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TOP ABSTRACT
ORAL PRESENTATIONS

Presenting: Saturday, June 17, 2023
8:30 AM

CREATININE OUTPERFORMS CYSTATIN C-BASED EGFR EQUATIONS IN ADULTS WITH SICKLE CELL DISEASE

Authors: Mauricio Barreto, M.D.[1], Emily Limerick, M.D.[2], Neal Jeffries, Ph.D.[2], Julia Varga, RN, MN, CCRC[2], Ahmed M. Gharib, M.D.[3], Maureen Clark, MS, MLS[3], Helen Looker, MBBS[3], Robert Nelson, M.D., Ph.D.[3], Howard A. Austin III, M.D.[3], Meryl Waldman, M.D.[3], Courtney Fitzhugh, M.D.[2]

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Background: Sickle cell disease (SCD) progressively alters kidney structure and function, increasing morbidity and mortality. In the setting of recurrent and chronic renal tubular injury unique to SCD, established estimating equations to determine glomerular filtration rate (GFR) have limitations in this patient population, partly due to increased tubular creatinine secretion and reduced muscle mass. This study compares estimated GFR (eGFR) derived from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C (Cys)- and creatinine (Cr)-based equations with iothalamate measured GFR (mGFR) to determine the noninvasive marker of kidney function in adults with SCD that most accurately reflects mGFR. We also examine the correlation of renal blood flow measured by MRI and a biomarker of tubular function and inflammation, β2 microglobulin (B2M), to mGFR.

Methods: Adults with SCD were recruited from the outpatient setting. Patients were free of vaso-occlusive crises with an eGFR > 30 ml/min/1.73m2. eGFR was calculated using the 2009 CKD-EPI Cr, 2012 CKD-EPI Cys, 2021 CKD-EPI Cr-Cys, and the 2021 CKD-EPI Cr equations; 2021 equations exclude race in the estimation. mGFR was obtained via the plasma decay method. Pairwise comparisons of the equations were made using the Wilcoxon signed rank test to evaluate the absolute value of the discrepancies between the estimated and mGFR. Bland Altman plots visually assessed the agreement and bias of different methods. Spearman correlations determined the association between renal blood flow and B2M with mGFR.

Results: Sixty-seven patients with SCD completed study laboratory evaluations (Male: 39, Female 28; median age 37 (Q1: 28, Q3 43.5); HbSS: 64, HbSβ0-thalassemia: 3). Most were on stable hydroxyurea doses (76%, n=51), and 22% (n=15) were on renin-angiotensin-aldosterone system inhibitors. Our cohort had a median mGFR of 124 mL/min/1.73 m2 (Q1: 102, Q3: 153, Range: 75 - 214) and a median urinary creatinine clearance of 142 mL/min (Q1: 102, Q3: 173). Of the estimating equations, the 2009 Cr-based equation had the lowest median absolute values of discrepancy: 25.6 mL/min/1.73 m2, followed by 2021 Cr: 26.4, 2021 Cr-Cys: 28.8, and 2012 Cys: 33.8. The 2012 Cys based equation was outperformed by all eGFR equations that used Cr in their estimations, $p < .05$ for all comparisons (Figure 1). Compared to the Cr-based estimates, both Cys-based equations produced higher discrepancies with a bias to under-predict mGFR when restricting the analysis to the subset of patients with albuminuria. Serum B2M ($r = -0.45$, $p = 0.0002$) showed a moderate negative correlation with mGFR. Finally, average renal blood flow positively correlated with mGFR ($r=0.34$, $p=0.009$) (Figure 2).

Conclusion: Of the four estimating equations, the 2012 Cys- based eGFR had the highest bias, lowest agreement, and highest absolute values of discrepancy with mGFR. These data suggest that Cys-based eGFR is inferior to Cr-based eGFR for reflecting mGFR in adults with SCD and preserved kidney function/hyperfiltration. The heightened chronic

inflammatory state in SCD may contribute to increased Cys concentrations, thereby underestimating eGFR and increasing the discrepancy. While prior data suggest Cys may have a role in predicting kidney disease progression, its accuracy at predicting mGFR in this population is limited. All equations showed increased bias to under-estimate mGFR when < 100 mL/min/1.73 m2 and in states of glomerular hyperfiltration (GFR > 150 mL/min/1.73 m2), a compensatory mechanism that occurs early in the development of sickle nephropathy. A larger dataset in patients with lower mGFR between 30-90 mL/min/1.73 m2 and longitudinal evaluations may better define the most accurate equations to assess kidney function in adults with SCD throughout the various stages of chronic kidney disease. Finally, increasing serum B2M and decreasing renal blood flow significantly correlated with worsening mGFR, suggesting their importance as potential early sickle cell nephropathy markers.

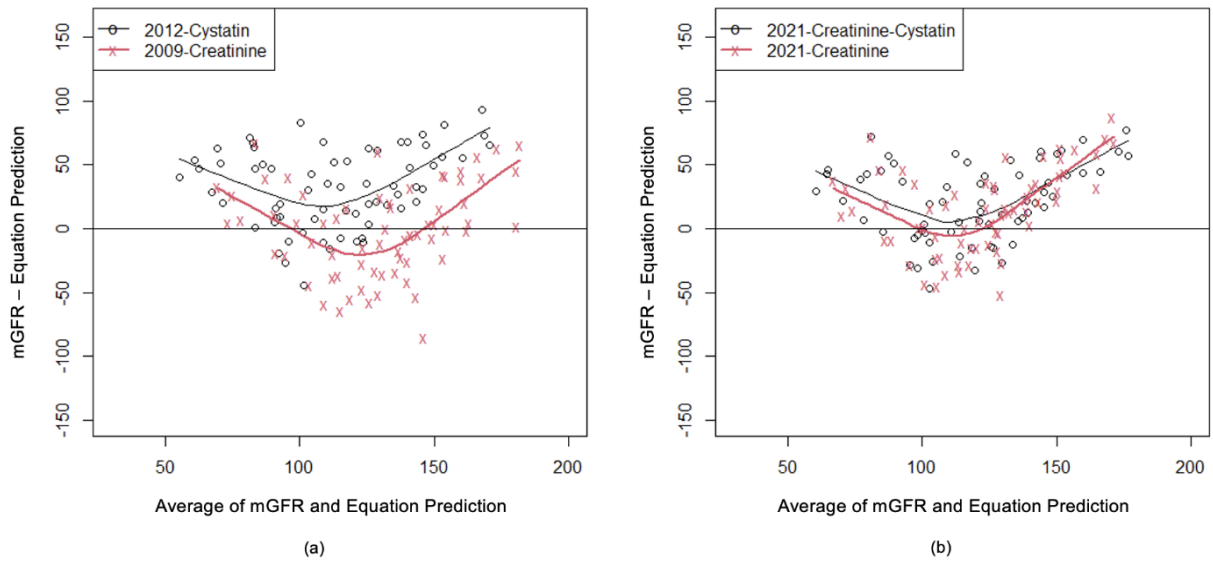

Figure 1.
Bland-Altman Plots for mGFR and (a) Cystatin 2012, Creatinine 2009 Measurements (b) Creatinine-Cystatin 2021, Creatinine 2021 Measurements (mL/min/1.73 m2)

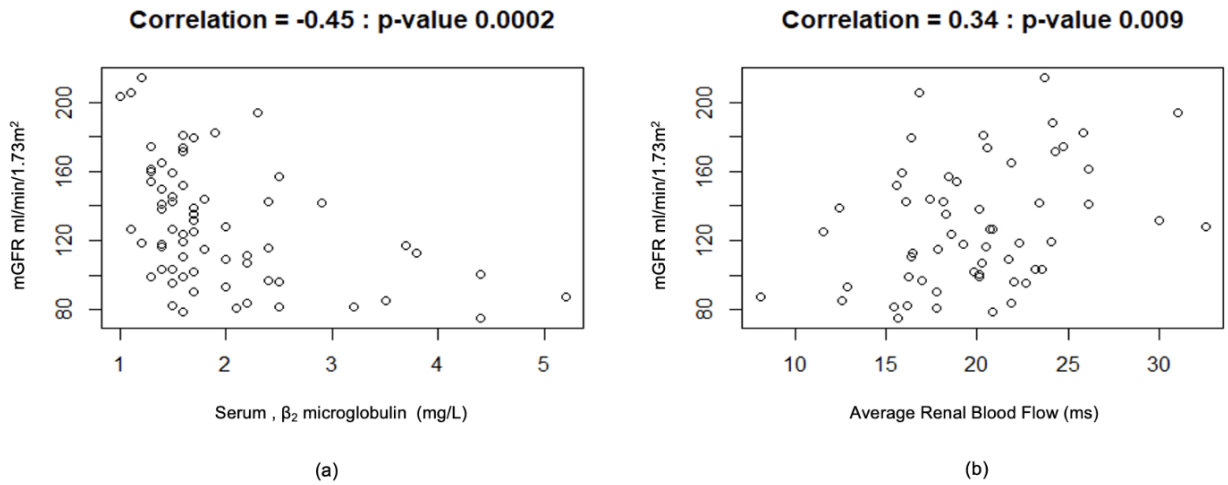

Figure 2.
Pearson Correlations between mGFR (mL/min/1.73 m2) and (a) Serum β2 microglobulin (mg/L) (b) Average Renal Blood Flow (ms)

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Background: A SCD HCT learning collaborative (SCD-LC) engaged 14 pediatric and adult paired sites (including community participation) using a standardized quality improvement (QI) process. Monthly virtual meetings provided coaching on clinical recommendations, QI methods, and practical implementation of Six Core Elements of HCT (6CE). We report here the results of this 5-year multi-stakeholder collaborative effort.

Methods: Implementation of 6CE was measured across 14 clinical sites (each site comprised of both pediatric and adult clinics) who care for 1625 individuals aged 16-25. Clinical programs varied: 12 urban, 2 rural; 12 academic, 2 non-academic; 6 small, 8 large. The HCT Process Measurement Tool (HCT-PMT) assessed 6CE implementation adherence using iterative QI strategies at baseline (2018) and every six months thereafter for 4.5 years (54 months). Pre-post results were compared for overall group and by type of practice.

Results: All 14 sites made substantial progress towards implementing a structured HCT process within 54 months. Overall HCT-PMT scores increased over time from 19.4 (SD 14.1) at baseline to 97.4 (SD 5.2) at 54 months. Pediatric site scores increased significantly from 24 (baseline) to 98.9 (54 months). Adult site scores also increased from 15 (baseline) to 95.8 (54 months). Pediatric sites scored higher at each assessment interval compared to adult sites. Large sites showed increased scores from 21 (baseline) to 97 (54 months) while small sites increased from 18 (baseline) to 98 (54 months).

Conclusions: All 14 pediatric and adult sites demonstrated significant progress with implementing a structured HCT process aligned with the 6CE within 54 months using quality improvement. This process can be applied to all genetic diseases and should be further explored.

JSCDH-D-23-1524863

PAIN SCREENING IN SICKLE CELL YOUTH (PASSKEY)

Authors: Dennis Vroom, MS[1], Samuel N. Rodgers-Melnick, MPH, MT-BC[2], Tracie Brown, CNP[3], Amma Owusu-Ansah, MD[3], Jeffery Dusek, PhD[2]

Affiliation: *[1]Case Western Reserve University, [2]University Hospitals Connor Whole Health, [3]University Hospitals Rainbow Babies and Children's Hospital*

Background: Children and adolescents with sickle cell disease (SCD) face several challenges as they age. Many of these challenges are related to pain as pain frequency, duration, and severity often increase as children with SCD age into adolescence. Though prior studies have 1) characterized pain frequency, duration, and risk factors for chronic pain and 2) described use of integrative health and medicine (IHM) modalities among youth with SCD, few studies have described the implementation of pain screening within real-world clinical practice to identify patients at risk for chronic pain and understand their resources and preferences for engaging in IHM modalities. Thus, the purpose of this study was to 1) determine the feasibility of routine comprehensive chronic pain screening within a pediatric SCD clinic; 2) identify and describe youth with SCD and chronic pain; and 3) understand preferences and resources related to engaging in IHM modalities for pain.

Methods: During routine visits to the outpatient hematology clinic, patients ages 8-18 with SCD were asked to complete measures of pain frequency and duration followed by the Pediatric Pain Screening Tool (PPST). Participants screening positive for 1) persistent pain (≥ 15 days of pain per month with duration of pain frequency < 6 months); 2) chronic pain (≥ 15 days of pain per month with duration of pain frequency ≥ 6 months); 3) medium risk for chronic pain (PPST total score ≥ 3, psychosocial score < 2); or 4) high risk for chronic pain (PPST total score ≥ 3, psychosocial score ≥ 2) were asked to complete the Pain Catastrophizing Scale – Child, the PROMIS Pain Interference 4a, and a survey regarding interest in and resources for engaging in IHM modalities. Providers utilized REDCap surveys administered via iPads to obtain patient data. Utilizing the REDCap system allowed for auto-scoring of pain classification (i.e., asymptomatic, episodic, persistent, or chronic), chronic pain risk category (i.e., low, medium, or high risk), and the generation of a pre-populated note, which was copied into the electronic health record (EHR) following screening. The following data were collected from patients' records: demographics, clinical characteristics (e.g., genotype and use of disease modifying therapies), referrals to specialty providers, healthcare utilization in last year, and analgesia prescriptions. Data analysis was limited to descriptive statistics of completed baseline screenings over the first year of the study.

Results: Between March 2022 and April 2023, 91/139 (65.5%) patients who attended at least one outpatient visit completed an initial screening. Patients (mean age 12.31 ± 3.13, 64.0% HbSS) were predominantly Black/African American (99.0%) and Non-Hispanic (99.0%), female (53.0%), and receiving hydroxyurea (62.6%). Of the 91 patients screened, 49 (53.8%) reported persistent or chronic pain or were at medium or high risk for chronic pain. Patients within this group reported overall mean pain interference scores of 53.0 ± 9.3, with higher mean scores among the chronic pain group (56.8) as compared to the asymptomatic group (45.1). Total pain catastrophizing scores increased by chronic pain risk, with the high-risk group reporting higher mean pain catastrophizing (30.3) than the low-risk group (19.7). Patients completing the survey on IHM modalities expressed highest interest music therapy (54.3%), art therapy (52.2%), and massage therapy (39.1%), preferred in-person (84.8%) over virtual

programming (23.9%), and mostly had smartphones for accessing virtual programs (76.1%)

Conclusions: Routine comprehensive pain screening is feasible within pediatric SCD care. Feedback from providers demonstrated that screening was a useful tool for detecting experiences such as pain catastrophizing that had not been reported in prior clinical assessments. This information was found at times to be novel data to parents and caregivers and served to add depth to the their understanding of patients' pain. Classifying patients by chronic pain risk also provided a means of triaging patients to appropriate services (e.g., psychiatry, music therapy, and other IHM modalities) and engaging patients in early intervention to address psychosocial factors related to risk of developing chronic pain.

DR. KWAKU “KOF” OHENE-FREMPONG EAST MEETS WEST GLOBAL SICKLE CELL DISEASE SYMPOSIUM

Presenting: Sunday, June 18, 2023
10:15 AM - 11:15 AM

JSCDH-D-23-1547603

SICKLE CELL HEALTH AWARENESS, PERSPECTIVES AND EXPERIENCES SURVEY: US PATIENTS/CAREGIVERS

Authors: Alan Anderson, MD[1], Regina Hartfield, BA[2], John James, OBE[3], Biba Tinga, MS[4], Elvie Ingoli[5], Mariane de Montalembert, MD, PhD[6], Fernando F. Costa, MD, PhD[7], Wasil Jastaniah, MBBS[8], Joachim B. Kunz, MD[9], Isaac Odame, MD[10], Belinda Lartey, MSc[11], Baba PD Inusa, MD[12]

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Background: Sickle cell disease (SCD) substantially impacts the physical and emotional well-being of patients and their caregivers, yet research into the impact of SCD on quality of life is limited. SCD affects an estimated 100,000 people in the US, occurring in 1 in ~365 Black/African American births and 1 in ~16,300 Hispanic American births. The Sickle Cell Health Awareness, Perspectives and Experiences (SHAPE) survey aims to improve our understanding of the global impact of SCD on patients and their caregivers. This analysis reports survey findings from the US within the context of insights obtained globally.

Methods: SHAPE was an online, 12-minute survey of patients and caregivers from the US, the UK, Germany, France, Brazil, Canada, Saudi Arabia, the United Arab Emirates, Bahrain, and Oman (patients only). Patients with SCD aged ≥12 years and caregivers aged ≥18 years supporting a patient with SCD were eligible. Participants answered close-ended questions regarding their circumstances and experiences with SCD, with the aim to build a robust and reliable dataset on which descriptive statistics were performed.

Results: Of 919 patients and 207 caregivers globally who responded, 295 patients and 30 caregivers were from the US. Fatigue/tiredness (84%) and vaso-occlusive crises (VOCs; 71%) were the symptoms most frequently reported in the past year by patients from all 10 countries; in the US, 80% reported fatigue/tiredness and 75% reported VOCs, comparable with all surveyed patients. Symptoms reported more frequently by US patients than by all patients were poor sleep (74% vs 60%), joint stiffness (63% vs 50%), poor appetite (48% vs 39%), and nausea (45% vs 37%). The average number of missed days of school/work in the past month was similar among US patients and all patients (6.4 vs 7.5 days) but was higher for US caregivers compared with all surveyed caregivers (7.9 vs 5.0 days). SCD symptoms that most impacted caregivers' lives in the US and globally were fatigue/tiredness (50% vs 49%) and VOCs (53% vs 43%); US caregivers reported a higher impact of poor sleep (30% vs 12%) and a lower impact of generalized pain (3% vs 20%) compared with all caregivers. More than half of US caregivers agreed that caring for someone with SCD affected their mental health (63% vs 52% globally) and ability to attend and succeed at school/work (70% vs 56% globally). Caregivers in the US were more optimistic

vs all caregivers about the future of the person they care for with SCD (83% vs 62%).

Conclusions: SHAPE survey findings provide insights into the broad impact of SCD on patients and caregivers in the US. Areas that need more support or improvement include treatments to address patient symptoms such as fatigue and VOCs and resources to improve health and well-being of patients and caregivers. Overall, these insights highlight areas that require improved patient and caregiver support in the US.

ABSTRACT BREAKOUT SESSION I
PSYCHOSOCIAL

Presenting: Sunday, June 18, 2023
1:15 PM - 2:45 PM

JSCDH-D-23-1529058

ACCESS TO MENTAL HEALTH SERVICES FOR SICKLE CELL PATIENTS USING MULTIDISCIPLINARY CLINIC

Authors: Charlene M. Sylvestre, MSN, MSW, NP-C, RN, CCAP

Affiliation: *Boston Medical Center/Boston University*

Background: The Center for Excellence in Sickle Cell Disease (SCD) at Boston University/Boston Medical Center (BMC) is the largest in New England, treating over 600 patients. Depression and Anxiety in the SCD population is 2-3 times higher than the national average with 35% of patients affected. Sickle cell patients with depression have higher mean healthcare costs versus patients without an affective disorder diagnosis. There is a high correlation between depression and low quality of life scores in the sickle cell population.

Methods: The majority of our adult SCD patients are seen in our multidisciplinary clinic (multi-D) where they have access to Hematology, Pulmonology, Nephrology, and Primary Care visits. Patients are more likely to see multiple disciplines in this setting as it is their Hematology "home". When referring patients to the Behavioral Health Center at BMC, the earliest time to first appointment averaged 10-16 weeks. Many patients who waited for these appointments would not show up when the time came, despite having ongoing symptoms of depression. In the fall of 2021 Behavioral Health hired a full-time clinician specifically for patients with chronic diseases, which prompted us to petition for 8 hours/week of services. The Psychologist would be in our multi-D clinic 4 hours per week for therapy sessions and would round with the Sickle Cell Team weekly- using the remaining time to visit with the inpatient population.

Results: Patients were more receptive to attending therapy sessions in the multi-D clinic well as remotely via video with our Psychologist. The majority of our SCD patients with depression who requested therapy engaged with this Psychologist 75% of the time versus approximately 50% when referred to the Behavioral Health Clinic.

Conclusions: Patients with a chronic, painful disease (SCD) have a higher risk of developing depression than the general population. In the sickle cell population, depression correlates to low scores on quality of life inventories and higher usage of acute medical services. Imbedding a mental health professional in our multi-D clinic allows for a warm hand off to psychological services and better access to care. In the 18 months since we recruited this Psychologist into our clinic, the demand for mental health access continues to escalate. We are currently in the process of recruiting a Social Worker with a specialty in counseling to add more visits for psychological support in the multidisciplinary setting.

JSCDH-D-23-1547915

A PATIENT PERSPECTIVE TO ADDRESSING CHALLENGES AT EDs THROUGH A FAITHBASED EDUCATION FORUM

Authors: Dominique C. Friend, Associate Degree, Inhua Chen, PHD

Affiliation: *Sickle International Family Coalition*

Background: The factors contributing to poor treatment care at Emergency Departments (EDs) for the SCD community have been well documented. A "cycle of distrust" epitomizes the problem as lack of understanding by healthcare professionals feed the distrust experienced by many SCD patients, leading to ineffective communication, negative provider attitudes and aggressiveness and disrespect by patients. Despite the intervening years since these first reports, many of the problems remain intact. To address these challenges, a two-year pilot project was initiated in collaboration with QSource and funded by the Centers of Medicare and Medicaid Services to respond to the factors that impede improved care delivery at ED during pain crises from a patient perspective.

The project entailed the application of faith-based educational events (Community SCD Learning and Action Networks (LANs)) to address foremost existing misunderstandings and/or lack of knowledge relating to disease burden, patient needs and preferences, and acute complications during time of pain crises, by providers, particularly those present in the EDs.

Methods: A qualitative approach was applied to leverage a patient- and faith-based approach to addressing barriers and challenges faced by sickle cell patients at EDs. This patient engagement strategy incorporated 4 in-person events and 4 webinar-like events at various geographical locations in the United States to educate and increase awareness of the plight of SCD patients at EDs. Two hundred stakeholders participated in the faith-based educational events. Stakeholders included patients, caregivers, physicians, healthcare professionals, interested community members and researchers.

Results: The patient perspective study uncovered three main themes of importance to the sickle cell community when addressing suboptimal care at EDs. These themes included dismantling stereotypes, supporting patient power, and emphasizing collaborative accountability. Among the survey respondents, an overwhelming positive evaluation (>75%) of the workshops and webinars was observed. The survey assessed three components, including (1) Part I which focused on the relevance of the content presented; (2) Part II which evaluated the faith-based methodology as an effective education tool, and (3) Part III which alluded to awareness of SCD challenges and collaborative accountability by all stakeholders to ensure high-quality care at EDs. Faith as a foundation for hope and perseverance was an important component to the satisfaction, motivation, and enthusiasm of those who attended the workshops and webinars.

Conclusions: The faith-based education series highlights the effectiveness of patient-driven education where "patient to patient" dissemination of knowledge is optimal when trust is implicit. In three months, over 200 patients and other stakeholders were assembled to discuss novel ways to work together "to move the needle," from a pragmatic and "realistic" approach. A clear conclusion of this work is the appreciation that the burden of better care at EDs stems from a collaborative accountability perspective. As such, the workshops aimed to uncover pragmatic tactics that patients can embrace to ensure that positive outcomes are attained at EDs. Awareness of the NHLBI and ASH guidelines was an important element reinforced throughout the education forum. In the age of doctor-patient shared decision-making, improvement of health outcomes is

based on collaborative, positive engagement by both physicians and patients. A new campaign “Rise up Ready” and “Do no Harm” has been formed to further implement the learnings from this study into actionable actions that can lead to better informed health decisions and improved, meaningful, and relevant health outcomes for sickle cell patients at EDs.

JSCDH-D-23-1512894

BUILDING A COLLABORATIVE CULTURE AMONG NORTHEAST SICKLE CELL COMMUNITY-BASED ORGANIZATIONS

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Background: As part of HRSA's Treatment Demonstration Project, a group of community-based organizations (CBOs) in the Northeast Region sought to establish and strengthen connections with each other and with providers in order to improve access to and quality of care for sickle cell patients and their families. The SiNERGe (Sickle Cell Improvement in the Northeast Region through Education) collaborative includes efforts in 13 states, the District of Columbia, the U.S. Virgin Islands, and Puerto Rico. Given the urgent, long-standing, unmet needs of sickle cell patients, partnerships and collaborations are essential for CBOs - many of which are small, resource-constrained organizations - to effectively provide direct services and support, replicate best practices, and amplify advocacy efforts.

Methods: Our approach to building collaborative relationships was informed by the collective impact model, which emphasizes five conditions: a backbone support organization, a common agenda, continuous communication, mutually reinforcing activities, and shared measurement systems. Executive Directors of the participating CBOs and/or their designees participated in regularly-scheduled conference calls, punctuated by annual opportunities to meet in-person. The backbone organization provided overall coordination and leadership for the effort, and acted as a liaison with SiNERGe leadership, provider organizations, and the HRSA Newborn Screening Program (NBS) Grantee. Participation in the collaborative was voluntary and did not conflict with CBO's existing memberships or affiliations.

Results: Key elements of the culture that evolved as the SiNERGe CBOs interacted were:

- Share learning – Information, insights, practices, and approaches were disseminated among the group.
- Share leadership – Opportunities to lead projects and processes were distributed among the CBO leaders.
- Share resources – Opportunities to obtain financial support were provided to participating CBOs.
- Develop talent – An emphasis was placed on acknowledging and supporting expertise by offering regional roles to interested leaders.
- Celebrate – Accomplishments were recognized, honored and celebrated.
- Honor the whole person – Interactions took place with a recognition of the multiple roles the leaders occupy.
- Have the group set the priorities and pace – The nature and timing of the work was determined by the group rather than by the backbone organization or providers.
- Accept challenges – Complications, both task-oriented and people-oriented, were acknowledged and processed with an emphasis on their long-term, group-level impact.
- Focus on abundance – Competition, though present, was de-emphasized by a focus on

the larger picture and availability of additional resources, roles, funds, opportunities, and recognition.

- Balance shared vision with varied implementation – Consensus-based goals and objectives included wide discretion for CBOs to enact those goals in ways that worked for their organizations, patients, and communities.
- Set high standards - A commitment to high-quality work was balanced with the importance of cultivating a safe space for "failing forward."
- Encourage innovation - New and creative ideas were welcomed, incubated, and replicated.

Key projects launched by the SiNERGe CBOs were:

- Shine the Light on Sickle Cell – Shine the Light is a day of community action on World Sickle Cell Day (June 19), began in 2019 with 40 participating organizations in 21 states and 1 country (outside the US), and grew in 2022 to 149 participating organizations in 29 states and 21 countries.
- CBO Project ECHO –Building upon the success of the provider ECHO sessions, the CBOs launched a regional CBO ECHO in 2018 and now have three CBO ECHOs in the region.
- Unaffiliated Patients – The group recently launched an effort to locate patients who have not been seen by a hematologist and/or CBO for a year or more.

The size of the SiNERGe CBO collaborative has expanded from 14 CBOs in 2014 to 30 CBOs in 2023. Since its inception the SiNERGe CBOs have also collaborated with the HRSA NBS Grantees. Currently, NBS grantees who also participate in SiNERGe CBO activities have introduced the collective impact model to their peer organizations across the U.S.

Conclusions: Intractable challenges in serving the sickle cell community make it necessary that small, resource-constrained community-based organizations work effectively together and with providers in order to bring about improved care for patients. Being intentional about the culture of collaboration can provide a foundation for results that exceed those that any one organization can accomplish – thus amplifying the positive impact on our capacity to serve patients and their families.

JSCDH-D-23-1525198

DEPRESSION IS ASSOCIATED WITH PAIN AND OPIOID MISUSE AMONG ADULTS WITH SICKLE CELL DISEASE

Authors: Charles Jonassaint, PhD MHS[1], Ektha Parchuri, MPH[2], Julia A. O'Brien, PhD, RN[3], Dima Hendricks, MA[1], Jonathan Lim, MS[1], Jude Jonassaint, RN[1], Michelle Quallich Lancet, BS[1], Christina Lalama, MS[2], Kaleab Adebe, PhD[1]

Affiliation: *[1]University of Pittsburgh, [2]University of Pittsburgh School of Medicine, [3]School of Nursing, University of Pittsburgh*

Background: Patients with sickle cell disease (SCD) experience both acute and chronic pain symptoms, leading to a disproportionately high use of health care resources. Depressive symptoms, including social isolation, defiance, feelings of helplessness, depressed mood, and suicidality, are frequently seen among both children and adults with SCD. Although the studies exploring depression and SCD are limited, there is evidence suggesting that depressive symptoms may increase patient risk for poor disease outcomes, particularly pain. The relationship between pain and depression is reciprocal; pain also contributes to increased risk of depression and negative affect. Despite this hypothesized association between depression and pain in SCD, there are few large studies examining the link between depressive symptoms and pain, and pain related outcomes. Therefore, the objective of this study was to test whether depressive symptoms are associated with average daily pain intensity, quality of life, and pain symptoms, in a large cohort of adults with SCD. We hypothesized that higher depressive symptom scores would be associated with more severe pain outcomes, pain catastrophizing, pain interference, and opioid misuse.

Methods: We performed a secondary analysis on baseline data from the "Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell via Mobile Application (CaRISMA)" Trial. This was a multisite randomized, controlled trial in adults (age 18yrs+) with SCD and chronic pain (i.e., pain at least 4 days/week for > 3 months, and/or being prescribed long-acting or daily opioid pain medication). Eligible patients were randomized 1:1 to either digital cognitive behavioral therapy or digital education. Both arms received at least 12 weeks of health coach support. At baseline, participants completed a battery of questionnaires and tracked their pain intensity (0-10 visual analog scale) and mood daily via a mobile app. For the purposes of analyses, participants were categorized into "high" (PHQ ³ 10) and "low" (PHQ < 10) depression. Baseline characteristics and demographics were compared between groups, and multivariable regressions were used to estimate covariate-adjusted associations with the following outcomes at baseline: daily pain, PROMIS Pain interference scale, Pain Catastrophizing Scale (PCS), Current Opioid Misuse Measure (COMM-9), and Adults Sickle Cell Quality of Life Measurement Information System (ASCQ-ME) pain severity and frequency.

Results: The trial enrolled 357 adults, mean age 36.3 (10.5), 66% female, 93% Black race. Mean PHQ score was 10 (SD=5.0; range 0-27) with 31(9%) respondents endorsing the item that indicates suicidal ideation. We compared baseline demographics, and pain and quality of life outcomes by depression group and found significant between-group differences for ethnicity, baseline suicidal ideation (PHQ-9), baseline anxiety (GAD-2 >0), and site (Table 1). PHQ score was associated with all outcomes in univariate analyses (all p< 0.01). After adjusting for the above covariates, depressive symptoms remained significantly associated with higher daily pain (B=0.096) intensity, less positive daily mood (B=-0.005), higher pain interference (B=0.572) and catastrophizing

(B=0.309), higher ASCQ-Me pain frequency (B=0.5043) and severity (B=0.456), and higher likelihood of opioid misuse (B=0.4919; all $p < 0.01$).

Conclusions: As hypothesized, patients with SCD reporting more severe depression were more likely to also report poorer pain outcomes, quality of life, and opioid misuse. This study confirms and extends prior studies showing poorer pain outcomes among depressed patients with SCD. Analysis of longitudinal data from this trial will help us determine whether treating depressive symptoms can decrease pain frequency and severity in SCD.

