SICKLE CELL

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Lanetta Bronté-Hall, MD, MPH, MSPH
Editor-in-Chief

THE FOUNDATION FOR SICKLE CELL DISEASE RESEARCH

CHANGE THE CONVERSATION.

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Released in Association with The Foundation for Sickle Cell Disease Research's 16th Annual Sickle Cell Disease Research & Educational Symposium and 45th National Sickle Cell Disease Scientific Meeting June 10 - 12, 2022

As the Founder and President, it is a pleasure to welcome you to the 16th Annual Sickle Cell Disease Research and Educational Symposium and 45th National Sickle Cell Disease Scientific Meeting. I would like to thank everyone here today for being part of this prestigious symposium. I believe your energy is crucial to the future of Excellent and Equitable Sickle Cell Disease Care.

I would like to thank Scientific Chair, Dr. Elizabeth Klings and Co-Chairs, Dr. Wally Smith and Dr. Andrew Campbell for their tireless energy to bring so many distinguished and high-level speakers on the agenda. Our Virtual and onsite speakers and attendees are from all over the world. I would also like to offer great thanks to all those who have been involved in organizing this event, under the expert guidance of Kyla Thorpe, the Symposium Director and Chief Operating Officer of the FSCDR. What we see before us today is a testament to their hard work.

The symposium allows us to examine and discuss the main issues and opportunities concerning sickle cell disease. It also provides an important forum for us to pause and take stock of where we stand today in the treatment and research landscape for sickle cell disease. Today, we will talk a lot about 'lessons learned' throughout this pandemic. And the first lesson I learned was how much we need each other. How much people in government need to work with people like you – clinicians, scientists, experts, health workers, pharmaceutical companies, foundations, and civil society organizations – all caring about sickle cell disease.

The logic behind this symposium has always been to turn the experience of the symposium into sustainable solutions that guide and inspire us for the continued growth and development of sickle cell care and research. Our Journal of Sickle Cell Disease and Hemoglobinopathies offers scholarly communication by which people involved in academic research can inform colleagues about the results of their work. The Journal is peer reviewed. A directive from the Board of Directors is to move toward indexing the journal as we continue to foster scientific rigor, impact and prestige.

It's a very exciting time for the Foundation for Sickle Cell Disease Research as we expand our satellite locations throughout the state of Florida. We first opened our doors in February 2015 ending the year with 279 patient visits. In 2021 we had 7,282 patient visits. We are already at nearly 4,000 visits for the months of January through June of this year. We have developed a strong clinical research program with a robust patient population, willing and eager to participate in clinical research. But, we sometimes lose track of the progress we've made with the mounting pressures we face daily in our efforts to deliver care, teach, and do research.

Lastly, I want to say a word about the tireless health professionals and frontline workers. I know a lot of it, because I am, by training, a medical doctor. You have worked in the most impossible conditions. You have saved countless lives. And even when there was nothing you could do, you gave your everything and you tried to alleviate your patients' suffering. You've done a great job. Thank you all for your support.

Best Regards,

Lanetta Bronté-Hall, MD, MPH, MSPH
Editor-in-Chief
Founder and President
Foundation for Sickle Cell Disease Research

On behalf of the organizing committee, I would like to welcome you to the 16th Annual Foundation for Sickle Cell Disease Research Symposium. This year's hybrid format marks the first time this conference has had a live component since 2019 and hopefully, marks the beginning of a return to normal daily life. We have assembled a program that showcases the research and clinical work that is taking place to improve the lives of our patients with sickle cell disease. This book contains the submitted abstracts that will be presented orally or via a poster. We are thankful to all of the submitters and reviewers of the abstracts and look forward to an exciting conference!

Best Regards,

Elizabeth S. Klings, MD
2022 Scientific Chair

cc:

Wally R. Smith, MD
2022 Scientific Co-Chair

Andrew D. Campbell, MD
2022 Scientific Co-Chair

TOP ABSTRACTS
ORAL PRESENTATIONS

Presenting: June 11, 2022
3:30 pm - 4:15 pm

JSCDH-D-22-1238443

EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS (PAHs) IN CHILDREN WITH SICKLE CELL DISEASE

Authors: Uzoamaka Obodo, BA[1], Jim Zhang, PhD[2], Heather Stapleton, PhD[2], Yan Lin, PhD[3], Dana Thompson, PhD[4], John J. Strouse, MD, PhD[5]

Affiliation: *[1]DeBusk College of Osteopathic Medicine, [2]Duke Nicholas School of the Environment, [3]Duke Global Health Institute, [4]Duke School of Medicine, [5]Duke University*

Background: Sickle cell disease is a severe hemoglobinopathy that affects approximately 40,000 children in the United States and over 300,000 infants worldwide each year, mostly in Africa and India. Outdoor air pollution is a potentially modifiable factor that has been associated with acute healthcare utilization in children and adults with SCD in ecological studies of exposure. Individual level exposure to tobacco smoke increases the rate of emergency department visits and hospitalizations in children and acute chest syndrome and mortality in adults with sickle cell disease. Short-term exposure to polycyclic aromatic hydrocarbons (PAHs) can be quantified by using silicone wristbands, which are worn by study participants and accumulate PAHs, and other organic contaminants, that are present in the ambient environment. In the body, PAHs can be metabolized and form adducts with proteins and DNA. Hemoglobin-PAH adducts are postulated to be a measure of longer-term exposure (~90 days) in people with normal red blood cell survival but have not been measured in people with sickle cell disease. The goal of this pilot study was to assess the feasibility of using silicone bands and hemoglobin adducts to measure PAHs in children with sickle cell disease.

Methods: We enrolled participants with sickle cell disease between 5 and 18 years of age in a prospective study of environmental exposures. We collected information on exposure by questionnaire, biospecimens (saliva, venous blood), and silicone wristbands worn by the participants for 5 days. We extracted semi-volatile organic compounds from the silicone wrist bands and hemoglobin adducts from red blood cells and characterized 23 PAHs from silicone wristbands by gas chromatography-mass spectrometry and 3 hemoglobin-PAH adducts by high-performance liquid chromatography-mass spectrometry. We measured salivary cotinine using a highly sensitive quantitative enzyme immunoassay (Salimetrics, Carlsbad, CA). We collected information on acute health utilization [ED visits, hospitalizations retrospectively (2 years) and prospectively (6 months)] and laboratory results from the electronic health record. We compared results using pairwise Pearson's correlation and calculated medians and interquartile ranges using Stata Intercooled 16.1.

Results: Our 30 participants were 60% female with a mean age of 12.5 ±3.6 years and hemoglobin concentration of 8.7 ± 1.5 g/dL. Most (84%) had homozygous sickle cell (HbSS), 13% were compound heterozygotes for HbS and C (HbSC) and 3% had sickle beta null thalassemia. Almost all (90%) were treated with hydroxyurea, 10% with voxelotor, and 3% with crizanlizumab. We detected quantifiable levels of 11 different PAHs on at least 50% of wristbands and hemoglobin benzo(a)pyrene (100%) and phenanthrene (90%) adducts in almost all children. The concentration of hemoglobin-PAH adducts was not correlated with markers of hemolysis (lactate dehydrogenase, reticulocytes, or hemoglobin concentration and there were no significant correlations between hemoglobin-PAH adducts and the PAHs measured from silicone wrist bands (Table 2). We identified salivary cotinine levels consistent with environmental tobacco smoke exposure (1 – 20 ng/ml) in 11 participants (44%) and primary tobacco use in 1 (4%). There were no significant differences in acute health care utilization by exposure.

Conclusion: This study demonstrates that individual level exposure to PAHs and tobacco smoke can be measured in children with sickle cell disease using silicone wristbands, hemoglobin-PAH adducts, and salivary cotinine. We identified detectable levels of multiple compounds and limited correlation among the three methods. This may reflect the different duration and types of exposure measured by the different methods or the small sample size. We plan

to assess the relationship among these exposures and disease severity in a larger and longer prospective cohort study.

JSCDH-D-22-1224674

MOMENTUM STUDY OF ARU-1801 GENE THERAPY FOR SCD: ROBUST ANTISICKLING OF HBFG16D

Authors: Michael Grimley, MD[1], Monika Asnani, MBBS, PhD[2], Michael Kent, MD[3], Archana Shrestha, PhD[4], Sydney Felker, PhD[5], Carolyn Lutzko, PhD[6], Paritha Arumugam, PhD[1], Scott Witting, PhD[6], Jennifer Knight-Madden, MBBS, PhS[2], Omar Niss, MD[1], Charles Quinn, MD, MS[1], Christopher Lo, BS[4], Courtney Little, BSN[4], Alisa Dong, PhD[4], Punam Malik, MD[1]

Affiliation: *[1]Cincinnati Children's Hospital Medical Center, [2]Caribbean Institute for Health Research, University of the West Indies, [3]Atrium Health/ Levine Children's Hospital, [4]Aruvant Sciences, [5]University of Cincinnati College of Medicine, [6]Cincinnati Children's Hospital*

Background: Sickle cell disease (SCD) is a genetic red blood cell (RBC) disorder that causes hemolytic anemia, painful vaso-occlusive crises, and life-threatening complications. Myeloablative allogeneic hematopoietic stem cell transplant (allo-HSCT) remains the only curative therapy for SCD, but has several limitations, including lack of donors, conditioning-related toxicities, and risk of graft-versus-host disease (GVHD). ARU-1801 is an autologous lentiviral gene therapy that utilizes reduced-intensity conditioning (RIC), designed to address these limitations and widen access for SCD patients. Updated data on an ongoing Phase 1/2 study (NCT02186418) are presented here.

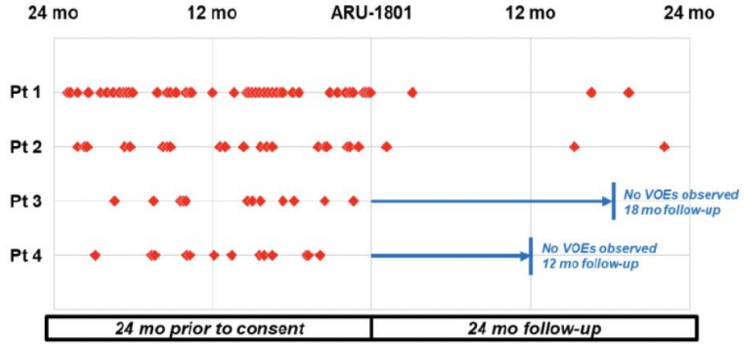
Methods: Adults (18-45 years old) with severe SCD (as defined by recurrent vaso-occlusive events [VOE] and acute chest syndrome) were screened for eligibility. Prior to infusion of ARU-1801, all patients received a single intravenous dose of RIC melphalan (140 mg/m2). Endpoints included measures of safety, engraftment, vector copy number (VCN), hemoglobin, and frequency of VOEs. Patients were weaned off transfusions 3-6 months after drug product (DP) infusion. Outcomes are reported at 24 months or latest follow-up for each patient.

Results: As of 1 Jan 2022, four patients (mean age [range], 26 [19-34] years old) have been treated and followed for ≥12 months post-transplant. Transient neutropenia and thrombocytopenia lasted a median of 7 days. There have been no other serious adverse events related to chemotherapy or ARU-1801 to date. Marked improvements in SCD manifestations include 80-93% reduction in annualized VOEs in the first two patients and complete absence of VOEs (100% reduction) in the next two patients to date.

Preclinical studies suggest HbFG16D may have superior anti-sickling potency compared to wild-type HbF. Clinically, patients in this study expressed a mean 42% HbFG16D per DP VCN, which appears more efficient at expressing anti-sickling globin (ASG) than other lentiviral vectors used for gene therapy, suggesting ARU-1801 may reach effective levels of HbF at relatively lower VCN. Combined, efficacy at low VCN and RIC may increase the safety profile of ARU-1801 over other SCD gene therapies. Furthermore, ARU-1801 appears to be a more potent ASG. At screening, Patient 4 had recurrent VOEs despite 16% HbF and 20% F cells; but, at 12 months following ARU-1801 gene therapy, had complete absence of VOEs with 18% HbF (15% HbFG16D) and 68% F-cells. Furthermore, Patient 4 showed a similar level of remarkable improvement in RBC sickling kinetics by oxygen gradient ektacytometry (Lorrca®) as seen in Patient 3 with 38% HbF.

Conclusion: ARU-1801 delivers a potent anti-sickling HbFG16D with RIC, making it a promising gene therapy alternative to therapies that require myeloablative conditioning and offering amelioration of SCD symptoms without the toxicities and resources associated with full myeloablation.

Figure 1. Reduction in VOEs from 24 months prior to consent to 24 months (or latest follow up) after treatment with ARU-1801



% VOE reduction	Change in VOEs	% total HbF*
93%	43 → 3	28%
80%	20 → 4	15%
100%	12 → 0	38%
100%	13 → 0	18%

*at 24 months or latest follow-up

JSCDH-D-22-1221467

SOLACE-KIDS: PHASE II TRIAL RESULTS OF CRIZANLIZUMAB IN PEDIATRICS

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Affiliation: *[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, [2]Department of Paediatric Hematology, King's College Hospital, [3]The Hospital for Sick Children (SickKids) and University of Toronto, [4]Children's Healthcare of Atlanta, Emory University, [5]Sultan Qaboos University, [6]Novartis Pharma S.A.S., [7]Novartis Pharmaceuticals Corporation, [8]Novartis Pharma AG, [9]University of Alabama Birmingham, Birmingham, AL, USA*

Background: Vaso-occlusive crises (VOCs) are the hallmark of sickle cell disease (SCD). The cell adhesion molecule P-selectin plays a key role in the multicellular interactions that can lead to VOCs. In the SUSTAIN trial in adults, crizanlizumab 5.0 mg/kg, an anti-P-selectin humanized monoclonal antibody, significantly reduced the median annualized rate of VOCs vs placebo and had a favorable safety profile. We describe initial safety/efficacy results for patients with SCD aged 12 to < 18yr treated with crizanlizumab 5.0 mg/kg, with or without hydroxyurea, in the SOLACE-kids trial.

Methods: SOLACE-kids is a Phase II study to confirm and establish dosing and evaluate safety of crizanlizumab in pediatric patients with SCD (any genotype) and ≥1 VOC leading to a healthcare visit within 12mo prior to screening. Patients (N≥100) are stratified by age: 12 to < 18yr, 6 to < 12yr and 6mo to < 6yr. Part A will confirm and establish dosing based on first-dose and multiple-dose pharmacokinetic (PK) results (targeting similar exposure to adults) and safety in each group; Part B will expand recruitment and evaluate long-term safety and efficacy of the PK-confirmed dose. Crizanlizumab is administered on Day 1, Day 15, then every 4wk (up to 2yr). Primary endpoints are PK and pharmacodynamic parameters (after starting dose and multiple doses) and frequency of adverse events (AEs). Secondary endpoints include the annualized rate of VOCs leading to healthcare visit, annualized rate of hospitalizations/emergency room (ER) visits and additional safety measures. This analysis focuses on safety/efficacy data of patients aged 12 to < 18yr receiving crizanlizumab 5.0 mg/kg.

Results: As of 28-August-2020, 50 patients aged 12 to < 18yr were enrolled in SOLACE-kids. Mean (SD) age of patients was 15.0yr (1.92), 29 (58%) were female, 44 (88%) had the HbSS genotype, 32 (64%) were Black/African American and 42 (84%) were receiving hydroxyurea. Median (range) duration of exposure to crizanlizumab was 36.6wk (6–98); 44 (88%) patients received treatment for ≥26wk.

The most commonly reported AEs were headache (n=14 [28%]), vomiting (n=12 [24%]) and back pain (n=9 [18%]). Grade ≥3 AEs were reported in 13 (26%) patients; most common were anemia (n=3 [6%]) and back pain (n=2 [4%]). Serious AEs were reported in 11 (22%) patients; none deemed treatment-related.

No AEs of special interest (Table 1; supplemental materials) led to treatment discontinuation except 1 patient who died of meningitis which was not treatment-related. No infusion-related reactions were serious; all resolved at data cut-off (except 1 case of Grade 1 dizziness). No anaphylactic reaction to crizanlizumab was reported. Pain events on the day of crizanlizumab infusion suspected to be treatment-related were reported in 3 (6%) patients. All pain events, regardless of relationship to treatment, were Grade 1/2, except for two Grade 3 events reported in the same patient (back pain and pain in extremity), which resolved on day of onset. All hemorrhage events were mild and not considered treatment-related.

Increase from baseline in total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was reported in 29 (58%), 17 (34%) and 20 (40%) patients, respectively. Two (4%)

patients had Grade 4 total bilirubin significantly above normal (1 patient was Grade 4 and 1 patient was Grade 3 at baseline); 21 (42%) patients had Grade 3 total bilirubin significantly above normal (5 patients were Grade 3 at baseline). Grade 3 increase in ALT and AST was reported in 2 (4%) patients each. All reported liver function parameters did not meet study criteria for severe drug-induced liver injury.

The median (range) number of VOCs leading to a healthcare visit was 3.0 (1.0–26.0) at baseline and 1.6 (0.0–12.7) on treatment (median absolute reduction: 1.0 [range: –13.3 to 5.8]). 18 (36%) patients did not experience a VOC leading to a healthcare visit while on treatment. The median (range) annualized rate of hospitalizations/ER visits at baseline was 4.0 (1.0–36.0) vs 1.54 (0.0–14.3) on treatment (median reduction: 2.35 [range: –21.7 to 5.3]) (Table 2; supplemental materials).

Conclusion: This initial analysis of SOLACE-kids shows crizanlizumab 5.0 mg/kg is safe and well tolerated in patients aged 12 to < 18yr, consistent with the established profile in adult patients. No new safety signals were identified. Compared with baseline, crizanlizumab 5.0 mg/kg treatment led to a median reduction of 1 VOC leading to a healthcare visit/year in this patient population.

Table 1. Adverse events of special interest

	Age 12 to <18 years (N=50)		
	Adverse events irrespective of relationship to study drug		Adverse events suspected to be related to study drug
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)
Effect on hemostasis – hemorrhage	5 (10.0)	0	0
Infections (all)	23 (46.0)	2 (4.0)	0
Infusion-related reactions (severe reactions search) at any time*†	6 (12.0)	0	4 (8.0)
Infusion-related reactions (standard search) on day of infusion*‡	15 (30.0)	1 (2.0)	11 (22.0)
Pain events on day of infusion*	8 (16.0)	1 (2.0)	3 (6.0)
Anti-drug antibodies to crizanlizumab (immunogenicity)	0	0	0

Numbers (n) represent counts of participants
*Individual preferred terms between the different search strategies overlap; hence, the same patient may be included in more than one category; †Search intended to identify events more likely to be caused by the infusion and to have a potentially more severe clinical course occurring any time after infusion (regardless of grade and causality); ‡Search excluded infusion-site reaction and investigated the most common, non-specific, potential signs and symptoms indicative of infusion-related reactions occurring on the day of infusion

Table 2. Annualized rate of VOC leading to healthcare visit and annualized rate of hospitalizations and ER visits

	Age 12 to <18 years (N=50)	
	Annualized rate of VOC leading to healthcare visit	**Annualized rate of hospitalizations and ER visits (total)**
Baseline*		
n	50	50
Mean (SD)	4.22 (4.34)	5.82 (6.25)
Median (range)	3.00 (1.00–26.00)	4.00 (1.00–36.00)
When receiving crizanlizumab treatment		
n	50	50
Mean (SD)	2.59 (3.15)	2.30 (3.26)
Median (range)	1.61 (0.00–12.70)	1.54 (0.00–14.30)
Absolute change from baseline		
n	50	50
Mean (SD)	−1.63 (3.51)	−3.52 (4.96)
Median (range)	−1.00 (−13.30 to 5.80)	−2.35 (−21.70 to 5.30)
Relative change from baseline		
n	50	50
Mean (SD)	−20.85 (119.67)	−49.10 (69.43)
Median (range)	−59.47 (−100.00 to 576.40)	−66.74 (−100.00 to 238.20)

*Baseline is defined as all VOCs leading to healthcare visits occurring within 12 months prior to screening until first dose

ER, emergency room; SD, standard deviation; VOC, vaso-occlusive crisis

ABSTRACT BREAKOUT SESSION I
PSYCHOSOCIAL

Presenting: June 12, 2022
1:30 pm - 3:00 pm

JSCDH-D-22-1237783

A SUCCESSFUL PILOT PROGRAM TO REDUCE STRESS FAMILIES IMPACTED BY SICKLE CELL DISEASE

Authors: Kemba Gosier[1], Naashon Ducille[1], Ofelia Alvarez, Medical Doctor[2]

Affiliation: *[1]Advancing Sickle Cell Advocacy Project, [2]University of Miami Miller School of Medicine*

Background: The disease process presents a burden to caregivers/parents of children with sickle cell disease (SCD) and can impact the child's self-esteem. Caregivers may be unable to work due to the frequent hospitalizations and pain episodes suffered by their children, resulting in stress and burnout among the caregivers. These medical and psychosocial factors have a significant effect on the individual's health and well-being and interfere with their ability to cope with everyday activities. The purpose of the Community of Parents Empowered (C.O.P.E) pilot designed by the community-based organization (CBO) Advancing Sickle Cell Advocacy Project (A.S.A.P) was to assist family members and pediatric patients with SCD learn about mindfulness and stress coping techniques. The interactive sessions discussed Community Building, Community Resources, Mindfulness, Music Therapy and Art Therapy. The group sessions were directed towards building relationships with other families living with sickle cell and to mitigate some of the caregiver burnout that can happen by engaging in creative therapy outlets.

