organ damage. In sickle cell disease, abnormal hemoglobin production causes the red blood cells to become rigid and sickle-shaped, leading to blood vessel blockages and subsequent pain and organ damage.

Betibeglogene autotemcel (beti-cel) and lovotibeglogene autotemcel (lovo-cel) are autologous ex vivo gene therapies in which a patient's own stem cells are collected, manufactured to add functional copies of a modified gene, and then infused back into the patient to engraft in the bone marrow and begin producing red blood cells with functional hemoglobin. The U.S. Food and Drug Administration (FDA) approved beti-cel for transfusion dependent beta thalassemia in 2022 under the name Zynteglo, and lovo-cel for sickle cell disease in 2023 under the name Lyfgenia.

To study the process and timing of real-world commercial implementation of these therapies, researchers analyzed data from 392 U.S. patients who enrolled to receive either beti-cel or lovo-cel between 2022 and 2025. To date, 29% (115) of these patients have received treatment, with 72% of beti-cel patients and 76% of lovo-cel patients having done so within a year of enrollment.

According to the findings, the median time elapsed from the decision to enroll and the one-time infusion of drug product was 9.8 months for beti-cel and 7.9 months for lovo-cel. Time for enrollment, scheduling, and cell collection varied across patients, with the most variability seen in the time elapsed between the decision to enroll in gene therapy and the collection of stem cells.

The median time to complete this step – during which centers prepare patients for therapy medically and financially – was 4.4 months.

Most patients required only one cell collection for both beti-cel (79%) and lovo-cel (63%), consistent with experience from clinical trials. The number of stem cell collection procedures played a role in the overall treatment timeline, with about 80 days added per collection cycle. Once stem cells were collected, the median time it took to manufacture, test, and deliver the gene therapy drug product to a treatment center was 3.2 months for beti-cel and 3.5 months for lovo-cel.

“We’ve identified areas of opportunity to enhance the treatment journey for patients and providers,” said Dr. Lager. “We recognize the importance of delivering our therapies to patients as soon as possible and remain committed to improving the treatment experience.”

The results showed some operational differences between the two gene therapies. The time between FDA approval and first commercial patient enrollment was about half as long for lovo-cel as for beti-cel. Since beti-cel was approved about 16 months before lovo-cel, the researchers suggest that early experience implementing beti-cel meant that more centers were prepared to begin treating patients with lovo-cel.

Researchers said that operational factors such as insurance approvals, the number of cell collections required, and manufacturing capacity play an important role in influencing treatment timelines. Finding opportunities for greater efficiency across these areas remains a key focus.

“Demand for our gene therapies continue to build. We are actively working toward ensuring that we have the manufacturing capacity to deliver gene therapy to all patients seeking a path to a cure,” said Dr. Lager.

The researchers noted that insurance coverage for these treatments has continued to expand. To facilitate further progress in overcoming barriers and increasing efficiency, they plan continued process improvements and collaboration with medical centers to share lessons learned and develop best practices.

Anjulika Chawla, MD, of Genetix Biotherapeutics Inc., will present this study on Monday, December 8, 2025, at 4:00 p.m. Eastern time in W311A-D of the Orange County Convention Center.

Early Results Suggest Exa-Cel Gene Therapy Works Well In Children
379: First results of exagamglogene autotemcel in pediatric patients aged 5-11 years with transfusion-dependent β-thalassemia or sickle cell disease with recurrent severe vaso-occlusive crises

Preliminary results from two trials of the gene therapy exagamglogene autotemcel (exa-cel) suggest the therapy offers an effective cure for beta-thalassemia and sickle cell disease in children younger than 12. Researchers say the therapy’s potential to offer a cure at an early age – before

organ damage accumulates – could make exa-cel even more beneficial in children than adults.

“All younger patients with sufficient follow-up met the primary endpoint of being transfusion independent in those with beta thalassemia and free of vaso-occlusive crises for those with sickle cell disease,” said lead study author Haydar Frangoul, MD, medical director of pediatric hematology/oncology at Sarah Cannon Research Institute at TriStar Centennial Children’s Hospital in Nashville, Tennessee. “A 100% success rate is rare in anything that we do.”

Exa-cel is approved for patients 12 years and older who have transfusion-dependent beta-thalassemia or sickle cell disease with recurrent vaso-occlusive crises (when blood cells become lodged in the vessels, causing severe pain and tissue damage). Both conditions are caused by genetic abnormalities that affect the ability for blood to carry oxygen throughout the body; exa-cel works by genetically modifying a patient’s own blood stem cells to correct this abnormality.

For the treatment, patients undergo a procedure to harvest their blood stem cells, which are then genetically edited in the lab using CRISPR/Cas9. The patient then undergoes a chemotherapy-based conditioning regimen to clear the bone marrow before the genetically edited stem cells are implanted back into the body, where they begin making healthy blood cells.

Researchers report preliminary results from two trials of exa-cel that are underway in children 5-11 years old. To date, the CLIMB THAL-141 trial has dosed 13 patients with beta-thalassemia, and the CLIMB SCD-151 trial has dosed 11 patients with sickle cell disease.

In CLIMB THAL-141, six of 13 patients to date have been evaluated for the primary endpoint of transfusion independence for 12 consecutive months, meaning that they maintained a weighted average hemoglobin of 9 g/dL or higher without a red blood cell infusion. All six met this endpoint. In addition, participants showed increases in hemoglobin and fetal hemoglobin production.

In CLIMB SCD-151, 4 of 11 patients to date have been evaluated for the primary endpoint of freedom from severe vaso-occlusive crises and the secondary endpoint of freedom from inpatient treatment for severe vaso-occlusive crises for 12 consecutive months. All four met these endpoints. No study participants have experienced a vaso-occlusive crisis after their exa-cel infusion to date. Increases in fetal hemoglobin production have been similar to the levels in teens and adults in previous studies, with mean total hemoglobin reaching a normal level by month six and remaining stable thereafter.

According to researchers, the results not only provide evidence that the gene therapy works in younger patients, but suggest it could be even more beneficial in this age group. “We think treating them at an earlier age may be better because you could potentially prevent some irreversible complications that lead to chronic issues,” said Dr. Frangoul.

Based on experiences to date, the safety profile of the therapy in these pediatric trials also appears to be consistent with trials in adolescents and adults and with the known side effects and complications associated with autologous stem cell transplantation and busulfan conditioning. One

study participant in CLIMB THAL-141 developed severe veno-occlusive disease, related to busulfan, with fatal multi-organ failure. Veno-occlusive disease is a known risk of busulfan that occurs more frequently in children. Despite several decades of research on busulfan and alternative conditioning regimens in the context of stem cell transplantation, there is no known strategy to completely eliminate this risk.

The CLIMB THAL-141 and CLIMB SCD-151 trials will continue to accrue participants and track outcomes to assess the safety and efficacy of the therapy over a longer period of time and in a larger patient group. Dr. Frangoul noted that a future study could test the therapy in children two to four years old.

The CLIMB THAL-141 and CLIMB SCD-151 trials are sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics.

Haydar Frangoul, MD, of Sarah Cannon Research Institute at TriStar Centennial Children's Hospital, will present this study on Saturday, December 6, 2025, at 4:00 p.m. Eastern time in W320 of the Orange County Convention Center.

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