Table 1. Baseline demographics, pain variables, quality of life and opioid misuse by PHQ-9 depressive symptoms group

			PHQ depression group		
Characteristic		**Total** (N=357)	**Low** (PHQ<10) (N=216)	**High** (PHQ ≥10) (N=141)	**P-Value**
Age at baseline (years)	Mean (s.d.)	36.3 (10.5)	36.7 (10.9)	35.8 (9.9)	0.632 (a)
Gender	Male	118 (33%)	79 (37%)	39 (28%)	0.155 (c)
	Female	237 (66%)	136 (63%)	101 (72%)	
	Prefer not to answer	2 (1%)	1 (0%)	1 (1%)	
Ethnicity	Hispanic/Latino	15 (4%)	6 (3%)	9 (6%)	0.046 (b)
	Not Hispanic/Latino	306 (86%)	193 (89%)	113 (80%)	
	Unknown	36 (10%)	17 (8%)	19 (13%)	
Education	Some high school	22 (6%)	10 (5%)	12 (9%)	0.253 (b)
	High school grad	69 (19%)	40 (19%)	29 (21%)	
	Some college	159 (45%)	94 (44%)	65 (46%)	
	College grad	60 (17%)	38 (18%)	22 (16%)	
	Graduate studies	47 (13%)	34 (16%)	13 (9%)	
Employment status	Yes, employed	130 (36%)	89 (41%)	41 (29%)	0.066 (b)
	No, not employed	63 (18%)	35 (16%)	28 (20%)	
	Disability	164 (46%)	92 (43%)	72 (51%)	
Suicidal ideation (PHQ item # 9)	Yes	31 (9%)	6 (3%)	25 (18%)	<.001 (b)
GAD-7 Anxiety Severity	Minimal (0-4)	46 (18%)	42 (35%)	4 (3%)	<.001 (b)
	Mild (5-9)	112 (45%)	63 (53%)	49 (38%)	
	Moderate (10-14)	61 (24%)	13 (11%)	48 (37%)	
	Severe (15-21)	30 (12%)	2 (2%)	28 (22%)	
	Did not complete	108	96	12	
Average pain intensity (2-week period)	Mean (s.d.)	4.4 (2.5)	3.9 (2.5)	5.1 (2.4)	<.001 (a)
Proportion of days in happy mood (2-week)	Mean (s.d.)	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.050 (a)
PROMIS: Pain Interference (T-score)	Mean (s.d.)	62.6 (7.1)	60.0 (7.3)	66.4 (4.7)	<.001 (a)
ASCQ-Me: Pain Episode Freq (T-score)	Mean (s.d.)	48.3 (12.3)	46.5 (12.5)	51.0 (11.6)	<.001 (a)
ASCQ-Me: Pain Episode Severity (T-score)	Mean (s.d.)	47.2 (13.4)	45.3 (13.8)	50.2 (12.0)	<.001 (a)
ASCQ-Me: Social Funct. Impact (T-score)	Mean (s.d.)	47.3 (7.9)	50.2 (7.6)	42.8 (6.0)	<.001 (a)
ASCQ-Me: Emotional Impact (T-score)	Mean (s.d.)	48.0 (8.8)	52.0 (7.6)	42.0 (7.0)	<.001 (a)
Pain Catastrophizing Scale score	Mean (s.d.)	9.3 (4.1)	8.0 (4.1)	11.3 (3.3)	<.001 (a)
Current Opioid Misuse Measure score	Mean (s.d.)	8.8 (5.4)	6.8 (4.5)	11.9 (5.3)	<.001 (a)

(a) Wilcoxon Test, (b) Chi-Square Test, (c) Fisher's Exact Test

JSCDH-D-23-1521192

TESTING A TAILORED DIGITAL MENTAL HEALTH PROGRAM FOR SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a chronic, genetic disorder that affects 100,000 Americans, predominantly of African ancestry. Adolescents and young adults with SCD are at high-risk to develop depression and anxiety, during a critical period in which they are building disease-related self-efficacy and are transitioning to the adult care team. Depression and anxiety among these patients are associated with more disease-related complications, poorer health outcomes, and decreased quality of life. It is crucial, therefore, that the mental health of patients with SCD is routinely screened, and that access to effective mental health treatment is provided in a timely manner using engaging platforms. Digital cognitive behavioral therapy (CBT) is an effective treatment for depression and anxiety; however, African American patients are not only less likely to receive digital CBT, but also are less engaged compared to non-minority groups. Personalization and tailoring digital CBT to the unique experience of SCD may be key to increasing treatment uptake, thus improving both mental and physical health outcomes. To bridge this gap in treatment of depression and anxiety in adolescents and adults with SCD, a mobile app that delivers digital CBT and provides a health coach was tailored specifically for patients with SCD. This study evaluated the effectiveness of these personalized treatments on anxiety, depression, and self-efficacy compared to the standard digital CBT treatment.

Methods: Adolescents and young adults with SCD ages 16 – 35 were recruited from the University of Pittsburgh Medical Center (UPMC) Children's Hospital and Adult Benign Hematology Clinic. Eligibility was determined by a mental health screener, and patients who had moderate to severe scores on the Patient Health Questionnaire 9 (PHQ-9) and/or Generalized Anxiety Disorder Scale (GAD) were approached for consent. Patients who agreed to enroll in the study were randomized either to the standard digital CBT treatment provided by UPMC's health system, or to an enhanced digital CBT app tailored towards minorities living with SCD (the PLUS group). Depression, anxiety, and sickle cell self-efficacy were measured prior to receiving digital CBT at baseline (T1) and a minimum of eight weeks post exposure (T2). To determine app engagement, we monitored the amount of CBT techniques completed and the amount of communication between the participant and their health coach. Dependent and independent T-tests were used to compare the improvement in depression, anxiety, and self-efficacy in both groups from T1 to T2, and to evaluate whether there was a significant difference in the change in scores between group. Descriptive statistics were used to explore engagement.

Results: Twenty-one eligible patients with SCD (standard group n = 11, PLUS group n = 10) were recruited, however only 19 completed the T2 interview (standard group n = 11, PLUS group n = 8). The standard and PLUS groups had similar numbers of male (36.4% and 36%, respectively) and female patients (63.6% and 70%, respectively). The PLUS group engaged with the app more frequently (M = 8.50 times) than the standard group (M = 5.64), but 40% of the PLUS group and 36.4% of the standard group only used the app once during the study period.

In addition, the PLUS group had significantly lower depression and higher self-efficacy scores at T2, whereas there were no significant changes in the standard group. Neither group had significantly improved anxiety scores post digital CBT treatment.

Conclusions: The patients in the PLUS group who received a tailored digital CBT intervention had higher engagement and significant improvements in their depression and self-efficacy, compared to the standard digital CBT group. Due to the limited sample size and poor overall engagement with the study and intervention, the study results should be interpreted with caution. Further research will be needed to confirm whether tailoring digital CBT is critical to improving engagement, and how tailoring improves health outcomes in patients with SCD. Nevertheless, tailoring digital CBT interventions to adolescents and young adults with SCD has great potential to improve engagement and effectively address their mental health needs and self-efficacy.

Demographics Table

Enrolled in study	**Standard (n=11)**	**PLUS (n=10)**	P value
Age (mean)	22.73	20.70	.464
SD	6.0	6.43	
Min-Max	16-35	16-34	
Gender			>.999
Male	36.4%	30%	
Female	63.6%	70%	
Education			
Some High School	36.4%	40%	.670
High School	27.3%	40%	.633
Some College	27.3%	10%	.586
College	9.1%	0%	>.999
Graduate	0%	10%	.476
Employment			
Yes	54.5%	30%	.387
No	45.5%	60%	.670
Other	0%	10%	.476

T-tests Comparing Standard and PLUS Groups

	Standard Arm				PLUS				Comparison
Variables	Pre	Post	Diff	P Value	Pre	Post	Diff	P Value	P Value
PHQ-9	11.18	10.09	1.091	.523	12.50	6.75	5.750	.016	.078
GAD	9.27	8.91	.364	.789	8.43	3.14	5.286	.128	.170
SCSES	29.70	31.30	-1.600	.345	28.29	32.14	-3.857	.007	.298

Authors: Charles Jonassaint, PhD MHS[1], Ektha Parchuri, MPH[2], Julia A. O'Brien, PhD, RN[3], Dima Hendricks, MA[1], Jude Jonassaint, RN[1], Michelle Quallich Lancet, BS[1], Christina Lalama, MS[2], Kaleab Adebe, PhD[1]

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Background: Adults living with sickle cell disease (SCD) most frequently seek medical care due to pain.

To determine the most efficacious treatment plan for patients presenting with pain, providers must first accurately assess and diagnose the pain. Unfortunately, the current approaches for assessing pain are inadequate or too complex. Combined with medical provider biases, patients can often have their pain symptoms misinterpreted, ignored, or blatantly dismissed.

To address the pain communication problem, we partnered with stakeholders, human-centered designers, and software engineers, to design an approach to pain assessment that does not rely on numeric scales, adjectives, or phrases. We developed an electronic tool called Painimation which allows patients to communicate their pain quality, intensity, and location using abstract animations and a paintable body image. Painimation has been validated in a general population with chronic pain but there is limited data validating this approach in SCD. Preliminary data on Painimation being used by adults with SCD (N=67) found that those who described their pain using the "throbbing" animation had less severe pain symptoms than those endorsing the "shooting" animation.

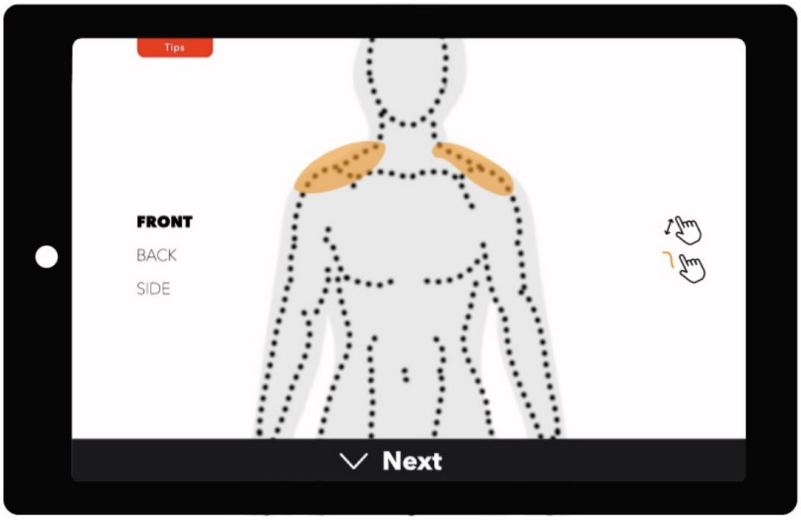
The objective of the current study was to replicate and extend prior findings by determining whether pain animations and body image data are associated with pain outcomes in a large cohort of adults with SCD. We hypothesized that the presence of shooting pain and greater body surface areas affected by pain would be associated with more severe pain outcomes and increased mental health symptoms.

Methods: We performed a secondary analysis on baseline data from the "Cognitive Behavioral Therapy and Real-Time Pain Management Intervention for Sickle Cell via Mobile Application (CaRISMA)" Trial—a multisite randomized, controlled trial in adults (age 18yrs+) with SCD and chronic pain (i.e., pain at least 4 days/week for > 3 months, and/or being prescribed long-acting or daily opioid pain medication). Eligible patients were randomized 1:1 to either digital cognitive behavioral therapy or digital education. Both arms received at least 12 weeks of health coach support. At baseline, participants completed a battery of questionnaires and tracked their pain intensity (0-10 visual analog scale) and mood daily via a mobile app. The Painimation app presents a front and back 2-dimensional body image that is paintable to indicate areas affected by pain. The app also presents eight abstract animations intended to represent different pain qualities (tingling, shooting, stabbing, throbbing, pounding, cramping, electrifying, and burning); the intensity of the animations can be adjusted, and up to three can be selected. The animations are not labeled, allowing for participants' interpretation of each animation. For the purposes of analyses, participants were categorized into "Shooting Pain" vs "No Shooting Pain" and "Throbbing w/ Shooting & Stabbing" vs "Throbbing Alone. Participants were also split into groups based on whether the proportion of the body image painted was less than the median (< 9.8% vs

>=9.8%). Baseline characteristics and demographics were compared between groups, and multivariable regressions were used to estimate covariate-adjusted associations with the following outcomes at baseline: daily pain, PROMIS Pain interference scale, Pain Catastrophizing Scale (PCS), Current Opioid Misuse Measure (COMM-9), and Adults Sickle Cell Quality of Life Measurement Information System (ASCQ-ME) pain severity and frequency.

Results: The trial enrolled 357 adults, mean age 36.3 (10.5), 66% female, 93% Black race. Both the "Shooting Pain" animation and greater body image scores were associated with all outcomes in univariate analyses (all $p < 0.01$). After controlling for age (Shooting Pain model only), depression, anxiety, % body image, and site, the shooting animations were independently associated with greater daily pain intensity ($p=0.04$); greater body image score was associated with daily pain intensity ($p < 0.001$), pain interference ($p < 0.001$), pain frequency ($p < 0.01$), and pain severity ($p < 0.01$).

Conclusions: As hypothesized, both the "shooting" animation and body image measures were associated with pain outcomes. This is the first study to test the use of animations and body image data for assessing pain in SCD. Future studies should explore whether pain location and animation selected are associated with pain etiology and determine whether this animation approach can differentiate different types of pain in SCD.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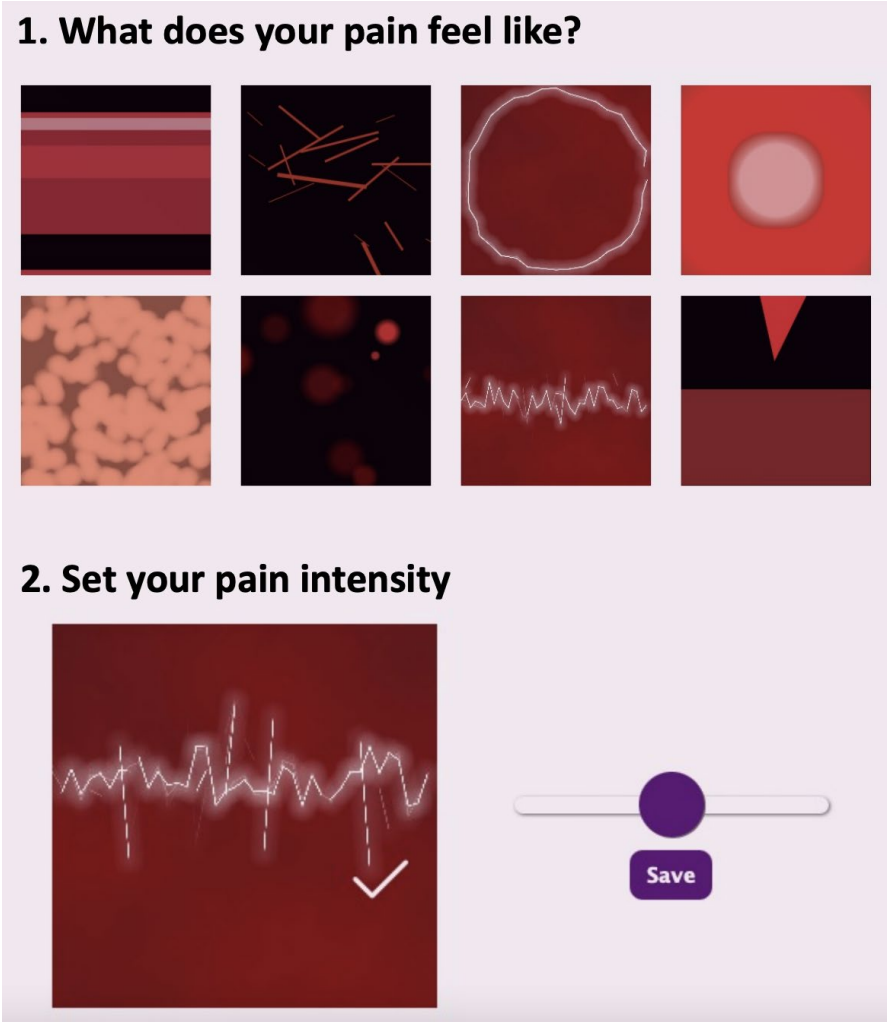
1. What does your pain feel like?
2. Set your pain intensity
Save

ABSTRACT BREAKOUT SESSION I
HEALTH SERVICES

Presenting: Sunday, June 18, 2023
1:15 PM - 2:45 PM

JSCDH-D-23-1500836

A CLINICAL PATHWAY FOR SICKLE CELL PAIN MANAGEMENT IN THE PEDIATRIC EMERGENCY DEPARTMENT

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Affiliation: *LSUHSC*

Background: Vaso-occlusive episodes (VOE) in pediatric patients with sickle cell disease often require emergency department (ED) visits for adequate pain relief. Inconsistencies in pain management strategies between healthcare providers during ED encounters for VOE can result in inadequately treated pain and subsequent need for hospitalization. Rapid assessment and administration of analgesia are critical in achieving effective pain control for these patients. Through standardized clinical guidelines, this project seeks to improve the timeliness of achieving optimal pain control in patients presenting to the ED for VOE.

Methods: The hospital clinical guidelines committee approved and published pain management guidelines into the electronic medical record (EMR) for use by Pediatric Emergency Medicine (PEM) faculty and residents in the Children's Hospital of New Orleans Emergency Department. The guidelines encouraged the use of intranasal analgesia as first-line therapy. Additionally, an order set was developed to improve the efficiency and effectiveness of acute pain management in sickle cell disease. Retrospective data was collected via chart review prior to the guidelines' initiation and compared to data collected five months after implementation. Each data set was comprised of 25 patients.

Outcome measures include the percentage of patients who received pain medication within one hour of presentation and the percentage of patients who received their first medication intranasally. Process measures include the time to IV access in minutes, and a survey to assess the percentage of pediatric emergency medicine (PEM) providers who referenced the clinical guidelines during management.

Results: Following implementation of the clinical guidelines and order set, patients receiving their first pain medication in less than an hour improved from 36% to 60% (p 0.07), with 12% of patients receiving their first pain medication within 30 minutes of triage. Use of intranasal pain medication as first-line therapy increased from 12% to 40% (p 0.008). Of the patients requiring admission for further pain management, 44% of patients received pain medication within one hour of presentation following implementation of the clinical guidelines compared to 33% prior to publication of the clinical guidelines (p 0.35).

Approximately 87% of providers reported referencing the clinical guidelines when caring for a patient presenting with a VOE. Choice of first-line pain medication and decreasing time from triage to the administration of the first pain medication were frequently reported as benefits of the clinical guidelines.

Conclusions: Initial results of our clinical pathway demonstrated improvement in timeliness of ED pain management after implementation of a standardized approach for SCD VOE. Implementation of the clinical pathway increased use of intranasal pain medication as first-line treatment, which appears to have contributed to decreased times to first medication administration. The pathway has been widely used by ED medical providers since implementation at our institution.

JSCDH-D-23-1525317

A PILOT STUDY OF A NURSE PRACTITIONER LED SHARED MEDICAL APPOINTMENT FOR SICKLE CELL

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Background: On any given day, as a nurse practitioner providing sickle cell care to adults, education and other interventions are repeated separately to at least seven or more individual patients. There is the urge to just bring everyone into the exam room at one time to save time. More importantly, I wonder how effective the visit was in impacting self-efficacy and health outcomes. A positive that is sometimes observed after visits is the comradery and positive synergy observed between patients that is very satisfying as a clinician and seemingly for the patients. To address improving visit efficiency and efficacy, the shared medical visit was identified as a model of care combining the elements of a medical visit with that of a support group conducted by a health care provider in groups of 5-10 patients in one setting. This paper describes a pilot study of a shared medical appointment (SMA) led by a nurse practitioner to adults living with sickle cell in a hospital-based sickle cell clinic that took place February 2020.

Methods: Setting: urban, safety net hospital based sickle cell clinic for adults.

The visit was structured after the VA's Shared Medical Appointments for Patients with Diabetes: Maximizing Patient and Provider Expertise to Strengthen Care Management and Group Health's Group Visit Starter Kit. Two of the theoretical models used were the Wagner Chronic Care Model and the biopsychosocial model.

Patients were individually approached either by phone or in person about having their visit conducted as a group rather than traditional one-on-one visit. Each patient was required to sign a confidentiality agreement prior to the start of the group session.

The appointment book was used as a registry of patients. Patient gender: 2 female, 3 male. Staff included: clerk, RN, NP, pharmacist, psychologist. Each patient received an approximately 10 minute one -on -one evaluation, medication review/adjustments, and group interaction with the NP, psychologist and pharmacist. Total time was 120 minutes. Evaluations were mix of verbal and printed evaluation form.

Results: All five patients voiced satisfaction with the shared visit and were eager for the next shared appointment. All the clinicians voiced satisfaction with the encounter stating not only did they learn from the patients more about sickle cell management in general. Total time of the visit with 120 minutes with the one-on one sessions lasting approximately 10 minutes each. The balance of the time was as a group. Post visit comradery and synergy was also observed. Other patients waiting for traditional appointments saw this and asked to be part of the next SMA. Regarding visit time overall: 5 patients were seen in span of 2 hours vs traditional 5 hours. Patients also had access to multidisciplinary team in one setting compared to traditional separate visit day/time and typically no direct access to a pharmacist.

Challenges included coordinating completion of all vitals such that everyone was present for the group interactions. COVID interrupted subsequent visits, a more detailed evaluation and being able to refine the whole process.

Conclusions: This study was not intended to be perfect example of a SMA but opportunity to get a general feel of implementing a shared medical appointment and general patient and provider acceptance of the model. Although a limited study, the SMA shows potential for increasing clinic visit efficacy, efficiency and patient/provider satisfaction. Areas of future study include other methods to coordinate intake of patients, decrease total visit time to 90 minutes, inclusion of other disciplines and identifying biological and psychosocial metrics to track over time, using more discussion as opposed to lecture and increasing group size and assessing increasing access to patients in areas without easy access to a sickle cell clinic via virtual participation.

JSCDH-D-23-1522758

EVALUATING SICKLE CELL DATA COLLECTION PROGRAM'S ADMINISTRATIVE CASE DEFINITION FOR ADULTS

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Background: Sickle cell disease (SCD) was first recognized in 1910 and identified as a genetic condition in 1949. However, there is not a universal clinical registry that can be used currently to estimate prevalence. The Sickle Cell Data Collection (SCDC) program, funded by the Centers for Disease Control and Prevention, funds state-level grantees to compile data within their states from various sources including administrative claims to identify individuals with SCD. The performance of the SCDC administrative claims case definition has been validated in a pediatric population with SCD, but it has not been tested in adults. The objective of our study is to evaluate the discriminatory ability of the SCDC administrative claims case definition to accurately identify adult SCD cases using Medicaid insurance claims data.

Methods: Our study uses Medicaid claims data in combination with hospital-based medical record data from the Alabama (AL), Georgia (GA), and Wisconsin (WI) SCDC programs to identify individuals 18 years of age or older meeting the SCDC administrative claims case definition. In order to validate this definition, our study included only those subjects that were identified in both Medicaid and the partnering clinical institution. We used clinical laboratory tests and diagnostic algorithms to determine the true SCD status of this subset. Positive predictive values (PPV) are reported overall and by state under several scenarios.

Results: There were 1,219 individuals (354 from AL and 865 from GA) who were identified using a 5-year time period. The 5-year time period yielded a PPV of 88.4% (91% for data from AL, 87% for data from GA), when only using data with lab-confirmed (gold standard) cases as true positives. With a narrower time period (3-year period) and data from three states (AL, GA and WI), there were a total of 1,432 individuals from these states included in our study. The 3-year time period PPV overall was 89.4% (92%, 93% and 81% for data from AL, GA and WI respectively) when only considering lab-confirmed cases as true cases.

Conclusions: Adults identified as having SCD from administrative claims data using the SCDC case definition have a high probability of truly having the disease especially if those hospitals have active SCD programs. Administrative claims are thus a valuable data source to identify adults with SCD in a state and understand their epidemiology and healthcare service utilization.

JSCDH-D-23-1505536

PRIORITY NEEDS OF THE US SICKLE CELL COMMUNITY: INSIGHTS FROM US ADVISORY BOARDS

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Affiliation: *[1]Sickle Cell Association of Houston, [2]New England Sickle Cell Institute, University of Connecticut Health, [3]Sickle Cell Community Consortium, [4]Sickle Cell Disease Association of America Inc., [5]Novo Nordisk, Inc., [6]Albert Einstein College of Medicine*

Background: Sickle cell disease (SCD) is an inherited chronic condition that is associated with pain, fatigue, hemolytic anemia, and organ damage. In combination with these clinical symptoms, psychosocial, economic, and structural social issues negatively affect quality of life and contribute to the reduced life expectancy of those affected by SCD. Although SCD was described in Western medical journals over a century ago, there has been a considerable lack of awareness and resources dedicated to the affected population. In the US and Europe, SCD predominantly affects racial and ethnic minorities, which contributes to disparities in health care access and quality of care. Despite recent advancements in the treatment of SCD, more investments are needed in researching novel therapies and in helping to disseminate effective care to the affected population, especially in view of valid historical mistrust and disparities in access to appropriate and comprehensive health care. The objective of this work was to identify and prioritize unmet needs of the US SCD population from the perspectives of sickle cell community leaders and hematologists who specialize in the care of people living with SCD.

Methods: Ten sickle cell advocates (7 patients living with SCD and 1 caregiver) and 9 hematologists were invited to participate in separate advisory boards for a workshop on "SCD Priority Needs" held in fall 2022. In preparation for the workshops, each participant was asked to submit his/her opinions on up to 5 priority needs of the US SCD community. Prior to the live session, advisor submissions were merged into 12 separate categories. Advisors agreed that the 12 final categories aligned with their submissions. Advisors then created an initial ranking of the needs by scoring each category based on 3 criteria: percentage of the SCD population affected by the need (0=0% and 5=100%), the impact of the need on quality of life (0=no impact and 5=most impactful), and the interdependence of the need relative to other needs (0=high degree of interdependency and 5=no interdependence). Finally, advisors adjusted the independent ranking, and a final list of the prioritized needs of the US SCD community was created.

Results: Hematologists and advocates agreed that the needs of the US SCD community were numerous and extended beyond the health care setting. The top 5 priority needs identified by each group are shown in the table. Although the lists of unmet needs were created de novo based on each group's pre-work submissions, both groups identified a need for more SCD specialists as among the top 5 priority needs of the community. According to hematologists, increasing the number of knowledgeable SCD specialists was a top priority. Patient advocates extended this need more broadly to increasing access to SCD specialists by having more trained health care professionals (HCPs), offering transportation and options for telemedicine, and ensuring access to compassionate care within the health care system, including improved awareness of social determinants of health among HCPs. The highest priority identified by advocates was legislative action to enforce established care guidelines, which are not followed uniformly across the country. Overall, the opinions gathered from hematologists and advocates provided

great insights and crucial groundwork for prioritizing the needs of the SCD community, and the next steps will be to start identifying solutions to address these needs and improve the care provided to people living with SCD.

Conclusions: The unmet needs of the US SCD community were amplified during separate advisory boards where hematologists and advocates prioritized the needs of the SCD community, which involve a combination of greater research, better treatment options, additional funding for SCD advancement, improved access to knowledgeable and compassionate care, and an overall increased awareness of SCD. Some of these needs can be addressed and have an impact now, such as better education and enforcement of guidelines that can enhance care without the need for additional research. Other needs are linked and should be addressed now but will require time to truly see the benefit. Increasing funding for SCD research would also expand our knowledge of SCD in the short-term and would provide the long-term benefit of increasing the number of knowledgeable SCD specialists. Lastly, creating more awareness for the SCD community can strengthen advocacy and help to broaden the knowledge of SCD among the public.

Hematologist Ranking		Patient Advocate Ranking	
1	Better treatments, both preventive and on-demand, for vaso-occlusive events	1	Legislation to enforce quality care guidelines
2	More funding for SCD research, education, and infrastructure support	2	Increased awareness of SCD among the general population and within the education system and workforce
3	Increased number of knowledgeable SCD specialists	3	Increased access to knowledgeable SCD specialists
4	Organized, stronger advocacy	4	Increased access to knowledgeable, ethical, and compassionate medical care within the health system (beyond the SCD specialist)
5	Improved reimbursement for therapies and SCD care	5	Improvements in SDOH for those with SCD and improved awareness of SDOH among HCPs

Top 5 Priority Needs of the SCD Community Identified by Hematologists and Patient Advocates
HCPs, health care professionals; SCD, sickle cell disease; SDOH, social determinants of health.

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THE SUNSHINE SICKLE CELL PROJECT

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Abstract

Education designed to raise basic awareness of sickle cell disease and its complications is essential, given a persistent, ongoing care gap exacerbated by a dearth of knowledgeable providers. Accordingly, many providers need education to appreciate that sickle cell disease is a significant global health concern, impacting up to 25 million individuals worldwide, while in the United States, approximately 8% of African Americans are sickle cell gene carriers and an estimated 100,000 individuals live with sickle cell disease To address critical clinical practice gaps related to the care of patients with sickle cell anemia, MediCom Worldwide, Inc. (MediCom) has partnered with The Foundation for Sickle Cell Disease Research (FSCDR) in the development of a quality-improvement educational curriculum titled The Sunshine Sickle Cell Project. The goal of initiative is to work towards closure of professional practice gaps among clinicians related to the care of patients with sickle cell disease.

Healthcare professionals who participated in the live education were provided with information on involvement in the quality improvement initiative and the opportunity to work through personal plans of action for QI during the live education. Each participant received a quality improvement checklist and encouraged to individualize measures based on their patient population. In addition, participants were also provided with tools and resources to facilitate implementation. Upon conclusion of all educational interventions, survey questions were developed and deployed to participants and subsequent key-informant interviews (60–90 minutes) were conducted.

Text

How can Practitioners Improve metrics for quality improvement initiatives in Sickle Cell Disease?

Sickle Cell Disease (SCD) is defined as a chronic hemolytic disorder characterized by the polymerization and deformation of the hemoglobin molecules within the red cells into a crescent shape, which results in vasoocclusive events and increased haemolysis (Adewoyin, 2015). Highquality treatment for people with sickle cell disease (SCD) should be evidence-based and backed by clear, quality measures that assess the quality and enhance performance. Well-trained personnel that is willing and able to provide the essential services should provide care. Due to a lack of knowledge and awareness regarding the clinical condition and the afflicted community, some healthcare practitioners may be hesitant to give SCD care (Sara, 2020). Clinical practice guidelines are a useful approach to standardizing care and alerting healthcare practitioners, particularly nonexperts, about the proper therapies that people with SCD require. Individual clinicians and systems can assess how effectively they follow existing standards in providing such treatment, as well as the consistency of this application to "every patient, every time" using commensurately validated quality measures (Sara, 2020).

The guiding framework for changing the way healthcare is delivered by evaluating performance on measures indicating the high-quality treatment, healthcare organizations and clinicians may determine how effectively they are reaching these quality goals. Healthcare providers require information and tools that integrate existing knowledge into clinical practice, and clinicians, organizations, and payers need the ability to monitor, recognize, and pinpoint areas for quality improvement in order to promote the delivery of high-quality SCD treatment. Tools that are pertinent include clinical practice guidelines, performance indicators, and quality metrics. These evidence-based SCD services may be categorized as quality metrics when there is a solid evidence foundation, which is defined as well-conducted randomized controlled trials and sufficient information to enable performance tracking (CMS, 2020). The capacity to offer high-quality healthcare and/or the achievement of one or more quality goals for healthcare can be measured or quantified by using instruments that take into account patient perceptions, results, organizational structure, and/or systems (CMS, 2020).

A multidisciplinary team of healthcare providers that provide comprehensive care is the best option for managing the treatment of persons with SCD, which includes multidisciplinary teams. Hematologists often supervise patient treatment and communicate with other disciplines since they are more knowledgeable about the many SCD problems and manifestations (Grosse et al., 2009). The comprehensive care team should also consist of behavioral health specialists (such as psychiatrists, neurologists, and psychologists), counselors, nutritionists, physical therapists, physiotherapists, community health workers (CHWs), care co-coordinators, and school support workers in addition to medical professionals. Furthermore, the chance of the interdisciplinary team's success is increased through building solid relationships with community health services and nonprofit organizations (Okpala et al., 2002). Numerous positive outcomes of comprehensive treatment include increased quality of life (QOL), fewer emergency department (ED) visits, and shorter hospital stays (Okpala et al., 2002; Vichinsky, 1991).
SCD may benefit from the recommendations made in the IOM study reworking for an Aging America: Building the Healthcare Workforce (IOM, 2008) to boost the number of healthcare professionals serving the elderly population. The following are some of these tactics:

The budget should be amended by the government to provide funding for worker monitoring.

- Hospitals should support resident training in all environments.
- All licensing, renewal and certification maintenance procedures should gauge proficiency in subject-related areas.
- The federal government and the states should raise the minimum training requirements in this area.
- Patients should support and honor care delivery approaches that have been proven successful.
- To improve the effectiveness and safety of care, federal authorities should push technological advancements.
- Organizations in the public, commercial, and community sectors should finance informal careers and make sure they have access to sufficient training opportunities.
- Financial incentives from both private and public sources should be used to boost the number of subject specialists across all professions.

The critical care team members (core team) should provide high-quality care for people with SCD, the duties that each member of the care team must play, the amount of education/experience required, and any potential obstacles to a ready and willing

workforce. The selection of team members must be done by a qualified committee using predefined checklists. The experts and professional services that have historically been involved in SCD care must be given priority in selection. Professional service providers and experts must be able to meet the regular, acute, and subacute care needs of people with SCD. The multidisciplinary medical team models must also be embraced from other severe, inherited disorders, such as cystic fibrosis (CF) (CFF, 2019).

National organizations and healthcare systems have made various steps to attract and keep the SCD workforce of the future. For instance, ASH provides a training program for internists and hematologists to help them launch an adult SCD clinic. However, more programmers and funding are required to promote the growth of a skilled workforce in the interdisciplinary SCD (Alsan et al., 2018). Disparities in health care service may also be caused by a lack of diversity among healthcare professionals (Cohen et al., 2002), which is another important aspect of the care of patients with SCD. Effective communication may be encouraged and patient-provider relationships may be improved by having physicians that are comparable to the patients in key respects, such as color, ethnicity, and language (Forbes Insights, 2011). In the healthcare industry as well as the workplace in general, diversity among instructors, staff, and trainees promotes innovative problem-solving, sound decision-making, and high levels of productivity (Hunt et al.,2015).

Based on their level of engagement in managing the clinical and psychological consequences of SCD or in reducing inequities in care, the SCD care team members are categorized as core or supplemental (e.g., CHWs). The medical specialties that are currently being used and are seen favorably by patients or medical professionals (e.g., financial counsellors) are another set of practitioners that may be considered while providing care to people with SCD. In the United States, certain members of the core team, including hematologists and emergency department doctors, currently care for both children and adults who have SCD. Moreover, given the appropriate degree of training, PCPs, nurses, and other advanced practice practitioners together can manage the treatment of patients with SCD. Second-level core team members support the management of SCD issues but are referred to as level 2 since they may not provide care for the whole SCD population but rather concentrate on those with a particular complication or requirement. Members of the ancillary team may offer services on an as-needed basis or may offer enabling services, but they have an impact on how care is provided or managed by addressing important social factors (Huntet al., 2015).

Moreover, despite the fact that this is often the time when family planning and choices regarding contraception take place, there are no standards or best practices for genetic counseling for people with SCD throughout adolescence or young adulthood. It is crucial to employ the right test to determine hemoglobinopathy trait status when offering genetic counseling to women about their likelihood of having a child with SCD. The best quantitative hemoglobin separation techniques include hemoglobin electrophoresis and others (Naik and Haywood, 2015). Inaccurate solubility tests include Sickled and Sickle Cell Screens. These tests cannot discriminate between SCD and SCT, nor do they identify additional hemoglobin variations that might put a couple at risk of producing a child with SCD, and they are subject to false negatives and positives.