Methods: Twelve families from the University of Miami Pediatric Sickle Cell Program and from Salah Foundation at Broward Health applied for the C.O.P.E Program. The Program consisted of thirteen free sessions distributed in eight weeks. All sessions were delivered virtually. A baseline survey of 10 questions using the Likert scale, asking participants to indicate their level of agreement, from strongly agree to strongly disagree was used to determine how confident the parents felt with stressors and available support and resource knowledge. The survey results were added up to determine the average response rate.

Results: Twelve adult participants (eleven females and one male; nine African Americans or Afro-Caribbean's, two Latinos and one mixed) completed an intake form and baseline survey. Nine children had SS and three had SC in the participating families. At the end, seven participants evaluated the program. The survey results for admission rates (0-10) and emergency room visits were variable over the previous year. Mindfulness was the most liked session (6 of 7 adults) whereas children enjoyed art therapy (5 of 7). Stress decompression and sharing with others were appreciated by participants. Meeting other families with children with SCD was the most helpful (7 of 7) part of the program. All respondents were satisfied with the program and learned about taking care of their child and self.

Coping skills, stress, and confidence managing stress N=12 participants

Coping with sickle cell disease: Yes: 5, Sometimes: 5, No: 2.

Expectations program will provide for participant: Balancing life: 5, Learning about school: 2, FMLA: 1, No answer: 4.

Available support system: Family and/or friend: 11, Church: 4, Mental health provider: 2,

Previous CBO support: Yes: 4, No: 7, No response: 1

Confident can take care of child with SCD with available resources: 6/12 strongly agree

Confident can access community and financial resources: 7/12 strongly agree or agree

Confident can access mental health resources for child: 8/12 strongly agree or agree

Confident can access mental health resources for self: 7/12 strongly agree or agree

Confident can use stress management techniques on self: 6/12 strongly agree or agree

Confident can use mindful breathing to reduce stress on self: 3/12 strongly agree

Confident can identify signs of caregiver burnout: 6/12 strongly agree or agree

Conclusions: Although this pilot program was limited in sample size, it provided valuable information about caregivers' lack of confidence knowing community resources and how to manage stress. The program met the objective of teaching coping strategies and mindfulness and contributed to decrease caregiver isolation and stress. Seven of the twelve participants initially did not have community-based organization support and at the completion of the program, now are all members of A.S.A.P. and are building community relationships by participating in monthly support groups. We plan to extend this program in the future, pending resources.

JSCDH-D-22-1214252

ENUMERATION OF HEALTH OUTCOMES AMONG ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE

Authors: Kristen E. Howell, MPH, PhD[1], Norma Pugh, MS[2], Jennifer Longoria, PhD, ABPP[1], Nirmish Shah, MD[3], Abdullah Kutlar, MD[4], Victor R. Gordeuk, MD[5], Allison A. King, MD, MPH[6], Jeffrey Glassberg, MD[7], Mariam Kayle, PhD, RN[8], Marsha Treadwell, PhD[9], Cathy Melvin, PhD, MPH[10], Jane S. Hankins, MD, MS[1], Jerlym S. Porter, PhD, MPH[1]

Affiliation: *[1]St. Jude Children's Research Hospital, [2]RTI, [3]Duke University School of Medicine, [4]Augusta University, [5]University of Illinois at Chicago, [6]Washington University School of Medicine, [7]Mount Sinai School of Medicine, [8]Duke University, [9]University of California, San Fransisco, [10]Medical University of South Carolina*

Background: Adolescents and young adults (AYA) with sickle cell disease (SCD) are vulnerable due to difficulties establishing adult care and worsening end organ damage. Young adults with SCD experience increased disease severity, healthcare resource utilization, and mortality, however the degree of these differences relative to age is not well characterized. The objective of this study was to identify differences in health-related outcomes between adolescents and young adults with SCD to better quantify the burden of aging during adult transition years. It was hypothesized that young adults with SCD experience increased severity of health-related outcomes compared to adolescents with SCD.

Methods: AYA participants (15 to 25 years of age) of the Sickle Cell Disease Implementation Consortium (SCDIC), a collaboration of eight multi-disciplinary SCD centers in the United States, were included in this study. Baseline data were gathered between 2016 and 2019 preceding two annual follow-up surveys. This study was approved by all eight institutional review boards and written informed consent was obtained. Participants were stratified by age at baseline as adolescents (age 15.0 to 17.9 years) and young adults (age 18.0 to 25.0 years). Outcomes of interest included clinical (number of dysfunctional organs, number of acute visits in the last 12 months), psychosocial (depression, depression treatment, anxiety, sleep, cognition, task management, reliance on others) and number of barriers to receiving medical care. Differences in participant characteristics were determined by Chi-square, Fisher's exact, Wilcoxon rank sum, or Negative binomial tests, as appropriate. Multivariable models were used to compare the clinical and psychosocial outcomes between adolescents and young adults.

Results: A total of 1,003 AYA participants were included (79% young adult, 54% female, and 72% severe SCD genotype). Young adults were more likely to receive regular blood transfusions (p=0.0139), have severe pain (p< .0001), have taken hydroxyurea (p=0.0284), and less likely to be seen by a SCD specialist (p=0.0347) compared to adolescents (Table 1). Young adults experienced significantly more organ dysfunction (OR [95% CI], 2.56 [1.77, 3.74]), increased acute healthcare utilization in the past 12 months (Point Estimate [95% CI], 2.57 [1.28, 3.85]), worsened depression (Point Estimate [95% CI], 1.74 [0.46, 3.03]), decreased sleep (Point Estimate [95% CI], -1.89 [-3.34, -0.45]), and increased barriers to medical care (Point Estimate [95% CI], 0.48 [0.29, 0.66]) compared to adolescents (Figure 1). There were no observed associations between age group and depression treatment or reliance on others.

Conclusions: This study found that young adults experience increased severity and frequency of SCD-specific complications, which is consistent with the literature. In the first few years of adulthood, young adults with SCD experience increased organ dysfunction and acute events, yet these patients are less likely to be seen by a SCD specialist. Despite worsening depression and sleep, young adults continue to receive low rates of mental health treatment, similar to adolescents with SCD. Depression seems to cause a disproportionate burden in young adulthood relative to adolescence

and does not seem adequately addressed. As patients with SCD are transitioning to adulthood, it is important to anticipate the increased severity of health outcomes and have heightened attention to mental health. Surveillance and treatment of mental health provided by clinical psychologists must be implemented as an integral part of transition programming and continued throughout adult care.

Table 1. Baseline Characteristics

C=Chi-square test, F=Fisher's Exact test, W=Wilcoxon Rank Sum test, N=Negative binomial test All p-values are unadjusted comparisons between adolescents and young adults *Participants with both private and public insurance are categorized as 'private'. *'Engaged' employment includes participants who are students and/or employed. 'Unengaged' employment includes participants who are unemployed and/or disabled. *Dysfunctional organs include ever experiencing: Avascular Necrosis, Chronic kidney disease, Stroke, Pulmonary arterial hypertension, skin ulcers, retinopathy, and Chronic refractory pain. *For T-scores (Sleep Impact, Cognitive Functioning, Task Management, Depression, Reliance on others): higher scores indicate more impairment. *Barriers to medical care included: costs, insurance, time/availability, distance to clinic, severity of the problem, bad experience with health care system, language

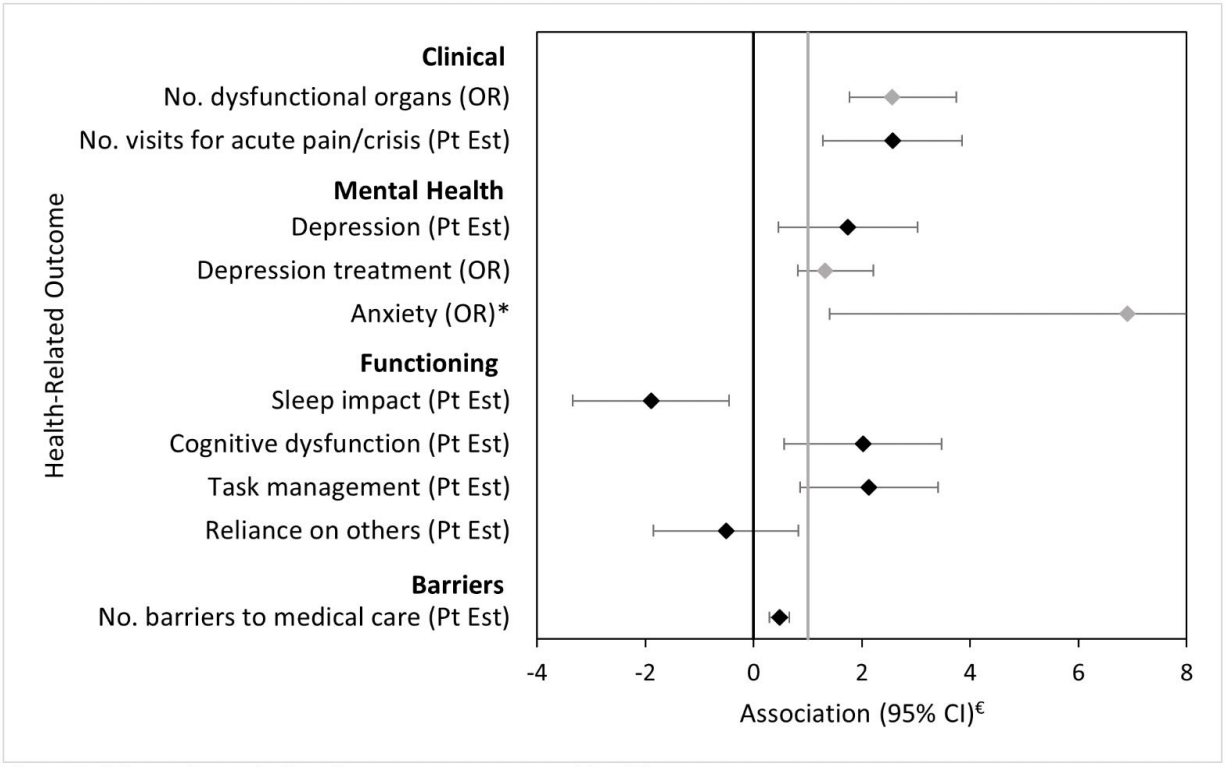

Figure 1. Adjusted associations between age group and health outcomes
*Anxiety upper confidence limit is 125.14 €Reference line for Point Estimates (Pt Est) is 0 (black) €Reference line for Odds Ratios (OR) is 1 (gray)

MEDICAL RISK FACTORS FOR ACADEMIC ACHIEVEMENT AND EMOTIONAL/BEHAVIOR OUTCOMES

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Background: Sickle cell disease (SCD) is a genetic red blood cell disorder that occurs in approximately 300,000 births each year (Colombatti et al., 2021). SCD has been linked to cognitive deficits, lower academic achievement (Hijmans et al., 2010), emotional and behavioral problems (Trzepacz et al., 2004), and intense physical pain (Connolly et al., 2019). Research demonstrates that lower full-scale intelligence (FSIQ) is associated with increased behavioral problems in youth with SCD (Prussien et al., 2020; Prussien et al., 2019). However, there has also been limited research on the relationship between medical characteristics of SCD and academic achievement, or emotional/behavioral wellbeing. The current study aims to examine the relationship between demographic and medical characteristics of pediatric SCD and academic achievement (i.e., reading and math), emotions (i.e., internalizing problems), behaviors (i.e., externalizing problems), and somatic concerns.

Methods: Chart review was conducted for a final sample of 108 youth with SCD at a southeastern medical center. Pediatric patients were clinically referred for neuropsychological evaluation due to concerns for inattention or learning difficulties. Patients completed measures of intelligence (Wechsler Intelligence Scale for Children—Fifth Edition or Wechsler Abbreviated Intelligence Scale—Second Edition) and academic achievement (Wechsler Individual Achievement Test—Third Edition, Reading Comprehension, Word Reading, and Pseudoword Decoding). Caregivers completed the Child Behavior Checklist, from which the internalizing problems, externalizing problems, and somatic complaints scales were used. Demographic covariates include age at time of testing, gender, insurance type, and SCD disease genotype. Medical variables extracted from chart review included hydroxyurea medication prescription and history of stroke/silent infarct or asthma. Descriptive statistics were conducted to examine the characteristics of the sample. Hierarchical linear regression analyses were conducted to examine primary study aims.

Results: Among all patients, 54.6% (N=59) were male, 77% (N=83) had Hbg SS/Hbg SBeta 0 genotype; 88% (N=95) either did not have any insurance or were on government insurance coverage; 42% (N=45) were prescribed Hydroxyurea; 23% (N=25) had a history of either stroke or silent infract; and 24% (N=26) were prescribed an asthma medication. Mean age of patients was 10.7 (SD=3.8) years. The average FSIQ score for all patients fell at the Borderline/Low Average range (M=80, SD=14.4). Average academic achievement scores fell in the Low Average range: M=84.5 (SD=18.2) for reading comprehension, M=86.2 (SD=16.4) for word reading skills, M=88.5 (SD=15.6) for pseudoword reading skills, M=83.6 (SD=17.1) for numerical operations skills, and M=80.5 (SD=16.9) for math reasoning skills. Average T-scores on the caregiver reported CBCL measure were in the Normal range: M=62.5 (SD=10.0) for somatic complaints, 58.9 (SD=11.1) for internalizing problems, and 54.2 (SD= 12.0) for externalizing problems.

Controlling for gender and age at testing, results of the hierarchical linear regression indicate that patients with lower family income (b= -10.30, t = -2.85, p = .005) and Hbg SC/Hbg SBeta+ genotype have more frequent externalizing behavior problems (b= 6.2, t = 2.23, p = .024). Patients from low-income families also report more frequent somatic complaints (b= -8.19, t = -2.85, p = .005) and internalizing emotional concerns (b= -10.17, t = -3.03, p = .003).

Regarding academic achievement, controlling for FSIQ, gender and age at testing, patients with a history of stroke/silent infract had lower scores on reading comprehension (b= -8.5, t = -2.41, p = .018), numerical operations (b= -6.44, t = -2.04, p = .044), and math reasoning (b= -8.53, t = -4.55, p< .001). Patients prescribed asthma medication had lower math reasoning scores (b= -7.15, t = -2.1, p = .039). No other medical characteristics were related to academic, emotional, behavioral, or somatic outcomes.

Conclusions: This clinically referred sample of youth with SCD exhibited overall Low Average intelligence and academic achievement scores. Youth with SCD, type SC/SBeta+ genotype had more behavioral problems than youth with SCD, type SS/SBeta0. Children from families with lower income had more somatic complaints, emotional concerns, and behavioral problems. Consistent with the literature, youth who experienced a stroke/silent infract had lower reading and math scores. Additional medical complications, such as asthma, may also be a risk factor for lower academic achievement but more research is needed to confirm these findings. Identifying demographic and medical risk factors for poorer academic achievement is important so that clinicians can monitor those youth at highest risk more closely.

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PATIENT AND PROVIDER PERCEPTIONS OF STIGMA IN THE EMERGENCY CARE OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a genetic disorder where red blood cells assume a sickled shape, potentially impeding blood flow and causing vaso-occlusive crises. When experiencing a vaso-occlusive crisis many must visit the emergency department (ED) for pain management and treatment. Many people with SCD are of African ancestry and the intersection of having the disease while being a visible minority in Western society may have implications on healthcare provider-patient interactions in the ED. Stigma, biases, and attitudes can all impact the quality of care that an individual with SCD receives. Our scoping review seeks to gather available evidence on stigma in the emergency care of SCD in Canada, the United States, and Europe. The objective is to detail the experiences of adult and adolescent SCD patients as well as the attitudes of ED nurses and physicians to truly understand the similar or conflicting perspectives contributing to this provider-patient interaction.

Methods: The literature review was conducted using the Joanna Briggs Institute (JBI) scoping review methodological framework. A search of the MEDLINE, EMBASE, Web of Science, and Sociological Abstracts databases from January 1, 2000, to January 1, 2022, was used to retrieve eligible studies. Two independent reviewers have screened the titles and abstracts, followed by a full-text review. The search yielded 30 articles meeting the eligibility criteria. Findings will be organized in a descriptive numerical summary as well as a qualitative thematic analysis, where themes, quotes, and conclusions will be identified.

Results: A preliminary analysis of the included studies has identified key themes within the literature. Common concerns reported by SCD patients regarding negative experiences in ED care included perceptions of mistreatment (i.e. lack of respect, dignity and empathy), lack of communication, and distrust of inpatient expertise. SCD patients also experience great delays in treatment initiation and assessment upon arrival to an ED. These delays in timely ED care were associated with the race of SCD patients as well as their status as SCD patients and were identified as a prominent concern among multiple studies. In addition, across the literature, patients report that stigma associated with provider perception of drug-seeking behaviour is a persistent problem in the ED. This stigma often caused disbelief of the level of pain the participants reported and led to inadequate pain control. Consequently, SCD patients shared that ED is often avoided and considered a last resort due to prior bad experiences. Age-specific differences were identified in patient and provider perceptions of ED care, with adolescent SCD patients and pediatric providers reporting more positive ED experiences and less negative attitudes toward SCD patients respectively.

Conclusions: This scoping review highlights the perceptions and implications of sickle cell disease-related stigma on provider-patient interactions in ED care. The factors identified may serve as key barriers to SCD patients seeking emergency care. These findings underscore the need to systematically address the gaps in quality acute care for this population.

Table 3. Number and percent of dyad and YA use by app component and timeframe

JSCDH-D-22-1238746

SOCIAL DETERMINANTS OF HEALTH AND THEIR IMPACT ON FAMILIES OF CHILDREN WITH SICKLE CELL

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Affiliation: *[1]Children's National Hospital, Center for Cancer and Blood Disorders, [2]Children's National Hospital, [3]Howard University School of Medicine, [4]Division of General and Community Pediatrics, [5]Cincinnati Children's Hospital Medical Center, [6]Center for Cancer and Blood Disorders,*

Background: A convenience sample of caregivers of children with SCD completed a 30-question survey reporting their experiences with SDOH that included the USDA Food Security Scale and the We Care housing screening tool in RedCap during clinic visits and hospitalizations. Parents were allowed to skip questions during the survey.

Results: Ninety-nine caregivers of children with SCD completed the survey. Eighty-one percent of respondents were female. Nearly all (95.9%) of respondents were Black or African American. About one quarter of respondents graduated college (29%) and 17.5% were unemployed. Of respondents, 66% had Medicaid and 33% had private insurance. Twenty-six percent endorsed food insecurity and 27% relied on low-cost food. Thirty-one percent lived in an apartment, 67.7% lived in a house, and 1% lived in a shelter or transitional housing. Sixteen percent lived in subsidized or public housing. Thirty-seven percent reported being unable to pay the mortgage or rent on time at least once, 9% reported living with other people because of financial difficulties, 5% reported their home not being heated and 7% reported being evicted from their home.