According to the findings of research on doctors' perspectives on patients' decisional requirements and methods of decision-making, doctors often employ two methods when making decisions about patient care (Bakshi et al., 2017). One strategy involved the doctor promoting a certain course of therapy to persuade the patient to accept it. According to Bakshi et al. (2017), a doctor's choice of method may be impacted by a variety of variables,

including the patient's features, the severity of the sickness, the types of therapies being employed, institutional frameworks, and other decision characteristics.

Another essential aspect to enhance care among people with SCD is by providing shared decisionmaking (SCD). SDM is defined as a way of communicating in which physicians and patients work together to make knowledgeable judgements about the patient's needs and their unique concerns, preferences, objectives, and values (NQF, 2020). To guarantee that SDM in clinical practice is a quality treatment for all patients, the NQF issued a nationwide call to action (NQF, 2020). SDM is essential but developing in SCD care.

Making choices concerning SCD disease-modifying medicines that either include considerable risks or need patient adherence to be successful at their best (such as HU) is common. Patients and families should be informed about and participate in making these decisions since they are complicated and preference-sensitive. This calls for a strong collaboration between physicians, patients' families, and patients that are built on trust and open communication (NQF, 2020).

Analysis: Status of quality improvement initiatives in Sickle Cell Disease:

Survey Results

A survey has been conducted to understand the perceptions of healthcare practitioners in managing Sickle Cell Disease. A total of 14 responses have been received, and their responses are analyzed in this report. Moreover, at the end of the survey questionnaire, the respondents were asked to provide their consent to participate in a one-to-one interview, to be held at the convenience of the respondent and the interviewer. Out of 14 respondents, six respondents agreed to participate. Using telephonic conversation, a suitable time for an appointment has been fixed with all these six respondents individually. Since the interviewees disagreed and felt uncomfortable with the recording of the interview, notes were prepared and the excerpts from the interviews are presented along with the survey analysis in this section. Moreover, to present the privacy of the respondents, the interviewees' names are kept anonymous and they are denoted as R1 (Respondent 1) to R6 (Respondent 6) respectively.

The section, thereby, shows the overall analysis of the survey and the interview to understand the perceptions and beliefs of the health practitioner about care in patients with sickle cell disease.

Reason for using healthcare

The respondents were questioned about the reason for which they use health care for patients with SCD. Out of the 34 respondents, about 50% stated that made visits to the emergency departments for acute Vaso occlusive crises. About 56% of the respondents avail the health care for adhering to primary care, and finally, approximately 59% utilize health care services for hospital admissions.

Furthermore, the interviewees were questioned about the reasons why patients with SCD use healthcare services. The interviewees majorly respond to the key reasons including bone pain crisis, Vasoocclusive crises, and abdominal pain. These responses are presented in the following extracts from the interviews-

“There are many reasons for which the patients require health services…most of the people suffer from pain, in bones and acute abdominal pain. Many of the patients visit emergency departments to seek care for most of these symptoms and acute issues.” R3

"I would say that it all depends…people with SCD may suffer from acute or chronic symptoms. Acute complications associated with SCD are higher than chronic….if I would recollect, I would say that the most important reasons for which people seek healthcare are Cerebrovascular Disease, pain management, vasocclusive crisis,…and yes, very recently, I encountered two patients who suffered from Cerebrovascular Disease." R5

"I feel it all depends…generally it's about the management and quality of life. Pain is a common issue faced by many. But yes, in children, the parents are most concerned with delayed growth and development, Chronic Pain Syndromes, and Immunological and Infectious Complications." R6

Measures for routine healthcare maintenance

Next, the respondents have been enquired about the measures considered in undertaking routine health care maintenance for patients suffering from SCD. A wide number of measures have been recognized by the respondents for routine health care maintenance, which include Penicillin prophylaxis, immunizations, vaccinations, Transcranial doppler (TCD) screening, and management, Care planning and management, Mental health screening and follow-up, blood pressure screening, and Ophthalmologic exam. The responses for healthcare maintenance among patients with SCD are presented in Figure 2

From figure 2, it can be found that the majority of the respondents, accounting for about 62% stressed undertaking proper vaccinations as routine healthcare maintenance among people with SCD. Other important measures include immunization, Penicillin prophylaxis, care planning, and management and blood pressure screening, as stated by approximately 53%, 53%, 47%, and 50% of the respondents, respectively. The other measures considered important by the respondents are mental health screening and follow-up, Ophthalmologic exam, and Transcranial doppler (TCD) screening and management, as recognized by 44%, 44%, and 21% of the respondents, respectively.

Furthermore, the same question was put to the interviewees to understand the measures considered by them for routine healthcare maintenance for people with SCD. The responses have been similar to the survey findings, which are stated in the excerpts from the interviews-

"Yeah, routine healthcare is of utmost importance for such subjects. Well, it actually depends on the symptoms of the patients and my main aim is to relieve the patients with any kinda symptoms suffered by them….i think some of the key aspects that I track at all times are the immunization and vaccination charts for the children, tracking the normal development and growth, and screening of their mental health. Counseling is another key aspect one can't ignore..so that they and their parents can manage the best of health outcomes even at home." R1

"Well, it depends on the complaints they face. Like when patients are suffering from bone pain crisis, some of the routine maintenance include analgesia, ensuring that they remain hydrated, or prescribing therapeutic or prophylactic antibodies. Similarly, in hypoxic cases, oxygenation becomes important. Another consideration is tracking for cardiac decompensation, and that's when blood transfusion is needed…so basically, you know, it all depends on the individual cases…and the severity of the complications suffered. each case is different…we meet them, track their historical records, and check for routine care accordingly." R2

"For every case, I believe checking for the vaccines, blood pressure levels, and comparison with past records are needed. After that, some of the routine tests performed range from penicillin prophylaxis to Transcranial Doppler screening, ophthalmologic test,

and mental health screening. But yes, these tests may even go up or down, depending on the issues faced by the patients and the severity of their disease, the pace at which it is progressing." R4

Newborn screening & Follow-up

Moving forward, the respondents were questioned about the measures to be undertaken for newborn screening and follow-up. 32 respondents answered this question, while two did not answer it. Some of the measures provided by the respondents have even discussions with the providers, communication about results, connection to follow-up care, and genetic counseling.

These responses are further analyzed and presented in Figure 3, as under 62.5% of the respondents (out of 32 who responded) perceived that discussion with the providers is the most important aspect of screening and following up the newborns with SCD. Follow-up care is perceived to be the next important measure, as stated by about 59% of the respondents, while more than 56% of each of the respondents considered communication about results and genetic counseling to be important.

This question was also asked by the interviewees, and three respondents provided their answers, which are stated as under:

"This is really of great concern. Though rare, but I would never want any newborn to suffer from SCD. In the cases with symptoms and confirmation, first thing is to counsel and inform the parents. It's important that they understand the problem, its magnitude and the likely development…so that proper care can be delivered to the newborn. Parents are also advised about follow-up care, checking on the symptoms and the development. They are also advised to maintain all health records and keep the pediatrician and other health professionals aware of the same." R5

"I feel public education and definite strategies are two key measures that must be provided so that the trait can be managed well. Another piece of advice remains the injection of penicillin daily, which is known to reduce the mortality rates significantly." R6

"Announcing the diagnosis of SCD in the newborn is not easy. It's a mental trauma for the parents, and I have even witnessed cases of severe sequelae. I think this should be done face-to-face, and in moderate to severe cases, I prefer the presence of a psychologist as well. Then, informing the parents about the expected achievements in the life of the child, checking and paying close attention to the clinical signs as well as when to visit the emergency department. I feel proper management, especially among newborns, is not possible without the ideal combination of Psychological help, therapeutic education, and parent associations" R1.

Acute chest syndrome & Acute Pain Crisis

Next, the respondents were questioned about acute chest syndrome and acute pain crises for managing individuals with SCD. 33 respondents answered this question, while one did not answer it. Some of the measures provided by the respondents have been discussed as prevention and treatment of acute chest syndrome; assessment, treatment, and management of acute pain crises, and fever management. These responses are further analyzed and presented in Figure 4, as under About 76% of the respondents (out of 33 who responded) perceived that assessment, treatment, and management is the most important aspect of acute pain crisis.
Prevention and treatment of acute pain crisis, followed by Fever management is perceived to be the next important measures, as stated by 67% and 57% of the respondents, respectively.

Interviewing the respondents on this question provided additional meaningful information, which is stated as under-

"Fever and respiratory symptoms are two vital aspects of ACS. Though it is acute, can become fatal and need immediate intervention for people of all ages. Also, checking the genotype is important, like the more severe SCD genotypes (hemoglobin S [Hb S] and Hb S-beta-thalassemia) are at a higher risk. Evaluation generally includes checking the fever, respiratory symptoms, pain in chest or back and Vacoocclusive pain in any part of the body." R2
"Pain, fever and respiratory symptoms even if the last chest radiograph is normal, in my opinion, are the initial maintenance care among people with ACS in SCD." R3

"Checking on the lower respiratory symptoms including hypoxemia or a new lung infiltrate is needed among such patients…also, they should be closely monitored as well as their respiratory status must be quantified using clinical respiratory score…and based on this score, the treatment stage should be escalated and decided." R4

Chronic Care Maintenance

Next, the respondents have been enquired about the measures considered in undertaking chronic care maintenance for patients suffering from SCD. A wide number of measures have been recognized by the respondents for chronic care maintenance, which include chronic transfusion management, prevention of stroke, Hematopoietic stem cell transplant, Asthma care, Hydroxyurea treatment, and prevention and management of splenic complications. The responses for chronic care maintenance among patients with SCD are presented in Figure 5.

From figure 5, it can be found that 51.5% of the respondents (out of 33 respondents), perceived that chronic transfusion management is an important aspect of chronic care maintenance in SCD.

Asthma care and Hydroxyurea treatment are other important measures, as stated by 46% of the respondents each approximately, while more than 42% of each of the respondents considered the prevention of a stroke to be important. Furthermore, 27% of the respondents considered that hematopoietic stem cell transplant is an important measure in chronic care maintenance and finally, about 18% of respondents accounted for the prevention and management of splenic complications.

The interviewees are then probed about the management of chronic SCD in the Patients. The responses of the interviewees highlight some of the chronic complications and their treatment plans highlighted as under-

"Once again, it depends on the symptoms and the progression of the disease. Some of the chronic complications one may suffer can be chronic pain syndromes, Immunological and Infectious complications, Sickle Cell Chronic Lung Disease, Hepatobiliary or liver damage Complications, and can be others like renal or abdominal-related complications. The treatment of each of these condition basically depends on their symptoms, requires regular follow-up, blood transfusion, wherever necessary and other management." R2

"Chronic SCD becomes one of the reasons for morbidity and we try to lessen the symptoms and the progression of the disease. The treatment depends on a multitude of factors, which are highly individualistic. It is tried that further complications like splenic issues do not erupt, or the condition of hydroxyurea is timely treated, for respiratory issues, proper asthma care must be provided….in some cases, transplantation of hematopoietic stem cell, and chronic blood transfusion management is done…" R4

"Blood and stem cell transfusion and stroke presentation and management are the main management plan for patients suffering from chronic SCD." R5

Pediatric to adult care

Moving forward, the respondents were questioned about the measures to be undertaken for the transition from pediatric to adult care. This question was answered by 32 people, while two people were unable to respond. Some of the responses' actions have even been discussed with the providers, such as patient self-efficacy, communication between pediatric and adult providers.

Timing of first adult visit, quality of life, and trust with their adult provider. These responses are further analyzed and presented in Figure 6, as under-
Figure 6 shows that the majority of respondents, accounting for approximately 62%, believe in patient self-efficacy. About 56% and 53% of respondents show other important measures including timing of the first adult visit and communication between pediatric and adult providers is crucial in the transition from pediatric to adult care, respectively. Quality of life and trust in their adult providers were deemed important by 31% each of those polled in the transition from pediatric to adult care.

This question was also discussed with the respondents about the measures considered by them while transitioning from pediatric to adult care. The responses are centered around keeping a track of the progression of health conditions, open discussion with the guardians and the patient, open communication, and discussion with the pediatric health professional.

"I feel this is an important phase of the life of the patient and the family member. Building trust is essential and hence, regular sessions of meeting to discuss the health, psychological feelings and overall condition of the patient must be done. Before and even sometimes after meeting the patient, talking with the pediatric health provider also makes it valuable." R6

"Transition must be made as smooth as possible for the patient, they not only undergo a different phase of life, but the disease and the underlying changes may be different by now. That's why the first meet with the service provider must be properly planned….cos it marks the building of the relationship…its necessary that the patient makes the same trust as with the previous health provider. What I generally do in such cases are pre-preparation by talking with the registered nurses and practicing pediatric doctor to learn about the patient, check his or her health records, history of any emergency visits and also try to know about the family background etc. then at the time of the meeting, I ensure that I become a good listener and let him or her speak about anything…be it health, experiences or their feelings. By the end of the session, I aim to build some trust and ingrain the feeling of self-confidence among the patients, which I feel is very important for fighting the health conditions and making any treatment successful." R1

Monitoring Preferences

In the next question, the respondents were questioned about their preferred mode of monitoring. Five respondents opted to answer this question, while nine skipped. The first respondent reflects that he/she wants to use "Oral medication usage at home", other respondents classify that he/she wants to use "new medications used for patients". Additionally, one of the respondents stated that

"My sicklers are primarily managed by Dr. Rodriquez and his Hematology team at BGMC. Since 3/2021, I am no longer admitted to BGMC. My responsibility is to maintain and prevent crises.

Another respondent added that he would like to monitor the "Length of time to treatment onset of Sickle Cell acute pain crisis in ER, best practices in the treatment protocol of acute pain crisis one accountability of MDs for noncompliance with established guidelines in ER and hospital." Two other respondents endorsed satisfaction with the current treatment and monitoring.

The interview responses further added some insights about the preferred mode of monitoring patients with SCD. These responses are provided as under-

"Basically the condition of the patient becomes the deciding factor for the monitoring mode. For acute or preliminary stages, I would say that staying at home is best. Hospital settings, though are equipped with the necessary equipment and resources to provide the best health and treatment, but become scary or gloomy and taxing on the pockets of the people. In chronic cases, definitely staying at hospitals is a must, so that proper monitoring, lessening of the symptoms and pains can be provided to the patients." R3

"Its not easy to live with the thought of living with the SCD. I would try that oral medications work best…the person living with the family in their homes helps preserve their mental health. But for this, regular follow-ups, checking on the symptoms, and events, when visit to emergency department may be needed, should be properly known to the patient as well as the family members." R4

Personal Information of Respondents

Next, the respondents were enquired about their qualifications and degrees. The questionnaire contained the options of Advanced Practice Registered Nurse (APRN), Registered Nurse (RN), Doctor of Osteopathic Medicine (DO), Doctor of Medicine (MD), Nurse Practitioner (NP), Physician Assistant (PA), and others. Nine respondents answered this question, while the others skipped the same.

The responses are presented in Figure 7.

It can be found that the majority of the respondents, about 16 respondents are MDs, while two each are registered nurses, nurse practitioners, and APRNs. This profiling shows that these medical professionals are experience holders and deal with SCD management. Hence, their responses are relevant and can be attributed to and representative of the population.

Conclusion

The paper discussed the qualitative improvement initiative in managing sickle cell disease (SCD). An in-depth literature review has been conducted to study the existing metrics for studying quality improvement initiatives in SCD. It is found that high-quality treatment for SCD should be evidence-based, backed by clear quality measures, and capable to enhance overall performance. Other important aspects covered in the literature include well-trained service providers, clinical proactive guidelines to standardize care, engagement of a multidisciplinary team of care providers, the role of effective communication and a shared decision-making process. The paper also presented the findings of a primary study to understand the status of quality improvement initiatives in SCD. The survey gauged responses from about 14 respondents, and the key findings explored the reasons for using healthcare use in SCD, considerations for routine and chronic healthcare maintenance, newborn screening, managing acute chest syndrome and acute pain crisis, the transition from pediatric to adult care, and monitoring preferences. Overall, the research explored new insights in the area of care and management of SCD, which can help augment the quality of care.

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Dr. Lanetta Bronte-Hall has disclosed no relevant financial relationships.

About The Foundation for Sickle Cell Disease Research

www.FSCDR.org

The Foundation for Sickle Cell Disease Research (FSCDR) is the United States' first outpatient center exclusively dedicated to the treatment of and innovative research for SCD. Florida has the highest population of individuals living with SCD in the U.S. In 2015, we opened the center in Hollywood, FL, offering focused care and collecting data through clinical trials. We utilize a human-centric, community-based, rigorously scientific approach to caring for our patients and finding better solutions to treat them.

For the past eight years, we have grown strong roots in the South Florida community and have taken great strides toward our mission of resetting the narrative around SCD through specialized care and innovative research. Our next challenge is building a state-of-the-art facility that provides ground-breaking treatment to more people living with SCD—offering more support to our patients, their families, and the broader sickle cell trait and advocate communities while creating a center for collaborative research that encourages scientists, medical professionals, and physicians researching and treating SCD to work toward new, life-improving solutions. This innovative research facility will be equipped with all the tools necessary to provide life-altering treatment and care. It will be a safe haven for patients, families, and communities desperate to alleviate the burden of this disease.

About MediCom Worldwide, Inc.

www.MediComWorldwide.com

Established in 1993, MediCom Worldwide, Inc. is an award-winning, accredited, independent medical education company that has educated more than one million healthcare professionals through more than 800 diverse educational activities. MediCom is dedicated to developing quality, robust activities for healthcare professionals and has been an accredited provider of continuing medical education (CME) for physicians since 1999. For the previous 12 years, MediCom has focused on the development of live activities and online communities as sources of innovative, engaging education, utilizing principles of integrated communication and adult learning theory to ensure that learners are able to meet their educational needs in their preferred learning formats. MediCom has built robust communities in oncology, pain management/addiction medicine, and migraine, with combined utilization of more than 1,200,000 unique visitors and more than 38,000 clinician members. Central to MediCom's practice is the emphasis on compliant, scientifically rigorous, and performance-improving outcomes-based, quality content built on demonstrated educational gaps, together with cutting-edge technological delivery mechanisms in multiple formats that facilitate learner-centered education.MediCom supports the ongoing educational needs of physicians, nurses, pharmacists, and other healthcare professionals and is an accredited provider of the following:

1. CME credit for physicians by the Accreditation Council for Continuing Medical Education (ACCME) through March 2021 (Accreditation with Commendation)

2. CPE credit for pharmacists by the Accreditation Council for Pharmacy Education (ACPE) through 2024
3. CNE credit for nurses by the California Board of Registered Nursing through 2019

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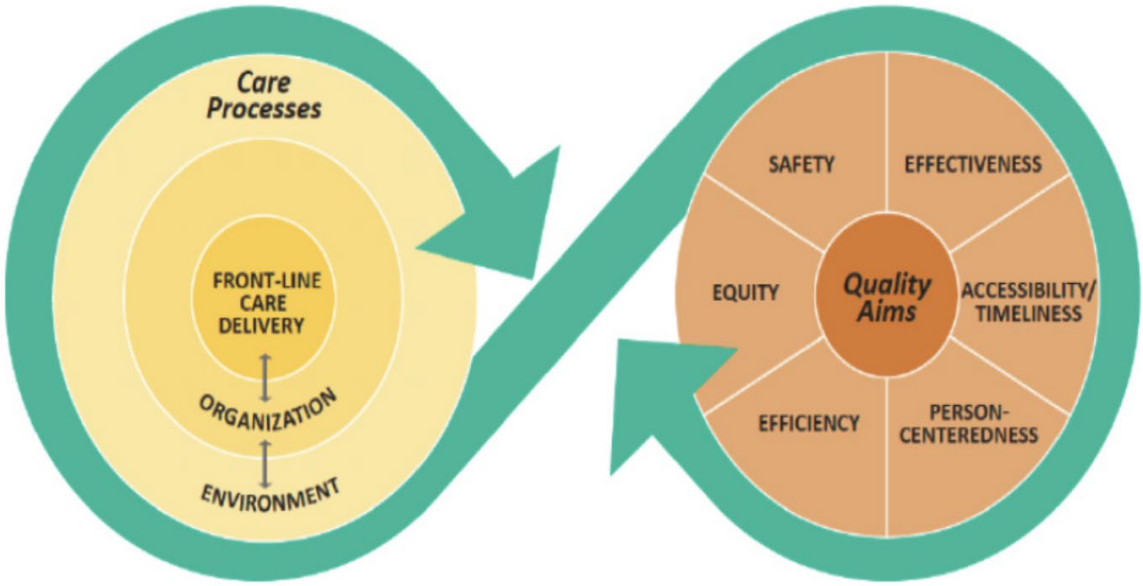


Source: NASEM, (2018).

Guiding framework for the transformation of care delivery.
Crossing the Global Quality Chasm: Improving Health Care Worldwide.

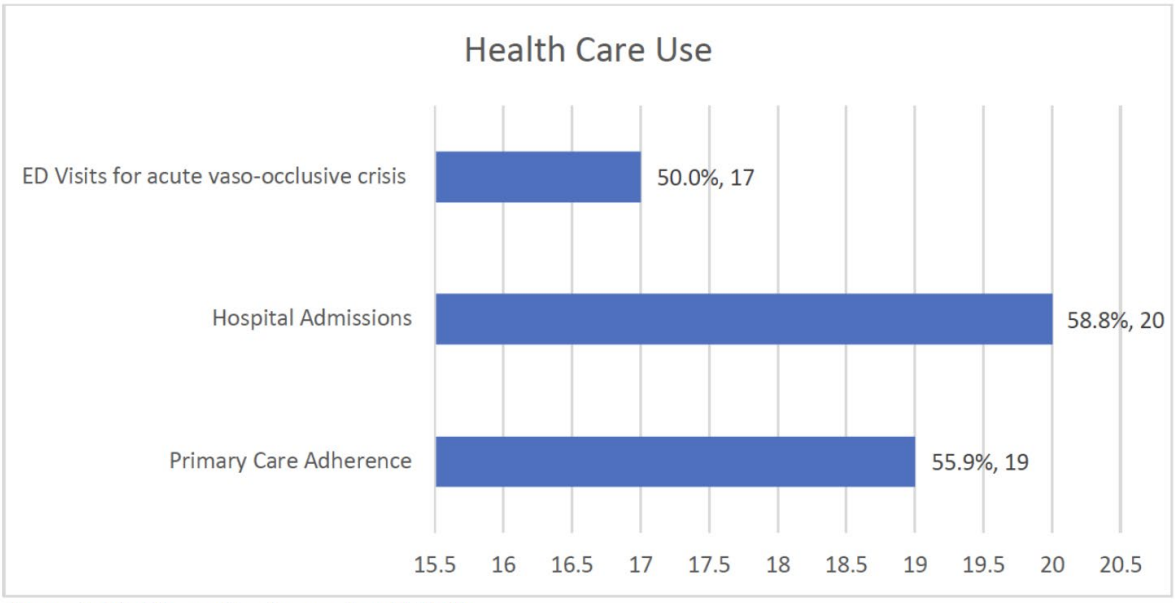


Figure 1: Healthcare Use for people with SCD

Healthcare use for people with Sickle Cell Disease
Figure 1. Reasons for healthcare use

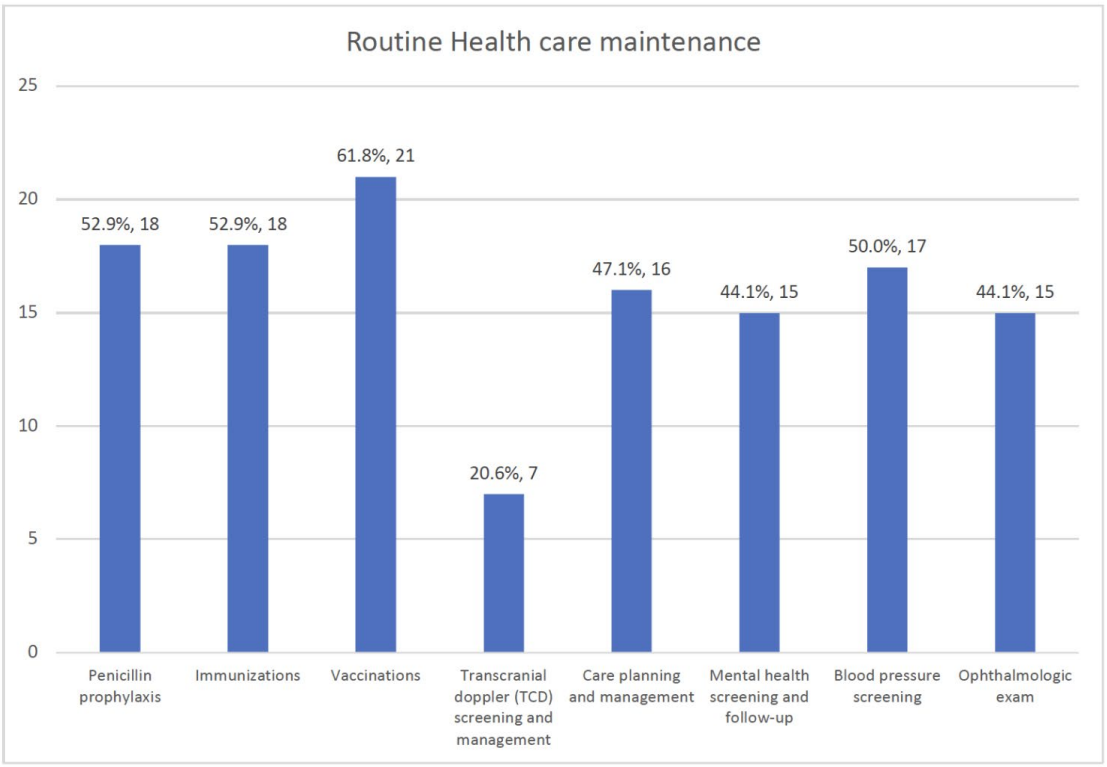


Figure 2: Reasons for routine healthcare maintenance

Routine healthcare maintenance
Figure 2. Reasons for routine healthcare maintenance

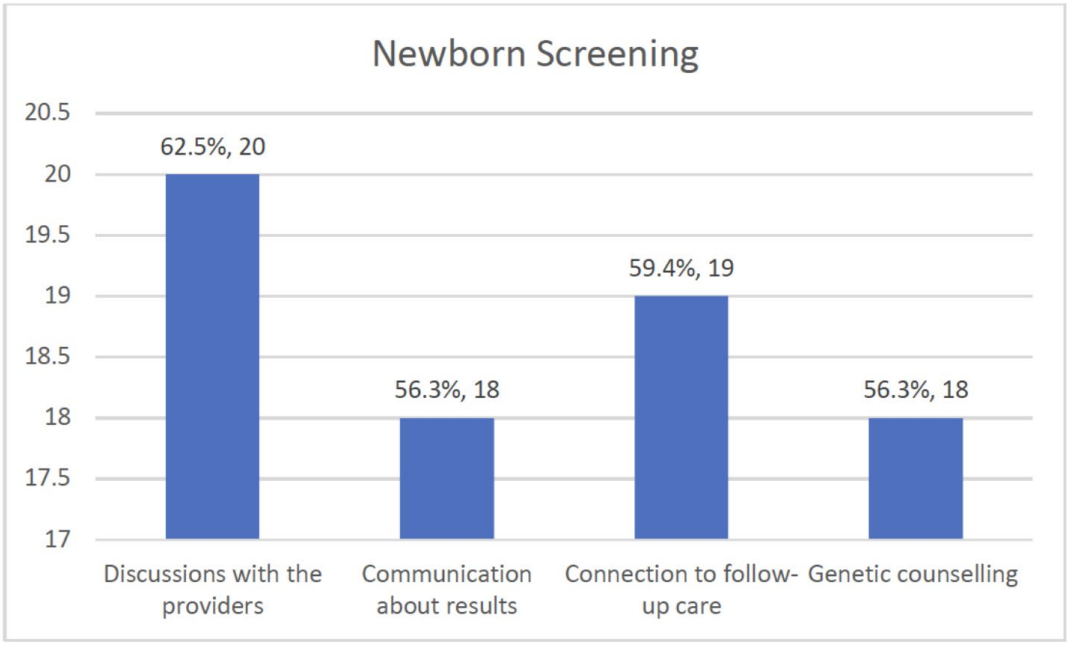


Figure 3: Newborn screening & follow-up

Newborn screening and follow-up
Figure 3. Newborn screening and follow-up

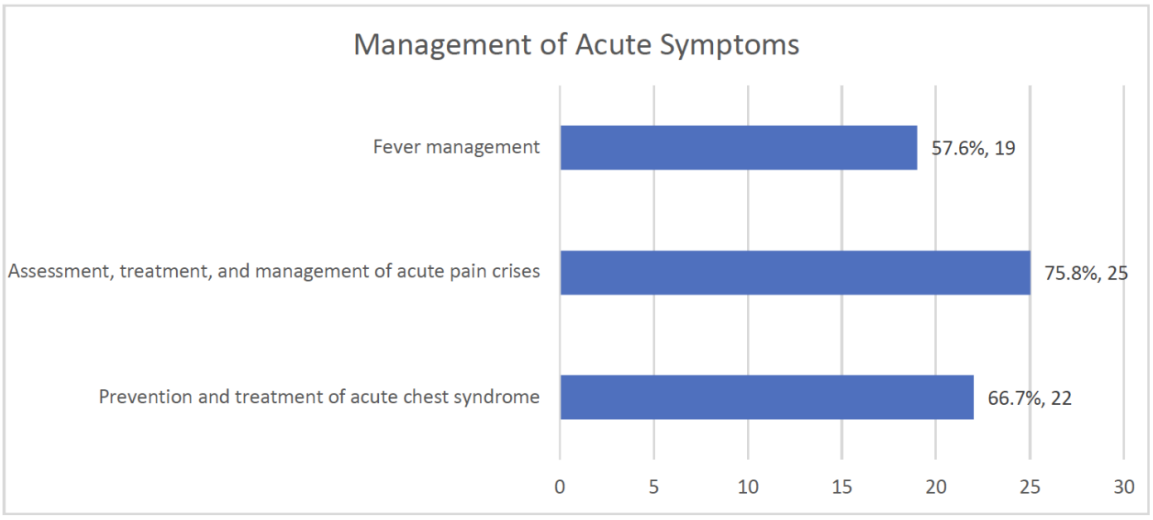


Figure 4: Management of acute symptoms

Acute chest syndrome and acute pain crisis
Figure 4. Management of acute symptoms

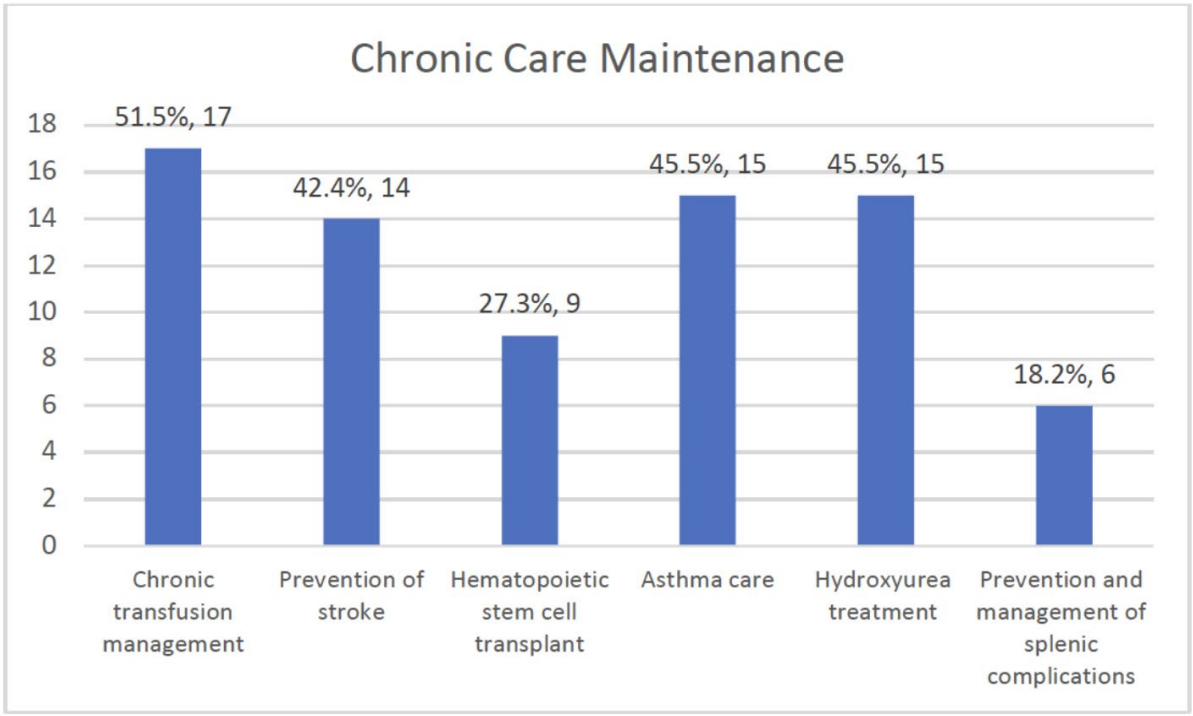


Figure 5: Chronic Care Maintenance

Chronic care maintenance
Figure 5. Chronic care maintenance

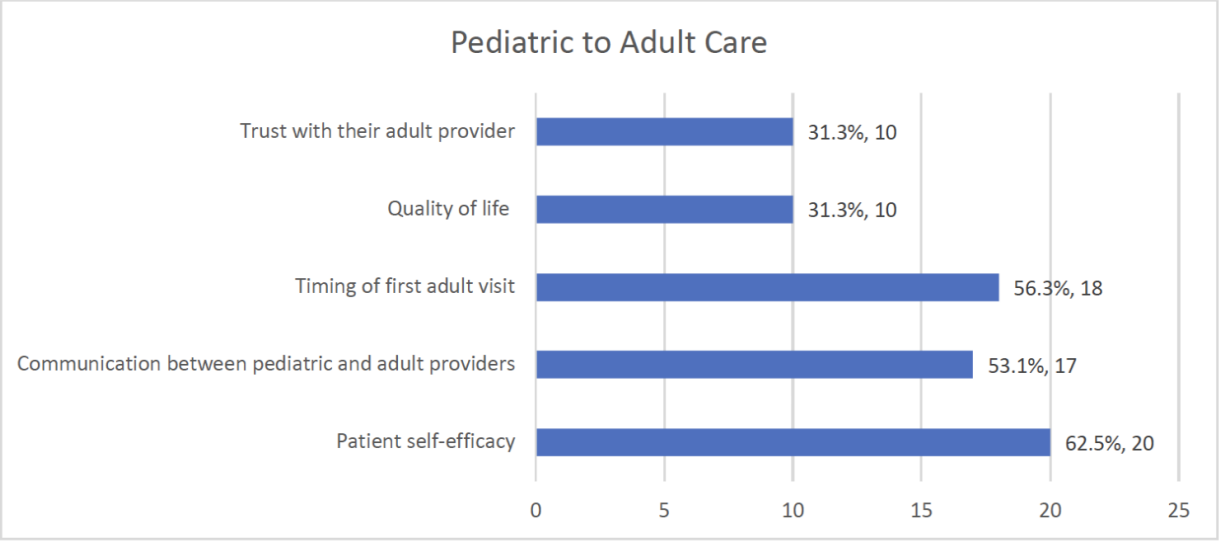


Figure 6: Transition from pediatric to adult care

Pediatric to adult care
Figure 6. Transition from pediatric to adult care

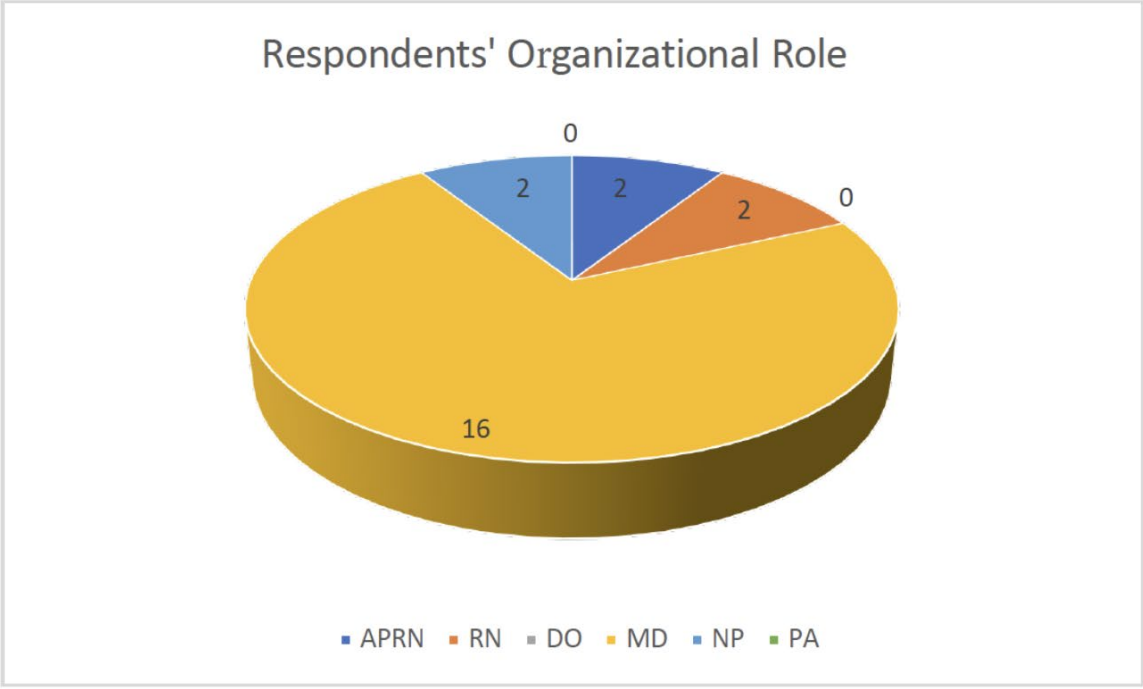


Figure 7: Respondents' qualifications

Respondents' organizational role
Figure 7. Respondents' qualifications

JSCDH-D-23-1517748

TIMELY OPIOIDS IN ADULTS WITH SICKLE CELL DISEASE PAIN CRISIS AFFECTS HOSPITALIZATION

Authors: Terrell D. Coring, Sr., PharmD, MD, Nikita Chintapally, MD, Reshmi Nair, PH.D, Hedy Smith, MD, PH.D

Affiliation: *Medstar Washington Hospital Center,*

Background: Vaso-occlusive crisis (VOC) is the most common complication seen in sickle cell disease (SCD) and accounts for the majority of SCD related emergency department (ED) visits and hospitalizations. Per American Society of Hematology (ASH) recommendations, acute pain related to SCD, in the acute care setting, warrants rapid (within 1 hour of ED arrival) assessment and administration of analgesia to optimize pain control. Our objective is to assess if there is an association between the time to administer IV opioids and length of hospital stay (LOS) and readmissions.

Methods: This is a retrospective chart review study including all adult patients presenting to our ED and admitted with a confirmed diagnosis of SCD and VOC between December 2016-February 2023. Data regarding gender, time of ED triage, timing, type, dose, and route of initial analgesia, length of stay, complications, and readmissions within 90 days were collected. The patients were stratified into five cohorts based on time to administer IV opioids and further stratified based on gender. The patients LOS measured in days were analyzed based on time to administer IV opioids amongst genders within specified cohorts (See tables 3 and 4). Analysis: Based on the time to administer IV opioids, patients were stratified into five cohorts. We used the Kruskal-Wallis test to compare the medians across the five cohorts. Readmission within 90-day was examined for all the stratified cohorts using Chi-squared test.

Results: 213 patients were included, 43% males and 57% females. There were no significant gender differences amongst cohorts and the time to administer opioids and LOS were not affected by gender (See Tables 3 and 4). The time to administer IV opioids ranged between 7 minutes to 918 minutes with a mean time of 169 minutes and median time of 143 minutes. LOS ranged from 1 day to 39 days with a mean of 7.4 days and median of 6 days. Trends in the data suggest that the LOS was more when time to administer IV opioids was longer (See Table 1). Readmissions within 90-days were higher when time to administer IV opioids was less than 1-hr or more than 4-hrs (See Table 2).

Conclusions: Our study indicates that administration of analgesia within 60 minutes of ED assessment as recommended by American Society of Hematology (ASH) and the National Institute of Health (NIH) guidelines may reduce the LOS by >1 day without any relation to gender. However, this cohort had a higher 90-day readmission rate when compared with the second and third treatment time points. The study limitations are the sample size, variability in patient cohort sickle genotypes, patterns of complications such as chronic pain, chronic opioids, psychosocial factors and institutional bias when treating pain. Standardized protocols have the potential to improve care and reduce variability in care delivery. Our study can inform institutional policy when managing sickle patients with VOC, by aligning our protocols with the recommended ASH and NIH guidelines.

Table 1: Time to administer IV opioids amongst the five cohorts and their LOS in days

Time to administer IV opioid (minutes)	N (%)	Mean days (SD)	Median Days (IQR)	Minimum days	Maximum days
0 to 60	35 (17%)	6.1 (7.1)	4 (2, 7)	1	38
61 to 120	52 (24%)	7.3 (7.0)	6 (3, 9)	1	37
121 to 180	49 (23%)	7.3 (6.7)	6 (3, 10)	1	36
181 to 300	51 (24%)	7.8 (7.1)	7 (3, 9)	1	34
More than 300	26 (12%)	8.7 (5.9)	6.5 (4,13)	1	23
p=0.140					

ABSTRACT BREAKOUT SESSION I
BASIC SCIENCE / HEALTH SERVICES

Presenting: Sunday, June 18, 2023
1:15 PM - 2:45 PM

JSCDH-D-21-1529766

IF YOU BUILD IT, THEY WILL ENROLL: MINORITY PARTICIPATION IN CLINICAL TRIALS

Authors: Sindy Mora-Garavito, MD, Sabahete Zeqiraj, Kelli Roe, PA, Francisco Castano, MPH, Aline Baday, Raven Dwyer, MPH, Kenneth Rivlin, MD, PhD

Affiliation: *NYC Health + Hospitals/Jacobi*

Background: The underrepresentation of minorities in clinical trials has long hindered the development of equitable healthcare interventions. This disparity is frequently attributed to individual-level factors such as mistrust, fear of experimentation, socioeconomic status, and cultural and language barriers. However, research on sickle cell disease clinical trials shows that minority underrepresentation cannot be explained by their "unwillingness to participate." Disparity research highlights the importance of "place" in healthcare inequities, suggesting that access to clinical trials at minority-serving healthcare institutions is a crucial systems factor.

Objective: To evaluate minority participation in pharmaceutical-sponsored sickle cell clinical trials at an inner-city public hospital and highlight the role of location in increasing minority enrollment in clinical trials.

Methods: We retrospectively analyzed enrollment data from sickle cell disease clinical trials at the public hospital between 2021 and 2023.

Results: During this period, we initiated six pharmaceutical-sponsored clinical trials, enrolling 22 patients aged between 04 years and 65 years. Willingness to participate was operationally defined as the ratio between subjects enrolled and the number eligible. Participation ranged from 33% to 100%. A comprehensive summary of the data is presented in the accompanying table.

Conclusions: Our findings underscore that providing access to clinical trials in community hospitals is critical for increasing minority enrollment. Despite the proximity of major academic medical centers, many minority patients opted for care at the public hospital, emphasizing the importance of offering clinical trials in community settings. We contend that prioritizing place is pivotal for reducing systemic healthcare disparities and ensuring that clinical research can be extended to diverse populations.

Star Day	Clinical Trial #	# Screened	# Enrolled other study	# Did not meet criteria	# Unable to contact	# Out Of stated	# of Eligible patients	# Not Interested	# Screen failure	# Enrolled	% Of Enrolment
19-Mar-22	1	65	-	17	40	-	8	5	0	3	37%
15-Jun-22	2	22	4	6	3	1	6	4	1	2	33%
31-Jan-22	3	53	6	37	2	1	4	2	-	2	50%
7-Oct-21	4	49	1	37	2	1	8	2	1	6	75%
10-Mar-22	4.a	3	-	-	-	-	3	-	-	3	100%
26-Apr-21	6	66	4	51	1	1	9	3	2	6	67%

Table

JSCDH-D-21-1523061

ISOLATION IMPAIRS PSYCHOSOCIAL FUNCTION IN SICKLE CELL DISEASE

Authors: Reina A. Lomeli, B.S., Donovan A. Argueta, Ph.D., Stacy B. Kiven, BIS, Natalie R. Garcia, B.S., Kalpna Gupta, PhD.

Affiliation: *University of California, Irvine*

Background: Chronic and unpredictable acute pain coexist with cognitive dysfunction in sickle cell disease (SCD). Managing chronic pain is crucial, though efforts are complicated by both physiological and affective contributors to pain. Affective state, which is severely impacted by the environment including stigma and social isolation, play a substantial role in pain perception and may further exacerbate psychological factors. Therefore, we examined if companionship and social isolation influence cognitive function and pain in SCD. In the present study, we examine the effects of social isolation on hyperalgesia, learning memory, and anxiety in a humanized mouse model of SCD.

Methods: The study utilized male HbSS-BERK sickle mice. The sickle mice are homozygous for knockout of both murine α and β globins and express human α and βS globin chains. Male mice were paired with opposite sex, age-matched companions at approximately 2 months of age for 8 weeks, at which point half of the male subjects were placed into isolation (one male/cage) or maintained with a companion of opposite sex (1 male + 1 female/cage). Isolation and companionship groups were maintained in general housing conditions and monitored. At 20 months of age, mice were assessed for hyperalgesia and cognitive behaviors. Mechanical hyperalgesia was assessed by counting paw withdrawal frequency (PWF) following 10 applications of a 1.0 g von Frey (Semmes Weinstein, Stoelting Co., Wood Dale, IL, USA) monofilament to the plantar surface of each hind paw. Cold hyperalgesia was assessed by measuring paw withdrawal latency (PWL, in seconds for the lifting of the paw the first time) and PWF following placement of mice onto a 4°C cold plate chamber (Stoelting Co.) over a 2-minute period. Musculoskeletal hyperalgesia was measured by testing grip force of each mouse's peak forepaw grip to a computerized grip force meter (SA Maier Co., Milwaukee, WI, USA) and normalizing by body weight. The cognitive behavioral assessment consisted of an open field test to assess anxiety-related behavior, which measured time spent and number of crosses through a central region. Working memory was assessed using novel object recognition and novel placement recognition tests to measure discrimination of novel objects and locations. Data shown as mean ± SEM and comparisons between companionship and isolation groups were completed using unpaired, two-tailed T-tests to determine statistical significance ($P< 0.05$)..

Results: Isolated male sickle mice experience greater hyperalgesia than male mice housed with an opposite-sex companion. Isolation induces greater PWF to mechanical (~80%, $P< 0.001$) and cold (~20%, $P< 0.1$) stimuli and reduces PWL to cold (~40%, $P< 0.05$), indicating exacerbated sensitivity. Spontaneous, non-evoked musculoskeletal hyperalgesia was not significantly altered by isolation ($P >0.05$).

Isolation also appeared to impact working and learning memory. Novel object recognition and novel object placement tests revealed reduced discrimination ratios in isolated mice (~25%, $P< 0.05$ and ~25%, $P< 0.05$), which are suggestive of impaired learning and memory function compared to mice with companionship. Open field test showed no significant differences ($P >0.05$) between isolation and companionship mice in time spent and number of crosses in the open field center area, indicating no detectable differences in anxiety-like behaviors.

According to cognitive tests, mice in companionship showed greater exploratory behavior and greater cognitive ability compared to those in isolation. Open field measures the percentage of time spent in exploration habits.

Conclusions: Herein we evaluated the role for social isolation on hyperalgesia and cognitive function in a humanized mouse model of SCD. Our data suggest that social environment through social isolation may play a dramatic role in exacerbating chronic hyperalgesia in SCD. As well, we provide novel findings that prolonged social isolation may also impact psychosocial functioning evinced by cognitive impairment. It is likely that that pain and cognitive function promote each other through brain's perception-based mechanisms from the higher brain centers. Thus, companionship and social interactions may be supportive of improving psychosocial function and reducing pain perception.

JSCDH-D-23-1523100

PALMITOYLETHANOLAMIDE MODULATES GAIT AND HYPERALGESIA IN SICKLE MICE

Authors: Kendall O'Daniel, B.S., Kristen Peterson, B.S., Donovan A. Argueta, Ph.D., Mya A. Arellano, B.S., Raghda T. Fouda, M.D., PhD, Natalie R. Garcia, B.S., Kalpna Gupta, PhD

Affiliation: *University of California, Irvine*

Background: Chronic pain is a major comorbidity of sickle cell disease (SCD). We observed that hyperalgesia correlated with gait impairment in humanized sickle mice, which show several clinical features of SCD including chronic pain. Gait impairment in SCD may comprise both peripheral and central mechanisms, including motor impairment and increased pro-apoptotic and pyknotic cerebellar Purkinje cells (Kiven et al., Front Immunol 2020). Cannabinoids are often used by subjects with SCD for pain relief but social stigma and intoxicating effects represent major barriers. The endocannabinoid palmitoylethanolamide (PEA) is a non-intoxicating lipid mediator produced throughout the body, which has demonstrated safety and efficacy in multiple clinical evaluations of treatment for chronic arthritic pain and may act via cannabinoid receptor activation. Herein, we evaluate the effect of chronic PEA administration on hyperalgesia and associated gait in a humanized 'sickle' mouse model of SCD.

Methods: We utilized the well-established ~6-month-old female, humanized sickle, transgenic mice HbSS-BERK which expresses >99% human α- and ßS- sickle hemoglobin (Hb) and complete knockout of murine α- and β-globins. Sickle mice recapitulate many of the clinical features of human SCD, which include spontaneous chronic pain, motor dysfunction and end organ damage. Mice were treated with PEA (ip, 20 mg/kg/d, Cayman Chemical, Ann Arbor, MI) or vehicle (7.5% DMSO, 7.5% Tween20, in sterile saline) for 14 days. For gait measurements, each mouse was individually placed in a transparent corridor (8 × 80 cm2) with acrylic glass floor panel mounted with LED lights, which produced a detectable touch sensor. Frustrated total internal refraction (fTIR) of the light path is evoked by physical contact of paw pads with the acrylic surface allowing for high-sensitivity detection (99 FPS, Lumenera Lt425C high-speed CMOS camera, Lumenera Corporation, Ottawa, Ontario) of walking behaviors. The MouseWalker software for video analysis was run in Matlab (The Mathworks, MA, USA). Both the program and manual are available online (biooptics.markalab.org). Mechanical hyperalgesia was analyzed as paw withdrawal frequency (PWF) in response to 10 applications of 1.0 g von Frey monofilaments. Following 2-week treatment, blood was analyzed for CBC (VetScan HM5, Zoetis, NJ, USA) to evaluate impact of PEA treatment on RBC and other cellular components.

Results: Treatment with PEA for 2 weeks ameliorates features of dysfunctional gait in adult female sickle mice. Mouse Walker evaluation was completed 14 days from start of treatment, and PEA-treated mice show increased limb swing speed (~30%, $P< 0.01$) and shortened swing duration (20%, $P< 0.05$) without affecting walking speed ($P >0.05$) compared to vehicle-treatment, which are suggestive of improved limb coordination and reduced sensitivity to mechanical forces during walking. Complementary to gait changes PEA treatment significantly decreased mechanical hyperalgesia, indicated by lower PWF, 1-hour following initial treatment and following 14-day treatment schedule (~55%, $P< 0.001$ and ~65%, $P< 0.001$, respectively) compared to baseline. PEA treatment decreased number of circulating white blood cells (WBCs, $P< 0.05$), with greatest reduction in circulating lymphocytes ($P< 0.1$). PEA had no

adverse effects on organ weight compared to vehicle treatment.

Conclusions: Dysfunctional gait associated with chronic pain is a debilitating comorbidity of SCD. Neurological, neuropathic, and immunological factors may contribute to peripheral and central mechanisms that drive gait dysfunction, including Purkinje cell damage and chronic inflammation. PEA has analgesic and anti-inflammatory effects on chronic pain in several clinical conditions, which includes reduction of mast cell activation – a key mechanism underlying pain and hypersensitivity in SCD. We provide the first evidence that PEA administration in a humanized sickle mouse model improves features of gait and inflammation. Future studies are required to investigate whether targeting neurological and/or immunological features of SCD with PEA may have a disease modifying effect.

JSCDH-D-23-1525257

PB-04 REDUCES MULTI-ORGAN PATHOLOGY IN TRANSGENIC SICKLE MICE

Authors: Betty S. Pace, MD[1], Monika Pilichowska, MD, PhD[2], Mayuko Takezaki, MS[1], Biarou Li, PhD[1], Aidan D. Faller, BS[3], Susan Perrine, MD, SM[4]

Affiliation: *[1]Augusta University, [2]Tufts University School of Medicine, Tufts Medical Center,Pathology & Laboratory Medicine, [3]Phoeniica Bioscince, Massachusetts General Hospital, [4]Phoenicia BioSciences, Boston Univ School of Medciine*

Background: Patients with sickle cell disease (SCD) experience morbidity in diverse organ systems. Hydroxyurea (HU) induces HbF and reduces many complications, but many adult subjects do not receive optimal doses due to myelosuppression. In a recent large utilization review, only 25% of US patients received HU; recently approved therapeutics were utilized in <3% of patients. As orally available small molecule therapies, particularly suitable for use with HU, are considered most feasible for wide application, we have evaluated 5 generations of HbF-inducing agents in preclinical and clinical studies. A repurposed candidate with a benign safety profile, PB-04, suppresses 4 repressors of the fetal globin gene promoter, has high-level inducing activity alone and additively with HU in patients' erythroid progenitors, nonhuman primates, beta YAC transgenic mice, and in patients with beta thalassemia intermedia (BTI) in an ongoing Phase 1b trial. Although Townes transgenic sickle mice do not induce HbF with many proven inducers, PB-04 was evaluated here for clinical effects.

Methods: Townes transgenic SCD mice, 4-7 months old, were treated intraperitoneally (IP) in 6 mice/ group for 4 weeks with PB-04 (30 mg/kg/once daily 3 days/week), HU (100 mg/kg/once daily, 5 days/week), PB-04 + HU, or water for untreated controls. At baseline, week 2 and 4, weights, complete blood counts (CBC), and flow cytometry were performed for percent reticulocytes (by acridine orange), HbF positive cells (F-cells), and mean fluorescence intensity (HbF/cell), and fetal globin mRNA was analyzed by RT-qPCR analysis. Pathology examinations performed on the lungs, liver, and spleen of all at the end of dosing.

Results: No adverse effects in behavior or growth were observed with HU or PB-04 treatments. HU treatment alone resulted in significantly decreased platelet, granulocyte, and monocyte counts; in contrast, PB-04 produced no significant decreases in peripheral blood counts. At 4 weeks, PB-04 and HU significantly increased F-cells by 2.3- and 2.2-fold and MFI by 4.8 and 5.2-fold, respectively. Spleen size decreased slightly in HU and combination treatments.

Marked pathologic abnormalities were observed in untreated sickle mice, including severe vascular congestion in pulmonary vessels, multiple large hemorrhagic splenic infarcts, and patchy hepatic necrosis. Widespread splenic extramedullary hematopoiesis (EMH) solely with erythroid precursors was observed in spleens of untreated and HU-treated mice, consistent with severe anemia. PB-04 treated mice had significantly less pulmonary vascular congestion, rare and small splenic infarcts, and EMH with all hematopoietic lineages present. Irreversibly sickled cells (ISCs) were predominant intravascularly in the untreated sickle controls, while normal-appearing RBCs were predominant in pulmonary vasculature of HU + PB-04 treated mice, as shown in Figure 1.

Conclusions: In these studies, F-cells and fetal globin mRNA expression were increased with HU and PB-04 treatments. Pathologic examinations demonstrate reduced multi-organ pathology and preservation of

all hematopoietic lineages in severe transgenic sickle mice treated with HU and PB-04 compared to decreased myeloid and platelet precursors with HU alone. With increased fetal globin expression observed in patients with BTI with PB-04 treatment, and evidence now of reduced clinical pathology in transgenic sickle mice, enrollment has begun in a cohort of patients with SCD on our clinical trial (NCT044326231).

JSCDH-D-21-1523565

ROLE OF RED CELL EXCHANGE AND RESTRICTED OPIOID CARE PLAN IN REDUCING HOSPITALIZATION

Authors: Sheinei Alan, MD, PhD[1,2], Chad Zik, MD[1], Rania Fusisi, RN[1], William Ershler, MD[1]

Affiliation: *[1]Inova Schar Adult Sickle Cell Center, [2]Inova Fairfax Hospital*

Background: Red cell exchange (RCE) is a therapeutic procedure that aims to reduce the number of sickle-shaped red blood cells in circulation and replace them with healthy donor cells. The use of RCE in sickle cell disease is primarily aimed at preventing or treating acute complications such as acute chest syndrome, stroke or priapism. However, by reducing the number of sickle-shaped cells in circulation, red cell exchange can help minimize episodes of vaso-occlusive pain crises (VOCs). In Patients with poor disease control and frequent pain crises and hospitalizations requiring parenteral opioids, RCE can be beneficial. Therefore, implementation of red cell exchange protocol with limitation of parenteral opioid use can potentially help reduce hospitalizations and achieve overall better disease control.

Methods: In our Center, we identified ten individuals with frequent hospitalizations and significant daily oral morphine equivalent use. These patients were then placed on a monthly RCE protocol resulting in suppressed hemoglobin S levels to below 40%. They were then instructed that only home oral opioids would be resumed if admitted to the hospital. Prior to initiation, patients were educated at length and during frequent clinic visits regarding the difference between chronic pain management and acute vaso-occlusive crisis. Individualized care plans for emergency department (ED) and inpatient pain management were revised and providers in the ED and hospitals were informed of this process. Each patient was also seen weekly to adjust to this change in disease management as well as identity and address psychosocial and comorbid complications impacting overall quality of life.

Results: We demonstrate that the implementation of red cell exchange protocol and restricted oral opioids only plan in the inpatient setting leads to reduced hospitalization among patients with sickle cell disease regardless of genotype, age and gender. For each patient placed on restricted care plan, acute care utilization was reduced compared to each patient's previous year's monthly admission rates. For example, in one patient with an average of 9 days of admission monthly in the five months preceding RCE and restricted care plan implementation, the total number of admitted days dropped to nearly zero. In another individual, the frequency and duration of hospital admissions reduced by nearly 50%.

Conclusions: Prolonged uncontrolled SCD with frequent VOCs will undoubtedly result in high acute care utilization, high opioid requirements and risk of development of chronic pain with subsequent opioid induced hyperalgesia and opioid failure. Sickle cell providers and patients need to be hypervigilant about this aspect of sickle cell disease and its management. We believe the implementation of red cell exchange protocol to help mitigate complications of VOC while focusing on chronic pain management is critical in subset of sickle cell patients. It is imperative that such patients are identified and educated when they reach a state of opioid failure and opioid induced hyperalgesia. The implementation of restricted oral opioids only plan will minimize behaviors leading to parenteral opioid use and help patients manage chronic pain in the outpatient setting. The implementation of this process should be accompanied with weekly clinic visits for close monitoring as well as tapering of outpatient oral opioids. In our center, we have seen not only a reduction in acute care utilization but also total oral

morphine equivalent use. Some of our patients on this protocol also report an improved sense of wellbeing. While the impact of the RCE program and the observed reduction in total morphine equivalents on overall quality of life needs to be further elucidated, we do note patient's reported improvement in sense of disease control and qualify of life.

JSCDH-D-23-1521465

TARGETING SICKLE CELL DISEASE PATHOBIOLOGY AND PAIN WITH NOVEL TRANSDERMAL CURCUMIN

Authors: Yugal Goel, PhD[1], Mya A. Arellano, B.S.[1], Raghda T. Fouda, M.D., PhD[1], Natalie R. Garcia, B.S.[1], Reina A. Lomeli, B.S.[1], Graham J. Velasco, HTL (ASCP) QIHC, MSHCA[2], Daniel J. Kerr, PhD[3], Probal Banerjee, PhD[3], Donovan A. Argueta, Ph.D.[1], Mihir Gupta, M.D.[4], Joel M. Friedman, M.D., PhD[5], Kalpna Gupta, PhD[1]

Affiliation: *[1]University of California, Irvine, [2]VA Long Beach Healthcare System, [3]City University of New York, [4]Johns Hopkins University, [5]Albert Einstein College of Medicine*

Background: Both acute and chronic forms of pain are major comorbidities of sickle cell disease (SCD). Chronic pain occurs in majority of adults with SCD and frequently requires long-term opioids. There is thus an urgent need to develop safe, non-opioid-based integrative approaches to prevent and/or treat chronic pain. The pathobiology of SCD includes inflammation, oxidative stress, neuroinflammation, hemolysis, and glial activation. Curcumin can attenuate all these pathobiologic mechanisms as well as inhibit nociceptor activation, offering the potential of an anti-nociceptive and disease-modifying therapy in SCD. We examined whether a novel topical curcumin gel, which promotes efficient transdermal systemic delivery, can ameliorate SCD pathobiology and prevent/treat chronic pain.

Methods: The present study utilized ~6-month-old male, humanized 'sickle', homozygous transgenic mice; the well-described HbSS-BERK preclinical model expresses >99% human sickle hemoglobin (Hb) and complete knockout of mouse α- and β-globins. These mice mimic the pathobiology and features of pain observed in persons with SCD. VasceptorTM (Vascarta Inc.), a gel containing 0.1 M of curcuminoids (derived from Curcugen, Dolcas, Inc.), or vehicle were applied (0.1 ml) topically to the abdomen on alternating days for 3 weeks.

Results: We first evaluated the bioavailability of topically applied curcumin (VasceptorTM) using high performance liquid chromatography. We found that curcumin levels peaked in the plasma (7.87 µg/ml) and blood cells (6.78 µg/ml) 60 min following administration. Thus, topically applied novel curcumin preparation VasceptorTM shows efficient bioavailability.

We next examined the anti-nociceptive efficacy of VasceptorTM in sickle mice. We observed that VasceptorTM application led to a significant decrease in paw withdrawal frequency (PWF) on a cold plate at 4˚C and PWF in response to von Frey monofilaments of 1.0 g at 1-hour post-treatment compared to baseline (BL) or vehicle treatment ($p < 0.05$), suggestive of a decrease in cold and mechanical hyperalgesia, respectively. This acute anti-nociceptive response of curcumin could be due to its known vasoregulatory effect. Compared to BL, mechanical hyperalgesia significantly decreased after 14 days of treatment and continued to decrease until 21 days ($p < 0.05$ and 0.01, respectively vs BL). Following 21-day treatment, mechanical (~29.4%, $p < 0.001$) and cold (~64%, $p < 0.001$) hyperalgesia were significantly reduced compared to vehicle. Significant amelioration of non-evoked cold avoidance at day 14 ($p < 0.01$ and 0.001 vs BL and vehicle, respectively), which continued through day 21 ($p < 0.001$ vs BL or vehicle), further suggest improvements in cold hyperalgesia. Together, these data indicate that topical VasceptorTM may have a disease modifying and/or direct anti-nociceptive effect in significantly reducing chronic hyperalgesia in sickle mice. Indeed, we observed a significant increase in hematocrit ($p < 0.05$), a reduction in reticulocytes ($p < 0.05$), and an

appreciable increase (43.2%) in hemoglobin in the blood of VasceptorTM-treated sickle mice vs vehicle. Lactate dehydrogenase (LDH) activity in the plasma of VasceptorTM-treated sickle mice was significantly lower vs vehicle ($p< 0.01$). Thus, improvement in red cell outcomes may be due to decreased hemolysis leading to a disease modifying effect.

VasceptorTM also significantly reduced global inflammatory marker serum amyloid-P (SAP; $p< 0.05$) and inflammatory cytokines in the skin secretome with a significant concomitant reduction in interleukins [2 ($p< 0.05$), 4 ($p< 0.01$), and 6 ($p< 0.01$)], monocyte chemoattractant protein 1 (MCP-1; $p< 0.01$), interferon-gamma (IFN-γ; $p< 0.05$), granulocyte macrophage-colony stimulating factor (GM-CSF; $p< 0.01$), and regulated on activation, normal T-cell expressed and secreted protein (RANTES; $p< 0.05$) compared to the vehicle treatment. MCP-1 has been shown to contribute to neuropathic pain, in addition to its role in inflammation. GM-CSF is known to stimulate granulocyte differentiation and growth and correlates with mast cell degranulation in sickle mice. Both RANTES and MCP-1 may also activate mast cells. We found that VasceptorTM treatment led to a significant decrease in cutaneous mast cell degranulation ($p< 0.001$) compared to vehicle. These data suggest an anti-inflammatory effect of VasceptorTM by targeting the release of cytokines and inhibiting granulocyte activity.

Conclusions: Transdermal curcumin significantly ameliorates hyperalgesia (chronic pain), inflammation and hemolysis and improves hematological parameters, which demonstrate its disease modifying and anti-nociceptive effects. The ease of topical application, increased bioavailability and non-toxic properties of transdermal curcumin suggest that if started early in age it may prevent chronic pain in SCD by targeting sickle cell pathobiology without any adverse effect.

ABSTRACT BREAKOUT SESSION II
HEALTH SERVICES

Presenting: Sunday, June 18, 2023
3:00 PM - 4:30 PM

JSCDH-D-21-1522084

ACCESS TO DENTAL CARE IN SICKLE CELL DISEASE PATIENTS IN AN URBAN HOSPITAL SETTING

Authors: Barbara Speller-Brown[1], Mark J. Nunes, DDS[2], Anupama R. Tate, DMD, MPH[2]

Affiliation: *[1]Childrens National Hospital, [2]Childrens National Hospital/ George Washington University*

Background: It is estimated that Sickle Cell Disease (SCD) affects approximately 100,000 Americans. Its incidence is especially profound in the African American community, affecting 1 in 365 births, and 1 in 13 Black children carry the Sickle Cell Trait 1. It is documented that there are barriers in access to healthcare for persons with SCD, specifically in comparison to individuals with genetic disorders such as hemophilia and cystic fibrosis 2. Because most patients with SCD are on prophylactic penicillin therapy until at least the age of 5, caries risk in this population has been documented at a lower rate than their otherwise healthy peers 3,4. Despite the documented association between SCD and oral health, there is no good data to reflect whether this patient population experiences increased barriers to access to dental care. The purpose of this project was to determine if significant barriers exist between patients with SCD and access to dental care in the Children's National Hospital system, and to work with stakeholders to offer potential solutions to these barriers.

Methods: After obtaining IRB approval, data was collected during routine Sickle Cell Disease clinic visits at two different sites for Children's National Hospital in the District of Columbia via parental questionnaire from July 2022 – November 2022. Domains included ability to access oral healthcare, previous access to oral healthcare, family attitudes toward oral healthcare, history of dental caries, history of dental fillings, and history of dental pain. Descriptive statistics were utilized to narrate attitudes and ability to access dental care. Simple quantitative statistics were utilized to describe disease prevalence.

Results: One hundred fifty-four patient responses were recorded. Forty-five percent of patients identified as female, 55% male. Ages ranged from 1 to 21 years.

Twenty-two percent of respondents (N=34) reported distaste for attending dental visits or only going to the dentist if absolutely necessary.