Conclusions: Addressing health disparities in marginalized groups can be challenging but it is essential. Our findings demonstrate high rates of food and housing insecurity among patients with SCD and their families. Further research is needed to determine the impact of SDOH in high-risk patients, such as those with SCD, and to determine how these factors impact health outcomes.

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SUSPECTED MUNCHAUSEN SYNDROME IN A PATIENT WITH FEIGNED SCD AND REPORT OF AN ACUTE STROKE

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Affiliation: *[1]Inova Schar Adult Sickle Cell Center, [2]Inova Fairfax Hospital, [3]Inova Schar Cancer Institute and Adult Sickle Cell Center, [4]Benign Hematology and Adult Sickle Cell Center*

Background: Approximately 100,000 Americans are living with sickle cell disease (SCD) every day. SCD patients experience debilitating physiological and psychological impairment, especially with regard to the incidence and management of vaso-occlusive pain crises (VOC). In this opioid epidemic, physicians have become more cautious in prescribing opioids, which subsequently affects management of VOC and chronic pain. Thus, the opioid epidemic has not only presented a significant challenge for SCD patients, but also in the mismanagement of chronic pain, leading to innovative attempts to obtain opioids.

We report an unusual case of a 27 year old male presenting with clearly-stated SCD-related complaints including symptoms of stroke. He was urgently treated with red cell exchange (RCE) only to be found as the laboratory studies returned, that he did not have sickle cell disease.

Methods: We carefully reviewed the 48 hour admission of this patient as well as conducted interviews with providers who had previously encountered this patient.

Results: A 27 year old male who stated he had SCD presented to a nearby facility with left face, arm and leg numbness, weakness and pain. Initial testing revealed a hemoglobin (Hb) of 12 g/dL, a comprehensive metabolic panel within normal limits and a mildly elevated lactate dehydrogenase (LDH). CT angiography of the head and neck were negative for large vessel occlusion or acute abnormality. He was transferred to our tertiary center for RCE. During the emergency department evaluation, he reported a diagnosis of HbSS genotype with home medications including hydroxyurea 500mg twice daily, folic acid, morphine 60mg twice daily, hydromorphone 10mg twice daily as needed and enoxaparin. He reported prior complications of acute chest syndrome, pulmonary embolism and frequent VOC and that he received prophylactic transfusions twice monthly. He also provided name and phone number of his hematologist in his home state as he claimed he was in the area working as a traveling nurse. He was admitted to the neurosciences intensive care unit and underwent urgent RCE. Prior to the exchange, a sickle cell screen and hemoglobin electrophoresis were sent but had not yet resulted. His normal Hb on admission and lack of any alloantibody despite extensive transfusion history raised suspicions about the diagnosis but the decision was made to proceed with emergent RCE in light of neurologic presentation. The following morning, his sickle cell screen was negative and later, hemoglobin electrophoresis revealed an AA genotype. The out of state hematologist referenced by the patient was contacted and he reported that the patient does not have SCD and has inappropriately used him as a reference many times.

Of note, while patient did initially receive intravenous opioids for his reported VOC, he was not discharged on any medications. He was informed that he did not have SCD and was discharged with outpatient medicine and hematology follow up.

Conclusions: Frequent VOC crisis is the hallmark of SCD and management includes opioids, transfusion when indicated and hydration. Our center has recently seen cases of patients with pain seeking behavior feigning symptoms and diagnosis of SCD, including another patient with numerous aliases presenting with a declared history of SCD and requesting opioids. However, this particular patient encounter is more unusual with a behavior consistent with Munchausen syndrome. The DSM V classifies factitious disorder, also known as Munchausen

syndrome, as the falsification of illness without any obvious gain. This patient underwent invasive central line placement and RCE without any clear gain. However, he also reported significant pain and requested IV opioids consistent with malingering for the purpose of obtaining opioids. It remains unclear if the patient was truly a travelling nurse, though plausible given his significant knowledge of SCD pathophysiology and treatment. The case raises awareness for the potential of Munchausen syndrome to overlap with underlying malingering in patients presenting with reported complications of SCD. In the era of opioid epidemic, we need to be judicious and evaluate patients carefully when providing care for those with SCD. We propose requesting a sickle cell screen for all patients new to the institution who present with a declared history of SCD with acute pain or other complications. This would not preclude emergent, life saving intervention but may avoid inappropriate treatment for patients with chemical substance abuse disorder who do not have sickle cell disease.

ABSTRACT BREAKOUT SESSION I
HEALTH SERVICES

Presenting: June 12, 2022
1:30 pm - 3:00 pm

JSCDH-D-22-1237213

ADHERENCE OUTCOMES OF A LIQUID HYDROXYUREA DELIVERY PROGRAM IN A PEDIATRIC POPULATION

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Affiliation: *[1]Boston Medical Center, [2]Boston Children's Hospital, [3]Brigham and Women's Hospital*

Background: Hydroxyurea remains underutilized in the pediatric sickle cell population despite its well-known efficacy in decreasing sickle cell complications and hospitalizations. Access to refills and liquid formulation remains a critical barrier for adherence to hydroxyurea.

Objective: To determine the clinical impact of home delivering compounded Liquid Hydroxyurea (LHU) on pediatric patients with sickle cell disease.

Methods: A retrospective cohort study was conducted using electronic health records and pharmacy databases. Pediatric patients aged < 21yrs at the time of initiation of hydroxyurea from March 2016 to July 2020 receiving compounded LHU from Boston Medical Center Pharmacy were included. The primary outcomes of the study were medication adherence by measuring the proportion of days covered, rates of acute care utilization, laboratory values, growth metrics before and after enrolling in the LHU delivery program.

Results: The final cohort included 41 patients. Laboratory outcomes showed a statistically significant increase in Hb 0.34 g/dl (95% CI: 0.04-0.63, p=0.02) and MCV 3.2 Fl (95% CI: 0.92-5.4, p=0.007). Hospitalizations decreased by 51.3% (p=0.01), and ACS episodes decreased by 86.4% (p=0.02) post-initiation of the LHU delivery program. Drug adherence, as measured by the proportion of days covered, had a median vale of 0.95 one-year post initiation of LHU.

Conclusions: Home delivery of compounded LHU from the pharmacy improved drug adherence, decreased hospitalizations, and improved laboratory outcomes in pediatric patients with sickle cell disease by overcoming the barriers to access. Implementation of similar home delivery programs across the country can significantly improve outcomes among pediatric sickle cell patients.

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Affiliation: *[1]New York Health + Hospitals, [2]New York Health + Hospitals/Queens and Elmhurst, [3]New York Health + Hospitals/Kings County Hospital, [4]New York Health + Hospitals/Queens, [5]NYC Health + Hospitals/Metropolitan, [6]NYC Health and Hospitals/Jacobi*

Background: Sickle cell disease (SCD) is a complex chronic disease that causes anemia, pain, organ damage, and early death. As a genetic disorder affecting predominantly people of color, the low priority SCD receives results in poor patient experience, poor outcomes, and high social and economic costs. Quality improvement studies have led to significant gains in survival and quality of care for many other complex chronic diseases. The strategy to implement evidence-based interventions through SCD quality improvement studies (QI) is championed by the National Institute of Children's Health Quality, American Society of Hematology, Health Resources and Service Administration's Sickle Cell Treatment Demonstration Program, and the National Alliance of Sickle Cell Centers.

The challenge is QI requires resources, time, effort, leadership commitment, and a system to monitor effectiveness. Many small or resource-limited centers do not have the necessary electronic medical record (EMR) tools in place. Our objective was to develop an SCD registry and documentation toolkit/navigator within our EMR to monitor the effectiveness of quality improvement studies.

Methods: We set up a team of pediatricians, ED providers, and pediatric hematologists that worked with our EPIC Healthy Planet team to create a sickle cell disease registry, documentation toolkit/navigator, and reports to monitor QI effectiveness.

Results: We created a database of all patients with SCD in our system, our EPIC registry, which can be refined through EPIC's "Slicer/Dicer."

We designed our EPIC documentation toolkit to:

1) Support and encourage quality care and complete documentation of key clinical information
2) Allow capturable clinical data to inform and facilitate quality improvement studies
3) Enhance communication between staff and community health workers
4) Destigmatize and encourage a more humanistic approach to care.

The toolkit includes:

1) history and assessment documentation smart forms (disease-modifying drugs, interval history, complication history, and health maintenance guidance
2) an individualized pain plan, including patients preferred profile
3) a transition of care assessment and planning tool

In addition, the tool kit has:

1) smart set for labs, immunizations, referrals, follow-up, and patient instructions
2) patient educational materials
3) community health worker referral and documentation

We launched the toolkit together with an educational module and tip-sheets. The customized navigator views are available for pediatric emergency medicine, pediatric primary care, and pediatric hematology

providers. From this standardized documentation, we can generate reports for various process and outcome measures for different QI studies.

Conclusions: To improve the patient experience, quality of care, outcomes, costs, and equity, we need to drive QI studies across all centers seeing individuals living with SCD. A critical first step is developing and sharing EMR toolkits that facilitate complete documentation and inform meaningful QI studies.

JSCDH-D-22-1237403

DEDICATED KIDNEY CLINIC FOR PATIENT WITH SICKLE CELL DISEASE: INITIAL OBSERVATIONS

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Affiliation: *[1]Emory University School of Medicine, [2]Grady Memorial Hospital, [3]Emory University, [4]Winship Cancer Center*

Background: Chronic kidney disease (CKD) and rapid decline in kidney function are associated with increased mortality in adults with sickle cell disease (SCD). With increasing age, the prevalence of CKD also increases. To provide comprehensive multi-disciplinary care of patients with SCD and CKD we piloted a dedicated SCD kidney clinic at an urban sickle cell center. We propose that this clinic will improve early recognition and management of CKD for patients with SCD. Here, we present our observations from the pilot phase of this project.

Methods: Between January 2021 and December 2021, a pilot was conducted at the Georgia Comprehensive Sickle Cell Center. A single nephrologist was assigned to see all the adult SCD patients that were referred to the SCD kidney clinic. Demographics, clinical characteristics, features of kidney dysfunction [albuminuria and estimated glomerular filtration rate (eGFR)], blood pressure trends as well as other laboratory data were collected at the time of enrollment and on subsequent visits. Data analysis and figures were generated using R-statistical software.

Results: During the study period, 44 adult African American patients with SCD were enrolled in the SCD kidney clinic pilot. 28 (64%) were females and 16 (36%) were males. The median age of the cohort was 45 years (IQR 38-55). The most common sickle cell phenotype was SS with 38 patients (86%) followed by SC subtype 4 (9.1%). Hemoglobin S/high fetal hemoglobin 1 (2.3%), Sickle cell beta thalassemia 1 (2.3%) were other phenotypes. Median serum creatinine on the initial visit was 1.2 mg/dl (IQR 0.8-1.6). The median eGFR at the initial visit was 59 ml/min/1.73m2 (IQR 38-106). 4 patients had an eGFR < 30 ml/ml/min/1.73m2. Hypertension was present in 23 (52%) patients at enrollment. The median albumin to creatinine ratio (ACR) was 330 mg/g (IQR 75-941). 24 (55%) patients were on either angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy at the initial visit. Microscopic hematuria was a common finding, present in 33 (75%) patients. The median hemoglobin was 8.1 mg/dl (IQR 6.9-9.3). 28 (63%) patients had elevated bilirubin, suggesting a hemolytic phenotype. In patients with SS phenotype, age was strongly correlated with initial eGFR (R=-0.59, p< 0.001) but there was no correlation between age and ACR at presentation (p >0.9) (Figures 1 and 2). Macroalbuminuria (ACR >300 mg/g) was present in 61% of patients with hypertension and 43% of patients with no history of HTN (p=0.23) (Figure 3).

Conclusions: This study describes the baseline characteristics of patient with SCD and CKD enrolled in our SCD kidney clinic. Albuminuria, hypertension, decreased eGFR, and elevated bilirubin were common at the time of inclusion. The implementation of this clinic has improved access and timeliness to nephrology care in this vulnerable population. It serves as a great platform to evaluate longitudinal trends and outcomes, engage in clinical and basic science research targeting preservation of kidney function in patients with SCD and CKD.

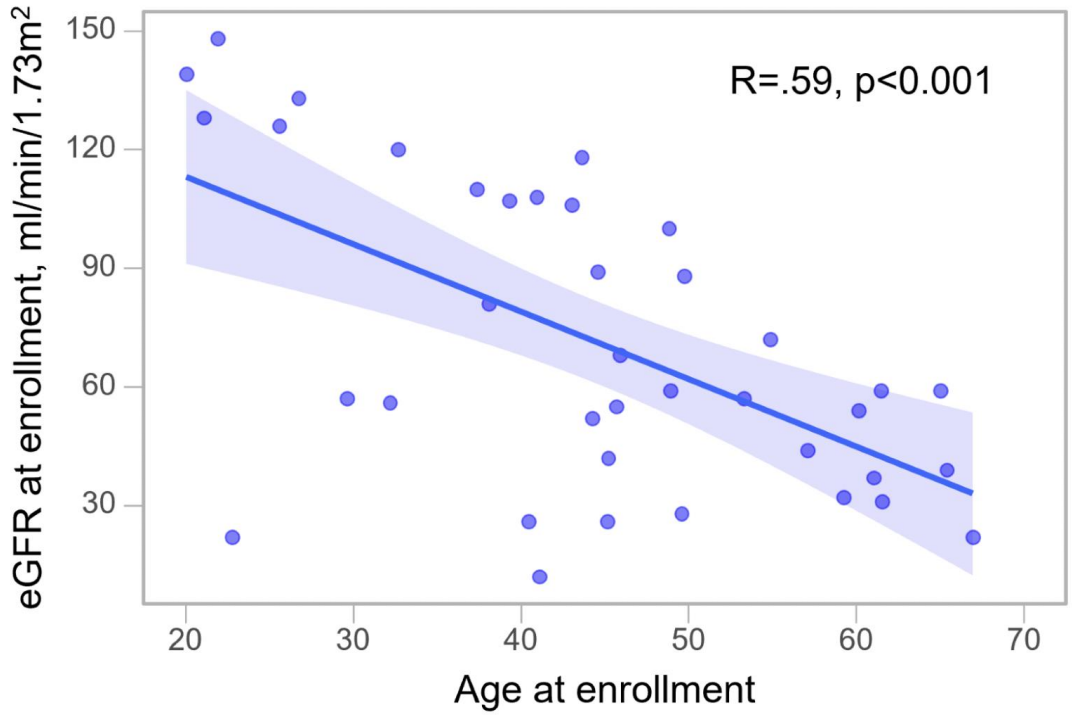

Figure 1: Correlation between eGFR and age at enrollment

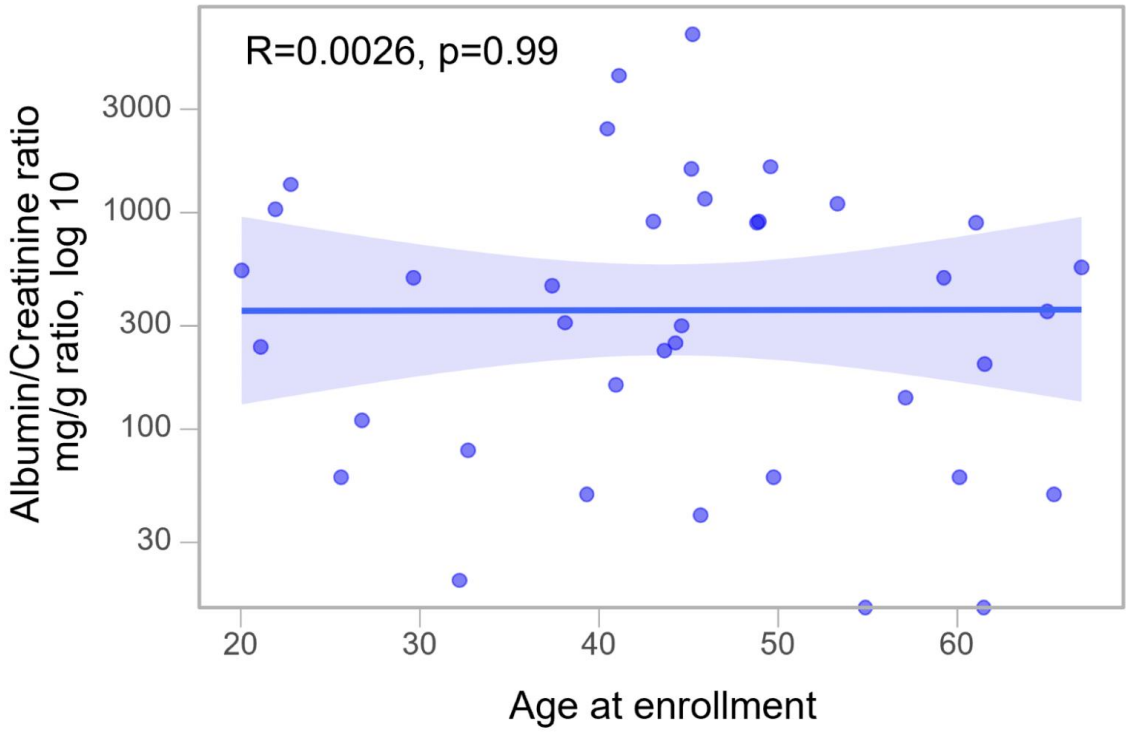

Figure 2: Correlation between eGFR and albuminuria at enrollment

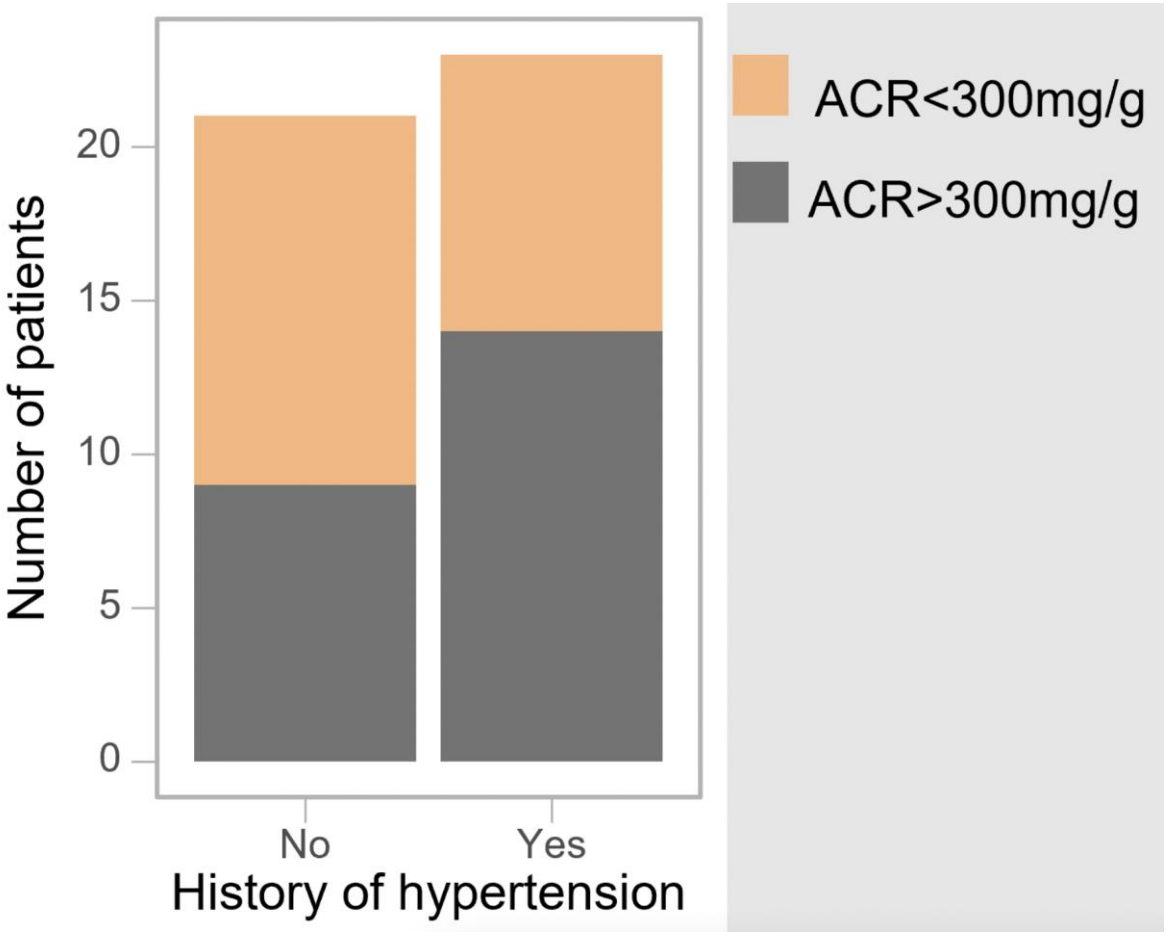

Figure 3: Incidence of albuminuria in SCD patients with and without hypertension

JSCDH-D-22-1211288

HYDROXYUREA POSSESSION PATTERNS FOR SICKLE CELL DISEASE PATIENTS IN MEDICAID

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Affiliation: *[1]Susan B. Meister Child Health Evaluation and Research (CHEAR) Center, [2]University of Michigan, [3]Public Health Institute, [4]Tracking California, [5]Duke University,*

Background: Hydroxyurea is the primary pharmaceutical intervention to decrease sickle cell disease (SCD) related complications—specifically vaso-occlusive pain episodes—for people living with sickle cell anemia and those with other SCD genotypes who have reoccurring SCD-complications. Despite the effectiveness of hydroxyurea in preventing SCD related complications and comorbidities, there has been low uptake of the medication. The objective of this analysis was to identify the patterns of hydroxyurea possession among Medicaid enrollees with SCD in California in order to provide a greater understanding of the most prevalent HU utilization behaviors.