Thirty-five percent of respondents (N=52) report their child has been diagnosed with dental caries and 21% of these respondents (N=11) report no history of dental restorations.

There was no significant difference between pre-adolescent (1-12y) and adolescent (13-21y) persons in accessing dental care. The adolescent group experienced a higher lifetime caries burden.

Conclusions: Subjectively, the majority of families in the CNH SCD clinic have similar dental access to otherwise healthy peers.

This study population had a lower overall caries rate, but a higher rate of untreated decay compared to the national average. This study highlights the importance of interdisciplinary care in patients with sickle cell disease. More studies are needed to validate this data outside of the Children's National Hospital System.

JSCDH-D-21-1524016

A NURSE-LED EDUCATION INITIATIVE TO IMPROVE INFUSION CENTER MANAGEMENT OF SICKLE CELL PAIN

Authors: Jessica Groesbeck, RN, BSN, OCN, Stefanie Sacknoff, PA-C, Srila Gopal, MD,

Affiliation: *UC San Diego Health*

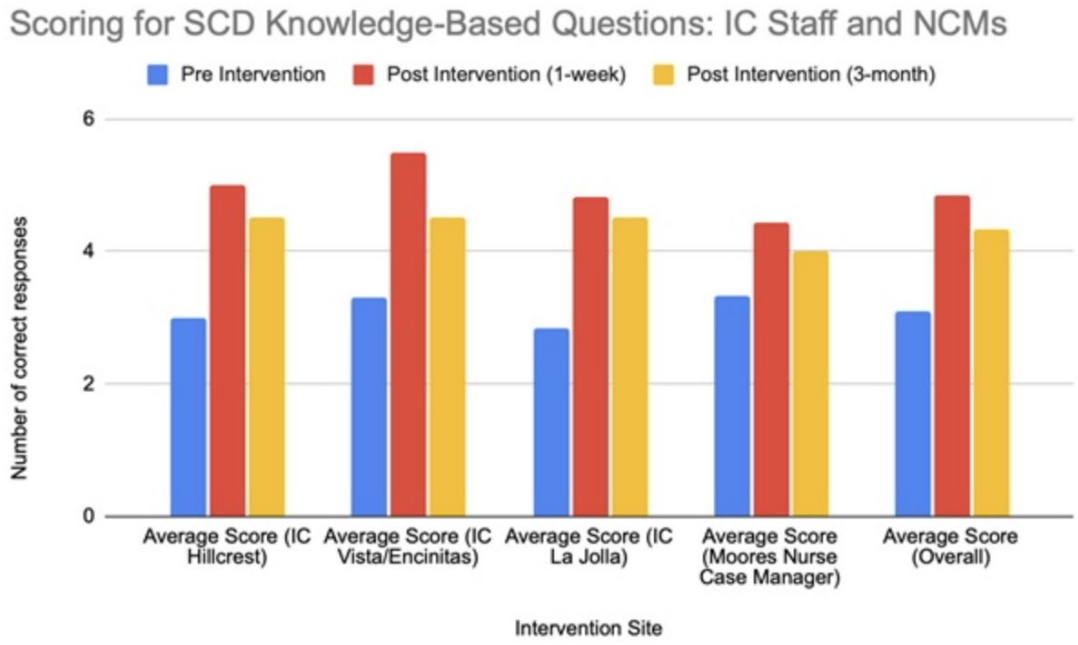
Background: Patients with Sickle Cell Disease (SCD) experience acute pain episodes for which they seek care in the Emergency Department (ED). SCD predominantly affects African Americans, and adults with SCD face significant disparities and bias when seeking care in the ED (Haywood, et al., 2013; Mills, et al. 2011). In January 2019, the Sickle Cell team of a large academic hospital in Southern California established a same-day infusion center (IC) management strategy for SCD pain crises as an alternative strategy to seeking care in the ED. This program was well accepted by patients, and the IC volume of sickle cell patient visits grew (270 visits in the two years pre-IC vs.1076 visits in two years post-IC).

Importantly, at the health system's sickle cell center, infusion services are embedded within the cancer center. As such, the majority of staff are trained in oncology and not SCD. As IC volume grew, a need was identified to increase staff knowledge and comfort level managing sickle cell pain in the ambulatory IC setting.

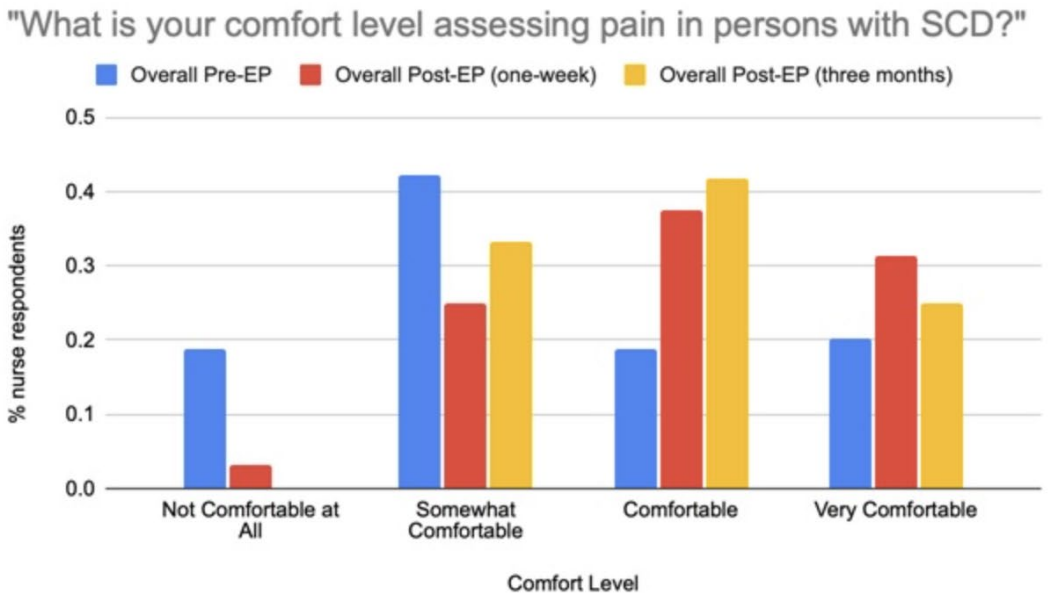
Methods: A Quality Improvement (QI) project with Plan Do Study Act framework was implemented: an educational presentation (EP) and 9-question survey were created and administered in a hybrid (in-person/virtual) format to IC staff and nurse case managers across the health system's 3 IC sites. Survey responses were collected pre-EP, post-EP(1-week) and post-EP(3-month). The metrics used to evaluate the project's impact were: (1) respondents' overall scores on knowledge-based questions; (2) reported comfort level assessing pain; and (3) reported comfort level administering pain interventions in patients with SCD. Finally, IC visit volume pre-/post-EP intervention was evaluated as an outcome measure using retrospective chart review in the electronic health record.

Results: Out of 81 attendees, 64, 31 and 12 surveys were returned pre-EP, post-EP(1-week) and post-EP(3-month), respectively. The overall average scores of knowledge-based questions answered correctly (out of 7) increased from 3.09 (pre-EP) to 4.84 (post-EP(1-week)) and 4.33 (post-EP(3-month)). The total responses of "Comfortable" and "Very comfortable" increased for both comfort level assessing pain (39.1% pre-EP v. 68.8% post-EP(1-week) v. 66.7% post-EP(3- month)) and comfort level administering pain interventions (39.1% pre-EP to 71.9%% post-EP(1-week) v. 75% post-EP(3-month)). Overall IC visit volume increased by 39.1% when comparing the 3 months preceding and following the intervention period.

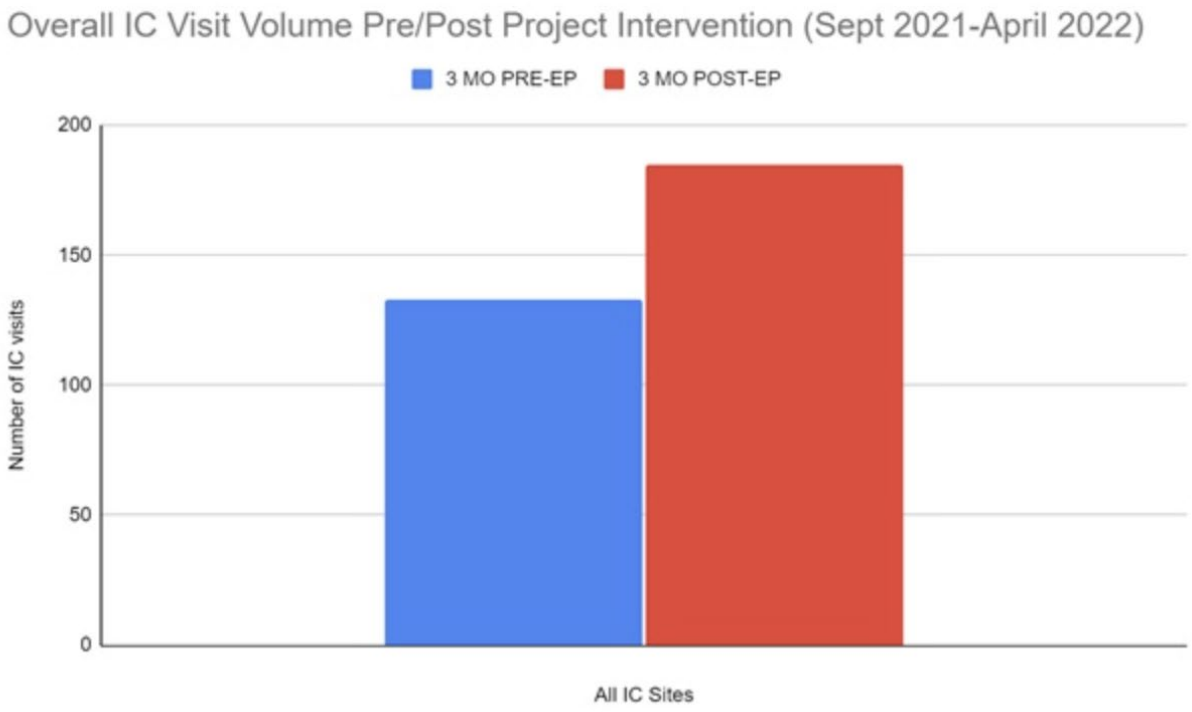
Conclusions: Implementing an education intervention creates an opportunity to optimize staff competence and confidence in treating patients with SCD. The observed impact on visit volume suggests a role for nurse-led education in facilitating broader institutional acceptance of an evidence-based IC strategy. Overall, the project promotes the integration of evidence-based guidelines into clinical practice in order to improve care for a vulnerable patient population.



Scoring for SCD Knowledge Questions: IC Staff & NCM, pre-EP v. post-EP(1-week) v. post-EP(3-month)



IC Staff & NCM Comfort Level Assessing Pain in Persons with SCD, pre-EP v. post-EP(one-week) v. post-EP (three-month)



Overall IC Visit Volume Pre/Post Project Intervention (Sept 2021-April 2022)

JSCDH-D-21-1525301

IMPLEMENTING SICKLE CELL TRAIT EDUCATION AND COUNSELING INTO PEDIATRIC CARE: A QI PROPOSAL

Authors: Nizar Tangour, MD, MS[1], Deena Shaltout, MD[1], Ginger Davis[2], Kristina Emeghebo, MD[3], Kathrin Balaoura, MD[3], Jason Mack, MD[1], Kenneth Rivlin, MD, PhD[4]

Affiliation: *[1]NYC Health + Hospitals/Metropolitan, [2]Sickle Cell Thalassemia Patients Network, [3]NYC Health + Hospitals/Queens, [4]NYC Health + Hospitals/Jacobi*

Background: In 1975, New York State (NYS) became the first in the nation to incorporate sickle cell disease (SCD) testing into its newborn screening program (NBS). By 2006, all 50 states had adopted this practice, leading to a significant reduction in SCD-related morbidity and mortality. NYS developed an extensive tracking system and established 28 hemoglobinopathy centers to deliver expert care for infants identified with SCD through newborn screening.

A notable consequence of this screening process is the identification of individuals with sickle cell trait (SCT), which has essential ethical, social, reproductive, and clinical implications. Although NYS Department of Health recommends informing parents of their child's SCT status and providing education, counseling, or referral to pediatric hematologists or genetic counselors, preliminary data and literature reveal that these non-mandatory recommendations are not consistently followed.

Objective: To utilize quality improvement methodology in developing an implementation plan to ensure that individuals with SCT identified through NBS receive appropriate education and counseling across New York City's public hospital system.

Methods: Through our SCD quality improvement Project ECHO, we designed a QI initiative with the following aims: 1) increase the proportion of infants with SCT whose parents receive appropriate education and counseling to 85% by June 2024, and 2) enhance the percentage of 16-year-olds with SCT who obtain suitable education and counseling to 50% by June 2024. We identified key metrics, barriers, drivers, and change ideas to be implemented to achieve these objectives. We have begun to pilot this plan across 4 of the 6 NYS-designated hemoglobinopathy centers within our system.

Results: Our current state is defined only by the recommendation that primary care providers document and provide counseling and education if SCT found on NBS. Preliminary baseline evaluations show wide variations in actual practice for infants. For adolescents, SCD identification and counselling and education is essentially done for filling out forms or participation in sports. Our targeted state is that this becomes part of our standard workflow for infant and adolescent care.

Our approach is summarized in our driver diagram (figure). The primary drivers are prepared proactive practice team, informed, engaged patients and parents, and a supportive integrative community. Key change ideas include SCT trait education (reproductive implications and rare complications) for providers and community including “talking points,” decision support and standardized documentation in electronic medical records, streamlined referral systems to pediatric hematology, genetic counseling, and community health workers, and improved SCT handouts for patients/family and community.

Conclusions: While there is growing consensus within the sickle cell community that SCT education and

appropriate counseling should be integrated into the standard workflow of pediatrics, challenges remain in its implementation. We have found that appropriate documentation, education, and counseling for SCT identified as part by newborn screening is lacking in our practice. We have developed a model for its implementation in infancy and adolescents and are working to implement it through our quality improvement Project ECHO across 4 NYS designated hemoglobinopathy centers. We expecting to be able to expand this across our healthcare system.

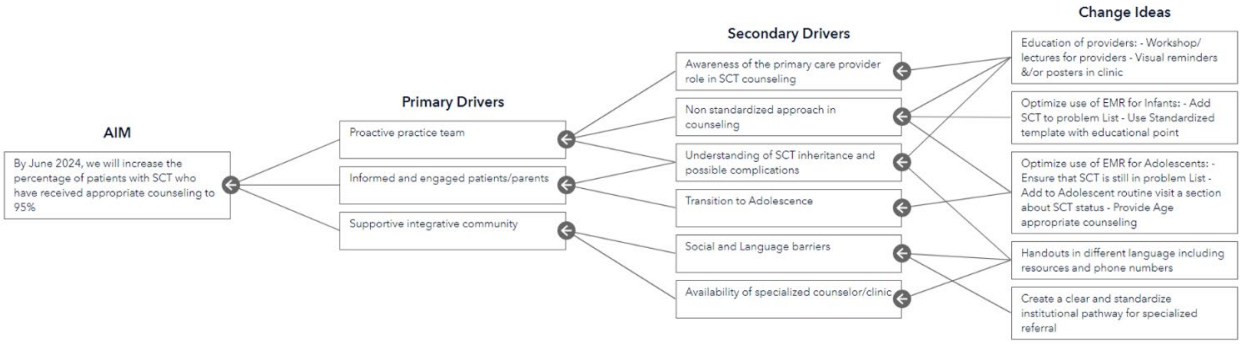


Figure 1: Driver Diagram
SCT: Sickle cell trait, EMR: Electronic Medical Records

JSCDH-D-21-1516960

MEDICAID ENROLLMENT PATTERNS IN THE FIRST 3 YEARS FOR CHILDREN WITH SCD

Authors: Sophia Horiuchi[1], Sarah L. Reeves, PhD, MPH[2], Hannah K. Peng, MPH[2], Jhaqueline Valle, MPH[3], Mary Hulihan, DrPH[4]

Affiliation: *[1]Sickle Cell Data Collection Program, [2]University of Michigan, [3]Tracking California, [4]CDC/NCBDDD/DBD*

Background: Secondary data analyses focused on children with sickle cell disease (SCD) often use Medicaid data as it is a rich source of prescription, outpatient utilization, and eligibility information. However, little is known regarding the population of children with SCD that are not enrolled in Medicaid given limited availability of healthcare data for this population.

Since 2006, all babies born in the United States are screened for SCD through their states' newborn screening (NBS) programs. NBS is the only consistent way in which to identify a population-based cohort of children with SCD irrespective of severity, healthcare utilization, or insurance coverage. Importantly, NBS data includes information on disease variant, which is not included within Medicaid data. Disease variant may be associated with disease severity and determines specific care recommendations such as transcranial doppler and hydroxyurea prescription.

The objective of this analysis was to leverage NBS and Medicaid data within two states' Sickle Cell Data Collection programs, California (CA) and Michigan (MI), to determine patterns of Medicaid enrollment and length of coverage among children with SCD in the first three years of life, and to assess variation in enrollment and coverage by sex and disease variant.

Methods: The inclusion criteria for this retrospective cohort study were individuals identified by the California and Michigan NBS programs with a confirmed diagnosis of SCD and born in the years 2015 to 2017. Within each state, newborn screening records were linked to Medicaid enrollment data to determine monthly Medicaid enrollment status, starting at the month of birth (i.e., zero months of age) and continuing for an additional 36 calendar months. Medicaid enrollment was stratified by sex and sickle cell disease variant (sickle cell anemia vs other). Sickle cell anemia was defined as the variants Hemoglobin SS or Sβ0-thalassemia. For those that were ever insured by Medicaid in the first three years, enrollment and coverage patterns were described by age of first enrollment, total months of enrollment, and gaps in coverage after enrollment. Counts less than eleven for California and less than five for Michigan were suppressed in accordance with data use agreements.

Results: Newborn screening programs identified 246 (CA) and 184 (MI) children born with SCD within each state from 2015 to 2017 (Table 1). Among these children, 54% (CA) and 48% (MI) were male, and 57% (CA) and 54% (MI) had sickle cell anemia.

In California, 66% of children were enrolled in Medicaid in the first three-years of life. These children had a median of 33 months (IQR =13) of Medicaid coverage. The median age at first Medicaid enrollment was 2 months (IQR =10), and 84% were continuously enrolled after first enrollment (Table 2). Among those enrolled in Medicaid, 59% had sickle cell anemia.

In Michigan, 94% of children were enrolled in Medicaid in the first three-years of life. These children had a median of 37 months (IQR=7) of Medicaid coverage. The median age at first Medicaid enrollment was 0 months (IQR=0), and 60% were continuously enrolled after first enrollment. Among

those enrolled in Medicaid, 57% had sickle cell anemia.

Conclusions: Medicaid enrollment and coverage patterns for children with SCD differed between the two states. These results provide key context to interpret results from studies that use Medicaid data by providing the proportion of the SCD population that are not included in the data, as well as the distribution of disease variant that affects disease severity and care. However, Medicaid is a significant provider of insurance for children with SCD, reflecting its utility as a rich source of information for SCD researchers.

	California		Michigan	
	SCD Births	Ever Enrolled in Medicaid	SCD Births	Ever Enrolled in Medicaid
Total SCD Births, n (row %)	**246**	162 (66%)	**184**	173 (94%)
SCD Type, n (col %)				
Sickle Cell Anemia	139 (57%)	96 (59%)	99 (54%)	92 (57%)
Other Sickle Cell Disease Genotype	107 (43%)	66 (41%)	85 (46%)	81 (43%)
Sex, n (col %)				
Male	132 (54%)	89 (55%)	88 (48%)	82 (54%)
Female	114 (46%)	73 (45%)	96 (52%)	91 (46%)

Table 1: Medicaid enrollment in the first 3 years of life for individuals with SCD born in 2015-2017

	California	Michigan
Total ever enrolled in Medicaid	**162**	**173**
Age of first enrollment into Medicaid (months)		
Median (IQR)	2 (10.0)	0 (0)
Gaps in Enrollment, n (col %)		
Continuously enrolled	136 (84%)	104 (60%)
Not enrolled for 1-5 months after first enrollment	--*	27 (16%)
Not enrolled for 6-12 months after first enrollment	15 (9%)	22 (13%)
Not enrolled for >12 months after first enrollment	--*	20 (12%)
Months of Medicaid Enrollment in first 3 years		
Median (IQR)	33 (13)	37.0 (7.0)

*Counts less than 11 are suppressed

Table 2: Patterns of Medicaid Coverage

JSCDH-D-23-1525197

USE OF PRIOR AUTHORIZATION FOR STATE MEDICAID MANAGEMENT OF SICKLE CELL DISEASE THERAPIES

Authors: Mariah J. Scott, MS, MPH, Emma Andelson, MPA, Maggie Jalowsky

Affiliation: *Sick Cells*

Background: Past studies have shown that over half of people living with sickle cell disease (SCD) use Medicare or Medicaid as their primary payer (Brousseau et al., 2010). Sick Cells undertook a landscape analysis of Medicaid coverage and access policies to identify barriers to accessing sickle cell disease (SCD) therapies. The research illuminates the state of access to SCD therapies across Medicaid programs and highlights discrepancies across coverage criteria. Findings illustrate the variation in coverage management and high frequency of utilization management techniques such as prior authorization (PA) to limit Medicaid beneficiaries' access to newer disease-modifying treatments for SCD.

Methods: Sick Cells identified six sickle cell disease therapies (Adakveo, Endari, Oxbryta, Siklos, Droxia, and Hydroxyurea) for study inclusion. Sick Cells worked with a healthcare consulting firm to analyze 2023 Medicaid preferred drug lists and coverage policies for state Medicaid programs. Current drug policies for each state, specific to sickle cell disease, were reviewed as of February 2023. Coverage policies for both medical and pharmacy benefits were included. The project team evaluated the PA landscape through product-specific analyses of utilization management strategies and state-by-state definition of PA requirements. Only coverage policies for state fee-for-service (FFS) programs were used in this analysis; managed Medicaid plans in states were excluded.

Results: Newer disease-modifying therapies for SCD are infrequently listed with open access on preferred drug lists (PDL) across states (Endari (4 states); Oxbryta (2); Adakveo (0)). Results demonstrate the high prevalence of PA requirements by drug across states (Adakveo (37 states); Oxbryta (31); Sikos (26); Endari (25); Droxia (7); Hydroxyurea (6). Inconsistent PA criteria were identified, including discrepancies in requirements related to diagnosis confirmation, specialist prescriber, number of vaso-occlusive crises within the past 12 months, trial and failure of hydroxyurea, and reauthorization requiring a reduction in pain crises from baseline.

Conclusions: Sick Cells' results find that state Medicaid programs have taken various approaches to manage SCD therapies, highlighting opportunities for increased consistency and transparency. These differences in state coverage approaches can lead to access barriers for SCD patients and may have unintended impacts, including delays in treatment.

JSCDH-D-21-1525208

VALUE-BASED PAYMENTS AND SICKLE CELL DISEASE: A RAPID LITERATURE REVIEW

Authors: Francisco Castano, MPH[1], Jean-Bernard Poulard, MD[2], Marcy Stein-Albert, MD[2], Kenneth Rivlin, MD, PhD[1]

Affiliation: *[1]NYC Health + Hospitals/Jacobi, [2]NYC Health + Hospitals/Queens*

Background: The National Academy of Science, Engineering, and Medicine's strategic plan for addressing sickle cell disease (SCD) highlights the need to develop reimbursement models that support coordinated healthcare delivery and support services for SCD patients. Currently, reimbursement models for healthcare services can be divided into fee-for-service payment models and value-based payment (VBP) models, which reward providers based on quality goals and cost savings. VBP includes a range of reimbursement arrangements such as pay-for-performance, bundled payments, shared savings programs, and capitation. Evidence supporting VBP comes from clinical effectiveness, cost-effectiveness, improved patient experience/satisfaction, and improved provider satisfaction/engagements which define quality measures that inform payers.

Objective: To conduct a rapid literature review and synthesize existing evidence and identify knowledge gaps regarding the application of VBP models for SCD population, ultimately informing payers.

Methods: We conducted a rapid semantic search using the AI search engine “elicit.org” and a citation search using “litmap.com.” Our search questions addressed the challenges in implementing value-based payments, different reimbursement outcomes and key quality indicators. We reviewed the titles and abstracts and selected papers useful to meet our objective.

Results: The literature supports that comprehensive care and disease-modifying drugs for SCD patients are both clinically and cost-effective. Various models of comprehensive sickle cell centers have been developed, and quality of care indicators have been established, providing critical information for payers. However, the major gap identified is the lack of sickle cell-specific examples of successful implementation of VPB models.

Conclusions: The rapid literature review reveals that value-based payment models show promise in improving quality of care and cost-effectiveness for SCD patients. However, the current lack of SCD-focus on the implementation of VPB models, highlights the need for additional research and case studies. These findings can serve as a foundation for the adoption of VBP models tailored to the unique needs of the SCD population, ultimately increasing the use of disease modifying drugs and enhancing care coordination, patient outcomes, and the patient experience.

ABSTRACT BREAKOUT SESSION II
CLINICAL RESEARCH

Presenting: Sunday, June 18, 2023
3:00 PM - 4:30 PM

JSCDH-D-23-1525304

BIOMARKER RESPONSE TO ADMINISTRATION OF ADAKVEO IN A "REAL WORLD" CLINICAL SETTING

Authors: Jennell White, PhD[1], Corrine Packer, MBBS[2], Xiufeng Gao, MD[3], Andrekia Williams-Montgomery, NCPT[2], Gershwin Blyden, MD/PhD[2], Lanetta Bronte-Hall, MD/MPH/MSPH[2], Patrick Hines, MD/PhD[3]

Affiliation: *[1]Wayne Stae Univesity, [2]Foundation for Sickle Cell Research, [3]Functional Fluidics*

Background: Sickle cell disease (SCD) is characterized by frequent and unpredictable vaso-occlusive episodes (VOEs) often associated with microvascular blood cell adhesion. P-selectin adhesion has been shown to be a mediator of pathologic adhesive interactions involved in VOEs and is a therapeutic target for SCD-modifying therapies. Adakveo is an FDA-approved (2019) P-selectin monoclonal antibody (mAB) therapy shown to reduce the annualized frequency of VOEs in SCD patients. Due to the lack of clinically available blood-based biomarkers to define an individual's cellular-level response to therapeutic p-selectin inhibition, providers often rely on the clinical assessment of VOE frequency and intensity to assess an individual's response to anti-p-selectin therapy. This may have contributed to the recently failed Phase 3 clinical trial. In this report, we monitored the cellular-level response to the therapeutic p-selectin inhibition by Adakveo administered in a real-world clinical setting using the flow adhesion of whole blood to P-selectin (FA-WB-Psel) assay.

Methods: This study was a retrospective assessment of clinical blood function biomarkers [FA-WB-VCAM, FA-WB-Psel, and mechanical fragility index (MFI)] in individuals with SCD who were administered Adakveo at the Foundation for Sickle Cell Disease Research (FSCDR) between January 2019 through June 2022. Flow adhesion assays were performed using pulsatile, shear flow (1.67Hz, 1.0 dyne/cm2). Mechanical fragility (MF) tests measure labile RBC sub-populations (MFI_S) and the cumulative hemolysis (MFI_L) followed by applied mechanical shear stress. SCD patients that received at least 3 biomarker evaluations within 1-year pre-Adakveo and up to 1-year post-Adakveo treatment were included in this analysis. FSCDR received an IRB waiver to confirm therapy start/stop dates and patient-reported pain/fatigue in patients who received care. Pain scores >7 was considered severe pain. We also calculated the annualized rate of clinic visits where patients presented with severe pain by quantifying the number of clinic visits with patient-reported pain intensity >7 and adjusted for time (months). The non-parametric Wilcoxon matched pairs signed rank test was used to test the statistical differences between groups. Data are presented as mean ± standard error of mean. A p-value < 0.05 was considered statistically significant.

Results: Out of a total of 3070 clinical samples obtained, 557 samples were analyzed from 15 unique patients who met study criteria. The average whole blood flow adhesion to P-selectin (FA-WB-Psel) was significantly lower post-Adakveo treatment (meanpre=84.80±8.28 cells/mm2, meanpost=48.05±9.49 cells/mm2, p=0.002); however, there was no significant change in FA-WB-VCAM (p=0.53), MFIS (p=0.55), and MFIL (p=0.50), or fatigue (Figure 1A and B). SCD patients with FA-WB-Psel critical values pre-Adakveo treatment were completely resolved in 71% (10 of 14) of patients and unresolved in 29% (4 of 14). One of the 15 patients had a pre-adakveo FA-WB-Psel level below the critical threshold, and this individual had an increase in FA-WB-Psel post-Adakveo treatment. The annualized rate of clinic visits with severe pain post-Adakveo

treatment was unchanged (2.1±0.52, 1.5±0.27, p=0.63) (Figure 1C).

Conclusions: We provide the first description of functional cellular-level monitoring of patient response to Adakveo administration in a real-world clinical environment. We observed a statistically significant decrease in whole blood adhesion to p-selectin, suggesting that FA-WB-Psel may be an effective monitoring biomarker to assess cellular-level responses to Adakveo administered in clinically. Most (94%) clinic visits and 82% of pre- and post-Adakveo treatment visits were to manage SCD acute pain crisis which may have contributed to the lack of significance reported in the annualized clinic visits with severe pain post-Adakveo treatment. One patient was below the critical range pre-Adakveo treatment but exceeded the critical value post-treatment similar to pre-clinical adhesion models. These data suggest treating SCD patients with low FA-WB-Psel levels may place these patients at risk for stimulated adhesion while taking Adakveo therapy. Ongoing analyses are underway to establish whether FA-WB-Psel may be a potential surrogate endpoint for VOEs in clinical trials of anti-p-selectin therapy as well as for anti-p-selectin therapy administered in the real-world clinical setting.

JSCDH-D-23-1521118

IMPACT OF IV CONTRAST EXPOSURE DURING VASO-OCCLUSIVE CRISIS ON SICKLE CELL DISEASE (SCD)

Authors: Olivia Perez de Acha, MD, Terrell Coring, MD, Shuchi Pandey, MBBS, Krishna Shah, MBBS, Nikita Chintapally, MD, Jhanvi Dave, MBBS, Hedy Smith, MD, PH.D,

Affiliation: *MedStar Georgetown/Washington Hospital Center*

Background: Sickle cell disease (SCD) affects more than 100.000 Americans, that can experience vaso-occlusive crisis (VOC). It can present with signs and symptoms that overlap with pulmonary embolism (PE), e.g. pleuritic chest pain, shortness of breath, hypoxia or sinus tachycardia. Hence, it is not uncommon that patients with SCD are exposed routinely to IV contrast (IV-cx) to rule out PE with every VOC recurrence. We hypothesized that exposure to IV-cx increases blood viscosity temporarily and therefore exacerbates RBC sickling with worsening oxidative stress and VOC.

Methods: This was a retrospective chart review study, where we analyzed all encounters for VOC at the ED of MedStar Washington Hospital Center in between 2021-2022. We excluded those not admitted to the inpatient service and discharged from the ED, those not exposed to IV-cx to rule out PE and those without 3 other VOC admission without IV-cx exposure to compare as control. Herein, will discuss 33 patients' results. A total of 132 admissions were analyzed for 33 patients (1 with IV-cx + 3 regular admissions without IV-cx exposure), each patient serving as their own control, acknowledging the heterogeneity of SCD VOC. For control admissions we looked at the 3 closest in time from the admission with IV-cx exposure. Severity of each VOC (with or without IV-cx exposure) was determined by the composite of lab results, clinical and treatment data for each admission, creating our own scoring system "VOC Severity Index" (Table 1). Scores were given from 0-4, >3 representing end-organ-damage, and 4 reserved for RBCs exchange transfusion. Maximum score was 39. We collected data on new PE, new DVT, therapeutic anticoagulation, basic demographics and SCD genotype. Results were analyzed through Graphpad Prism software, using paired t test. This study received IRB approval from MedStar Health Research Institute.