Methods: The cohort for this analysis was Californians living with SCD, identified by the Sickle Cell Data Collection Program by linking and applying a validated case definition to administrative, newborn screening, and clinical case data sets. The Sickle Cell Data Collection Program is a public health surveillance at the population level. Participants were included if they had at least one hydroxyurea prescription claim from 2010 to 2017. The cohort was restricted to those with continuous Medicaid enrollment one year prior to and after their first hydroxyurea prescription. Prescription claims were used to construct a hydroxyurea possession history for the twelve months following a patient's first hydroxyurea prescription claim. A medication possession ratio (MPR) was calculated for each month. MPR is the ratio of the days a person possessed a hydroxyurea prescription to the total days in the month, excluding any days the person was hospitalized. Group-based trajectory modeling was used to identify subgroups with distinct hydroxyurea possession patterns over the twelve-month follow-up period.

Results: 713 Medicaid enrollees were included in this analysis; the cohort was 57% pediatric (under 21 years) and 50% male. Three statistically significant groups of hydroxyurea possession patterns were identified: persistently high, moderate decreasing to low, and low dropping to no compliance (Figure 1). The distribution across the three groups were similar between sex. 72% of adults and 56% pediatric patients had trajectories that decreased over the twelve-month follow-up period. However, these individuals fell into two distinct trajectories: moderate decreasing to low and low dropping to no compliance.

Conclusions: This investigation of hydroxyurea uptake based on claims data for those with SCD suggests a high rate of non-compliance among people who have been prescribed the medication and shows the utility and importance of data tracking systems for rare diseases such as SCD. Almost three fourths of the identified adults had a possession pattern that decreased to low or no possession over the 12-month period. Furthermore, this analysis illustrates distinct hydroxyurea utilization behaviors. These possession patterns can be used to target and inform interventions to increase hydroxyurea adherence. Further analysis is planned to identify patient characteristics associated with each possession pattern.

Table 1: Hydroxyurea Possession Patterns for Medicaid Patients with SCD

	N (%)	Hydroxyurea Possession Patterns		
		Group 1 Moderate decreasing to low	**Group 2** Low dropping to no compliance	**Group 3** Persistently high
Total	**713**	253 (35%)	197 (28%)	263 (37%)
Age				
Adult (21+)	304 (43%)	111 (37%)	108 (36%)	85 (28%)
Pediatric (<21)	409 (57%)	142 (35%)	89 (22%)	178 (44%)
Sex				
Male	358 (50%)	118 (33%)	106 (30%)	134 (37%)
Female	355 (50%)	135 (38%)	91 (26%)	129 (35%)

JSCDH-D-22-1222536

MASSAGE THERAPY FOR YOUTH WITH SICKLE CELL DISEASE: A RETROSPECTIVE STUDY

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

Background: Children and adolescents with sickle cell disease (SCD) have complex needs during hospital admissions that include managing stress, anxiety, and the physical and psychosocial dimensions of pain.1 A recent review of five experimental studies found that massage therapy can provide significant pain reduction; improve functional status; reduce depression, anxiety, and stress; and potentially reduce analgesic use and length of stay among individuals with SCD.2 To our knowledge, no studies have examined the effectiveness of inpatient massage therapy provided by a Certified Pediatric Massage Therapist (CPMT) among children and adolescents with SCD. The purpose of this retrospective study was to examine the effects of massage therapy on patient-reported outcomes among children and adolescents with SCD admitted on an inpatient hematology/oncology unit.

Methods: With philanthropic support, University Hospitals Connor Whole Health began providing massage therapy to pediatric patients on an inpatient hematology/oncology unit in 2019. The full-time CPMT worked in collaboration with the medical team and child life services to enhance patient care and psychosocial support. The CPMT provided massage therapy sessions (approximately 20-30 minutes) upon patient/family request or referral from the medical team, documented all sessions in the electronic health record (EHR), and collected patient/family testimonials on the impact of sessions. Investigators conducted a retrospective chart review on all massage therapy sessions provided to inpatients with SCD at University Hospitals Rainbow Babies and Children's Hospital and documented in the EHR between December 2019 and June 2021. Data analysis included 1) counts and percentages of patients' demographics and clinical characteristics, and 2) means, standard deviations, and paired t-tests of single-session effects on numeric rating scale measures of pain, stress, and anxiety in sessions where the pre-session score was ≥ 1.

Results: Between December 2019 and June 2021, 222 massage therapy sessions were provided to 44 children and adolescents with SCD during inpatient admissions. Patients (mean age 11.14 ± 5.33) were mostly Black/African-American (95.5%) and Non-Hispanic (97.7%). Equal numbers of male (50%) and female (50%) patients received massage therapy, and most (79.5%) had HbSS disease. Of the 222 massage therapy sessions, complete pre-session (≥ 1) and post-session (≥ 0) scores were available for pain (90 sessions), stress (35 sessions), and anxiety (30 sessions). On average, patients receiving massage therapy with pre-session scores ≥ 1 rated their pain at 7.02 ± 1.98, stress at 7.40 ± 1.99, and anxiety at 7.27 ± 2.07. These patients reported clinically and statistically significant ($p < .001$) mean reductions in pain (-1.34 ± 1.55), stress (-2.11 ± 2.01), and anxiety (-2.30 ± 1.97). Additionally, several patient/family testimonials described the positive impact and support provided by massage therapy services.

Conclusions: This study provides initial evidence for the clinical effectiveness of massage therapy provided by a CPMT for addressing the physical and psychosocial needs of inpatient children and adolescents with SCD. Within a large pediatric academic medical center, massage therapy services can be integrated within inpatient care and medical team meetings to enhance symptom management and psychosocial support. More research is needed to determine the efficacy of massage therapy, both individually and in collaboration with other

treatments, for addressing the needs of inpatients with SCD.

JSCDH-D-22-1236661

TRANSCRANIAL DOPPLER SCREENING IN CHILDREN WITH SICKLE CELL ANEMIA-REVIEW OF BEST PRACTICE

Authors: Jane Zepeda, PA[1], Alecia Nero, MD[2], Caroline Rogers, PA[1], Lakisha Bennett, RN[3],

Affiliation: *[1]UT Southwestern Medical Center, [2]University of Texas Southwestern Medical Center, [3]Childrens Medical Center,*

Background: Sickle cell anemia (SCA) is a disorder of hemoglobin and specifically refers to hemoglobin SS and hemoglobin Sβ0 genotypes. Stroke is one of the most debilitating sequelae of SCD and can occur in early childhood [1]. Transcranial Doppler (TCD) is a noninvasive ultrasound-based method of measuring the rate of blood flow in the vessels of the brain that predicts increased stroke risk in children with SCA. National guidelines recommend annual TCD screening of children with SCA beginning at age 2 years and continuing until 16 years [2] to allow for interventions for primary stroke prevention. Despite the nationally recommended guidelines, the annual rate of TCD screening ranged only from 7 to 54% among states in a 2015 study of 4887 children [3]. This implies that many children with SCA are not being assessed for stroke and likely not offered appropriate medical intervention.

This project aims to assess adherence with national TCD screening guidelines in patients with SCA ages 2-14 years receiving care at a single institution to determine whether differences exist between performing these assessments within the general radiology department or a family-centric clinic model to inform best practice for this high risk patient population.

Methods: Children's Health Center for Cancer and Blood Disorders (CCBD) Sickle Cell Program currently delivers care to 455 patients with SCA ages 2-14 years old who are deemed eligible for TCD screening. The program standard to screen until age 14 years is due to the inability to accurately insonate the vessels beyond that age with the non-imaging clinic TCD. Screening TCDs have been performed in two locations:

1. Non-imaging TCD, completed within the hematology clinic on same day as a scheduled clinic visit with the sickle cell provider, or
2. Imaging TCD, completed in the radiology department at a separate time and potentially separate date from scheduled clinic visit with a sickle cell provider

We examined the number of TCDs completed in eligible patients over a 2 year period in clinic from February 2017 - February 2019. In 2019, all screening TCDs were moved to the radiology suite. We evaluated those performed in radiology from February 2020 - February 2022 to avoid confounding based off transitioning to a new practice change within that first year.

Using the electronic health record, we compared aggregate data of the number of patients eligible for TCD screening to the number of completed TCDs during these two-year intervals.

Results: Hematology clinic TCDs: 195 of 365 eligible patients completed screening TCDs (53%). 54% of the completed TCDs were in female patients.

Radiology TCDs: 211 of 455 total eligible completed screening TCD (46%). 55% of these completed TCDs were in female patients.

Conclusions: The CCBD Sickle Cell Program performed TCDs on the upper end of the range published in the literature regardless of location. However, there was a 7% decrease in the number of completed TCDs in the radiology suite compared to the hematology clinic. The factors leading to this noted decrease are unclear. We question whether the TCDs performed in the clinic were more family-centric leading to fewer missed days of work or school since these were always paired with hematology provider visits. Also,

it is possible that having these services performed by the primary team/medical home was a factor contributing to higher adherence with the clinic-based TCDs.

Screening for stroke in children with SCA should be an urgent medical priority. Identifying barriers to effectively screening these children should be evaluated and addressed to further decrease the morbidity and mortality of severe SCA. We describe our experience that location and/or team performing the TCD screening may affect the adherence with national guidelines. Our next steps are to formally and rigorously evaluate barriers to full adherence with national guidelines so that these can be corrected.

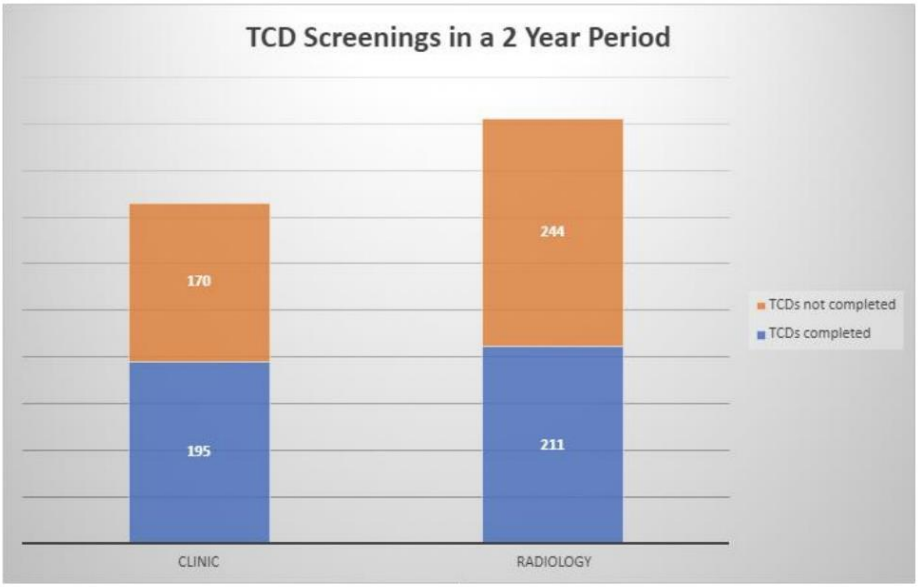


Figure. Number of screening TCDs in patients with SCA performed in 2 year intervals within the hematology clinic and radiology department

ABSTRACT BREAKOUT SESSION I
BASIC SCIENCE

Presenting: June 12, 2022
1:30 pm - 3:00 pm

JSCDH-D-22-1239107

AN ODE MODEL FOR PREDICTING PEDIATRIC PATIENT PAIN IN SCD BASED ON PATIENT SLEEP DATA

Authors: Quindel D. Jones, B.S.[1], Rebecca Segal, PhD[1], Reginald McGee, PhD[2], Cecelia Valrie, PhD[1], Angela Reynolds, PhD[1]

Affiliation: *[1]Virginia Commonwealth University (Richmond, VA, US), [2]College of the Holy Cross*

Background: Sickle Cell Disease (SCD) is a family of genetic blood disorders that affects over 20 million people worldwide, whose prevalent complication is pain. Severe, acute pain episodes, characterized as unanticipated pain periods ranging from hours to weeks, usually occur a few times a year during childhood and adolescence for individuals with SCD. They are primarily due to vaso-occlusion , and result in tissue damage and inflammation, and thus, are characterized as nociceptive pain (i.e., pain due to an identifiable pain stimulus that is potentially or actually damaging). Valrie et al. 2019 study that involved 88 pediatric SCD patients who reported sleep quality and pain revealed a correlation between sleep and pain using actigraphy. This connection between sleep and pain has yet to be fully explored as a precursor of pain presentation. Pain is a subjective experience, making it difficult to quantify and monitor. Mobile technology has been a major aid in this quest since it allows continuous monitoring of several self-reported patient factors, such as sleep quality, pain onset and severity, affect, medication use, and activity levels. The patient data collected by Valrie et al. reflects that sickle cell pain in childhood presents differently than adulthood, without chronic pain, and that poor sleep quality is correlated with increased SCD pain.

Methods: In this study, we investigate this sleep-pain connection using mathematical tools that incorporate a dynamical systems approach. Dr. Valrie investigated the temporal relationship between SCD pain and sleep in the prospective study of 88 pediatric SCD patients aged 8 to 17 years using twice daily electronic surveys (e-diaries) for up to 4 weeks with concurrent sleep actigraphy for 2 weeks. Sleep is defined as self-reported sleep quality, and actigraphy assessed sleep duration and efficiency. This resulted in 4473 total e-diary assessments completed across the sample. Data sets from some of those patients were excluded because of excessive sparsity. Based on the results in Clifton et al. 2017 and Yang et al. 2019, we created a mechanistic (ordinary differential equations) ODE model for predicting subjective pediatric patient SCD pain levels using the aforementioned data. Our model is a deterministic set of ODEs that aims to understand how pain level is impacted by sleep quality and pain medication.

Results: Preliminary fitting of the patient data to the model has confirmed the correlation seen in Valrie et al. 2019 but with significant discrepancies. The current aim is to employ iterated parameter estimation for each patient to capture the quantitative relationship between sleep and pain and then use that relationship to have sleep history predict pain onset and duration.

Conclusions: Our model aims to be a warning system for upcoming pain events for pediatric SCD patients, given the proper pain and sleep data. This is advantageous in the digital age as noninvasive monitoring will allow physicians to treat chronic pain in patients anywhere based on personalized, data-driven recommendations.

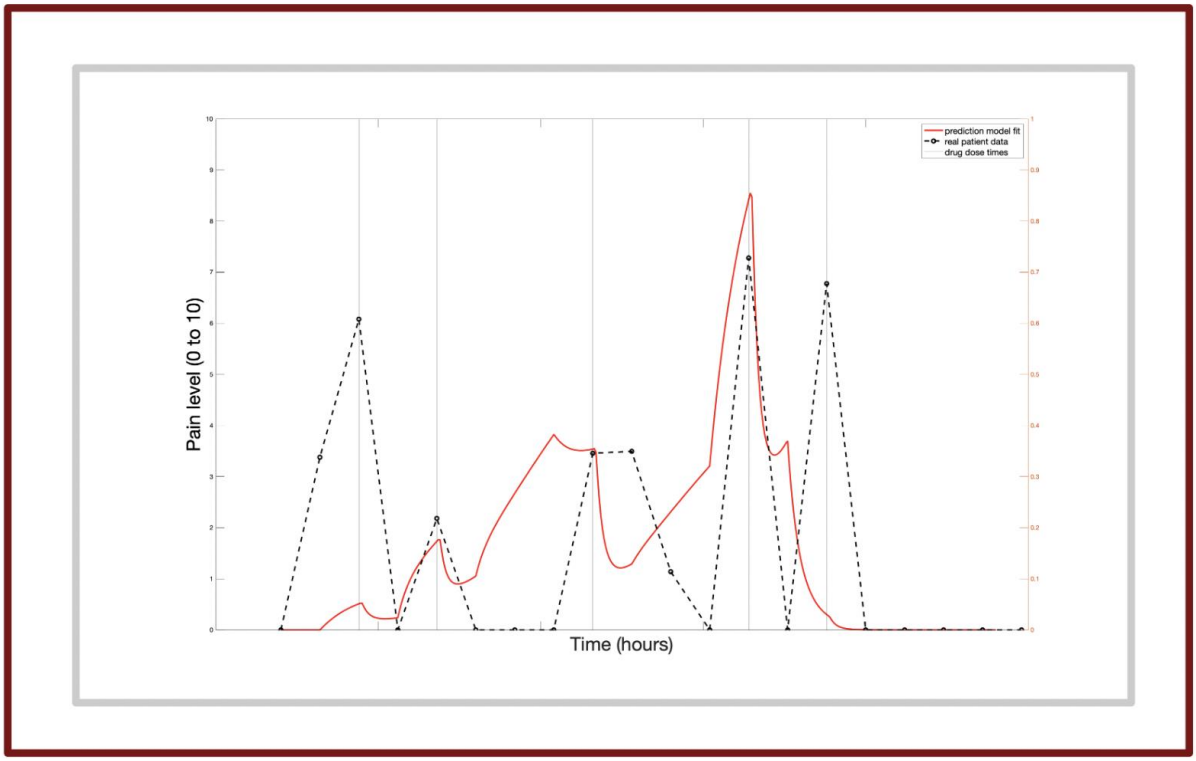
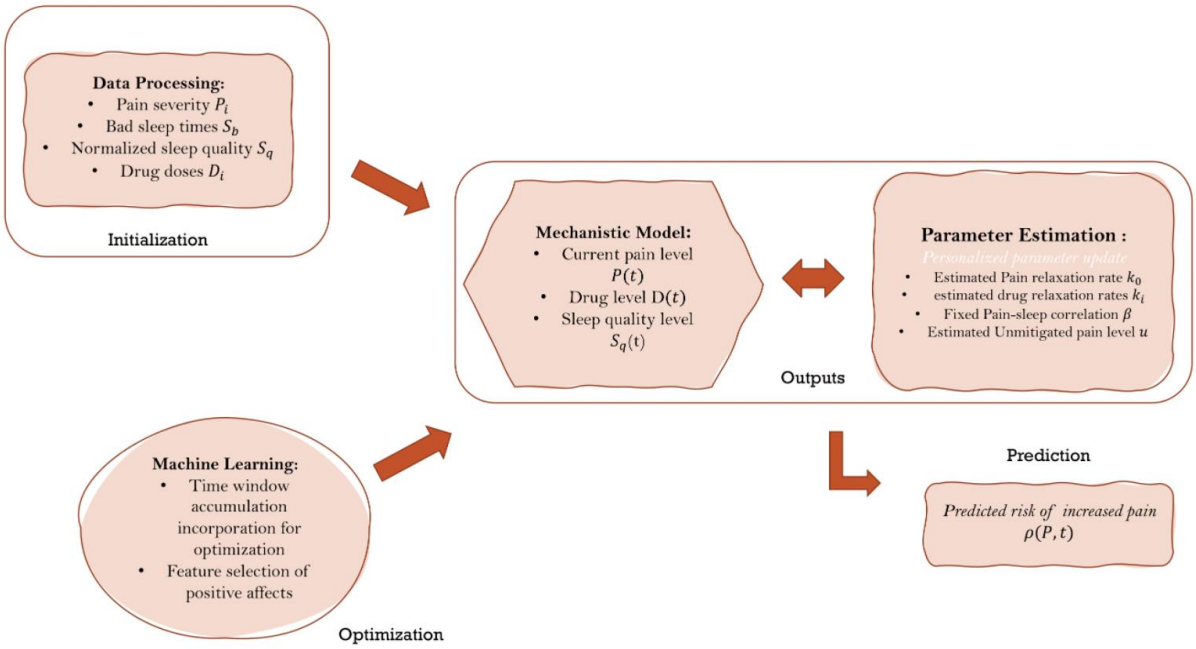


Figure 1: Sample pain and medication data from an individual patient
Pediatric patient pain episode model prediction (in red) compared to the patient's reported pain (black dashes) and reported drug dose times (vertical lines) over 10 days (240 hours). This is patient A10, whose pain pattern is classified as pain onset. This is one patient example of the preliminary model fitting.