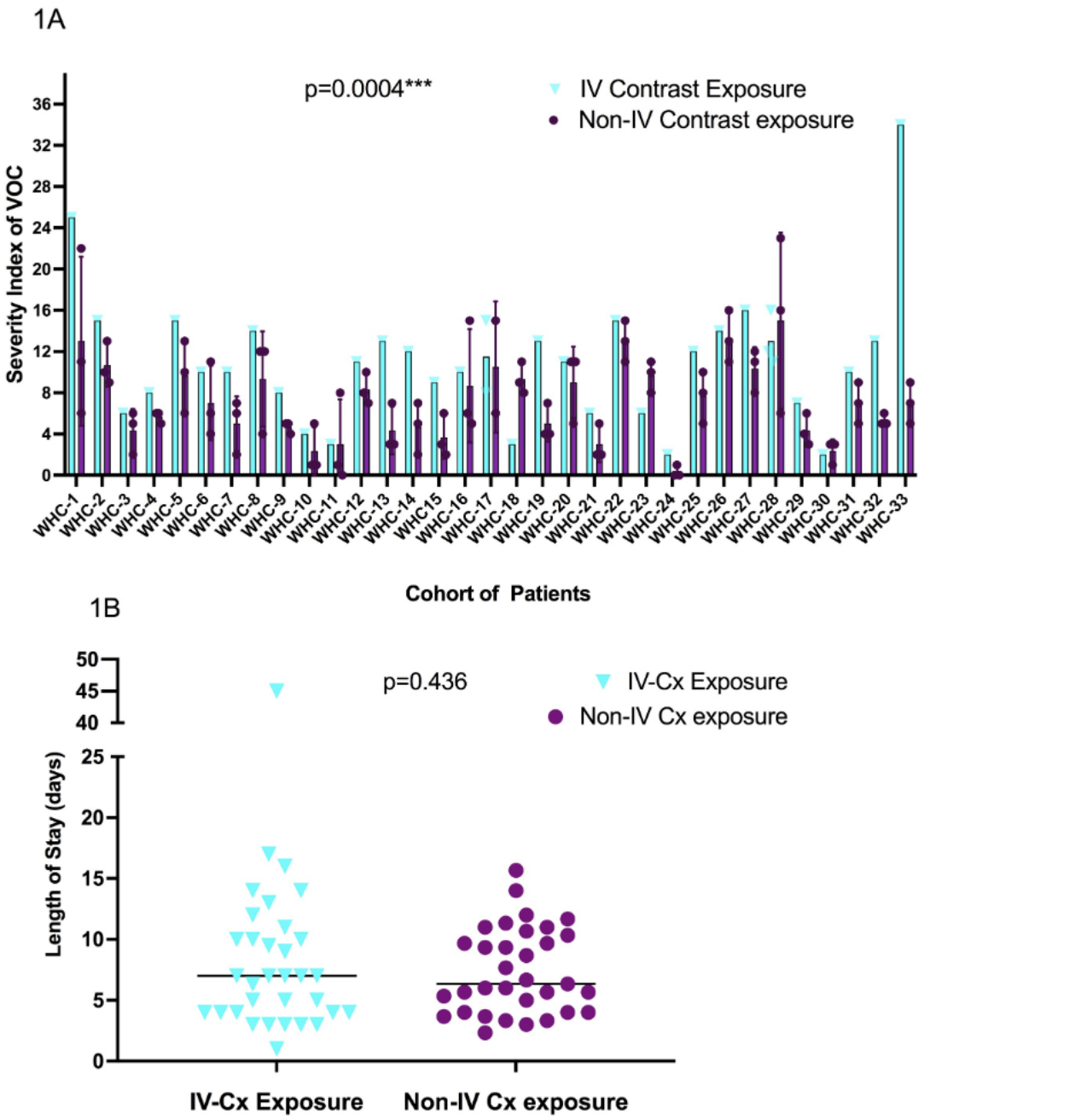
Results: 54.5% (18/33) were female, mode of age was 25, 86% were HbSS, and 100% were Black. We compared the severity index of the admission with IV-cx exposure against the mean severity index score of the 3 other VOC admissions without IV-cx exposure. VOC severity index was higher for the admission related with IV-cx exposure in 90% (30/33) patients (p= 0.0004***) (Fig 1A). CT chest with PE protocol was negative in 100% (33/33). No DVT was reported in the totality of 132 encounters. Acute Kidney Injury (AKI) was noted in 15.0% (5/33) of patients when IV-cx was used, vs 7.0% (7/99) when no IV-cx was used. Length of stay was not significantly different (p=0.436) (mean IV-cx stay: 8 days vs. mean non-IV cx stay: 7.8 days) (Fig 1B). RBCs exchange transfusion happened in 10% of total encounters analyzed (14/132), being 42% (6/14) of the situations when IV-cx was used. Acute chest syndrome (ACS) developed in 19 admissions of 10 patients (6 female/4 male). Interestingly, 42% (8/19) of ACS happened when IV contrast had been used, and only 7/19 were managed with RBC exchange transfusion. In 1 encounter with IV-cx exposure, patient developed ACS and acute respiratory distress syndrome (ARDS) requiring extracorporeal membrane oxygenation (ECMO), which is an end-organ damage and treatment modality not reflected in our severity index score.

VOC Severity Index means were similar in female vs male patients. Likewise, gender was not related to higher frequency of AKI, exchange transfusion or length of stay.

Conclusions: IV-cx exposure is associated with worsening in the severity of the VOC, manifested as more severe pain, and need of escalation of treatments, albeit with no increase in the LOS. Iv-cx should be avoided in SCD patients in VOC, when possible. PE should remain low in the differential in the setting of VOC, despite overlapping symptoms. Our findings are limited in the nature of retrospective chart review and small number of patients. Further analysis with prospective larger cohorts are needed for a better understanding on the role of IV-cx exposure and VOC.

VOC Severity Index	Variables	Score			
ON ADMISSION			**DURING ADMISSION**		
Sat02%	<92	3	Development of AKI	Yes	3
	> 92	0		No	0
Temperature	>37.8	1	PCA pump (Dilaudid)	Yes	1
	>39	2		No	0
Heart Rate	>105	1	Ketamine gtt	Yes	3
	>120	2		No	0
	>140	3	Exchange transfusion	Yes	4
Hemoglobin	<9	1		No	0
	<8	2	Simple transfusion	Yes	2
	<7	3		No	0
WBC	>13.1	1	Acute Chest Syndrome	Yes	3
	>18	2		No	0
	>20	3	Total hemoglobin drop	>1.0	1
Total bilirubin	>3	1		>2.0	2
	>6	2		>3.0	3
LDH	>300	1	MAXIMUM SCORE		39
	>450	2			
	>650	3			
Lactic Acid	>2.6	3			
Acute Chest Syndrome	Yes	3			
	No	0			
Reticulocytes absolute count	>0.400	1			

Table 1: Calculations for the Vaso-Oclusive Crisis Severity Index Score.
Chart review was done in 132 admissions. Score system ranged from 0-4, 3 reflecting end-organ-damage. 4 was reserved for the most aggressive treatment represented in exchange transfusion. Maximum score was 39, which indicate multi-organ failure. AKI; Acute Kidney Injury, defines as increase in serum creatinine by ≥0.3 mg/dl (=26.5 kmol/l) within 48 h. LDH; Lactate Dehydrogenase. PCA, Patient-Controlled Analgesia. Sat02%, Saturation of Oxygen. WBC; White Blood Cell count.



Vaso-ooclusive crisis severity index

Figure 1. A) Vaso-occlusive crisis Severity Index calculations. Analysis for 33 patients was done by pairs. Each IV-contrast exposure admission (33 encounters) was given a severity index score, and was compared against the mean average of 3 other VOC admissions (99 encounters) where patient had not been exposed to IV-contrast to rule out PE. Triplicates were chosen to account for heterogeneity as SCD manifest different in each patient, but usually follows a pattern within the same patient. Mean VOC Severity Index scores were significantly different (p=0.0004***). Individual values are represented with mean SD. B) Length of stay analysis. Analysis of 132 encounters by length of stay were not significantly different when compared admissions with IV contrast exposure vs non IV contrast exposure within the same patient. Mean LOS was 8 days for IV contrast exposure vs 7.8 when the patient was not exposed to IV contrast (p=ns).

JSCDH-D-23-1530206

LEG ULCER PREVALENCE AND OUTCOMES IN A REAL-WORLD STUDY OF PATIENTS TREATED WITH VOXELOTOR

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Background: Sickle cell disease (SCD) is an inherited disorder driven by the polymerization of sickle hemoglobin in the deoxygenated state, leading to chronic hemolytic anemia. Leg ulcers are a severe, chronic, and often recurrent complication of SCD and occur in approximately 14% to 18% of patients in the US and more commonly in men and those with the HbSS genotype. Leg ulcers are painful and decrease physical function, increase pain interference, and cause psychosocial impacts. Symptoms and complications associated with leg ulcers include chronic hemolysis, edema, impaired endothelial function, venous incompetence and vaso-occlusion. Leg ulcers in SCD are commonly treated with standard wound care, including mechanical/autolytic debridement and various dressings. Studies on local and systemic treatments have been inconclusive. Voxelotor is a sickle hemoglobin polymerization inhibitor approved in the United States and the United Arab Emirates for the treatment of SCD in patients aged ≥4 years, and in Oman, Saudi Arabia, and Kuwait for patients aged ≥12 years. Voxelotor is approved in the European Union and Great Britain for the treatment of hemolytic anemia in patients with SCD aged ≥12 years. Phase 3 clinical trials have shown that voxelotor increases hemoglobin and reduces markers of hemolysis with an overall favorable safety profile. The Retrospective Real World Oxbryta Data Collection and Analysis Study (RETRO; NCT04930328) aimed to characterize real-world safety and the effectiveness of voxelotor in patients aged ≥12 years. RETRO expands upon our understanding of voxelotor, providing valuable insights to drive future studies that will investigate descriptive results. Here we present leg ulcer prevalence and data before and during voxelotor treatment in the RETRO study.

Methods: RETRO is a post-marketing study designed to collect and characterize real-world, retrospective laboratory and clinical data from patients aged ≥12 years with SCD (all genotypes) treated with voxelotor as part of their usual care. The study was conducted at 9 US sites. Data from patients treated with voxelotor for ≥2 consecutive weeks and with available medical records 1 year before and up to 1 year after their first voxelotor dose were included.

Results: A total of 216 patients with a mean (SD) age of 33.5 (14.21) years were included. Overall, 8.8% (19/216) of patients had an active or previous leg ulcer any time during the 1-year period before voxelotor initiation and up to 1-year post-treatment. Of these patients, 57.9% (11/19) reported 1 leg ulcer, and 42.1% (8/19) reported ≥2 leg ulcers; the mean (SD) age of these 19 patients was 40.5 (10.9) years, 36.8% (7/19) were female, and 79.0% (15/19) were Black or African American. Most patients (84.2% [16/19]) had the HbSS genotype, and 57.9% (11/19) were taking hydroxyurea. Five leg ulcers in 4 patients resolved before voxelotor initiation. A total of 23 leg ulcers were ongoing at treatment initiation, meaning

the ulcer either occurred before the first dose of voxelotor or occurred after treatment initiation. A total of 14/23 (60.9%) leg ulcers occurred before voxelotor initiation, with half of them (7/14) resolving after voxelotor initiation. The other 9 leg ulcers (39.1% [9/23]) occurred after voxelotor initiation; of these, 5 (55.6%) resolved during voxelotor treatment. Further descriptive analyses of leg ulcer events and resolutions are ongoing.

Conclusions: RETRO is the largest multicenter, retrospective study of voxelotor to date. Data reported here describe the prevalence and incidence of leg ulcers in this cohort and the reported outcomes before and during voxelotor treatment. The limitations of this retrospective study include small sample sizes, reliance on data captured in medical records, and the lack of a control group. To address this gap in knowledge, the Resolution of Sickle Cell leg Ulcers with Voxelotor (RESOLVE) study, which is designed to investigate the impact of voxelotor on leg ulcers, is currently underway (NCT05561140).

JSCDH-D-23-1511450

LOW ARGININE BIOAVAILABILITY AND CLINICAL OUTCOMES IN CHILDREN WITH SICKLE CELL PAIN

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Affiliation: *Emory University*

Background: Global arginine bioavailability ratio (GABR) (Arginine/[Citrulline+Ornithine]) is associated with clinical outcomes including pain, pulmonary hypertension risk and mortality in SCD. Arginine replacement therapy demonstrates opioid-sparing effects, improved blood pressure and cardiovascular function, and shorten length of hospital stay. We have previously shown that patients with SCD-VOE have an altered arginine metabolome associated with pain severity. Arginine is a conditionally essential amino acid synthesized from citrulline in the kidneys. During VOE, hemolysis leads to the release of erythrocyte-arginase (arginine-metabolizing enzyme) that converst arginine into ornithine. Arginine-to-ornithine ratio (arg/orn) is a biomarker of arginase activity, while GABR incorporates the impact of kidney function on global arginine bioavailability. The association between arginine bioavailability and clinical outcomes has not been sufficiently explored in children with SCD-VOE. This study objective is to evaluate associations between arginine bioavailability and clinical outcomes in children with SCD-VOE receiving intravenous (IV) arginine replacement therapy (ART) compared to placebo.

Methods: Prospective single-center double-blind randomized controlled trial (RCT) of IV ART (TID, up to 7 days) in children with SCD age 3-21 years hospitalized for VOE requiring IV opioids. Patients with significant liver/renal dysfunction or those previously enrolled were excluded. Subjects were randomized into 1 of 3 arms: 1) 100 mg/kg/dose Arg, standard dose (SD), 2) loading dose: 200 mg/kg followed by SD or 3) placebo. Demographics, total parenteral opioid (TPO) use (morphine equivalents, mg/kg) time to crisis resolution (time of study drug delivery to last IV opioid in hours), pain scores and targeted amino acids were obtained before treatment & at discharge. A biorepository for future mechanistic studies was also created. Mean±SD, paired t-tests and Pearson correlation analyses between groups were performed where appropriate.

Results: Safety results of this RCT have been previously reported (Reyes et al, Am J Hematol 2022). Plasma arginine levels were low at VOE presentation (mean 50±28 µM), with low arginine levels (< 60 µM) found in 74% of patients. ART increased arginine concentration by 182% ($p< 0.0001$) compared to 26% ($p=0.24$) in placebo. Arg/orn correlates to arginase concentration ($r= -0.38$, $p< 0.0001$). Time-to-crisis-resolution strongly correlates with TPO ($r=0.72$, $p< 0.0001$). Arginine bioavailability at presentation inversely correlates to time-to-crisis-resolution for both arg/orn and GABR ($r= -0.39$ $p=0.01$) in the placebo arm only, which was lost after arginine therapy (arg/org: $r= -0.04$, $p=0.7$; GARB: $r= -0.03$, $p=0.7$). Similar trends are observed for TPO. Time-to-crisis-resolution correlates with age ($r=0.2$, $p=0.03$). When patients were stratified into two groups based on age ≤12 and >12 years, subjects >12 years old showed a strong negative correlation between plasma arginine levels and time-to-crisis resolution ($r= -0.5$, $p=0.02$) in the placebo group only. Pain scores at presentation positively correlate with TPO ($r=0.33$, $p=0.04$) in the placebo arm only, which was lost after arginine therapy ($r=0.03$, $p=0.76$).

Conclusions: In the absence of ART, low arginine bioavailability predicts worse clinical outcomes in patients with SCD-VOE, including a longer time-to-crisis resolution and a higher use of IV opioids. Arginine bioavailability may represent a novel biomarker of SCD-pain severity. This data further confirms arg/orn as a surrogate for arginase activity reflective of hemolytic rate as previously described. ART ameliorates the influence of arginine deficiency on clinical outcomes related to pain in SCD. An NHLBI/PECARN supported Phase-3 multi-center trial of ART enrolling 360 children with SCD (SCD Treatment with Arg Therapy – STArT) is ongoing.

JSCDH-D-23-1547931

PAIN SENSITIVITY AND CENTRALIZED PAIN IN ADULTS WITH SICKLE CELL DISEASE AND CONTROLS

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Background: In Sickle cell disease (SCD), chronic pain is prevalent, debilitating, and significantly impactful. Understanding the underlying mechanisms of pain sensitivity in individuals with SCD is crucial for developing targeted interventions and personalized pain management strategies. In particular, the degree of central, or nociplastic pain has now been measured using descriptive surveys, and brain center connectivity patterns on MRI imaging have been associated with nociplastic pain.

Methods: Therefore, to gain deeper insights into the complex pathophysiology of pain in SCD, we explored in adults with SCD the potential relationship between pain sensitivity, assessed by a questionnaire, cerebral blood flow (CBF) assessed by imaging, and centralization or chronification of pain as measured by the PainDETECT questionnaire. A total of nine adults diagnosed with SCD (mean age = 33.2 years, 55.6% female) were recruited for this study. Pain sensitivity was evaluated using a non-disease specific standardized pain sensitivity questionnaire (PSQ), which included self-report measures assessing pain threshold, pain tolerance, and pain perception. Cerebral blood flow was assessed using magnetic resonance imaging. Furthermore, participants were also assessed using the PainDETECT questionnaire to detect centralized or nociplastic pain.

Results: Preliminary findings indicated a consistent trend suggesting that higher pain sensitivity, as measured by the pain sensitivity questionnaire, was associated with lower cerebral blood flow; however, the observed correlation did not reach statistical significance ($p > 0.05$), likely due to the small sample size. Additionally, there was a positive correlation between the PainDETECT questionnaire results, reflecting neuropathic pain components, and the pain sensitivity questionnaire, although statistical significance was not achieved due to the limited sample size.

Conclusions: This hypothesis-raising pilot study provides initial insights into the potential link between pain sensitivity and cerebral blood flow in adults with SCD. It provokes research with larger cohorts and more robust study designs, to establish a significant association between pain sensitivity, cerebral blood flow, and neuropathic pain components. Such studies may lead to improved pain treatment approaches and enhanced patient care in SCD.

JSCDH-D-23-1522173

SAFETY AND EFFICACY OF VOXELOTOR IN CHILDREN AGED 2 TO < 4 YEARS WITH SICKLE CELL DISEASE

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Affiliation: *[1]Children's Hospital of Philadelphia, [2]Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Center, [3]Department of Paediatric Haematology, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, [4]NOVO NORDISK A/S, [5]East Carolina University Brody School of Medicine, [6]Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, [7]Barts Health NHS Trust, [8]University College London NHS Foundation Trust, [9]Pfizer Inc, South San Francisco, [10]Children's Healthcare of Atlanta*

Background: Sickle cell disease (SCD) is driven by polymerization of deoxygenated sickle hemoglobin (HbS), resulting in chronic hemolytic anemia and vaso-occlusive crises. Ischemic injury and inflammation that begins early in children with SCD are associated with progressive end-organ damage, substantial morbidity, and early mortality. Voxelotor, a HbS polymerization inhibitor, is approved in the US for patients aged ≥ 4 years. Here we report the safety and efficacy of voxelotor in children with SCD aged 2 to < 4 years.

Methods: Patients with baseline hemoglobin (Hb) ≤ 10.5 g/dL received once-daily voxelotor 1500 mg weight-based–equivalent dosing for up to 48 weeks (HOPE-KIDS Part D; NCT02850406). Concomitant hydroxyurea was allowed if stable for ≥ 1 month at enrollment. Efficacy outcomes included change from baseline to week 24 in Hb and markers of hemolysis. Safety was assessed by treatment-emergent adverse events (TEAEs).

Results: As of July 29, 2022, 23 patients aged 2 to < 4 years (median [range] age, 2.0 [2–3] years; median [range] weight, 14.6 [10–19] kg; 60.9% male) were enrolled; 82.6% were HbSS and 17.4% were HbSβ0 in genotype; 69.6% were receiving hydroxyurea. At baseline, mean (SD) Hb was 8.4 (1.0) g/dL. Efficacy evaluation was performed in 20 patients with hematology measurements who completed the week 24 assessment. At week 24, the mean (SD) increase in Hb from baseline was 0.6 (1.0) g/dL, with 45% (95% CI: 23.1–68.5) of patients achieving a Hb response > 1 g/dL. Seventy-five percent of patients (15/20) achieved a Hb response > 1 g/dL at some time point during the study. Reductions in hemolysis markers—indirect bilirubin (mean change from baseline: –24.5%; n=18) and reticulocytes (mean change from baseline: –3.65%; n=19)—were observed. At least 1 non–SCD-related TEAE occurred in 91.3% of patients (21/23). The majority of TEAEs were grade 1 or 2. Three patients had ≥ 1 TEAE considered related to study drug (nausea, abdominal pain, diarrhea). No patients permanently discontinued treatment due to TEAEs.

Conclusions: Voxelotor increased Hb and decreased markers of hemolysis in children with SCD aged 2 to < 4 years. Voxelotor was well tolerated, and no new safety signals were detected. These results, which are consistent with those in children aged 4 to < 12 years (HOPE-KIDS Part C) and adolescents and adults aged ≥ 12 years (HOPE trial), support the use of voxelotor as a potential strategy for early mitigation of hemolysis and anemia associated with SCD in children aged ≥ 2 years.

ABSTRACT BREAKOUT SESSION II
CLINICAL TRIALS/CLINICAL EPIDEMIOLOGY

Presenting: Sunday, June 18, 2023
3:00 PM - 4:30 PM

JSCDH-D-23-1524041

ARGININE THERAPY FOR CHILDREN WITH SICKLE CELL DISEASE PAIN: A RANDOMIZED CONTROLLED TRIAL

Authors: Claudia R. Morris, MD[1], Nitya Bakshi, MD[1], Deb Leake, CPNP[1], Scott Gillespie[1], Lou ann Brown, PhD[1], Frank Harris[1], Dunia Hatabah, MD[1], Kirshma Khemani, MD[1], Alexus Locke[1], Chris A. Rees, MD[1], Mark Griffiths, MD[1], Loretta Reyes, MD[1], Polly Kumari[1], Sruti Shiva, PhD[2], Carlton Dampier, MD[1]

Affiliation: *[1]Emory University, [2]University of Pittsburgh*

Background: Vaso-occlusive pain episodes (VOE) are the leading cause of emergency department (ED) visits & hospitalization in patients with sickle cell disease (SCD). During SCD-VOE, patients develop an acute arginine (Arg) deficiency. Arginine replacement therapy (ART) has shown opioid-sparing effects, improves blood pressure & cardiopulmonary function & decreases length of hospital stay. Though we have previously demonstrated that intravenous (IV) ART improves mitochondrial function, the precise mechanisms by which Arg mediates these positive effects remain unclear. The study objective is to determine the role of IV ART as adjuvant in the management of SCD-VOE

Methods: Prospective single-center double-blind randomized controlled trial (RCT) of IV ART (TID, up to 7 days) in children with SCD age 3-21 years hospitalized for VOE requiring IV opioids. Patients with significant liver/renal dysfunction or those previously enrolled were excluded. Subjects were randomized into 1 of 3 arms: 1) 100 mg/kg/dose Arg, standard dose (SD), 2) loading dose: 200 mg/kg followed by SD or 3) placebo. Demographics, total parenteral opioid (TPO) use (morphine equivalents, mg/kg) time to crisis resolution (time of study drug delivery to last IV opioid in hours), pain scores, patient reported outcomes (PROMIS) & mitochondrial function were obtained before treatment & at discharge. The primary outcome measure was TPO use between study arms. Hypothesis tests & unadjusted & covariate-adjusted fixed & mixed effects generalized linear regression models were used, as appropriate, to compare cross-sectional & longitudinal outcomes within & between randomization arms. This protocol utilized IND#66943 (Sponsor-Morris), registered with ClinicalTrials.gov (NCT02536170).

Results: 1,548 patients were screened, 266 were eligible, 114 consented, & 108 were randomized. Safety results of this RCT have been previously reported (Reyes et al, Am J Hematol 2022). Demographics & clinical outcomes of subjects randomized by treatment arm are provided in Table 1. While statistically insignificant, there was a clinically relevant decrease in TPO & time to crisis resolution in both ART arms compared to placebo. The placebo group required 45% higher TPO & experienced >15 hours longer mean time to crisis resolution compared to combined ART-treated groups when adjusted for HU use, continuous age and sex. Among children < 17 years, the placebo group (n=33) required 80% more TPO compared to combined ART groups (n=57; p=0.075). No differences in ED vs discharge pain scores or patient/parent PROMIS reports across arms were found. Mitochondrial Complex V activity was higher (p=0.02) & protein carbonyl levels were lower (p=0.003) at ED visit in patients on Hydroxyurea (HU). Notably mitochondrial Complex IV & V activity increased significantly in both ART arms while there was no change in the placebo group (Fig 1A &B, p< 0.001); protein carbonyl levels in platelet rich plasma decreased in both ART groups (Fig 1C, p< 0.001), suggesting a decrease in oxidative stress that increased in the placebo arm (p=0.02). Greatest

mitochondrial improvement occurred with ART loading dose.

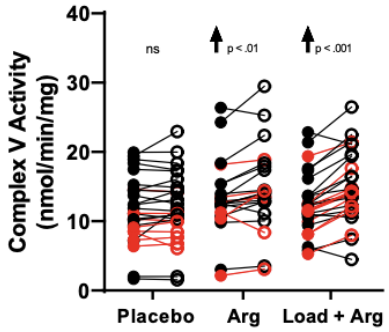
Conclusions: ART increases mitochondrial activity & decreases oxidative stress in children with SCD-VOE. This is the first report to suggest a HU-related impact on mitochondrial activity in SCD. Prior reports show that Complex V inhibition leads to increased mitochondrial oxidant production in platelets from SCD patients. Acute improvements in Complex IV & V function & decreased oxidative markers with ART are consistent with Arg-induced reductions in mitochondrial oxidant generation. ART improves symptoms associated with MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) suggesting an impact of Arg on mitochondrial activity that may be beneficial in SCD. Given emerging data supporting a link between mitochondrial function and pain, improved mitochondrial activity may mechanistically contribute to decreased pain & ultimately less opioid requirement with IV ART , as well as have further implications for improved metabolism and oxidative signaling in SCD. In this RCT, ART also demonstrated clinically relevant opioid-sparing & a decreased time to crisis resolution that was statistically insignificant. A larger sample size may elucidate potential differences; we are currently enrolling 360 children in an ongoing PECARN-endorsed multicenter Phase 3 RCT (SCD Treatment with Arg Therapy – STArT).

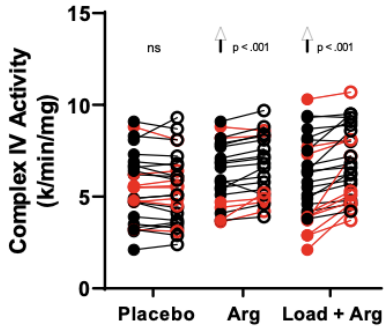
Table 1: Demographics and clinical outcomes by study group

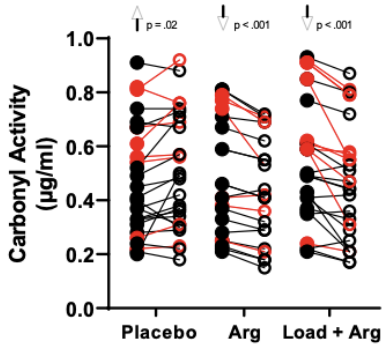
Characteristic	Overall Cohort	Arginine	Loading Dose Arginine	Placebo
	N=108	N=36	N=36	N=36
Age, Mean ± SD	12.7 ± 3.8	13.1 ± 3.7	13.1 ± 3.7	11.8 ± 4.0
Sex, n (%)				
Male	52 (48%)	17 (47%)	19 (53%)	16 (44%)
Genotype, n (%)				
HbSs/HbS-β^0 thalassemia	78 (72%)	26 (72%)	25 (69%)	27 (75%)
HbSC/HbS-β^+ thalassemia	30 (28%)	10 (28%)	11 (31%)	9 (25%)
Race				
African American	108 (100%)	36 (100%)	36 (100%)	36 (100%)
Ethnicity				
Hispanic/Latino	1 (1%)	0 (0%)	0 (0%)	1 (3%)
Hydroxyurea use, n (%)				
Yes	73 (68%)	24 (67%)	24 (67%)	25 (69%)
HCU in prior year, Median (IQR)	3.0 (2.0, 6.0)	2.5 (2.0, 6.0)	4.0 (2.0, 6.5)	3.0 (1.0, 5.0)
HCU for pain in prior year*, Median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	2.5 (1.0, 5.5)	2.0 (1.0, 4.0)
Had ≥3 pain episodes HCU in prior year, n (%)	51 (47%)	17 (47%)	18 (50%)	16 (44%)
Highest pain score at presentation, Median (IQR)	9.0 (8.0, 10.0)	9.0 (8.0, 10.0)	10.0 (8.0, 10.0)	9.0 (8.0, 10.0)
Laboratory values at enrollment, Mean ± SD				
WBC (X 10-9/L)	12.3 ± 5.1	13.03 ± 5.15	13.2 ± 5.3	10.7 ± 4.6
Hemoglobin (g/dL)	9.3 ± 1.7	9.47 ± 1.70	9.27 ± 1.51	9.28 ± 1.83
Mean Corpuscular Volume (fL)	86.8 ± 12.6	86.6 ± 12.4	86.2 ± 12.1	87.6 ± 13.6
Platelets (X 10-9/L)	368 ± 167	359 ± 136	383 ± 174	361 ± 189

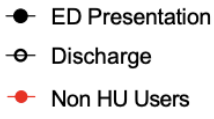
Clinical Outcomes, Mean (95% CI)	**Type****				***p-value***
Total IV opioids (mg/kg IV morphine equivalents)	Unadjusted	1.78 (1.15, 2.41)	1.97 (1.29, 2.66)	2.49 (1.40, 3.58)	0.534
	Adjusted	1.55 (0.96, 2.15)	1.75 (1.06, 2.45)	2.40 (1.32, 3.48)	0.391
Total IV opioids < 17 years	Unadjusted	1.44 (0.93, 1.95)	1.66 (1.07, 2.26)	2.65 (1.47, 3.82)	0.180
	Adjusted	1.20 (0.67, 1.74)	1.52 (0.97, 2.08)	2.44 (1.30, 3.59)	0.140
Time to Crisis Resolution (hours)	Unadjusted	57.3 (40.5, 4.0)	55.1 (40.9, 69.3)	69.3 (41.2, 97.5)	0.670
	Adjusted	51.8 (35.3, 8.3)	49.6 (35.1, 64.0)	66.3 (39.1, 93.4)	0.550
Time to Crisis Resolution < 17 years	Unadjusted	53.0 (35.0, 70.9)	49.0 (34.9, 63.1)	71.9 (41.2, 103)	0.407
	Adjusted	47.4 (28.8, 65.9)	45.3 (31.0, 59.5)	67.2 (37.7, 96.7)	0.402

**HCU – healthcare utilization (ED visits & hospitalizations); ** Regression adjusted for HU use, continuous age and sex*









JSCDH-D-23-1526188

ASCENT1: A PHASE 2 TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ORAL DECITABINE-TETRAHYDROURIDINE (NDEC) IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is driven by the polymerization of mutated hemoglobin (HbS) in red blood cells (RBCs). Fetal hemoglobin (HbF) mitigates the effects of HbS polymerization, but the HbF gene expression is silenced in infancy by DNA methyltransferase 1 (DNMT1). Decitabine induces HbF expression by direct inhibition of DNMT1. NDec is an innovative combination treatment with decitabine, the active component, and the pharmacokinetic enhancer tetrahydrouridine (THU). Hydroxyurea (HU), the current standard of SCD care, indirectly induces HbF by inducing bone marrow stress. As the indirect effect of HU on HbF is clinically variable, the direct HbF induction of NDec is hypothesized to provide a sustainable treatment option for patients with SCD.

In a previous trial in high-risk patients with SCD by Molokie R et al. (2017), oral decitabine (0.16 mg/kg) and THU vs placebo significantly increased total Hb, HbF, proportion of HbF-enriched RBCs (%F-cells) and improved RBC health markers, without triggering grade ≥3 non-hematologic toxicity. NDec formulations were further investigated in 2 phase 1 trials in healthy people. The ASCENT1 trial (NCT05405114) aims to study the efficacy and safety of once- or twice-weekly NDec vs placebo in patients with SCD. This study will provide proof of concept and determine the optimal dose for future trials.

Methods: ASCENT1 is a randomized, placebo-controlled phase 2 trial with an additional exploratory open-label HU block (Figure). To ease the operational aspects for patients and sites, trial design, visit schedule and trial materials were developed together with patient groups, study nurses and coordinators. The HU non-eligible block will include those who are HU-naïve or who cannot be treated with HU for any reason. Participants randomized to NDec in the HU active block will discontinue HU during a 4-week washout period.

All SCD genotypes are eligible for inclusion; other criteria are ≥18 years of age, 2–10 documented vaso-occlusive crises (VOCs) ≤12 months before screening, Hb ≥5.0–≤10.5 g/dL and reticulocyte count >1.5x upper limit of normal at screening. HU active participants are eligible only if deemed inadequately controlled by investigators despite being prescribed HU in the preceding 6 months and being on a stable dose >3 months.

Exclusion criteria include chronic transfusion therapy or treatment 28 days before screening/during trial with hematopoietic growth factors and treatment with voxelotor, crizanlizumab or L-glutamine 12 weeks before signing informed consent.

HU non-eligible (n=60) and HU active (n=24) participants will be randomized 1:1:1 to NDec once weekly, NDec twice weekly (2 consecutive days) or placebo/open-label HU. The trial consists of a main and extension phase (24 weeks each). NDec will be administered orally, with a meal, according to body weight intervals to attain a decitabine dose level of 0.16−0.25 mg/kg and THU dose level of 8−12.5 mg/kg.

The primary endpoint is change in total Hb (g/dL) from baseline (BL) to Week 24. Secondary efficacy endpoints include change in HbF (g/dL and %HbF of total Hb), change in %F-cells of total RBCs, and change

in hemolysis markers from BL to Week 24. Secondary efficacy endpoints also include numbers of VOCs, acute chest syndrome and transfused RBC units from BL to Week 48. The secondary safety endpoint is the number of adverse events (grade ≥3) from BL to Week 52. Changes in patient-reported outcomes from BL to Week 48 will be assessed using 5 validated questionnaires for SCD.

The primary endpoint will be analyzed using an ANCOVA model with treatment, historical VOC rate and sex as fixed factors, and BL Hb as covariate. Treatment policy estimand will be used to handle intercurrent events.

In this trial, VOCs are defined as ≥1 predefined clinical events requiring a medical visit, including home and telemedicine visits, for those with limited regular access to medical management at a clinic/hospital.

Results: Results are not yet available for this trial. The recruitment to ASCENT1 started in summer 2022.

Conclusions:VNDec and HU both induce HbF and will not be given together due to a theoretical potentiation of hematologic toxicity. The exploratory HU active block enables preliminary comparisons of the efficacy and safety between NDec and HU. The extension phase allows for analyses that may require longer follow-up to show clinical benefits and sustainability of NDec in SCD.