Schematic flowchart showing model framework
This model framework shows the modeling process. The project is currently in the box with two steps since that process is iterative.

JSCDH-D-22-1237566

GUT MICROBIOME AND SICKLE CELL DISEASE: IMPACT OF HYDROXYUREA IN ANGOLAN CHILDREN

Authors: Mariana Delgadinho[1], Catarina Ginete[1], Carolina Fernandes[1], Brigida Santos[2], Jocelyne Vasconcelos[2], Miguel Brito[3],

Affiliation: *[1]H&TRC ESTESL/IPL, [2]CISA, [3]Escola Superior de Tecnologia da Saude de Lisboa,*

Background: Sickle cell disease (SCD) is one of the most prevalent genetic diseases, affecting approximately 300,000 newborns every year. It is particularly common in the African continent, with nearly 80% of the SCD births occurring in Sub-Saharan Africa, contributing to 50-80% of under-5 mortality. The SCD clinical manifestations are quite diverse, and the gut microbiome has recently been shown to be important in the control of inflammation, cell adhesion, and the production of aged neutrophils, which are major interveners of recurrent vaso-occlusive crises experienced by the patients. Furthermore, it has been proposed that hydroxyurea (HU), the most commonly used treatment for SCD, has a multimodal effect and could help to reduce aged neutrophils and microbiome dysbiosis. Given this, our main aim is to understand how the disease and HU treatment modulates the microbiome and if these changes could be related with severity.

Methods: In order to characterize the gut microbiome, we sequence the bacterial 16SRNA gene for the V3-V4 regions using NGS. A total of 66 stool samples were collected, which consisted of SCD children before and after initiation of the HU treatment. Hematological and clinical data were also obtained during the consultations. After DNA extraction and sequencing, the EzBioCloud pipeline was performed in the fastq files for microbiome taxonomic profiling and quality control. The differences between the two groups were assessed with the STAMP software, using Welch's t-test.

Results: Significant differences in alpha-diversity were found between the two groups, with higher values for the children naïve for HU in a number of parameters, including OTU species count ($p< 0.001$), phylogenetic diversity ($p=0.004$), and microbial richness ($p< 0.001$), as measured by the ACE, Chao1, and Jackknife indices. When compared to the beginning of the trial, children after HU treatment had larger proportions of beneficial bacteria, such as Roseburia inulinivorans, Lactobacillus rogosae, Blautia luti and Faecalibacterium.

Conclusions: To our knowledge, this is the first study to show alterations in the gut microbiome in SCD children before and after HU treatment. Nevertheless, further studies about the microbiota in SCD populations will be crucial to demonstrate the importance of specific bacteria and their function in this disease. Ultimately this could provide new insights for developing treatments to reduce gut microbiota-driven inflammation, which may attenuate the chronic symptoms. This work was supported by FCT/Aga Khan (project nº330842553) and FCT/MCTES (UIDB/05608/2020 and UIDP/05608/2020) –H&TRC.

JSCDH-D-22-1238852

MONOACYLGLYCEROL LIPASE INHIBITION AMELIORATES HYPERNOCICEPTIVE PHENOTYPE IN SICKLE MICE

Authors: Kennedy Goldsborough, BSc[1], Karan Muchhala, PhD[1], Atuahene Adu-Gyamfi[1], Sara Herz[1], Donald Jessup, BSc[1], Bryan Mckiver, MS[1], Kalpna Gupta, PhD[2], Imad Damaj, PhD[1], Joyce Lloyd, PhD[1], Hamid Akbarali, PhD[1], Wally R. Smith, MD[1], Aron Lichtman, PhD[1]

Affiliation: *[1]Virginia Commonwealth University, [2]University of California - Irvine*

Background: Sickle Cell Disease (SCD) is a major cause of morbidity and mortality worldwide, and affects more than 100,000 people in the US. Recurrent episodes of acute, vaso-occlusive pain crisis, a hallmark of the disease, lead to chronic pain for many patients, though the mechanisms of this transition are poorly understood. Although opioids remain the standard of care to treat SCD chronic pain, their myriad adverse side effects (e.g., constipation, respiratory depression, abuse liability, dependence) as well as the fact that SCD chronic pain requires prolonged opioid treatment that results in tolerance, severely limit their therapeutic utility. Thus, a pressing need exists to identify effective non-opioid analgesic strategies to reduce SCD chronic pain. Humanized mouse models of SCD, such as the Berkeley (BERK) model, mimic features of sickle cell pain and therefore provide a useful tool to investigate disease pathophysiology and evaluate novel therapeutic strategies. Dorsal Root Ganglion (DRG) neurons are peripheral sensory neurons essential for the transmission of nociceptive stimuli to the CNS. DRG neurons from sickle mice show hyperexcitability. Furthermore, sensory nerve conduction studies are a clinical diagnostic tool for peripheral neuropathologies, and in rodent models of neuropathic pain serve as an indicator of peripheral neuropathy. Inhibitors of the major degradative enzyme of 2-arachidonoylglycerol, monoacylglycerol lipase (MAGL), reduce nociceptive behavior in neuropathic and inflammatory preclinical models of pain through cannabinoid receptor-dependent and -independent mechanisms. Therefore, we examined if MAGL inhibitors will ameliorate the hyper-nociceptive phenotype of HbSS-BERK sickle mice.

Methods: Male and female HbSS-BERK (SCD) and HbAA-BERK (control) (5-6 months old) mice were used for these experiments. Nociceptive behaviors were assessed using the von Frey and Hot Plate tests. Spontaneous, musculoskeletal and motor-functional behaviors were assessed using the Grip Strength and Nesting assays. Neuronal hyperexcitability was assessed using whole cell patch clamp electrophysiology of L4-S1 DRG neurons. Peripheral neuropathy was assessed using sensory nerve conduction studies of the dorsal caudal tail nerve. The latency of the compound sensory action potential and the corresponding amplitudes were recorded. Data were analyzed as two- and three-way ANOVAs followed by Tukey post-hoc analysis when appropriate ($p < 0.05$ considered significant).

Results: HbSS-BERK mice displayed profound mechanical and thermal hypersensitivity. HbSS-BERK mice also exhibited deficits in forepaw grip strength and nest-building behavior. Patch clamp studies revealed that DRG neurons harvested from HbSS-BERK mice displayed extreme hyperexcitability. Moreover, HbSS-BERK mice exhibit reduced sensory nerve conduction velocity and amplitude compared to control mice. MJN-110 reduced mechanical allodynia and thermal hyperalgesia in HbSS-BERK mice in a dose-dependent manner. Importantly, seven days of daily injections of MJN-110 (5 mg/kg) continued to ameliorate the hyper-nociceptive phenotype of HbSS-BERK mice, which did not undergo tolerance. Finally, DRG harvested from the MJN110-treated HbSS-BERK mice showed similar DRG neuronal activity as seen in control mice. Ongoing studies are examining the effects of repeated administration of MJN110 on nesting behavior and sensory nerve conduction.

Conclusions: These findings validate that HbSS-BERK mice show hypersensitive responses to mechanical and heat stimuli, and exhibit musculoskeletal/motor-functional deficits in grip strength and nest building behavior. Additionally, this work demonstrates hyperexcitability of sensory neurons from the lower lumbar region of the spine and a reduction in sensory nerve conduction amplitude and velocity in the dorsal caudal nerve of the HbSS-BERK mice. Finally, the observations that MJN110 reduces these hyper-nociceptive behaviors and ameliorates neuronal hyperexcitability in HbSS-BERK mice suggest that MAGL inhibition is a promising strategy to prevent/reduce chronic pain related to sickle cell disease.

JSCDH-D-22-1269771

SURGICAL REVASCULARIZATION REDUCES STROKE RISK IN CHILDREN WITH SCD AND MOYAMOYA SYNDROME

Authors: Sabrina H. Han, BHS[1], *Joseph Piatt, MD[2], Ricardo Hanel, MD, PhD[3], Corinna Schultz, MD, MSHP[2], Manisha Bansal, MD[4,5], Philipp Aldana, MD[4,6],*

Affiliation: *[1]UF College of Medicine, [2]Nemours/AI duPont Hospital for Children, [3]Baptist Health System Jacksonville, [4]University of Florida College of Medicine - Jacksonville, [5]Nemours Children's Specialty Care, [6]Wolfson Children's Hospital*

Background: Recent studies have suggested that surgical revascularization may be a safe and effective therapy to reduce the risk of cerebrovascular complications in patients with sickle cell disease and moyamoya syndrome (SCD-MMS). However, these studies have been limited by small sample sizes and lack of a control group for comparison. Through a multi-center, retrospective cohort of children with SCD-MMS, we sought to investigate whether the addition of revascularization surgery reduces the risk of cerebrovascular events (CVEs) in comparison to conservative management alone (chronic transfusion therapy and/or hydroxyurea).

Methods: A retrospective review was performed at 15 major U.S. pediatric neurosurgery centers with established hematology programs for children with SCD-MMS (age < 18 years old) treated between 1993 and 2017. A limited data set of patients' clinical and surgical histories were extracted and entered into a central registry. The incidence of CVEs (stroke and TIAs) between patients treated with surgical revascularization was compared to those with conservative management alone. Multivariable logistic regression was used to compare CVE occurrence and multivariable Poisson regression was used to compare incidence rates between groups. Covariates in multivariable models included age at treatment start, age at moyamoya diagnosis, antiplatelet use, CVE history, and the risk period length.

Results: A total of 141 patients with SCD-MMS were studied. 78 (55.3%) were treated with conservative management and revascularization surgery (Surgery group) and 63 (44.7%) were treated with conservative management alone (Conservative group). Both cohorts were similar in terms of sex and use of CTT and HU. Those in the Surgery group had an earlier onset diagnosis of MMS, a greater proportion of patients with CVE prior to treatment start, and worse baseline mRS scores - all indicative of a worse clinical course of cerebral ischemia. After revascularization, patients in the Surgery group had reduced odds of developing a CVE over the duration of their risk period (odds ratio = 0.27, 95% CI: 0.08-0.94, P = .040). Furthermore, when comparing patients in the Surgery group during their pre-surgical periods and post-surgical periods, patients had markedly reduced odds of developing a CVE after surgery (odds ratio = 0.22, 95% CI = 0.08-0.58, P = .002). Postoperatively, 3 patients had CVEs and 4 had non-CVE complications. Of the 13 patients with no prior history of CVE who underwent surgery, 100% continued to be free of CVEs post-operatively.

Conclusions: Our retrospective study provides strong evidence that revascularization surgery, when added with conservative treatment, can be performed safely and reduce the risk of CVEs in pediatric patients with SCD-MMS. As the largest study of its kind to date, these results support the role of revascularization surgery in stroke and TIA prevention in this population; nevertheless, a prospective study will be needed to validate our findings.

Table 1. *Patient Characteristics by Group.*

Characteristic	Conservative N = 63	Surgery N = 78	*P* value
Baseline age, years	5.2 ± 3.6 4.7 (2.9 – 6.6)	5.9 ± 3.7 5.2 (3.2 – 7.9) [n=77]	.22[1]
Age of Moyamoya Diagnosis, years	10.3 ± 4.7 9.9 (6.7 – 14.2) [n=62]	9.1 ± 4.2 8.7 (6.0 – 12.0) [n=77]	.14[1]
Sex			.61[2]
Male	31 (49.2%)	34 (43.6%)	
Female	32 (50.8%)	44 (56.4%)	
Baseline mRS	1 (0 – 1)	1 (1 – 2)	<.001[1]
0	15/33 (45.5%)	12/74 (16.2%)	
1	14/33 (42.4%)	30/74 (40.5%)	
2	0/33 (0%)	19/74 (25.7%)	
3	2/33 (6.1%)	11/74 (14.9%)	
4	2/28 (6.1%)	2/74 (2.7%)	
Age of treatment start, years (Conservative or Surgery)	6.8 ± 4.0 6.2 (4.1 – 8.8)	11.0 ± 4.7 10.5 (7.4 – 14.5)	<.001[1]
Age of conservative start, years	6.8 ± 4.0 6.2 (4.1 – 8.8)	6.3 ± 3.7 5.5 (3.3 – 8.3)	.39[2]
Treatments			
CTT	61 (96.8%)	74 (94.9%)	.69[2]
HU	28 (44.4%)	29 (37.2%)	.39[2]
AP	34 (54.0%)	59 (75.6%)	.008[2]
Length of treatment, years			
CTT	9.2 ± 4.85 9.2 (4.7 – 12.5) [n=58]	7.8 ± 4.9 6.7 (3.9 – 12.2) [n=74]	.098[1]
HU	2.7 ± 2.7 2.2 (0.4 – 3.8) [n=28]	3.1 ± 3.1 1.8 (0.7 – 4.3) [n=28]	.74[1]
AP	4.3 ± 2.7 4.1 (1.7 – 6.5) [n=32]	5.0 ± 4.0 4.05 (2.1 – 7.0) [n=57]	.75[1]
CVE history prior to treatment (Conservative or Surgery)	33/62 (53.2%)	65 (83.3%)	<0.001[2]
CVE history prior to conservative management	33/62 (53.2%)	42 (54%)	>.999[2]
Length of risk period, years	11.8 ± 4.7 11.9 (9.3 – 15.1)	8.7 ± 4.8 7.9 (5.0 – 12.7)	<.001[1]

Data are mean ± standard deviation, median (interquartile range), or count (percentage). Adjusted sample size values are provided when missing data was present. AP = Antiplatelet; CTT = Chronic transfusion therapy; CVE = Cerebrovascular event; HU = Hydroxyurea; mRS = modified Rankin Scale. [1]Wilcoxon rank sum test; [2]Fisher's exact test

Table 2. *Cerebrovascular Events by Treatment Group.*

Outcome	Conservative N = 62*	Surgery N = 77*	Effect Size (95% CI)	*P* value
CVE Occurrence: ≥1 CVE per patient	27 (43.5%)	7 (9.1%)	0.27 (0.08 – 0.94)[1]	.040
0 CVE	35 (56.5%)	70 (90.1%)		
1 CVE	21 (33.9%)	4 (5.2%)		
2 CVE	3 (4.8%)	1 (1.3%)		
3 CVE	3 (4.8%)	1 (1.3%)		
4 CVE	0 (0%)	1 (1.3%)		
No. CVEs per 100 patient years followed	5.7	4.7	0.53 (0.18 –1.61)[2]	.19
Total CVEs	36	13		
Hemorrhagic stroke	3	0		
Ischemic stroke	23	6		
TIA	4	7		
Unknown	6	0		
Ischemic stroke/TIA Occurrence: ≥1 CVE per patient	21 (33.9%)	7 (9.1%)	0.34 (0.10 – 1.22)[1]	.10
No Ischemic strokes/TIAs per 100 patient years	4.5	4.7	0.59 (0.19 – 1.94)[2]	.40

Regression models are adjusted for age of treatment start, age of moyamoya diagnosis, use of antiplatelets, history of CVEs, and length of risk period (see **Supplementary Tables S1-4** for the full regression analysis outputs). CI=Confidence interval; CVE = Cerebrovascular event; TIA=Transient ischemic attack.

*Adjusted sample size; 1 patient in the Conservative group had an unknown time of treatment start and 1 patient in the Surgery group had surgery at last known follow-up

[1]Odds ratio from a logistic regression model; [2]Rate ratio from a Poisson regression model

Table 3. *Cerebrovascular Events by Pre-Surgery and Post-Surgery Groups.*

Outcome	Pre-Surgery N = 77*	Post-Surgery N = 77*	Effect Size (95% CI)	*P* value
CVE Occurrence: ≥1 CVE per patient	36 (46.7%)	7 (9.1%)	0.22 (0.08 – 0.58)[1]	.003
0 CVE	38 (49.4%)	70 (90.1%)		
1 CVE	22 (33.9%)	4 (5.2%)		
2 CVE	10 (13.0%)	1 (1.3%)		
3 CVE	6 (7.8%)	1 (1.3%)		
4 CVE	1 (1.3%)	1 (1.3%)		
No. CVEs per 100 patient years followed	17.8	4.7	0.34 (0.17 – 0.66)[2]	.002
Total CVEs	64	13		
Hemorrhagic stroke	2	0		
Ischemic stroke	32	6		
TIA	18	7		
Unknown	12	0		
Ischemic stroke/TIA Occurrence: ≥1 CVE per patient	32 (41.6%)	7 (9.1%)	0.26 (0.09 – 0.69)[1]	.010
No. Ischemic strokes/TIAs per 100 patient years	13.9	4.7	0.59 (0.28 – 1.19)[2]	.15

Regression models are adjusted for age of treatment start, history of CVEs, and length of risk period (see **Supplementary Tables S5-8** for the full regression analysis outputs). CI=Confidence interval; CVE = Cerebrovascular event; TIA=Transient ischemic attack.

*Adjusted sample size: 1 patient in the Surgery group had surgery at last known follow-up; this patient was excluded from both the Pre-Surgery and Post-Surgery groups to preserve balancing of groups and the repeated measure nature of the analysis.

[1]Odds ratio from a logistic regression model; [2]Rate ratio from a Poisson regression model

ABSTRACT BREAKOUT SESSION II
HEALTH SERVICES

Presenting: June 12, 2022
3:15 pm - 4:45 pm

JSCDH-D-22-1216882

A QUALITATIVE STUDY TO EXAMINE PROVIDER'S KNOWLEDGE & PERCEPTIONS OF HYDROXYUREA

Authors: Jonathan Hooshmand, MPH[1], Paloma Luisi, MPH[1], Marcy Stein-Albert, MD[2], Jean-Bernard Poulard, MD[2], Kenneth Rivlin, MD, PhD[3], Lindsay Cogan, PhD[4]

Affiliation: *[1]New York State Department of Health, [2]NYC Health + Hospitals/Queens, [3]NYC Health and Hospitals/Jacobi, [4]New York State Department of Health: Office of Quality and Patient Safety*

Background: While evidence supports hydroxyurea (HU) as a safe and effective treatment for sickle cell disease (SCD) in children and adults, utilization and adherence remain suboptimal (Badawy et al., 2017). Previous research found that low awareness of or agreement regarding the benefits of HU by providers led to under prescribing of HU or low adherence to the National Heart, Lung, and Blood Institute (NHLBI) guideline for HU treatment counseling (Lanzkron et al., 2008; Cabana et al., 2019).

Methods: Participants for the key informant interviews were identified from a survey of pediatric emergency department, primary care, and hematology physicians and clinical providers who are part of New York City's Health and Hospitals system. The semi-structured interviews were conducted via WebEx using questions approved by the NYC H+H IRB and lasted between 20 and 45 minutes. Thematic analysis was applied to the interview transcripts with the researcher coding for themes.

Results: When asked about challenges with HU adherence, teens or adolescents were mentioned frequently. When discussing the process of a SCD consult and HU conversation, most providers discuss the treatment option and provide materials with information during the first consult, let the patient review the information at home, and then initiate a follow-up consult for a treatment decision. Social workers and support with care coordination for families emerged as a theme when providers were asked what supports were/could be helpful for patients with SCD. Lastly, there was strong agreement among providers about the quality of the HU and SCD educational resources available to providers and patients by the health system.