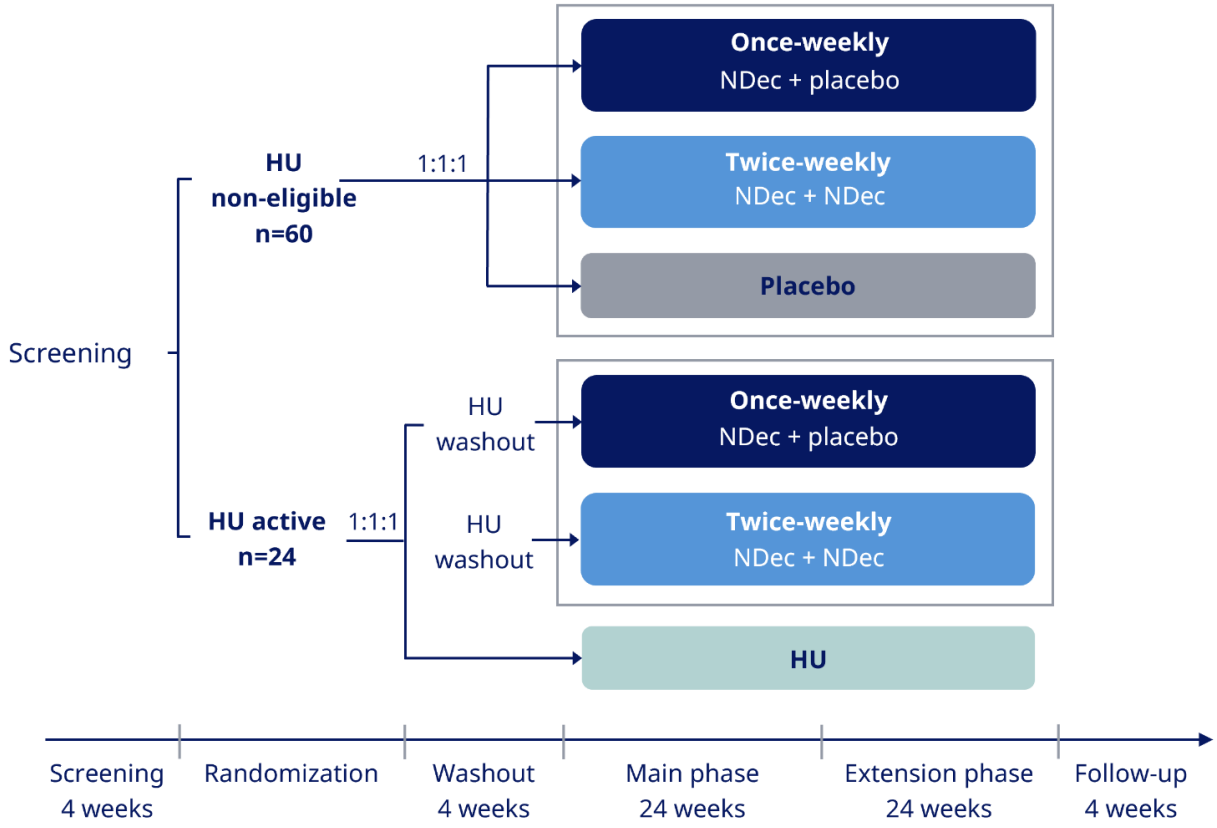

Figure
ASCENT1 is a multicenter, randomized, parallel-group, double-blinded, double-dummy, placebo-controlled phase 2 trial with an additional exploratory open-label HU block. HU, hydroxyurea; NDec, oral decitabine–tetrahydrouridine.

JSCDH-D-23-1520656

EFFICACY AND SAFETY OF EXAGAMGLOGENE AUTOTEMCEL FOR SICKLE CELL DISEASE

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Background: Elevated fetal hemoglobin (HbF) is associated with improved outcomes in patients with sickle cell disease (SCD). Exagamglogene autotemcel (exa-cel; formerly known as CTX001) is a cell therapy designed to reactivate HbF via non-viral, ex vivo CRISPR/Cas9 gene-editing at the erythroid enhancer region of BCL11A in autologous CD34+ hematopoietic stem and progenitor cells (HSPCs). Recent data from the pivotal CLIMB SCD-121 (NCT03745287) trial showed that a single dose of exa-cel increased HbF and total hemoglobin (Hb) sufficiently to eliminate vaso-occlusive crises (VOCs) in patients with severe SCD. Here, we report efficacy and safety data from the first 31 patients dosed with exa-cel in the ongoing CLIMB SCD-121 trial.

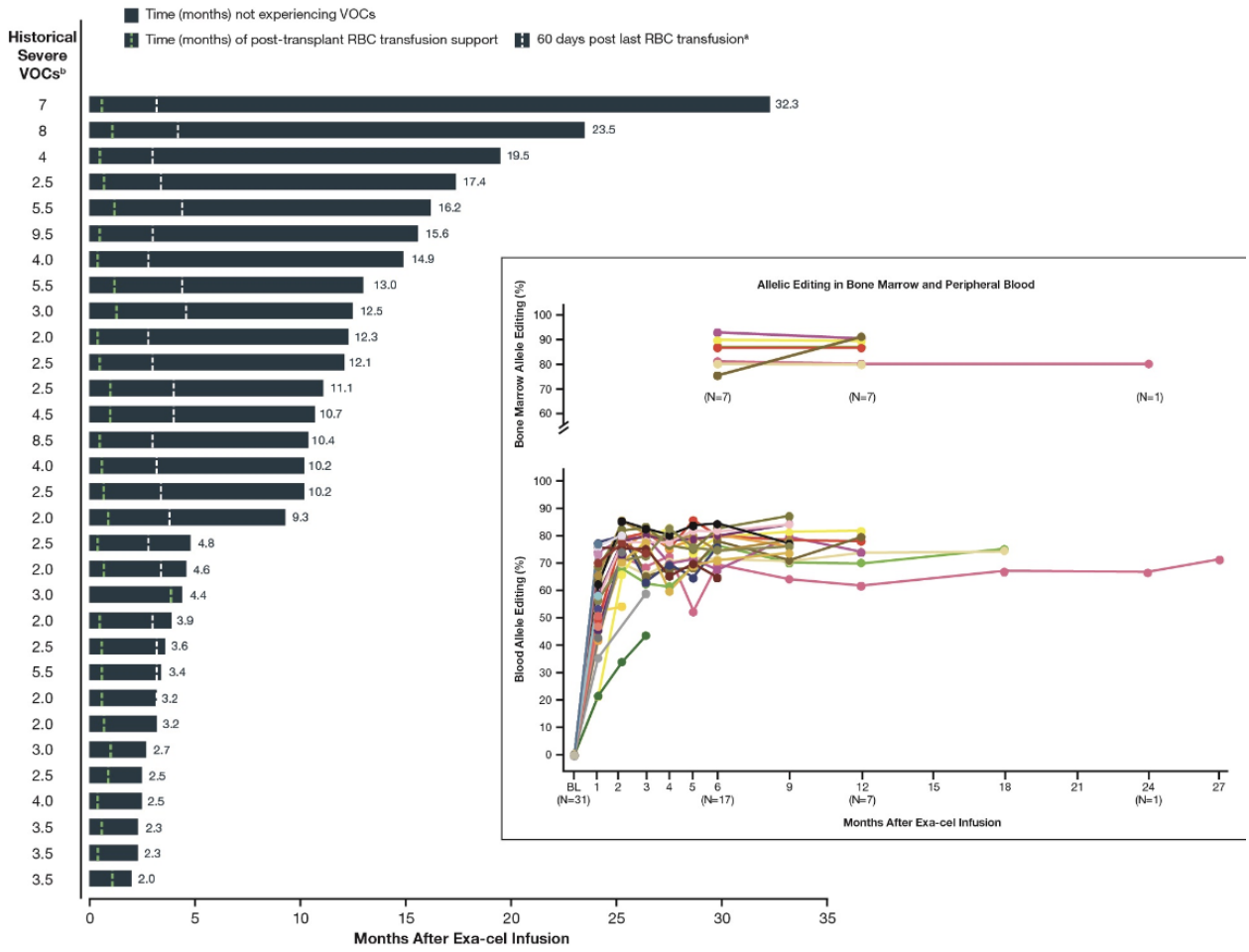
Methods: Patients aged 12 to 35 years with severe SCD and a history of ≥2 VOCs per year in the previous 2 years before screening were eligible. Following pharmacokinetic-adjusted, busulfan myeloablation and infusion of exa-cel, patients are monitored for engraftment, total Hb, HbF, BCL11A-edited alleles, transfusions, VOCs, and adverse events (AEs). The primary endpoint is the proportion of patients who have not experienced a severe VOC for at least 12 months after the infusion of exa-cel, starting 60 days after their last RBC transfusion. Updated efficacy and safety results on all dosed patients will be included in the presentation. Data are reported as mean (min–max), unless noted.

Results: At the most recent data cut in February 2022, 31 patients with SCD (age 22.5 [12–34] years) had been infused with exa-cel (follow-up 9.6 [2.0–32.3] months), of whom 6 (19.4%) were between the ages of 12 and < 18 years and 29 (93.5%) had the βs/βs genotype. In the 2-year period before screening, patients experienced 3.9 (2.0–9.5) severe VOCs per year. After exa-cel infusion, all patients engrafted neutrophils and platelets with a median time of 27 and 32 days, respectively.

All patients were VOC-free at the time of the data cut (duration of follow-up 2.0–32.3 months after exa-cel infusion; Figure). Median time from exa-cel infusion to last RBC transfusion was 19 (11–52) days. The mean proportion of HbF was >20% by Month 3, with mean total Hb levels >11 g/dL on and after Month 3. All 11 patients who have at least 12 months of follow-up after exa-cel infusion have maintained HbF levels >20% while experiencing no VOCs. At Month 6, the mean proportion of edited BCL11A alleles in bone marrow CD34+ HSPCs and peripheral blood mononuclear cells was 86.6% and 76.0%, respectively. These proportions remained stable in all patients who had ≥1 year of follow-up (Figure).

There were no patients who had serious AEs considered related to exa-cel. There were no deaths, discontinuations, or malignancies.

Conclusions: Exa-cel infusion led to the elimination of VOCs in all patients with SCD, with associated clinically meaningful increases in HbF and total Hb that were maintained over time. Proportions of CRISPR/Cas9-edited BCL11A alleles have remained stable after ≥1 year, indicating that long-term HSCs were successfully edited. The safety profile was generally consistent with that of busulfan myeloablation and autologous transplant. Exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a one-time functional cure for SCD. Updated data from this trial will be provided in the presentation.



BL, baseline; RBC, red blood cell; VOC, vaso-occlusive crisis.
Each row in the bar graph and each line in the inset represents an individual patient.
[a]Patients are evaluated for elimination of VOCs starting 60 days after their last transfusion.
[b]Pre-study severe VOCs annualized over 2 years.

JSCDH-D-23-1524504

EXPLORING TRAUMATIC INJURY RATES IN SICKLE CELL DISEASE PATIENTS: A US GEOGRAPHIC ANALYSIS

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Affiliation: *[1]University of Pittsburgh School of Medicine, [2]School of Nursing, University of Pittsburgh, [3]University of Pittsburgh School of Pharmacy, [4]University of Pittsburgh, [5]Center for Research on Health Care, University of Pittsburgh; Center for Behavioral Health and Smart Technology, University of Pittsburgh*

Background: Sickle cell disease (SCD) is an inherited hemolytic disorder resulting from the polymerization of hemoglobin S (HbS), affecting nearly one in 500 African Americans in the United States. External injury can cause an inflammatory response, leading to endothelial dysfunction and increasing the risk for vaso-occlusive events (VOE). Traumatic injury—caused by accidents, homicide, or self-inflicted injury—was the leading cause of death in individuals under age 44 in 2022, particularly affecting African Americans who face the highest risk of mortality and chronic pain following an injury. Since traumatic injuries and SCD share a patient demographic, patients with SCD are more likely to be vulnerable to trauma, resulting in an increase in annual VOE events. Trauma management for SCD patients varies by state, and the lack of established guidelines may increase the risk for poor trauma related outcomes, including readmissions, chronic pain, poor quality of life, and even mortality. Thus, identifying locations with the highest intersection between SCD and traumatic injury and understanding the patterns and necessary measures for adequate trauma-related pain management in SCD is critical for informing guideline development. This study aimed to compare the prevalence of injured SCD patients and injury mechanisms across regions in the US, as an initial step in understanding trauma treatment in SCD.

Methods: A retrospective study analyzed de-identified medical and prescription claims data from Optum's Clininformatics Data Mart Database in Eden Prairie, MN from January 2014 to September 2021. The study identified SCD adults with recent traumatic injuries from ages 18 to 65 in all 50 states using ICD-9/10 diagnosis codes for SCD and traumatic injury in both inpatient and outpatient settings within the study period. If an individual had multiple traumatic injuries, the most recent injury was used. Eligibility required 12 months of continuous enrollment. The study also noted sociodemographic and clinical characteristics. States with no data were noted as < 50th percentile based on the population distribution of SCD-injured individuals per state. Z-tests were used to compare mechanism of injury and demographic variables.

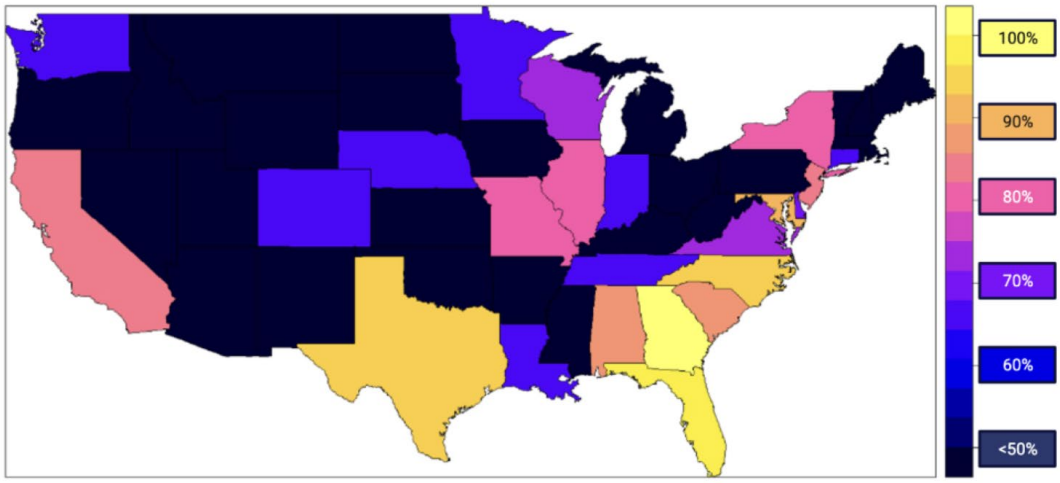
Results: A representative sample of 204 individuals had an SCD and traumatic injury diagnosis between 2014-2022. The average age was 48.4 ± 12.8 years; women were significantly overrepresented compared to men (81.4% vs 18.6%, p< .001). Blunt injuries were more common than penetrating injuries across all states (84.3% vs 15.7%, p< .001). States with over the 90th percentile of the total SCD-injury population include Maryland (92nd), North Carolina (94th), Texas (96th), Florida (98th), and Georgia (>99th); the intersection between SCD and traumatic injury is most prevalent in Florida and Georgia (Figure 1). Prevalence of penetrating injuries in these 90th percentile states is significantly higher than states below the 90th percentile (p=< .001); highest in North Carolina. Open penetrating wounds to the head (gunshot wounds, stabbing, etc) were

overrepresented amongst penetrating injuries (43.8%, p=0.007). No association between age and mechanism of injury.

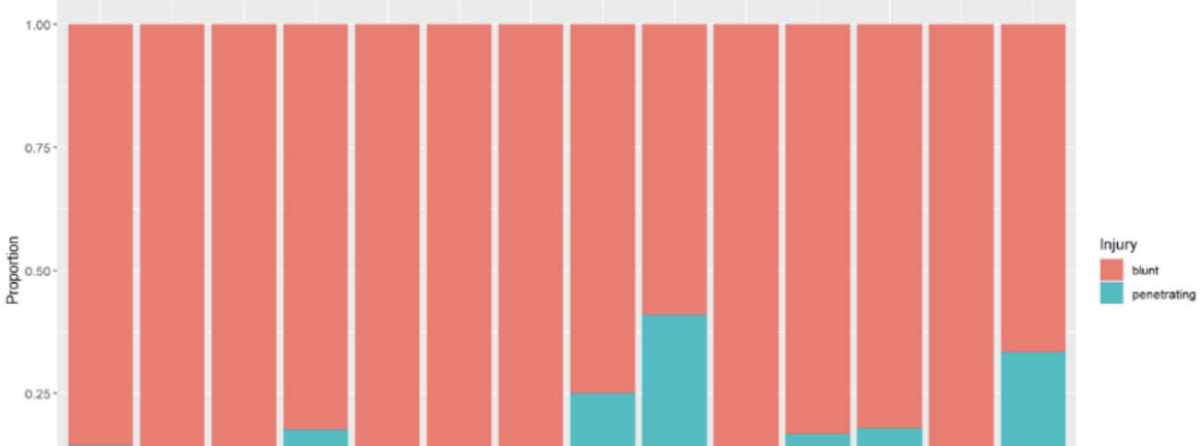
Conclusions: From this representative sample, the highest intersection between SCD and traumatically injury is noted in Southern regions of the United States, with an overrepresentation of penetrating head injuries. These regions also have the largest SCD populations with disparities in access to SCD centers and care. Tailoring prehospital emergency care, as well as developing and implementing care guidelines for SCD patients with violent injuries, are crucial steps to prevent early mortality, decrease readmission for SCD-related complications, and improve quality of life. Future research is critically needed to identify differences in the injury profile for SCD patients and other populations. In addition, clinicians and researchers should advocate for injury prevention strategies among SCD patients on a legislative level, especially in high-risk Southern states.

Demographics	N=204	P-value
Age (mean)	48.4	
SD	12.8	
Min-Max	18-65	
Gender		
Male	18.6%	<0.001
Female	81.4%	
Mechanism of Injury		
Blunt	84.3%	<0.001
Penetrating	15.7%	

Demographics of SCD Patients with Traumatic Injury from Representative US Sample



Prevalence of SCD Population with Traumatic Injuries from 2014-2021 in the United States (Percentiles per State)



JSCDH-D-23-1510708

HIBISCUS-KIDS PHASE 1/2 TRIAL IN PROGRESS: ETAVOPIVAT IN CHILDREN WITH SICKLE CELL DISEASE

Authors: Miguel R. Abboud, MD[1], Raffaella Colombatti, MD, PhD[2], Julie Kanter, MD[3], Eric Wu, PhD[1], Leila Jerome Clay, MD, MCTS[1], Adlette Inati, MD, FAAP[4]

Affiliation: *[1]NOVO NORDISK A/S, [2]Pediatric Hematology Oncology Unit, Department of Women's and Child's Health, Azienda Ospedale-University of Padova, [3]Division of Hematology and Oncology, University of Alabama Birmingham, [4]Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Center, Department of Pediatrics and Adolescent Medicine, Beirut, Lebanon*

Background: In sickle cell disease (SCD), a single β-globin gene mutation causes sickle hemoglobin (HbS) to polymerize and red blood cells (RBCs) to aggregate, leading to hemolytic anemia and vaso-occlusive events. These events generally present as a vaso-occlusive crisis (VOC), an acute episode of pain. With symptom onset in infancy, patients experience recurrent VOCs, chronic hemolytic anemia, long-term organ damage, and systemic co-morbidity occurrences through the years, resulting in a shortened lifespan. Therefore, novel, safe therapies are urgently needed for children with SCD to prevent organ damage and cumulative co-morbidity from early life on.

Etavopivat is a once-daily, selective erythrocyte pyruvate kinase (PKR) activator in clinical development to treat patients with SCD and other hemoglobinopathies. The hypothesis is that PKR activation will reduce HbS polymerization and improve RBC membrane function via decreasing 2,3-diphosphoglycerate (DPG) and increasing adenosine triphosphate (ATP). This will lead to a decrease in RBC sickling and hemolysis and hence reduce the cause of microvascular obstruction and anemia (Schroeder et al., J Pharm Exp Ther 2022; Telen et al., HemaSphere 2022).

Our aim is to describe the design of the HIBISCUS-KIDS study (PACTR202209604592389), a single-arm, open-label, phase 1/2 trial to evaluate the pharmacokinetic (PK) response, safety, and tolerability of etavopivat in pediatric patients with SCD.

Methods: Patients receive a 400 mg etavopivat dose daily for a 24-week primary treatment period followed by a 72-week extension period (Figure). For this study, up to 50 patients aged 12 to under 18 years will be enrolled at 15 sites in 6 countries (Canada, UK, Lebanon, Turkey, Nigeria, and Kenya). After a minimum of 12 weeks, data on safety, PK, and clinical activity including annual VOC rate, fatigue, central nervous system events, and patient-reported outcomes will be evaluated by the sponsor and shared with the safety review committee to inform further decisions on a potential inclusion of patients younger than 12 years.

Inclusion criteria are a confirmed diagnosis of SCD with any documented genotype, a hemoglobin value from 5.5 to below 10.5 g/dL, and at least two episodes of VOCs in the past 12 months. Key exclusion criteria are hospitalization, hospital or clinic visit for more than 10 VOCs within the 12 months before treatment start, or hospitalization for any SCD-related complication within 14 days of the screening period.

The primary objective is to assess etavopivat PK based on the primary endpoints: maximum concentration, area under the concentration time curve, and steady state etavopivat plasma exposure in children with SCD. Safety and tolerability of etavopivat during the 24-week primary treatment period is a co-primary endpoint and will be analyzed based on number of

reported adverse events (AEs), severe AEs, and AEs related to etavopivat, premature discontinuations, dose interruptions, and dose reductions of etavopivat.

Key secondary and exploratory study objectives are to assess the effects of etavopivat on Hb response, VOC occurrences, changes in fatigue and cerebral blood flow, silent cerebral infarct incidences, and functional capacity.

Results: This study is in progress and results are yet to be available. Enrolment has been started in Lebanon, with 3 patients screened and randomized for the study so far. Sites within Canada, UK, Turkey, Nigeria, and Kenya are planned to open for enrolment.

Conclusions: Etavopivat is a novel, investigational, selective PKR activator with the potential to improve RBC health and lifespan. This Phase 1/2 study will assess the safety and tolerability of etavopivat in children with SCD and add additional pediatric data along the phase 2/3 HIBISCUS trial (NCT04624659) in adults and adolescents with SCD.

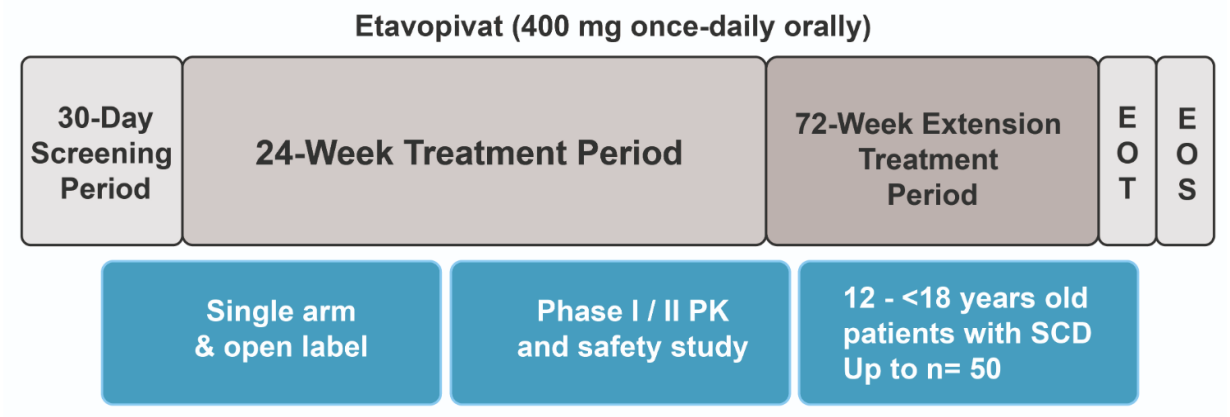


Figure. HIBISCUS-KIDS STUDY DESIGN
Abbreviations: EOS, End of Study; EOT, End of Treatment; PK, Pharmacokinetic; SCD, Sickle Cell Disease

JSCDH-D-23-1523570

TIP: PHASE 1B CROSSWALK-A TRIAL – CROVALIMAB FOR ACUTE VASO-OCCLUSIVE EPISODES IN SCD.

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Affiliation: *[1]University Paris-East Créteil, Henri Mondor University Hospitals, APHP, Sickle Cell Referral Center - UMGGR, Créteil, France and University Paris-East Créteil, IMRB, Laboratory of Excellence LABEX GRex, Créteil, France, [2]UTHSC Center for Sickle Cell Disease, [3]Division of Pediatric Heamatology/Oncology, Central Michigal University SOM, Children's hospital of Michigan,[4]Department of Medicine, University of Verona and AOUI Verona, Italy, [5]Albert Einstein College of Medicine, [6]Roche Products Limited, Welwyn Garden City, United Kingdom, [7]Certara, Inc., Paris, France, [8]Genentech, Inc., South San Fransisco, [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [10]Icahn School of Medicine at Mount Sinai, Department of Emergency Medicine, New York*

Background: Sickle cell disease (SCD) is a group of autosomal recessive red blood cell (RBC) disorders caused by a single point mutation in the β-globin gene, resulting in the production of hemoglobin S (HbS). HbS polymerizes within RBCs under certain conditions, leading to the distortion of the RBC membrane and generation of dense and sickle RBCs. These pathologic RBCs contribute to microvascular occlusions, which may present as acute, painful episodes called vaso-occlusive episodes (VOEs). Although most VOEs are managed at home, >70% of emergency department visits and >90% of hospitalizations for SCD are VOE-related.1,2 Additionally, acute chest syndrome is one of the most severe complications of VOEs and is a leading cause of mortality.3,4 As there are no targeted therapies for the management of VOEs, treatment is currently limited to pain management, blood exchange transfusion (with the risk of complications), and other supportive care, which represents a significant unmet medical need. Overall, accumulating nonclinical data suggest a multimodal role for complement dysregulation in the pathophysiology of SCD including vaso-occlusion, hemolysis, inflammation, thrombogenicity, endothelial activation, and end-organ damage.5 Complement pathway activation has been described in patients with SCD at baseline, in acute pain crises, and in patients with delayed hemolytic transfusion reaction. The complement pathway can be targeted with crovalimab, which is a novel, engineered, anti-complement C5 monoclonal antibody. In a Phase 1/2 study in patients with paroxysmal nocturnal hemoglobinuria, a complement-mediated disorder, crovalimab showed rapid and sustained complement inhibition with promising efficacy and safety.6

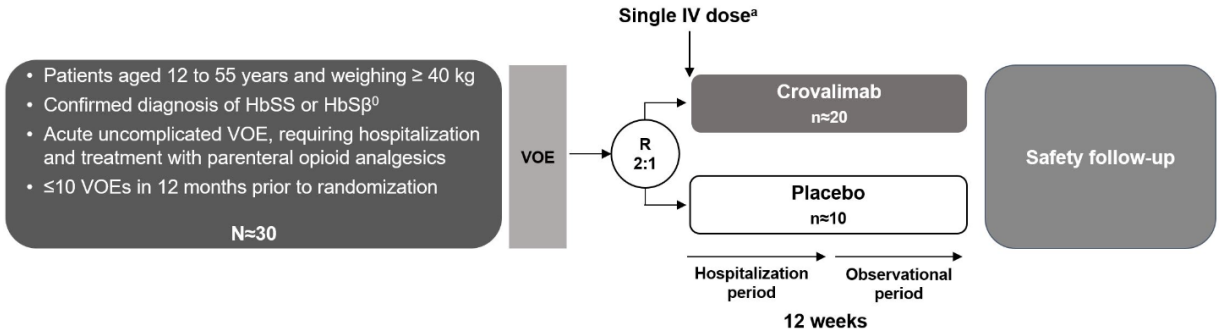
Here we describe the CROSSWALK-a trial (NCT04912869), a randomized, double-blind, placebo-controlled, Phase 1b study evaluating the safety of crovalimab in managing acute uncomplicated VOEs in patients with SCD.

Methods: Patients aged 12 to 55 years, weighing ≥40 kg, and with a confirmed diagnosis of SCD homozygous HbS (HbSS) or sickle cell β0 thalassemia (HbSβ0) will be enrolled (Figure). Patients must present with an acute uncomplicated VOE, requiring hospitalization and treatment with parenteral opioid analgesics. Vaccinations against Neisseria meningitidis, Hemophilus influenzae type B, and Streptococcus pneumoniae must be current. Eligible patients will be randomized 2:1 to receive either a single intravenous weight-based tiered dose of crovalimab or placebo. All patients will continue with

pain management and other supportive care for their VOE, and may continue concurrent SCD-directed therapies. Patients will be followed during hospitalization until discharge and will also be followed post-discharge during an observational period. The study duration for an individual patient for hospitalization and the post-discharge observational period will be 12 weeks, which will be followed by a safety follow-up period. The primary objective is to evaluate the incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0, incidence and severity of infusion-related reactions and hypersensitivity, and change from baseline in targeted vital signs and clinical laboratory test results. Efficacy, pharmacokinetic, pharmacodynamic, immunogenicity, and exploratory biomarker endpoints will also be evaluated. Protocol updates are in progress.

Results: CROSSWALK-a is scheduled to be completed in January 2025.

Conclusions: CROSSWALK-a is enrolling patients with SCD in six countries.



[a]Single dose of 1000 mg IV crovalimab for patients weighing ≥40 kg to <100 kg, over an infusion duration of 60 ± 10 minutes and 1500 mg IV crovalimab for patients weighing ≥100 kg, over an infusion duration of 90 ± 10 minutes. HbSβ0, sickle cell disease genotype of sickle cell beta zero thalassemia; HbSS, homozygous hemoglobin S; IV, intravenous; R, randomized; VOE, vaso-occlusive episode.

CROSSWALK-a study schema

POSTERS

JSCDH-D-21-1525073

CARE PLAN MEETING WITH FREQUENT CLINIC VISITS CRUCIAL TO IMPROVING SICKLE CELL DISEASE

Authors: Sheinei Alan, MD, PhD[1,2], Chad Zik, MD[1], Rania Fusisi, RN[1], William Ershler, MD[1]

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Background: Clinic visits are an essential part of managing sickle cell disease (SCD), as they allow for the timely detection of complications and the implementation of appropriate treatments. In addition to disease management, clinic visits are important to identify and addressing personal, emotional, psychological and caregiver needs of the patient. We demonstrate that comprehensive family care plan meeting coupled with weekly clinic visits are vital in patients especially in those with highest need for acute care and opioid utilization.

Methods: In our center, several patients with frequent hospitalizations and high opioid use were identified for comprehensive family/ care plan meeting. The patients consisted of both SS and SC phenotypes, males and females and predominately in the second and third decade of life. The family/ care plan meeting consisted of all sickle cell physicians, social work, case management and nurse navigator as well as patient and his or her identified caregiver(s). In this meeting, barriers to care including psychosocial support, food and housing insecurity and transportation needs were identified. Patient's sickle cell disease and comorbidities were reviewed comprehensively, and goals of care agreed upon. This was then followed by weekly clinic visits with the patient and provider to continue ongoing discussions and management of underlying disease, psychosocial support and monitoring of acute care/opioid use.

Results: Since implementation of family meetings and weekly visits, we demonstrate a reduction in hospitalizations and total daily oral morphine equivalent use as well as an improvement in patient's overall self-perceived quality of life. It is important to note that this observation is regardless of implementation of disease modifying therapies including red cell exchange program, sickle cell genotype or gender.

We demonstrate the case of two patients, with nearly monthly admissions in the last year and high opioid use. One patient has SC disease and another with SS disease. Both patients are highly intelligent, college graduates and with optimal family support. The weekly visits focused on reinforcing moving care from the inpatient to outpatient setting as well as achieving better disease control. Each clinic visits focused on helping patient become compliant with disease modifying therapies and improving barriers to care. Each week focused on providing "homework" which consisted of tasks needed for disease management including opioid tapering plan, compliance with medications, vaccines, eye screening, establishing care with primary care or other needed providers/ subspecialists. Clinic visits also allowed for optimizing provider patient relationship to help identify psychological barriers to compliance and addressing misconceptions. Furthermore, the need for managing disease was reinforced with each encounter. With ongoing reduction in hospitalization, overtime, each patient became more aware of personal barriers to optimal care and managing their disease at home. As each patient spent more time with family and focusing on their own personal goals, their motivation for improvement increased. Each patient became a more active participant in the care discussion and achieving goals outlined in the initial family meeting. In the case of the two mentioned patients in particular, both individuals are now employed and one is living

independently for the first time with the other making arrangements for independent housing in the fall.

Conclusions: Unfortunately, many individuals with SCD have faced many barriers to care including access to regular clinic visits where ongoing education and identifying gaps in care. Addressing patient's psychosocial support, basic housing and food insecurities and misconceptions about sickle cell disease is crucial for disease management and long-term positive outcome. Sickle cell disease has profound impact on one's physical, psychological and social wellbeing. It is important sickle cell providers to account for all aspects of a patient's wellbeing in devising each patient's individual care plan. We believe this is best done via frequent clinic visits that allows for ongoing close monitoring, especially in those with highest opioid use and acute care utilization. We believe there is a component of self-medicating and seeking respite in hospitalization in those with frequent admissions and thus it is important that those underlying contributing factors are identified and addressed as part of appropriate disease management.

JSCDH-D-21-1517511

CHRONIC KNEE JOINT PAIN FROM EXCESSIVE MARROW EXPANSION RESPONDED TO HYDROXYUREA

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Background: Compensatory bone marrow hyperplasia is common in sickle cell disease. Hydroxyurea, which is primarily indicated for decreasing painful episodes, can be used to treat bone marrow hyperplasia in sickle cell disease as it is an anti-metabolite. We present a case of severe chronic left knee pain that was due to hyperplastic bone marrow encroaching on the epiphysis and deforming the articular surface..