Conclusions: These findings will help inform future interventions and quality improvement initiatives for health systems and SCD patients.

JSCDH-D-22-1218166

ADOLESCENTS WITH SICKLE CELL DISEASE EXPERIENCE IMPACTS IN HEALTH-RELATED QUALITY OF LIFE

Authors: Andrew D. Campbell, MD[1], Avery A. Rizio, PhD[2], Kristen L. McCausland, MPH, PhD[2], Glorian P. Yen, PhD, MPH[3], Jincy Paulose, MD[3], Soyon Lee, PharmD[3]

Affiliation: *[1]Childrens National Hospital, [2]QualityMetric Incorporated LLC, [3]Novartis Pharmaceuticals Corporation,*

Background: Children and adolescents with sickle cell disease (SCD) experience disease-related complications such as chronic pain, vaso-occlusive crises, anemia, acute chest syndrome, and splenic sequestration. These complications, and their long-term effects, likely contribute to impairments in health-related quality of life (HRQoL). We compare the HRQoL of adolescents with SCD with a normative sample of adolescents from the US general population.

Methods: An online cross-sectional observational survey was administered to US adolescents with SCD, ages 12–17 years (n=247). Adolescents provided assent to participate, and their guardians provided permission. Adolescents completed the Child Health Questionnaire-Child Form 45 (CHQ-CF45) and the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) Pain and Sleep Impact domains. Average CHQ-CF45 scores were compared to developer-provided normative scores from a sample of adolescents ages 11–18 years representative of the US adolescent population. Adolescents' ASCQ-Me Pain and Sleep Impact scores were compared to benchmark scores from a sample of US-based adults with SCD. Differences between adolescent and normative/benchmark sample means were evaluated using Welch's t-tests. Differences were also compared to a minimally important difference (MID) threshold, calculated as ½ standard deviation of the normative/benchmark sample mean.

Results: Adolescents with SCD reported CHQ-CF45 scores that were significantly lower than normative scores ($p < 0.001$ for all domains). For 8 of the CHQ-CF45 domains, differences between the adolescent SCD sample and the normative sample were meaningful, as they exceeded the MID threshold. The greatest impacts were observed for the Physical Functioning, Role/Social Limitations due to Physical Health, and General Health domains. Differences for the Getting Along/Behavior and Family Cohesion domains were not meaningful, as they did not exceed the MID threshold. Adolescents reported ASCQ-Me Pain Impact scores that did not differ significantly from the benchmark sample of adults with SCD ($p=0.079$). While adolescents' ASCQ-Me Sleep Impact scores were significantly higher than those of the adult SCD benchmark sample (indicating that the adolescent sample experienced fewer sleep impacts, $p < 0.001$), the difference did not exceed the MID threshold.

Conclusions: Using adolescent-self report, these results demonstrate the significant detrimental impact of SCD on adolescents, relative to a normative sample of US-based adolescents of a similar age. Impacts were observed across many different areas of HRQoL. Results also indicate that adolescents with SCD experience pain and sleep-related impacts that do not meaningfully differ from those experienced by adults with SCD. Treatments and services for adolescents with SCD should focus on improving HRQoL.

Authors: Benjamin Jaworowski, BS, Taylor Crouch, Ph.D., Rachel Walls, LCSW, Daniel A. Sop, MS, Shirley A. Johnson, LSW, Wally R. Smith, MD

Affiliation: *Virginia Commonwealth University*

Background: Utilization behaviors in adult sickle cell disease (SCD) patients are driven by a complex mix of factors, many of them behavioral. Anxiety and depression- known to be prevalent in SCD- as well as substance misuse, adverse childhood experiences (ACEs), and resulting toxic stress, may all drive up utilization of hospital resources. Approximately 60% of US adults report at least one ACE, and Black people and the poor have disproportionately greater exposure to ACEs. ACEs have not been routinely assessed in adults with SCD. We hypothesized that adults in an SCD Adult Medical Home with ACEs and other behavioral risk factors would more often utilize Community Health Workers (CHWs) assigned for case management within the Medical Home.

Methods: We analyzed insurance claims to measure ICD10 diagnoses for anxiety and depression. We analyzed psychological assessment battery data from our trained LCSW to document not only these measures, but also the Adverse Childhood Experience (ACE) score. To assess outcomes, we analyzed detailed CHW logs of each patient contact. We documented the number of contacts per patient and the length of contact time per contact, in minutes. We tested the association of these two outcomes with mood and anxiety disorder diagnoses for all patients (N=409), as well as the ACE score for patients who completed an assessment battery (N=57). Analysis of variance was used to compare means of each outcome variable among patients with and without anxiety or mood disorders, and among patients with ACE scores of 0, 1-2, and 3 or more.

Results: We found significant differences in the mean number of contacts per patient among patients with vs. without a mood disorder, and with vs. without an anxiety disorder. Similarly, we found highly significant differences in the mean number of contacts per patient among patients with an ACE score of 3 or more vs. all other patients. P-values for both variables for mood disorders were 9.68E-05 and 3.66E05. P-values for anxiety were .0009 and .0003. P-values for ACE Scores of 3+ compared to all others were 1.39E-08 and 3.18E-08.

	All	Mood Disorder	No Mood Disorder
Total Contacts	3532	1450	1910
Total Patients	409	98	311
Avg time of contact (min)	16.44	17.26	15.81
Contacts per pt	**8.6**	**14.8**	**6.1**

	ACE Score = 0	ACE Score = 1-2	ACE Score = 3+
Total Contacts	64	181	709
Total Patients	8	16	33
Avg time of contact (min)	18.86	16.1	18.2
Contacts per pt	**8**	**11.3**	**21.5**

Conclusions: We conclude that behavioral risk factors- particularly adverse childhood experiences- predict not only hospital utilization but also CHW utilization in an adult SCD medical home. Expansion of ACE assessment screening is warranted to confirm

whether the dramatic impact of ACE score on CHW utilization holds among non-referred patients. Expansion of screening for toxic stress and substance misuse are also warranted. Our findings suggest SCD program leaders could reliably use behavioral risk factor assessment to assign CHW resources to SCD adult patients.

JSCDH-D-22-1238557

COMPLEMENTARY AND INTEGRATIVE MEDICINE USE IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

Authors: Lisa N. Thaniel, DSW, LICSW[1], Suvankar Majumdar, MD[1], Anqing Zhang, Ph.D.[1,2], Deepika S. Darbari, MD[1,3]

Affiliation: *[1]Children's National Hospital, [2]Division of Biostatistics and Study Methodology, [3]Center for Cancer and Blood Disorders*

Background: Pain or vaso-occlusive crisis is the hallmark of sickle cell disease (SCD). Standard treatment for SCD pain includes hydration, as well as non-steroidal anti-inflammatory drugs and opioid pain medications. While most studies show that opioids provide short-term relief, they are associated with side effects including constipation, opioid induce hyperalgesia, and risk of dependence and addiction. The objectives of this study were to assess the prevalence of complementary and integrative medicine use in a population of pediatric patients with SCD, the type of CIM used, and sociodemographic and health-related factors associated with their use of CIM.

Methods: Parents of children with SCD were approached about the study during clinic visits and hospitalizations. They were asked to complete a 22-item survey about their child's use of CIM. Descriptive statistics were used to generate frequencies or percentages for categorical variables. Chi square or Fisher's exact was performed with a p-value < 0.05 to test the association between CIM and sociodemographic characteristics in the collected sample.

Results: Of the 100 parents who completed the survey, 86% reported using CIM. The most commonly used techniques were prayer (68%), massage (53%), heat (30%), relaxation techniques (24%), aroma therapy (23%), exercise (21%), and herbal medicine (16%). Nineteen percent of foreign born and 15% of U.S. born parents reported using herbal and folk remedies. Twelve parents reported using spiritual healing, reiki, or laying on of hands and 8 parents reported using acupuncture and mindfulness. Nine percent of parents reported using cannabidiol products and 4% of parents reported using cannabis for their child's SCD.

Conclusions: Health care providers should be prepared to integrate CIM into their discussions with patients and families and provide opportunities for families to learn about safe CIM approaches.

JSCDH-D-22-1201535

PREVALENCE AND FACTORS ASSOCIATED WITH DEPRESSION AMONG ADULTS WITH SICKLE CELL DISEASE

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Affiliation: *[1]Head of Adult Medicine, [2]Department of Psychiatry University of Uganda, [3]The Center for Rapid Evidence Synthesis, [4]Makerere University*

Background: Depression amongpatients with sickle cell disease (SCD) is underdiagnosed and undertreated due to the overlap of symptoms and signs of SCD and depression. The study sought to determine the prevalence and factors associated with depression among adults attending the SCD out-patient clinic in Mulago Hospital, Uganda.

Methods: This was a cross sectional study in which 255 adults with SCD were enrolled. Participants were evaluated for depression using the Self Report Questionnaire (SRQ-20) and a score of 6 was considered diagnostic of depression. Demographic data was collected with a pre-tested study questionnaire. Perceived social support was measured using the 12-item multidimensional social support scale and self-esteem was measured using the Rosenberg Self-Esteem Scale. Blood samples were taken to obtain a complete blood count. Modified poisson regression analyses were used to determine associations of depression.

Results: The prevalence of depression was 68.2 % (95% C.I; 62-74) with a median age of 21 years. The factors independently associated with depression were pain crisis in the last month (prevalence ratio (PR)=1.07, 95% CI: 1.04-1.07, p=0.001), history of a hospital admission in the past 6 months (PR=1.04, 95% CI: 1.01-1.07, p=0.012), formal education (PR=0.79, 95% CI: 0.59-0.97, P=0.008) and a low social support rating (PR=0.67, 95% CI: 0.53-0.84, P=0.0019)

Conclusions: The prevalence of depression in adults with SCD is high with up to two thirds of patients having some form of depression. The major risk factors were low level of education, low social support, pain crises in the past month and hospital admissions in the last 6 months.

JSCDH-D-22-1221656

REAL-WORLD CHARACTERISTICS OF PATIENTS WITH SICKLE CELL DISEASE WHO INITIATE CRIZANLIZUMAB

Authors: Payal Desai, MD[1], Marie Yasuda, PharmD, MS[2], Chi-Chang Chen, MsPharm PhD[2], Catherine McGuiness, MA, MS[2], Yao Cao, MS[2], Jincy Paulose, MD[3], Soyon Lee, PharmD[3], Dionne Hines, MPH, PhD[2], Rolin Wade, RPh, MS[2], Glorian P. Yen, PhD, MPH[3]

Affiliation: *[1]Director of the Ohio State Sickle Cell Program, [2]IQVIA, Inc., [3]Novartis Pharmaceuticals Corporation*

Background: Sickle cell disease (SCD) is a genetic blood disorder characterized by vaso-occlusion that results in vaso-occlusive crises (VOCs) and progressive systemic manifestations. Treatment options have been historically limited. Approved in 2019, crizanlizumab is a humanized monoclonal antibody indicated to reduce the frequency of VOCs in patients ≥ 16 years of age with SCD. The objective of this study was to describe the real-world use of crizanlizumab.

Methods: This retrospective descriptive analysis used IQVIA's US-based Longitudinal Patient-Centric Pharmacy and Medical Claims Databases. Patients had a diagnosis of SCD between November 1, 2018, and April 30, 2021, and ≥ 1 claim for crizanlizumab (date of first crizanlizumab claim as the index date [ID]) between November 1, 2019, and January 31, 2021; were aged ≥ 16 years at ID; and had ≥ 12 months of pre-ID data. A subset of patients with ≥ 3 months of post-ID follow-up was identified (3-month cohort), as well as a subset with ≥ 6 months of post-ID follow-up (6-month cohort). Pre-ID patient demographics and SCD treatment, number of crizanlizumab doses received, and additional post-ID SCD treatment were collected.

Results: A total of 540 patients with SCD who received crizanlizumab were identified; 345 with 3-month follow-up and 262 with 6-month follow-up. A majority (64%) were female (3-month, 64%; 6-month, 62%); 57% were in the 16- to 34-year age group (3-month, 55%; 6-month, 53%); 48% had commercial insurance (3-month, 47%; 6-month, 47%); 31% had Medicaid (3-month, 29%; 6-month, 28%); and 21% had Medicare (3-month, 24%; 6-month, 24%). In the 12 months pre-ID, 305 patients (56%; 3-month cohort, 206 [60%]; 6-month cohort, 156 [60%]) had ≥ 1 hydroxyurea claim and 71 (13%; 3-month cohort, 45 [13%]; 6-month cohort, 37 [14%]) had ≥ 1 prescription L-glutamine claim. In the 3 months post-ID, 86% of 3-month cohort patients received ≥ 2 doses of crizanlizumab; in the 6 months post-ID, 66% of 6-month cohort patients received ≥ 4 doses. In the 3 months post-ID, 103 patients (30%) in the 3-month cohort had ≥ 1 hydroxyurea claim and 14 (4%) had ≥ 1 prescription L-glutamine claim, whereas in the 6 months post-ID, 92 (35%) of 6-month cohort patients had ≥ 1 hydroxyurea claim and 14 (5%) had ≥ 1 prescription L-glutamine claim.

Conclusions: Results from this analysis suggest that most patients initiating crizanlizumab are 16-34 years of age and received hydroxyurea prior to crizanlizumab. Hydroxyurea prescription fill frequency seemed to have decreased post initiation of crizanlizumab. Most patients who started on crizanlizumab continued to get regular-interval doses at 6 months. Due to the nature of claims data, the reason for discontinuation or gaps between doses is unknown. The impact of COVID-19 restrictions or other access barriers on crizanlizumab use is unknown. Given the relatively small sample, results may not generalize to all crizanlizumab users.

ABSTRACT BREAKOUT SESSION II
CLINICAL RESEARCH

Presenting: June 12, 2022
3:15 pm - 4:45 pm

JSCDH-D-22-1223322

CARDIAC MORPHOLOGY IN HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANT FOR SICKLE CELL DISEASE

Authors: Jennifer Shmukler, Emily Limerick, MD, Arlene Sirajuddin, MD, My-Le Nguyen, MD, Neal Jeffries, PhD, Vandana Sachdev, MD, Courtney Fitzhugh, MD

Affiliation: *National Heart, Lung and Blood Institute, National Institute of Health*

Background: Cardiopulmonary complications of sickle cell disease (SCD) include diastolic dysfunction, possibly associated with diffuse myocardial fibrosis,1 and elevated tricuspid regurgitant jet velocity (TRV≥2.5m/s) – both of which are associated with early mortality.2-4 Furthermore, iron deposition also contributes to morbidity/mortality.5 Matched sibling hematopoietic cell transplants (HCT) offer a potential cure.6,7 However, fewer than 20% of patients have a suitable donor.8 Haploidentical HCT regimens now have improved safety and efficacy and an increased donor pool, offering a more widely available potentially curative option for SCD.9,10 We previously used echocardiography to demonstrate improved cardiac morphology one year after HCT.11 This report describes the first use of cardiac magnetic resonance imaging (CMR), the gold standard for measuring volume, mass, and ventricular function in healthy patients,12 to evaluate changes in cardiac morphology post-HCT in adults with SCD.

Methods: We analyzed data from adults with SCD who received nonmyeloablative haploidentical peripheral blood HCT at the NIH after conditioning with oral cyclophosphamide, pentostatin, alemtuzumab, and 400 cGy total body irradiation. Graft-versus-host disease prophylaxis included post-transplant cyclophosphamide and sirolimus. Patients underwent non-contrast CMR at 3T, echocardiography, and laboratory studies at baseline and 1-year after HCT. This study used CMR to investigate measurements previously shown via echocardiography to improve after HCT: left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), cardiac output (CO), left ventricular end-diastolic mass (LVEDM) and left atrial volume (LAV).11 All measurements, except for LVEF, were indexed to body surface area (BSA). CMR myocardial tissue mapping (native myocardial T1 and T2*) were obtained to indirectly assess myocardial fibrosis13, and quantify iron overload, respectively.

Results: Nineteen adults with SCD were transplanted; 12 with available CMR images were included in the analysis. One patient died two months after HCT, 1 had severe claustrophobia precluding CMR, and the remaining five patients did not have images available for review. The median age of the patients was 29 years (19-51); 92% had HbSS and 67% were male. One patient experienced primary graft rejection with autologous recovery and was included in this analysis. Hemoglobin (g/dL) (8.9±0.9 to 11.7±2.0, p=0.002) and TRV (m/s) (2.7±0.3 to 2.3±0.5, p=0.01) both improved by 1-year after HCT.

Most CMR variables improved after HCT. LV size, as measured by LVEDV (mL/m2), improved by 1-year (116.9±19.0 to 94.3±16.6, p=0.001), as did LVEDM (g/m2) (69.6 ± 18.5 to 60.7±15.4, p=0.03) and LAV (mL/m2) (58.8±11.1 to 45.8±10.0, p=0.002). CO (L/min/m2) decreased but remained within normal limits (4.9±0.9 to 4.0±0.7, p=0.01), while LVEF (%) did not significantly change (59.5±4.0 to 57.6±6.4, p=0.2). Only two of these variables also showed improvement on echocardiography: LVEDM (91.5±17.1 to 76.2±12.2, p=0.005) and LAV (35.7±8.8 to 29.7±9.3, p=0.01).

Native myocardial T1 did not significantly change after HCT (1262.7±102.1 to 1214.5±77.4, p=0.053). At baseline, nine patients had abnormally elevated native myocardial T1 (>1250ms13), compared to four at 1-year. Although one patient in this cohort had myocardial hemosiderosis at baseline (T2*<20ms14) and showed minimal improvement at 1-year (16.2 to 18.8 ms), no significant change in iron burden in

either heart or liver occurred 1-year after HCT ($p > 0.05$).

Conclusions: One year after HCT, patients showed marked improvement in cardiac chamber morphology. Further, mean TRV significantly improved to a normal level by 1 year, suggesting that HCT may offer a survival benefit. Native myocardial T1 times shortened at 1-year; this change was not significant, more extensive studies are indicated to further assess changes in myocardial tissue characterization. Although measured iron burden remains unchanged after 1 year, patients receive therapeutic phlebotomy, which may continue beyond 1 year. In this small sample, CMR was very sensitive in detecting cardiac mass and volume changes after HCT and provided complementary information to echocardiography. Notably, improvement in cardiac parameters can be attributed only in part to the resolution of anemia; further studies are required to determine the role of myocardial fibrosis reversal, improved blood flow, and other changes after HCT.11

JSCDH-D-22-1238031

EVOLUTION OF COVID-19 IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE: ALPHA TO OMICRON

Authors: Olufunke Y. Martin, MD[1,2], Stefanie Margulies, MS[2], Barbara J. Speller-Brown, DNP,CPNP, MSN[2], Deepika S. Darbari, MD[1,2], Suvankar Majumdar, MD[2], Andrew D. Campbell, MD[2]

Affiliation: *[1]Center for Cancer and Blood Disorders, [2]Children's National Hospital*

Background: Approximately two years ago, COVID-19 was declared a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and through genomic surveillance, we have seen the emergence of variants of SARS-CoV-2. In the United States, there have been over 78 million cases and >900,000 deaths attributable to COVID-19 reported. Sickle cell disease (SCD) was identified as a risk factor for severe COVID-19 in adult and pediatric patients. The emergence of novel SARs-CoV-2 variants has led to challenges in diagnosing, treating, and predicting long-term sequelae in individuals with SCD and COVID 19.

Objective: We compare the overall seasonal variation of COVID-19 variants and patterns of healthcare utilization and clinical presentation over time in pediatric patients with SCD and COVID-19 at Children's National Hospital (CNH), which provides care to patients from Maryland, District of Columbia, and Virginia.

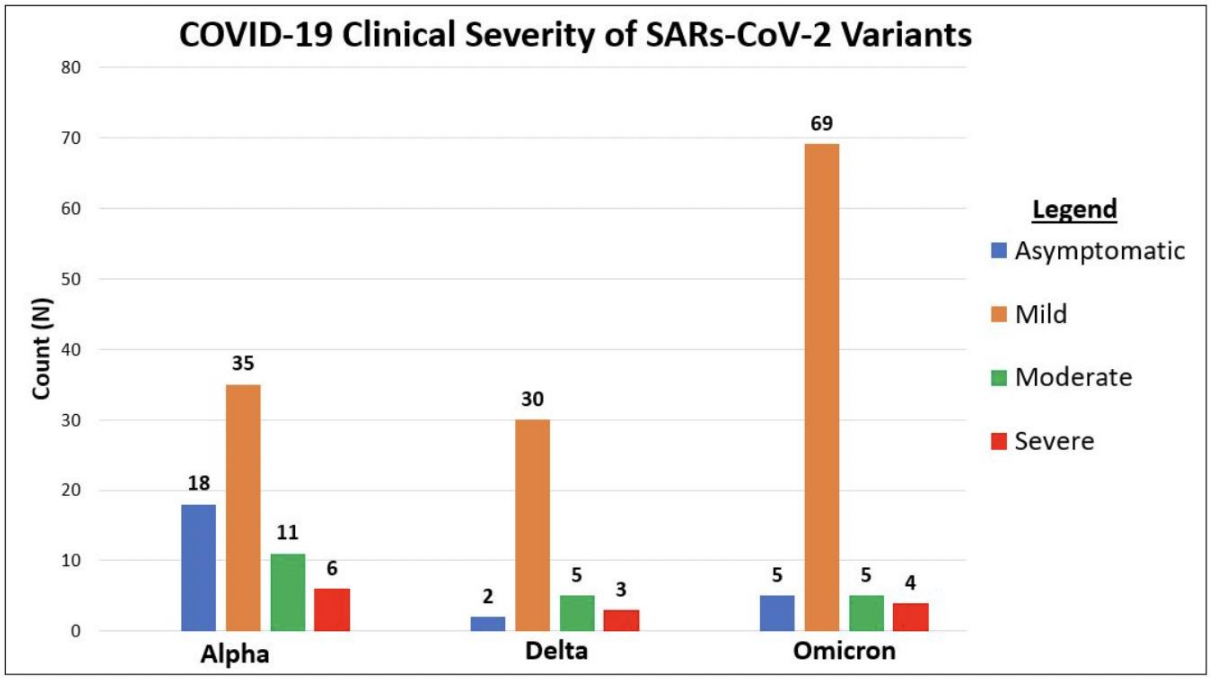
Methods: Our single-center, observational cohort study included 193 pediatric patients with SCD (0-21 years) with 80% with PCR confirmed SARS-CoV-2 infection at Children's National Laboratory, and 24% reported from an outside lab either rapid antigen testing or PCR between March 31, 2020, and January 31, 2022. Per the SECURE SCD Registry definitions, clinical severity was classified as asymptomatic - no clinical signs or symptoms during the positive COVID-19 period, mild - symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing or gastrointestinal symptoms or digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea, moderate - pneumonia, with or without clinical symptoms, no hypoxia, and severe - early respiratory symptoms or gastrointestinal symptoms followed by dyspnea and hypoxia (O2 saturation less than 92%).

Results: A total of 193 unique patients with SCD and positive SARS-CoV-2 PCRs were included in our registry. The majority of patients were female (51.8%), and the mean age of patients was 11.2 years (SD 6.5 years). Most of the cohort resides in Maryland (70%), and HbSS was the dominant genotype (69.4%). During the Alpha dominant variant of the COVID-19 pandemic (March 2020- June 2021), there were 70 cases, followed by 40 cases during the Delta variant (July 2021- December 19, 2021), and 83 cases during the Omicron variant dominance (from December 20, 2021-January 31,2022). There were 149 patients (77%) that presented to the emergency department (ED) or were hospitalized. There was a total of 80 hospitalizations (41.5%), and a relative comparison showed that the percentage of hospitalizations was highest during the Delta variant (47.5%) and lowest during the Omicron variant (36.1%) (p= 0.407). ED-only utilization was highest in the variant of Omicron (43.4%, N=36), followed by Delta (32.5%, N=13), and then Alpha (30%, N=21) (p=0.197).

The most common SCD related complication was acute vaso-occlusive (VOC) pain (33%, N=64) and accounted for half of all hospital admissions (51%, N=41 of 80). Acute chest syndrome (ACS) was reported in 40% (N=32) of admitted patients and was highest in the Alpha variant (54.8%, N=17). The use of blood transfusion therapy was highest in patients infected with the Alpha (N=17) and Delta (N=14) variants, while Remdesivir use was highest with the Omicron variant (N=15). A total of 6 patients received monoclonal antibodies (Delta, N=4; Omicron, N=2). Throughout all the variants, there was a significant difference in COVID-19 clinical severity (p< 0.005) [Figure 1]. Of the patients classified as asymptomatic

(13%, N=25), seventy-two percent (n=18) were diagnosed during the Alpha variant. Mild severity was the most prevalent (69%, N=134), with the Omicron variant having the highest cases (51.5%, N=69). Severe cases were observed in all variants (6.7%, N=13) but were most prevalent during the Alpha variant (46.2%, N=6).

Conclusions: Interestingly, while the relative percentage of hospitalizations was lowest during the Omicron wave, the highest percentages of ER utilization occurred, likely reflecting national trends of testing limitations. Overall, COVID-19 remains mild in pediatric patients with SCD, and notably, there was higher health care utilization in the Omicron variant, with the majority of patients having mild severity.



COVID-19 Clinical Severity of SARS-CoV-2 Variants

JSCDH-D-22-1234053

IMPACT OF A SINGLE MUSIC THERAPY SESSION ON PAIN PERCEPTION OF SICKLE CELL DISEASE PAIN

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Affiliation: *[1]Children's National Hospital, [2]Shenandoah University*

Background: Sickle Cell Disease (SCD) is one of the most common genetic conditions in the United States, characterized by severe pain crises that often result in hospitalization. The neuromatrix theory of pain suggests pain is a multimodal experience emphasizing interventions that address multiple dimensions of pain experience.

Methods: Twenty-one participants completed music therapy sessions, focusing on singing to address their pain followed by verbal processing of their experiences. Pain scores were collected immediately prior to, during, and after the sessions. A follow-up interview was conducted. Sessions and interviews were audio recorded, coded, and analyzed using qualitative content analysis.

Results: 22 English-speaking adolescents and young adults with SCD admitted to the hospital due to vaso-occlusive crisis and without significant visual and/or hearing impairments participated in the study. Participants reported an average 3.03-point difference between pre-intervention pain score and pain score during the intervention ($p < 0.001$). Comparing pre-intervention pain scores to post intervention scores, participants reported an average 1.9-point reduction in pain ($p < 0.001$). Analysis of interviews and session transcripts provided insights into the lived session experience and revealed 5 themes. Participants reported decreased pain and improved mood, demonstrating an openness to verbal engagement, increased insight, and expressive freedom, suggesting additional session benefits and potential agents of change.

Conclusions: The unique ways in which participants engaged in the music therapy session suggest the importance of interventions that simultaneously address the physical and emotional experiences of pain. When participants experienced themselves as agents of their own pain management, directly addressing their pain experience musically, it engaged them in a reflexive process that altered their pain perception, improved their mood, and changed their relationship with their illness. Music therapy is beneficial in reducing pain perception in patients with SCD, addressing physical and emotional dimensions of pain experience. Further research is needed to evaluate the full impact and benefits of this intervention.

Table 1 *Average Reported Pain and Change in Pain Scores*

	Mean	SD	Median	Interquartile Range	p-value
Pre	7.09	1.87	6.88	5.75 – 8.5	
During	4.05	2.23	3.62	2.56 – 5.5	
Post	5.19	2.87	5.56	4.00 – 6.81	
Pre - During	-3.04	1.36	-3.19	-4.07 – -2.12	< 0.001
Pre – Post	-1.9	1.96	-1.75	-2.94 – -0.32	< 0.001
During - Post	1.14	2.02	1.63	-0.43 – 2.52	0.010

JSCDH-D-22-1238904

MULTICENTER, RETROSPECTIVE REAL-WORLD EXPERIENCE OF VOXELOTOR-TREATED PATIENTS WITH SCD

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Affiliation: *[1]New England Sickle Cell Institute, [2]University of Connecticut Health, [3]University of Texas Health, [4]Duke University School of Medicine, [5]Rutgers Medical School, [6]Central Michigan University, [7]Brigham and Women's Hospital, [8]University of Texas Southwestern Medical Center, [9]Albert Einstein College of Medicine*

Background: Sickle cell disease (SCD) is an inherited systemic disorder, with pathology driven by polymerization of sickle hemoglobin (HbS). Voxelotor, a HbS polymerization inhibitor, is approved in the United States for treatment of SCD in adults and pediatric patients aged ≥4 years, and in the European Union for the treatment of hemolytic anemia due to SCD in adult and pediatric patients aged ≥12 years as monotherapy or in combination with hydroxycarbamide. Efficacy and safety data from the randomized, placebo-controlled HOPE trial demonstrated the effectiveness of voxelotor in increasing hemoglobin (Hb) levels and reducing markers of hemolysis. Real-world studies complement and expand upon information gathered in randomized clinical trials by providing evidence of treatment safety and efficacy in clinical practice. The Retrospective Study to Evaluate Outcomes in Patients With Sickle Cell Disease Treated With Oxbryta (RETRO) aims to characterize real-world safety and effectiveness of voxelotor in adults and adolescents (aged ≥12 years) with SCD treated with voxelotor as part of their usual care.

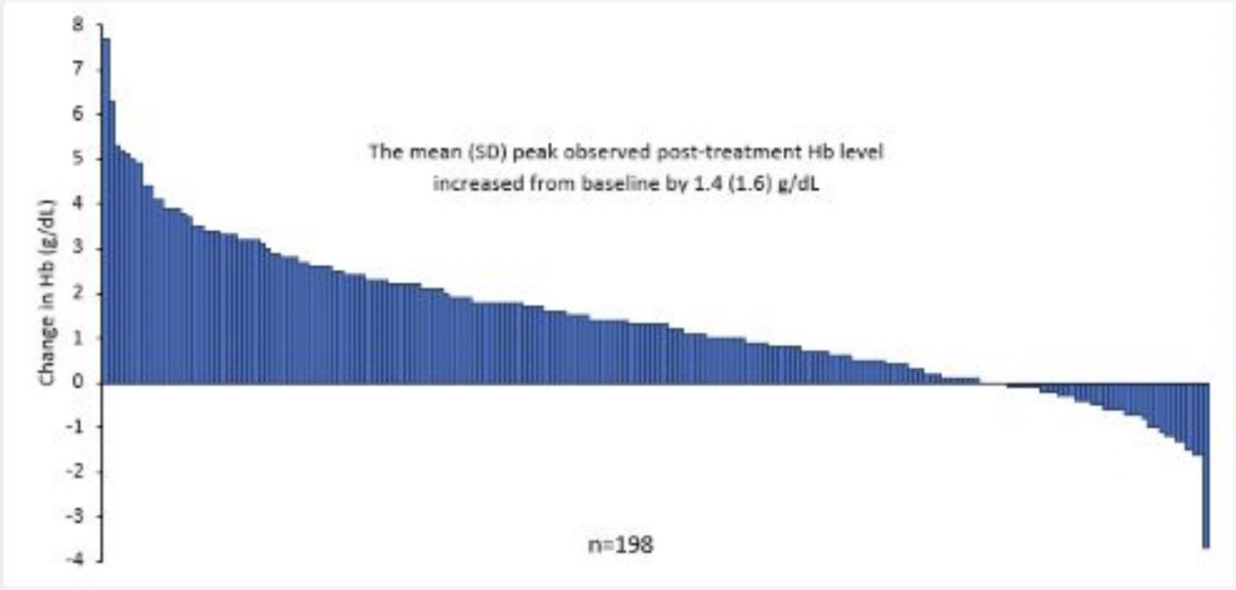
Methods: RETRO is a multicenter, post-marketing, retrospective study that collected laboratory and clinical data from patients' medical records 1 year before and 1 year or more after initiation of voxelotor treatment. Patients with documented SCD who received voxelotor for ≥2 consecutive weeks were included in this analysis.

Results: Data from 216 patients across 9 US sites were collected and analyzed. The mean (SD) patient age was 33.5 (14.2) years; 56% (n=120) of patients were female, and 44% (n=96) were male. The mean (SD) duration of voxelotor treatment was 51.1 (25.6) weeks. Reasons for voxelotor prescription (n, %) included reducing the following: anemia (151, 69.9%), pain (51, 23.6%), frequency of vaso-occlusive crises (45, 20.8%), and the need for blood transfusions (17, 7.9%); multiple reasons may have been selected. Most patients were prescribed an initial voxelotor dose of 1500 mg (n=187, 86.6%), and 68.1% (n=147) of patients used hydroxyurea concomitantly. A total of 25.0% (n=54) of patients had a dosage interruption or adjustment. Reasons for dosage change (n, %) included adverse event (AE; 37, 17.1%), other (22, 10.2%), pill burden (2, 0.9%), and lack of efficacy (1, 0.5%); multiple reasons may have been selected.

A total of 198 patients had recorded baseline and post-treatment Hb values. In these patients, the mean (SD) peak observed post-treatment Hb level increased from baseline by 1.4 (1.6) g/dL, from 7.8 (1.5) g/dL to 9.2 (2.0) g/dL (Figure). In the subset of patients for whom baseline and post-treatment indirect bilirubin levels were available (n=80), the mean (SD) minimum observed post-treatment value for indirect bilirubin decreased from baseline by 1.1 (1.9) mg/dL, from 3.1 (2.0) mg/dL to 1.9 (1.9) mg/dL. For patients with available reticulocyte percentage values (n=178), we observed a decrease from baseline by 3.8% (5.8%), from 11.6% (6.8%) to 7.7% (5.1%). The safety and tolerability of voxelotor in the real-world setting will be presented. The most common non–SCD-related treatment-emergent AEs were diarrhea, headache, and rash; 37.0% (n=80) of patients reported ≥1 non–SCD-related AE, and most AEs were mild in severity.

Conclusions: RETRO is the first multicenter study to collect and analyze retrospective data from patients with SCD treated with voxelotor in a real-world setting. These interim results are consistent with the HOPE trial, showing that voxelotor treatment was associated with increased Hb levels and decreased hemolytic markers. The safety data are also consistent with those from the HOPE trial.

Figure: Per-Patient Peak Hemoglobin Change From Baseline



Hb, hemoglobin.

JSCDH-D-22-1224885

PARTIAL RED CELL EXCHANGE FOR OUTPATIENT SCD PATIENTS DURING CRITICAL BLOOD SHORTAGE 1

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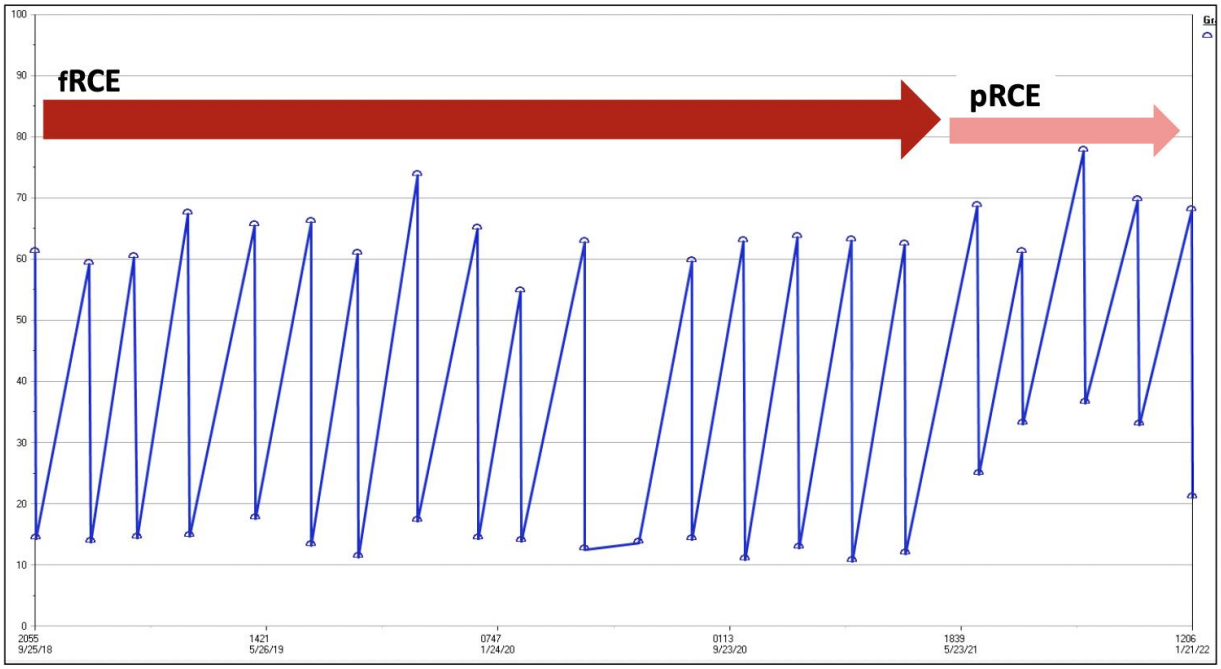
Background: Sickle cell disease (SCD) is a well-described genetic disorder resulting in an altered hemoglobin molecule (HbS) which has a tendency to polymerize in the deoxygenated state resulting in deformed red blood cells (RBCs). Clinically, patients with SCD are challenged with a number of complications including recurrent vaso-occlusive pain crises, chronic anemia, pulmonary hypertension, chronic kidney disease, cerebral vascular accidents (CVA) and priapism. There are certain clinical scenarios for which red cell exchange has proven benefit. These include for patients with acute chest syndrome (ACS) or CVA. Red Cell Exchange (RCE) has also proven effective for patients who require chronic transfusion who have developed secondary hemochromatosis and for selected patients with severe chronic pain. During the Covid pandemic there has developed a critical shortage of donor blood thereby influencing availability for patients on chronic RCE therapy. We currently report results from our institutional policy of providing partial RCE (pRCE) rather than full RCE (fRCE) during this period of reduced inventory.

Methods: We have reviewed data from 10 patients receiving chronic RCE therapy. These individuals had a prior diagnosis of CVA, refractory pain or recurrent priapism and were all treated between January 2021 and Mid-February, 2022. A total 36 pRCE were performed on these 10 patients using an automated extracorporeal continuous flow device Spectra-Optia ®. Each patient's pRCE was constituted with half the number of required red blood cell units (RBCs). The RBCs were phenotypically matched for red cell antigens: C, E and Kell antigens and administered at 4-8 week intervals. This was the same interval as before we instituted the pRCE protocol. Pre- and post RCE hemoglobin A (HbA) and S (HbS) were measured by gel electrophoresis.

Results: Of the 10 patients, 5 were males and 5 females. Ages ranged from 25 to 44 years, and all were on a prescribed RCE treatment protocol as recommended by their hematology providers. Three patients were on isovolemic hemodilution (IHD) and the rest were on standard RCE. For the group of 10 patients as a whole, the post pRCE HbS percent ranged from 21% to 35% and post RCE HbA was 61% to 75%. The post pRCE HbS levels were not as low as we previously experienced with fRCE (typically 10% to 25%). Nonetheless, over the approximate one year since we instituted pRCE, we have detected no adverse consequences including recurrent CVA, priapism or exacerbation of pain.

Conclusions: The SARS-CoV-2 pandemic has resulted in critical blood shortages nationwide affecting many clinical services including elective surgeries and ongoing RCE therapy. By instituting a pRCE protocol, we have been able to avoid cancellation of RCE. The patients tolerated the pRCE without neurologic event, breakthrough crisis or recurrent priapism despite a higher post-RCE HbS% and a lower HbA%. Future research will be undertaken to compare pRCE with fRCE in a systematic way to assess whether clinical outcomes are truly comparable. If so, patient safety and blood bank inventory will both be favorably affected.

Percent Hemoglobin S Before and After Prophylactic Red Cell Exchange



JSCDH-D-22-1197523

VENOUS THROMBOEMBOLISM AND RIGHT SIDED CARDIAC DYSFUNCTION IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a hypercoagulable state associated with an 11-12% risk of venous thromboembolism (VTE) by the age of 40; VTE increases mortality risk in these patients. Echocardiographic markers of right-sided cardiac dysfunction and pulmonary hypertension (PH) are also independent predictors of mortality. VTE is a PH risk factor in the general population; the association in SCD is unclear. We hypothesized that patients with SCD and VTE have a greater frequency of right-sided cardiac dysfunction on echocardiogram compared to those without VTE, which may impact the associated mortality risk.