Methods: Retrospective chart and literature review

Results: In conventional practice, the dose of hydroxyurea is not titrated to the maximally tolerated dose until mild myelosuppression (absolute neutrophil count 2,000/ mm3 to 4,000/ mm3) is achieved. The initial recommended starting dose is 15 mg/kg/day, and if blood counts remain within an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks until the maximum tolerated dose of 35 mg/kg/day, or the dose that does not produce toxic effects for 24 consecutive weeks, is reached. Acceptable ranges are: neutrophils 2,500/mm3, platelets 95,000/mm3, hemoglobin >5.3 g/dL, and reticulocytes 95,000/mm3. Toxic hematologic ranges are: neutrophils <2,000/mm3, platelets < 80,000/mm3, hemoglobin < 4.5 g/dL, and reticulocytes 80,000/mm3

In a study of myeloproliferative disorder treatment with hydroxyurea, a reduction in the ratio of granulopoieses/erythropoiesis was observed, and bone marrow aspiration showed decreased cellularity, indicating that there is suppression of erythropoiesis in the bone marrow. When patients do not experience a satisfactory clinical benefit from lower doses of hydroxyurea, higher doses may achieve the desired result by reducing the granulopoiesis/erythropoiesis ratio. In our case, the patient experienced clinical benefits with the titration of the hydroxyurea dose to 26 mg/kg/day, which achieved control of red bone marrow expansion and the causative factor of this patient's knee pain.

Caution must be used to prevent excessive bone marrow suppression when cytopenias occur with reductions in red blood cell counts and consequent total hemoglobin levels, while myelosuppression leads to a higher risk of infections and bleeding complications.

Conclusions: This proves that the beneficial effects of hydroxyurea in controlling pain in sickle cell disease can be due to multiple mechanisms, including hemoglobin F induction, lower neutrophil and reticulocyte count from ribonucleotide reductase inhibition, decreased adhesion of circulating neutrophils and reticulocytes, improved red cell rheology, and nitrous oxide release with local vasodilation.

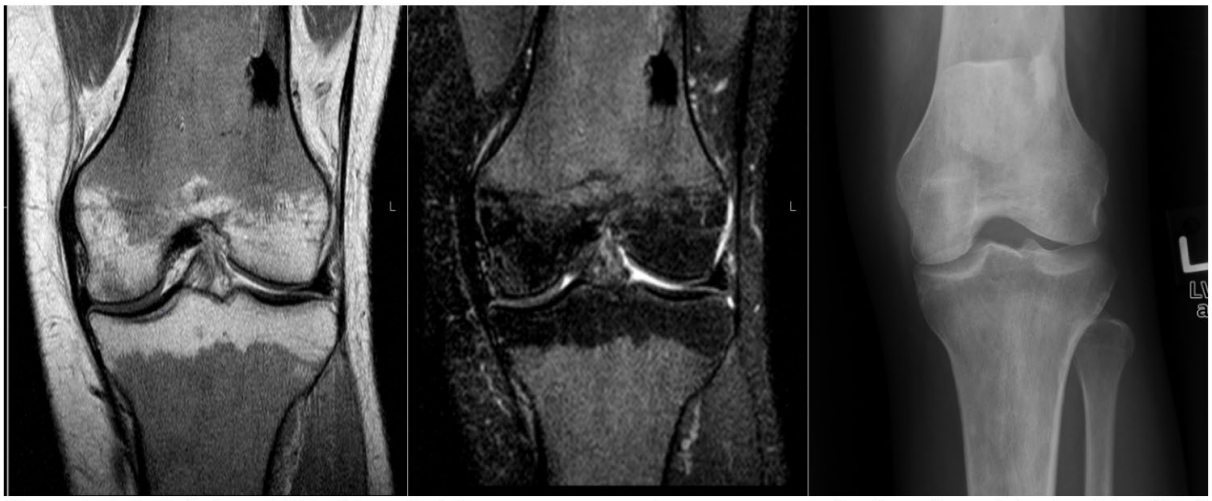

Figure 1. A, B - Left knee MRI with and without contrast - red marrow expansion into the epiphysis of the distal end of the left femur (yellow arrows). C. Left knee X-ray – no significant findings.

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COLCHICINE REDUCES MAST CELL DEGRANULATION AND INFLAMMATION IN SICKLE CELL DISEASE MICE

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Background: Inflammation, marked by a "cytokine storm" of circulating proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF-α), and C-reactive protein (CRP), and increases in intracellular NLRP3 inflammasomes, is an important component of sickle cell disease (SCD). Although current treatments have limited anti-inflammatory effects, targeting inflammation is a promising but unrealized treatment approach.

Colchicine, a tubulin inhibitor with a unique mechanism of action, inhibition of tubulin binding that prevents microtubule assembly, is a promising anti-inflammatory agent for SCD. It is useful in gout, familial Mediterranean fever, pericarditis, and other inflammatory diseases. In these contexts, it often reduces the same inflammatory proteins and cellular components that are elevated in SCD.

We sought preliminary evidence for colchicine as an anti-inflammatory treatment for SCD.

Methods: Humanized sickle mice (HbSS-BERK) are knockout for murine α and β globins and express human α and βS globins (>99% βS) on a mixed genetic background. HbSS-BERK have severe disease, including hyperalgesia. Experiments were performed following protocols approved by the Institutional Animal Care and Use Committee.

Female mice of ~ 3.5 months of age received either colchicine 100 µg/kg body weight or vehicle (phosphate-buffered saline) intraperitoneally daily for 14 d. Pain-related behavior testing was performed before treatment and 1 h, 24 h, 7 d, and 14 d after the 1st dose of the study agent. Mechanical hyperalgesia was tested by paw withdrawal frequency (PWF) in response to the application of a von Frey monofilament to the mid-plantar surface of the hind paw. Musculoskeletal/deep tissue hyperalgesia was tested by measurement of the peak tensile force exerted by a forelimb upon traction. Cold hyperalgesia was tested by PWF/2 min upon placement of mice on a cold plate maintained at ~4°C.

After the 14 d of dosing, mice were euthanized; blood and 4 mm diameter dorsal skin punch biopsies were collected for mast cell assessment by toluidine blue stain or incubated in culture media for 24 h to examine inflammatory cytokines. Plasma serum amyloid-P (SAP) and IL-6 were analyzed with enzyme-linked immunosorbent assays. Limited blood volumes prevented the assay of other circulating proteins. Automated and manual cytometry were used to characterize circulating blood cells. Skin secretagogue was assayed for cytokines IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, monocyte chemoattractant protein 1 (MCP-1), interferon-gamma (IFN-γ), TNF-α, macrophage inflammatory protein-1 alpha, granulocyte-macrophage colony-stimulating factor (GM-CSF), and regulated on activation; normal T-cell expressed and secreted protein (RANTES) using Q-PlexTM microarray. All behavioral tests were analyzed using two-way repeated measures ANOVA with Tukey's multiple comparisons tests; Cytokines, hematopathology, and

mast cell analysis were analyzed using Student's two-tailed t-test.

Results: As per usual laboratory practice, we considered mouse circulating SAP levels as surrogate for human CRP levels. Following 14 d of dosing, plasma IL-6 levels were ~67% lower (~130 v ~48 µg/g protein; $p < 0.01$), and plasma SAP levels were ~45% lower (~33 v ~18 µg/g protein; $p < 0.01$) in colchicine-treated mice. There were no significant differences in blood cell parameters. Concentrations of IL-3, IL-1, IFN-γ, and GM-CSF were 40% ($p < 0.05$), 20% ($p < 0.05$), 40% ($p < 0.01$), and 40% ($p < 0.01$) lower, respectively, in the skin secretagogue of colchicine-treated mice. Colchicine reduced skin MC degranulation by ~ 75% ($p < 0.0001$),and we attribute reductions in GM-CSF, IL-3, and IFN gamma to this effect. Given the chronic nature of inflammation in SCD, we did not anticipate phenotypic changes after only a 14 d exposure to colchicine. Indeed, no significant differences in hyperalgesia or mouse/organ weight were observed.

Conclusions: We think that the next steps should be dose-finding studies of colchicine in adults living with SCD followed by randomized, placebo-controlled trials with clinically relevant endpoints such as repeated measures of pain interference using a validated instrument. The anticipated lack of colchicine effect upon blood cell parameters suggests that patients would benefit more from a combination of a disease-modifying agent such as hydroxyurea in combination with colchicine.

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CULTURAL TRAINING FOR NURSES TO PROVIDE BETTER CARE OF SICKLE CELL PATIENTS: A LITERATURE REVIEW

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Background: Sickle Cell Disease (SCD) is the most common inherited blood disorder in the US. It is caused by a missense mutation in the b-globin gene, at the sixth codon position encoding for Valine instead of glutamic acid, giving rise to the abnormal sickle hemoglobin. This change makes the carrying of oxygen to the tissues by hemoglobin less efficient. SCD affects primarily individuals of African, Central and South American, Middle Eastern, Asian, Indian, and Mediterranean descent. According to the Center for Disease Control and Prevention, approximately 100,000 Americans have SCD, and according to the National Heart, Lung, and Blood Institute about 20 million people are affected worldwide. This literature review focuses on cultural training of nurses to provide better unbiased care for SCD patients and therefore achieve better patient outcomes.

Although SCD management is well established, there is still a stigma associated with SCD and race that often surfaces when treating the SCD patient.

Methods: An integrated review was utilized including databases Cochran Library, PubMed, and Google Scholar between years 2008-2023. The review was guided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting system. A total of 75 articles were screened and 10 articles selected as per the inclusion criteria.

Results: This review selected 10 articles with the levels of evidence ranging from level 1 to level V. The major findings of the articles addressed cultural competence, education, sickle cell, and stigma. The sickle cell population is tied directly to people of color which are more prone to experience racism and discrimination. As a result, cultural competence training in the ongoing nursing curriculum was found beneficial, and it may decrease the stigma of the disease leading to better health care outcomes for SCD patients during hospital admission.

Conclusions: The finding from integrative review suggests that there are barriers to culturally competent healthcare. SCD primarily affects African Americans and Hispanics in the United States. These patients are subject to bias and discrimination by nurses which lead to longer hospital admissions. Nurses' gaining a better understanding of the disease process is vital for patient care but understanding the multicultural aspects of cultural care benefits positive patient outcomes.

JSCDH-D-21-1525362

FACULTY NEEDS ASSESSMENT FOR TRAINEE EDUCATION ON SCD

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Background: Sickle Cell Disease (SCD), an inherited blood disorder that afflicts millions worldwide. It's caused by a mutation in the gene that codes for the hemoglobin and results in abnormal red blood cells that have a sickle shape. It can lead to various complications, including chronic pain, anemia, stroke, and organ damage. Despite the prevalence of SCD and its associated morbidity and mortality, there is a shortage of adequate education and training in SCD management for healthcare providers. Our project aims to develop and implement a comprehensive curriculum for residents to enhance their knowledge and skills in SCD in the long run. To achieve the above goal, it is paramount that we conduct a survey of faculty members who teach medical residents about this disease regarding their assessment and needs for educating residents regarding SCD management.

Methods: A descriptive research survey was administered online to faculty in primary care specialties (Internal Medicine, Med-Pediatrics combined, Family Medicine) at multiple institutions (1 large academic center, 2 small community hospitals). Each institution had over 50 SCD patients admitted to the hospital each year. Faculty included teaching attending physicians, cheif residents, and program directors.

Results: A total of 13 faculty took this survey. Response rate was 32%. The results from this survey show that sixty-nine percent of the faculty agree that there is a provider shortage for patients with sickle cell disease. Eight-five percent percieve that there is a knowledge deficit in health care providers in sickle cell disease management. Over ninety percent of faculty agree that learning about sickle cell disease is important for their residents and this will improve their ability and comfort level in caring for patients with SCD. One hundred percent of our respondents were interested in participating in a formal curriculum for sickle cell disease.

Conclusions: The results from our needs assessment indicate that there is interest from the faculty in training the trainees on sickle cell disease. There is a significant national provider shortage acknowledged by multiple organizations for sickle cell disease (SCD) especially in the adult population. This study further emphasizes the interest and need for formal curriculum in primary care residency programs to help expand the sickle cell workforce.

JSCDH-D-21-1525241

INEFFECTIVE ERYTHROPOIESIS AND ANEMIA IN ADULTS WITH SICKLE CELL DISEASE

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Background: The great majority of adult patients with sickle cell disease are anemic with hemoglobin (Hb) levels below 12 g/dL. Although it is well established that lower Hb levels are associated with increased adverse outcomes including pulmonary hypertension, stroke, cognitive decline, acute chest syndrome, frequency of vaso-occlusive crisis and shortened survival, a full understanding of the mechanisms accounting for anemia remains to be elucidated. Involved factors include chronic hemolysis, inflammation, renal insufficiency (blunted erythropoietin response) and nutritional inadequacy. Despite lacking a uniform explanation for anemia applicable to individual SCD patients, it remains a management goal to optimize Hb level as much as possible within constraints associated with secondary hemochromatosis. To better understand the mechanisms involved in SCD patients with moderate to severe anemia (Hb < 9 g/dL) we examined hematopoietic parameters in a series of SCD patients who visited our Center over a 3-month period.

Methods: Adult patients visiting Inova Schar Adult Sickle Cell Center clinic over a 3-month period (January through March 2023) with known Hb levels below 9 g/dL were evaluated by a contemporary hematologic panel that included complete blood count with differential, reticulocyte count, comprehensive metabolic panel (included total bilirubin and creatinine), lactate dehydrogenase (LDH), random urinary microalbumin and serum erythropoietin level. Reticulocyte proliferation index (RPI) was determined utilizing a readily accessible calculator (MedCalc). Briefly, the RPI = (Hematocrit/45) x reticulocyte count/maturation time. The maturation time takes into consideration the time for erythrocytes (in days) to develop. This varies with level of anemia (maturation = 1 for Hct >40%, 1.5 for Hct 30-39%, 2 for Hct 20-29% and 2.5 for Hct < 20%). A calculated RPI > 3 indicates a normal or near-normal marrow response to anemia. For our purposes, we considered an RPI < 2.5 to be a suboptimal response to anemia.

Results: 46 SCD patients had Hb levels below 9 g/dL. The mean age was 37.8 years. 44 were HbSS and 2 were HbSC. The mean Hb was 7.0 g/dL (+/- 1.2 g/dL) and mean RPI was 2.54. There were 29 SCD patients with RPI < 2.5 and 13 patients with RPI > 3 (Figure 1). 4 patients had RPI of 2.5-3 and were excluded from this analysis.

Conclusions: Over a 3 month period, 46 unique patients (44 HbSS, 2 HbSC) seen in our clinic were found to have Hb levels below 9 g/dL. Of these, 29 (63%) were reticulocytopenic (RPI < 2.5). As shown in Table1, patients with high RPI (> 3) were younger and had higher LDH and total bilirubin measures suggesting marrow response to chronic hemolysis. Although more patients with low RPI had evidence for renal insufficiency, most patients in both groups had normal serum creatinine levels. Patients in the low RPI group had less evidence for chronic hemolysis (lower LDH, total bilirubin). An explanation for the hypoproliferative response existing in the majority of SCD patients with moderate to severe anemia remains to be fully elucidated but may indicate some component of bone marrow failure.

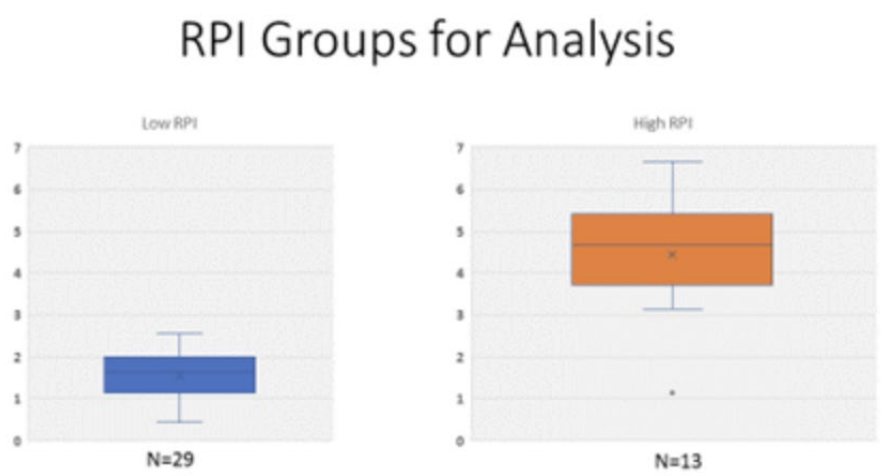

Figure 1
RPI groups

	Low RPI (<2.5) n=29	High RPI (>3) n = 13
Age	40.7 (+/- 12.89)	32.8 (+/- 10.13)
Hb (g/dL)	6.9 (+/- 1.26)	7.3 (+/- 0.95)
RPI	1.56 (+/- 0.54)	4.69 (+/- 1.14)
LDH (U/L)	447 (+/- 262)	636 (+/- 172)
Total Bilirubin (mg/dL)	2.3 (+/- 1.92)	4.6 (+/- 2.44)
Creatinine	0.8 (+/- 1.10)	0.74 (+/- 0.34)

Table 1
Summary data of variables for RPI groups

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ISCHEMIC STROKE IN A PATIENT WITH HEMOGLOBIN S-BETA + THALASSEMIA

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Background: The heterogeneous variant of sickle cell-beta thalassemia [Sβ+] is often associated with milder hemolytic disease(1). Ischemic strokes and silent cerebral infarctions are well-established neurologic complications of sickle cell disease [SCD], with a previous study estimating the prevalence of stroke in SCD patients at 3.75% [in the 4082 patients enrolled]. However, strokes are less commonly reported in Sβ+ population, the same study reported a 1.29% stroke prevalence in Sβ+ and significantly higher rates in other variants (2).

Case: A 41-year-old gentleman with known sickle cell disease [Sβ+ type], and multiple prior hospitalizations with vaso-occlusive crises presented to the emergency room with left-sided weakness, left-sided facial droop and right-sided visual deficits. Imaging confirmed multiple punctate areas of right MCA distribution infarcts. Secondary workup revealed right-sided proximal non-occlusive ICA thrombus, a small patent foramen ovale on echocardiogram, and significantly elevated triglyceride levels at 349 mg/dL [without any reported history of familial hypertriglyceridemia].

The distribution of his infarcts was consistent with ischemic/embolic etiology, presumed secondary to the proximal ICA thrombus. He was transferred to a tertiary hospital and started on a stroke-protocol heparin drip. Though the stroke was not due to an acute sickle cell crisis, he underwent RBC exchange transfusion to help minimize the surrounding brain tissue impact. After this event, he was initiated on aspirin, statin and routine exchange transfusions to decrease his risk for recurrent strokes. On serial outpatient labs, triglyceride levels remain significantly elevated, suggesting a potential role for traditional vascular risk factors in this patient's stroke risk.

Discussion: The co-inheritance of HbS with other globin gene mutations results in various SCD variants including Sβ+, wherein a person inherits both sickle cell and β-thalassemia traits. Patients with the Sβ+ variant tend to have milder clinical presentations; in particular, the stroke risk seems significantly lower than other genotypes (3)(4). Though SCD is most associated with ischemic strokes involving large vessel stenosis, the embolic presentation reported here is a downstream sequela of the patient's underlying sickle cell pathology and dyslipidemia.

Dyslipidemia is often seen in both SCD and β-thalassemia. Recently, Fekri et al studied lipid panel trends in 151 SCD patients [including 54 Sβ+ patients]. In comparison to both healthy controls and other SCD variants, Sβ+ is associated with hypocholesterolemia and significantly elevated levels of triglycerides (5). Though the mechanism is not entirely clear, hypertriglyceridemia in SCD patients is linked to exaggerated endothelial activation and vascular dysfunction. Hypertriglyceridemia increases the incidence of ischemic strokes by promoting atherosclerosis, thrombosis and blood viscosity (6)(7)(8). Consequently, in SCD patients inherently at a higher risk, hypertriglyceridemia adds an additional vascular risk factor.

As in the above-described case, patients with SCD are more likely to develop intra-luminal thrombosis than the general population. This occurs due to recurrent episodes of sickling resulting in pathologic adherence of red blood cells to vascular endothelium and subsequent vascular injury (9). In this case, SCD and hypertriglyceridemia both predisposed him to a

hypercoagulable state increasing the risk for embolic strokes.

Conclusions: This report describes a middle-aged patient with known Sβ+ sickle cell disease who presented with embolic strokes. Sβ+ is often considered as a milder variant of SCD, but this is a misleading characterization as seen in ours and other similar cases(10). While it's not commonly seen, when modifiable atherosclerotic risk factors such as hypertriglyceridemia are present in SCD, lifestyle modifications and lipid-lowering drugs should be considered to decrease the overall stroke risk. It also brings up the question of whether the long-term approach to stroke risk reduction in SCD patients should be modified in the presence of vascular risk factors. In conclusion, a higher degree of clinical suspicion and greater awareness of various stroke etiologies unique to this sub-type will improve the burden of morbidity in this patient population.

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PRE-CONCEPTION DISEASE MODIFYING TREATMENT AND PREGNANCY OUTCOMES IN SCD

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Background: Sickle cell disease (SCD) is known to affect pregnancy adversely. Pregnancy in patients with SCD is associated with increased morbidity and mortality in both the mother and the fetus. In addition, Women with sickle cell disease are at an elevated risk for infertility, miscarriages, VTE (Venous Thromboembolism), pre-eclampsia, pre-term birth, and other fertility and pregnancy-related complications. Adequate care throughout pregnancy with a multidisciplinary team is known to improve outcomes in SCD. However, research and clinical focus on pre-pregnancy care is limited in the SCD population. Pre-conception care offers a unique opportunity to reduce adverse outcomes by identifying modifiable risk factors and providing intervention and education prior to conception. The purpose of this study is to determine if SCD targeted disease-modifying therapy (DMT) prior to pregnancy had an impact on pregnancy outcomes in women with SCD.

Methods: This is a single institution retrospective cohort study at the UI Health Sickle Cell Center. All SCD female patients with a live pregnancy over a 3-years period (January 2020-December 2022) were selected for the study. Exclusion criteria included a history of hematopoietic stem cell transplant. The following data points were collected: age of mother, pre-pregnancy disease-modifying therapy, gravity and parity (GTPAL), mode of delivery, gestational age of the fetus, breastfeeding status, presence of pregnancy-related complications such as pre-eclampsia with or without severe features [pre-E, SF], VTE, vaso-occlusive pain episodes [VOE], ACS (Acute Chest Syndrome), IUGR (Intra Uterine Growth Restriction), and type of DMT (Hydroxyurea, Chronic Exchange transfusion, Voxelotor, L-glutamine, or Crizanlizumab).

Results: Patients not on any DMT were compared to patients on various treatments (chronic exchange or hydroxyurea). None of our patients were on the newer DMT prior to their pregnancy. There were 24 women with a live birth in the 3 years. Of these, 4 were on exchange transfusions before pregnancy, 8 were on hydroxyurea, and 12 were on no treatment. The median age of the patients was 27.0 (interquartile range 23.5-33.0) years. There was no significant difference in age at pregnancy between the two groups (P=0.99). 17 patients had severe Hb genotypes (SS or S-β0 thalassemia) and the other 7 had mild genotypes (SC or S-β+ thalassemia). No difference in Hb genotype severity between DMT and control groups (Fisher's exact test P=1). On average, patients on DMT had more total pregnancies (3.3 vs 2.7) and more live births (1.8 vs 1.6). The gestational age was 3.2 weeks older in the DMT group after adjusting for age at pregnancy and Hb genotype severity (P=0.032). There was no significant difference between the two groups in delivery through C-section, breastfeeding, VTE, ACS or VOE (Fisher's exact test P=1). Patients in the DMT group had a higher risk for pre-eclampsia-related complications after adjusting for age and Hb genotype severity (OR=27, 95% CI 1.9-380, P=0.0029).

Conclusions: Our findings indicate that patients on DMT prior to pregnancy have improved outcomes overall, with lower miscarriages and a higher likelihood of pregnancy. In addition, these women were more likely to carry their pregnancies to term. While our study had limitations, given the small

number and retrospective nature, these findings highlight the importance of comprehensive pre-natal care and DMT in women with SCD in improving pregnancy outcomes in the high-risk population.

Hb Type	Count of Hb Type
SS	13
SC	6
SS HPHF	2
SB0	1
SS HPFH	1
SS, ALPHA THAL CARRIER	1
SB+	1
Grand Total	**25**

Type of SCD

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SCOPING REVIEW OF SICKLE CELL TRAIT: IMPLICATIONS FOR EDUCATION, COUNSELING, AND POLICY

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Background: Newborn screening (NBS) for sickle cell disease has been a public health success, saving lives through early identification of infants with a potentially life-threatening disease. However, NBS also identifies individuals with sickle cell trait (SCT) – the child and at least one parent. The sickle cell community faces the challenge of addressing the ethical, reproductive, and potential healthcare implications of this incidental finding. Growing consensus suggests that families identified with an infant with SCT should be informed, educated, and counseled as part of pediatric practice. In NYS, pediatricians are recommended to inform parents of infants identified with SCT, but there is no formal system, mandate, or funding to facilitate information, education, and counseling. Scoping reviews map the available evidence and identify gaps in the literature.

Objective: To review the literature and provide recommendations for implementing SCT education and counseling within pediatric practice.

Methods: We searched PubMed and Web of Science using two broad search terms: "sickle cell trait" and "newborn screening." Titles and abstracts were screened for inclusion if they were in English, and informed about informing, education, counseling, or complications. Papers were excluded if they focused on prevalence or were unrelated to our objective.

Results: The search returned 118 unique papers; 72 were excluded, and 46 underwent full-text review. Nine papers were general reviews, nine focused on complications, and 26 discussed physician and patient attitudes, knowledge, and barriers. Two papers reported on program implementation using strategies such as nurse educators and the other letters.

Conclusions: This scoping review emphasizes the need for a standardized approach to address the information, education, and counseling needs of patients and families affected by SCT. Despite recommendations, there is currently no mandate or financial support for these essential services. Implementing a formal, evidence-based system within pediatric practice is crucial to ensure comprehensive and effective care for SCT families. Policymakers should consider allocating resources and establishing mandates to facilitate the provision of SCT education and counseling.

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TIP: PHASE 2A CROSSWALK-C TRIAL – CROVALIMAB FOR VASO-OCCLUSIVE EPISODES IN SCD

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Background: Sickle cell disease (SCD) is a group of autosomal recessive red blood cell (RBC) disorders caused by a single point mutation in the β-globin gene, with either homozygous inheritance or heterozygous co-inheritance with other pathogenic variants of the β-globin gene. Hemoglobin S, produced as a result of this point mutation, polymerizes within RBCs under certain conditions, distorting them and generating dense and sickle RBCs. These pathologic RBCs contribute to microvascular occlusions, which may present as acute painful episodes called vaso-occlusive episodes (VOEs). Patients with SCD may also have severe chronic anemia, chronic pain, immune dysfunction, and progressive multi-organ damage. Current therapies for SCD include hydroxyurea, as well as newer treatments such as L-glutamine, crizanlizumab, and voxelotor. Despite these treatments, considerable morbidity and mortality among patients with SCD represent a significant unmet medical need. Complement pathway activation has been reported in patients with SCD at baseline, in acute pain crises, and in delayed hemolytic transfusion reaction. Accumulating nonclinical data suggest the potential multimodal role for complement dysregulation in the pathophysiology of SCD, including vaso-occlusion, hemolysis, inflammation, thrombogenicity, endothelial activation, and end-organ damage.1 The complement pathway can be targeted with crovalimab, a novel anti-C5 monoclonal antibody that allows for small-volume subcutaneous (SC) self-injection. In a Phase 1/2 paroxysmal nocturnal hemoglobinuria (a complement-mediated disorder) study, crovalimab showed rapid and sustained complement inhibition with promising efficacy and safety.2

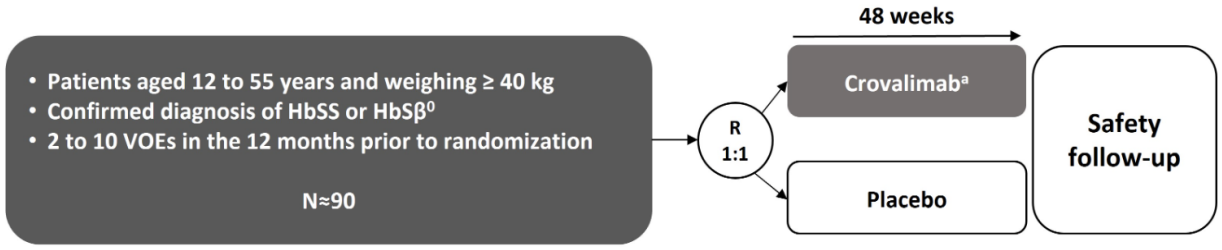
Here we describe the CROSSWALK-c trial (NCT05075824), a randomized, double-blind, placebo-controlled, Phase 2a study evaluating the efficacy and safety of crovalimab as adjunct therapy in preventing VOEs in patients with SCD.

Methods: Patients aged 12 to 55 years, weighing ≥40 kg, with a confirmed diagnosis of SCD, homozygous hemoglobin S (HbSS) or sickle cell β0 thalassemia (HbSβ0), and presenting with 2 to 10 VOEs are eligible, including patients on concurrent SCD-directed therapies. Vaccinations against Neisseria meningitidis, Haemophilus influenzae type B, and Streptococcus pneumoniae are required. Patients with a history of hematopoietic stem cell transplant will be excluded. Eligible patients will be randomized 1:1 to the crovalimab or placebo arms (Figure). An initial intravenous loading dose of crovalimab or placebo will be given on Week 1, Day 1, followed by SC dose on Week 1, Day 2, and then weekly SC doses on Weeks 2 to 4. Starting Week 5, a maintenance dose will be given every 4 weeks during the 48-week treatment period. All study treatment will be given according to a weight-based tiered dosing schedule

(patients weighing ≥40 kg to < 100 kg and patients ≥100 kg). The primary objective is to evaluate the efficacy of crovalimab vs placebo based on the annualized rate of medical facility VOEs. Key secondary efficacy objectives are the annualized rate of acute chest syndrome, the annualized rate of home VOE, and change in urinary albumin–creatinine ratio, tricuspid regurgitant jet velocity, and Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue score in adults, from baseline to Week 49. Safety, pharmacokinetic, immunogenicity, and exploratory biomarker objectives will also be evaluated. Protocol updates are in progress.

Results: Primary results are expected in July 2024.

Conclusions: CROSSWALK-c is enrolling patients with SCD and chronic VOEs in seven countries.



[a]Loading IV dose of 1000 mg (patients weighing ≥40 kg to <100 kg) and 1500 mg (patients weighing ≥100 kg) on Week 1, Day 1, followed by SC dose of 340 mg on Week 1, Day 2 and QW on Weeks 2 to 4. Maintenance doses of 680 mg SC (patients weighing ≥40 kg to <100 kg) and 1020 mg SC (patients weighing ≥100 kg) from Week 5 and Q4W thereafter. HbSβ^0, sickle cell disease genotype of sickle cell beta zero thalassemia; HbSS, homozygous hemoglobin S; IV, intravenous; QW, once every week; Q4W, once every 4 weeks; R, randomized; SC, subcutaneous; VOE, vaso-occlusive episode.

Figure: CROSSWALK-c study schema

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TO TRANSFUSE OR NOT TO TRANSFUSE? LONG-TERM STROKE MANAGEMENT IN PEDIATRIC HEMOGLOBIN SC

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Introduction: One of the most devastating complications in sickle cell anemia (SCA) is stroke. Stroke risk is as high as 11% in children with HgSS and HgS beta0-thalassemia. Chronic transfusions have been shown to prevent recurrent stroke in HgSS and HgS beta0-thalassemia. As stroke in patients with HgSC is very rare, there is no established standard of care for their long-term management. Here we present a case of a 6-year-old female with HgSC and stroke.

Case Description: A 6-year-old female with HbSC and no history of medical or sickle-related complications presented with headache, vomiting, and fever. No focal neurological deficits were identified. Headache was persistent and reported as 10/10 so MRI and MRA of the brain were performed. Imaging was concerning for subacute right inferior cerebellar infarct in the PICA distribution with evidence of edema and narrowing of the 4th ventricular outflow tract. Red cell exchange was performed. The patient was started on a chronic transfusion program as per guidelines for patients with HgSS with stroke to prevent stroke recurrence.

Discussion: Stroke in SCA occurs in up to 11% of pediatric patients. Differential diagnosis for the etiology of our patient's stroke included but not limited to infectious given fever, underlying sickle cell pathology or a thrombophilia (workup was negative). Typically following an acute stroke, a patient with HgSS receives scheduled chronic transfusions with the goal of preventing recurrent stroke by maintaining a hemoglobin S% less than 30% or a HgA% of 70%. The atypical location, the relative rarity in HgSC and questionable underlying etiology for this patient's stroke led to a discussion of whether to start chronic transfusions versus no transfusions. Chronic transfusions have significant side effects including transfusion reactions and effect on quality of life. Whereas long-term chronic transfusions in HgSS following a stroke is a gold standard recommendation to prevent recurrent stroke, it is less clear in this setting. Hydroxyurea has been shown to decrease risk of primary stroke in sickle cell and may be effective in this setting if chronic transfusions are not pursued. Ultimately the team, in collaboration with the parent and patient, chose to pursue chronic transfusions due to the potential morbidity associated with a recurrent stroke.

Conclusions: Given its rarity, there is limited literature regarding the treatment of stroke in HgSC patients. Shared decision-making is imperative. This case report is our institutional experience treating a patient with HgSC and stroke and our consideration of known tenets as applied to a subset of patients where there is no available standard of care.

TABLE OF AUTHORS