Methods: We performed a retrospective chart review of 402 SCD patients who received care at Boston Medical Center between 2003 and 2021. VTE was defined as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) by diagnostic imaging. Demographics, clinical and laboratory data, VTE diagnostic evaluation, and echocardiography were obtained. For patients with VTE, we recorded data pre-VTE and 5 years post-VTE. For those without VTE, we recorded data at entry into the database and 5 years later. Chamber size, right and left ventricular function, valvular function, and tricuspid regurgitant jet velocity were collected from echocardiograms. Data were analyzed using Fisher's exact, Sign-ranked and McNemar's tests.

Results: In our cohort, 251 (62%) were HbSS/HbSβ0 and 227 (56%) were female. VTE occurred in 75 individuals (19%) [DVT in 35 (47%), PE in 50 (67%), and both in 9 (12%)]. Those with a VTE had a higher frequency of prior acute chest syndrome, avascular necrosis, stroke, and surgical splenectomy compared to those without VTE ($p< 0.01$ for all comparisons). History of VTE conferred an increased mortality rate compared to those without VTE (13% vs 6%, $p=0.04$). Within our cohort, 183 patients had initial and follow-up echocardiography (58/75 in VTE group, 125/327 in non-VTE group). In the VTE group there was a significant increase in right atrial size ($p=0.034$) five years post-VTE compared to pre-VTE; in the non-VTE group, no change in right atrial size occurred. There was a non-significant trend towards decrease in right ventricular function over five years only in the VTE group ($p=0.08$).

Conclusions: Patients with SCD and VTE had an increased history of SCD-related complications reflective of more severe disease and mortality compared to those without VTE. In those with a VTE, there was an increase in subsequent right-sided cardiac dysfunction reflective of possible pulmonary hypertension. These findings need to be confirmed prospectively in a larger cohort.

ABSTRACT BREAKOUT SESSION II
CLINICAL TRIALS/CLINICAL EPIDEMIOLOGY

Presenting: June 12, 2022
3:15 pm - 4:45 pm

JSCDH-D-22-1238612

COVID-19 VACCINE RATES AMONG PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Affiliation: *St. Jude Children's Research Hospital*

Background: Immunization against SARS-CoV-2 has emerged as one of the most effective public health interventions to control the spread of coronavirus disease-2019 (COVID-19), especially among "high risk" individuals. Those with sickle cell disease (SCD) are at an increased risk for severe illness from COVID-19. Vaccines are effective in preventing COVID-19 disease, as well as preventing hospitalization and death. Historically vaccine hesitancy is prevalent among patients with SCD, particularly adolescents, as compared to those without SCD [1]. In this study, we sought to: (1) elucidate COVID-19 vaccine uptake among adolescents with SCD at our institution and their parents and (2) identify barriers, if any, to the vaccination.

Methods: To clarify caregiver and patient attitudes about COVID-19 vaccination, a qualitative survey about vaccine uptake and reason for declination (when applicable) was added to an ongoing cross-sectional survey of caregivers and adolescents with SCD in May 2021. We then analyzed data from the Sickle Cell Clinical Research and Intervention Program (SCCRIP) study database to look for potential associations [2]. Patients aged 13-18 years between May 2021 and February 2022 with any SCD genotype and who were enrolled on the SCCRIP study were included in the association analysis. The following variables were extracted: age, sex, race, ethnicity, economic hardship index (EHI), parental education level, household income, genotype, and COVID-19 vaccine status. Statistical analysis was carried out using the Fisher's exact test and Wilcoxon rank sum test to draw conclusions between vaccine refusal and these variables.

Results: 49 adolescents and 132 parents completed the survey. Among survey respondents, the overall vaccination rate among patients with SCD was 49% in adolescents and 53% among parents. Among those who were unvaccinated 60% of adolescents and 68% of parents preferred to remain unvaccinated (Figs. 1A and B). Survey response of non-vaccinated individuals was pooled into 3 main categories: perceived benefit to oneself (utility), lack of confidence (vaccine mistrust/belief in misinformation), and unanswered medical questions. Perceived lack utility/personal benefit was the primary reason for vaccine refusal among 53% of adolescents and 43% of parents (Fig. 1C). The second leading reason for vaccine refusal among both adolescents and parents were related to a lack of confidence/trust in the vaccine. Only a minority of patients gave unanswered medical questions as a reason to decline (7% and 12% among adolescents and parents, respectively).

Based on results from the SCCRIP database, we found a correlation between poorer EHI Education scores and vaccine refusal (Fig. 3). Among survey participants, there was no difference in sickle cell genotype and sex in either the vaccine refusal or vaccine compliant groups.

Conclusions: Vaccine hesitancy remains prevalent among individuals with SCD. Although the risks of severe COVID-19 complications are high among these individuals, there exists significant apprehension to COVID-19 vaccination. While many of our patients with SCD and their parents who participated in this study are vaccinated, 51% of adolescents and 47% of parents remained unvaccinated with less than half of this group interested in vaccination. To try and understand this apprehension, we used self-reported survey data which shows that many patients either perceive a lack of personal benefit from the vaccine or lack confidence in the vaccine itself. Interestingly, among those that refused, we found an association between vaccine refusal and poorer EHI Education

scores, suggesting that education less than high school may be a risk factor for vaccine hesitancy.

Figure 1. Pie chart of the distributions: (A) % vaccinated, (B) % unvaccinated who intend to be vaccinated, and (C) reasons for deferring the vaccine by parents and adolescents.

Figure 1A

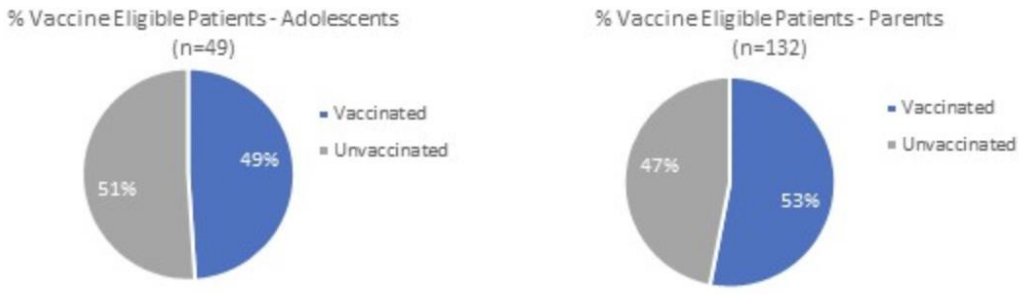


Figure 1B

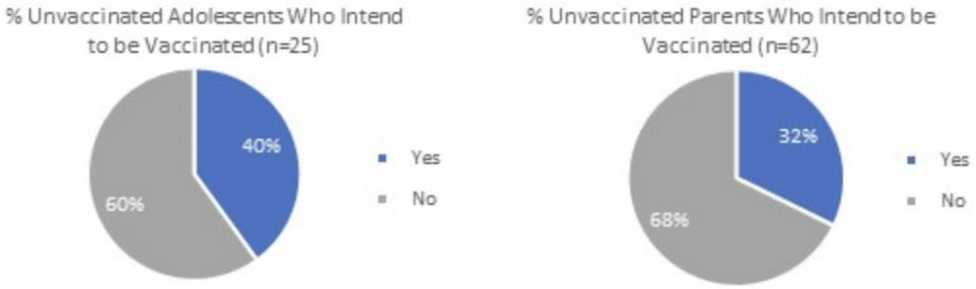


Figure 1C

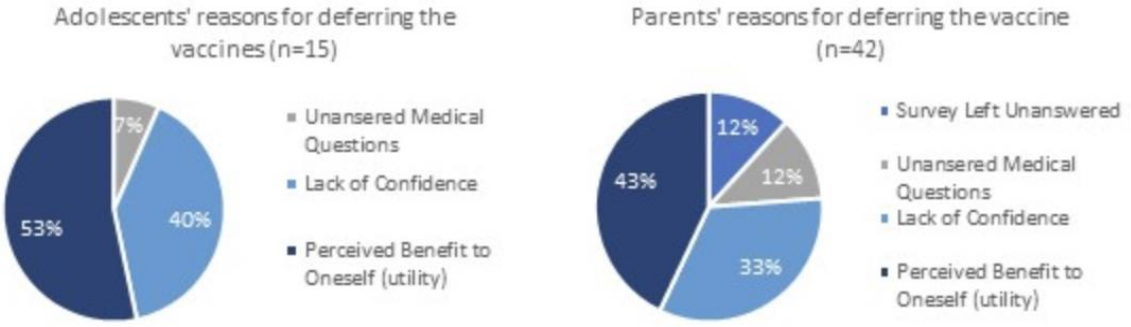
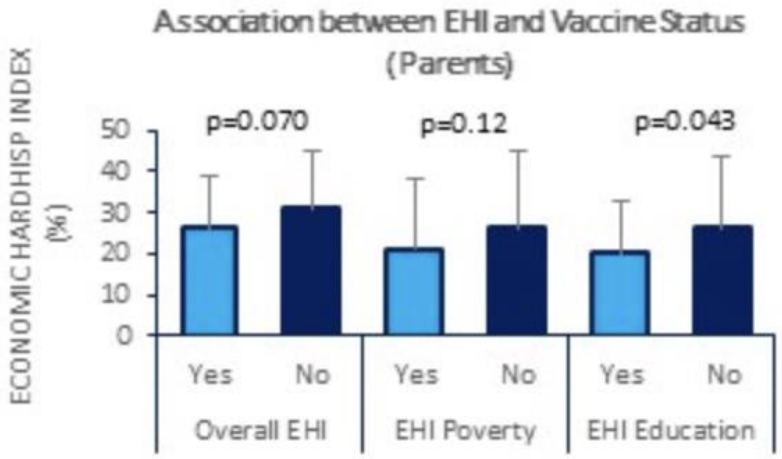


Figure 2. Bar plot of economic hardship index by vaccine status of parents along with the standard deviation P-value was calculated using Wilcoxon rank sum test.



JSCDH-D-22-1212715

ETAVOPIVAT IS WELL TOLERATED AND IMPROVES RED BLOOD CELL HEALTH IN SICKLE CELL DISEASE

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Affiliation: *[1]University of Illinois at Chicago, [2]Children's Healthcare of Atlanta, [3]Emory University. [4]UCSF Benioff Children's Hospital San Francisco, [5]University of Texas Health, [6]Levine Cancer Institute, [7]Atrium Health, [8]Cincinnati Children's Hospital Medical Center, [9]University of California, [10]Forma Therapeutics, Inc., [11]Duke University Medical Center*

Background: Etavopivat, an investigational, once-daily, selective, activator of erythrocyte pyruvate kinase (PKR) increases PKR activity, resulting in decreased 2,3-DPG and increased ATP in red blood cells (RBCs) of healthy volunteers and patients (pts) with sickle cell disease (SCD).1,2 Here, we report results of an open-label (OL) extension cohort from a Phase 1 study (NCT03815695) designed to characterize the safety and clinical activity of etavopivat at a maximal pharmacodynamic dose in pts with SCD.

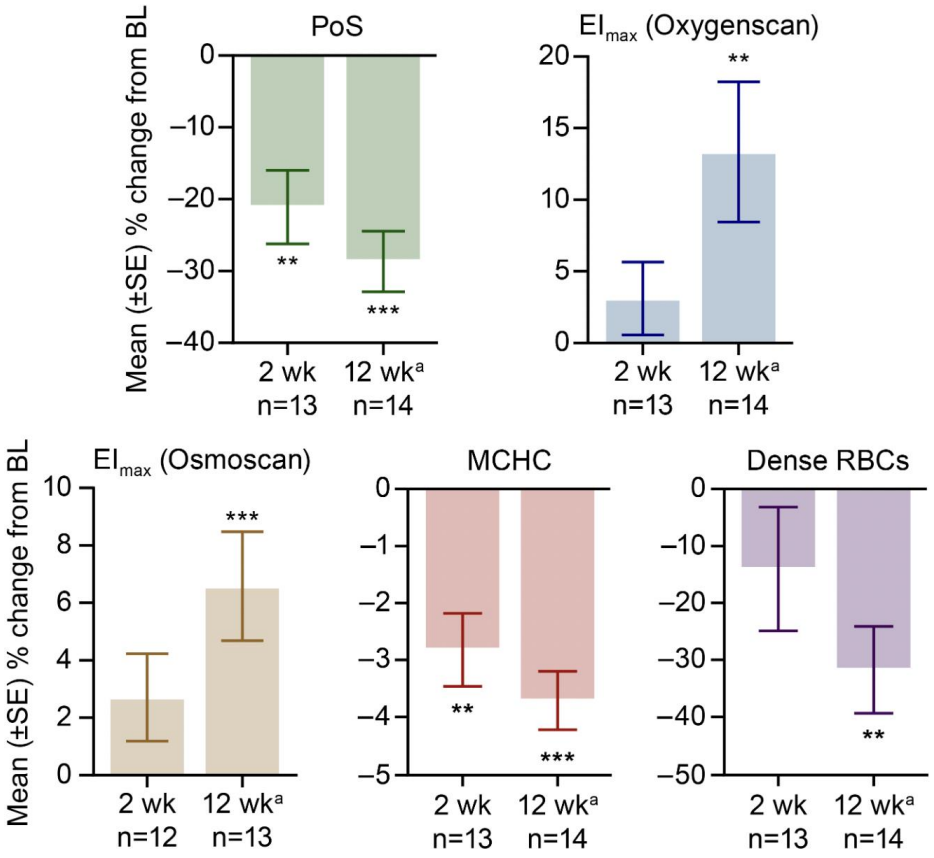
Methods: 15 pts were enrolled to receive etavopivat 400 mg once daily for 12 wks, followed by a 4-wk follow-up. Assessments included safety, pharmacokinetics, pharmacodynamics, RBC health parameters and systemic markers of SCD pathophysiology.

Results: Of 15 pts (age 32.3 ±10.1 yr; HbSS/SC n=13/2; male/female n=5/10), 14 completed 12-wks of treatment (tx); 1 pt discontinued tx after ~2 wks. Etavopivat 400 mg once daily was generally well tolerated. Adverse events (AEs) reported during tx and follow-up were commonly low grade (Gr) and consistent with pts' SCD. Gr1-2 AEs in >2 pts (n [%]) were sickle cell pain events (9 [60%]); headache (5 [33%]); and upper respiratory tract infection (3 [20%]). The Gr3-4 AE in >1 pt was sickle cell vaso-occlusion (VOC; 4 [27%]). On-tx serious adverse events (SAEs; 1 pt each) were Gr3 VOC post Gr3 COVID (not tx-related) and Gr3 left femoral deep vein thrombosis (possibly related, resulting in tx discontinuation as stated above). SAEs (1 pt each) during the 4-wk follow-up were Gr3 acute chest syndrome + Gr3 VOC, Gr3 non-cardiac chest pain and Gr3 syncope (all unrelated). Observed increases in ATP and decreases in 2,3-DPG were durable over 12 wks of etavopivat tx. Etavopivat tx normalized hemoglobin (Hb)S-oxygen affinity to that of HbA. Etavopivat tx over 12 wks improved overall sickle RBC health, demonstrated by a reduction in point of sickling as well as improved measures of deformability and hydration of sickle RBCs (all $P< 0.01$; Figure). Etavopivat tx over 12 wks was associated with a sustained significant increase in Hb compared with baseline (BL; $P< 0.0001$), with mean maximal increase of 1.5 (range 0.7-2.3) g/dL. On-tx increase in Hb >1g/dL was achieved in 11 (73%) pts, for whom the mean maximal Hb increase was 1.8 (1.2-2.3) g/dL. Absolute reticulocytes, indirect bilirubin and lactate dehydrogenase significantly decreased from BL and were sustained over the 12-wk period (all $P< 0.05$), indicative of increased RBC lifespan and decreased hemolysis. Several markers of systemic disease activity significantly decreased from BL during daily etavopivat tx, including the inflammatory marker tumor necrosis factor-α, which decreased by 35% ($P< 0.001$). Based on preliminary exploratory analysis with an aggregate duration of etavopivat exposure of 3.32 pt-yrs in the OL cohort, a decrease in the trend for VOC hospitalizations was observed: annualized historical and on-tx VOC hospitalization rates were 0.93 and 0.30, respectively; the 1 on-tx VOC hospitalization was COVID-related.

Conclusions: Etavopivat 400 mg once daily for up to 12 wks demonstrated a tolerable safety profile and showed improvements in various markers of RBC health in pts with SCD. Rapid and sustained increases in Hb were associated with decreases in reticulocyte

counts and markers of hemolysis, supporting increased sickle RBC lifespan and improved anemia. Together, these results support further evaluation of etavopivat in the Phase 2/3 Hibiscus Study (NCT04624659) currently enrolling pts.

Figure: Etavopivat improved sickle RBC PoS, deformability (EImax) and hydration (RBC Hb concentration [MCHC] and dense RBCs) during 12-wks of dosing



** *P*<0.01 or *** *P*<0.001 vs BL for all patients based on the Wilcoxon signed-rank test.
[a] Showing best response during 12 wks of etavopivat treatment.
BL=baseline; EI_{max}=maximum elongation index; MCHC=mean corpuscular hemoglobin concentration; PoS=point of sickling; RBC=red blood cell

JSCDH-D-22-1237781

OUTCOMES OF COVID-19 IN NEWBORN SCREENING COHORTS OF SICKLE CELL DISEASE AND TRAIT

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Background: Individuals living with sickle cell disease (SCD) are at risk for poor COVID-19 outcomes. People with sickle cell trait (SCT) may be unaware of their status; researchers hypothesize that differences in coagulation in SCT may partially account for the higher rate of severe COVID-19 outcomes for the Black population. There are no population-based surveillance data for those with concurrent SCD or SCT and COVID-19 infection.

Newborn screening (NBS) provides confirmation of SCD or SCT status and may be linked to COVID-19 data by state. This analysis investigates Georgians and Michiganders with NBS-confirmed SCD or SCT and their rates of COVID-19 infection and hospitalization and mortality related to COVID-19 compared to those with normal hemoglobin.

Methods: Our population-based cohorts included persons with in-state NBS results showing SCD, SCT, or normal hemoglobin in Michigan born 1987-2019 and Georgia born 2008-2020 who could be linked to COVID-19 data in the same state. Data regarding COVID-19 infections, hospitalizations, and mortality were obtained from the Michigan Disease Surveillance System and the Georgia State Electronic Notifiable Disease Surveillance System from March 10, 2020-November 30, 2021.

Data were analyzed by state using consistent methods and coding. Logistic regression with generalized estimating equations modeled odds ratios (OR) for hospitalization, adjusting for age and sex and stratifying by race. Subgroups were too small for adjustment in Georgia, but analyses were stratified by race. There were no deaths in the SCD or trait cohorts in Georgia; however, in Michigan, mortality was calculated for those with SCD or trait compared to normal hemoglobin, adjusted for age, sex, and race.

Results: Proportion of births linked to COVID-19 cases and ORs for hospitalization and mortality are shown in Table 1. In Michigan, there were 15x increased odds for hospitalization and 13x increased odds for mortality in SCD compared to normal hemoglobin among Black people. In Georgia, there was 21x increased odds for hospitalization in SCD compared to normal hemoglobin among Black people. After accounting for race in the SCT group, there were no differences in odds of hospitalization or death in Michigan data, nor of hospitalization in Georgia data.

Conclusions: In this population-based examination of NBS-confirmed cases of SCD and sickle cell trait, those with SCD were found to have a substantially higher occurrence of hospitalization and death related to COVID-19 than those with normal hemoglobin. Those with trait did not have higher odds of hospitalization and death than those with normal hemoglobin after accounting for race. These results suggest that SCD is an important risk factor for poor outcomes of COVID-19 infection, and that SCT may not contribute to the high rate of severe outcomes in the US Black population.

Table 1: Demographics, hospitalization, and mortality of individuals with COVID-19 (March 10, 2020 – November 30, 2021) and a newborn screening result of normal hemoglobin, sickle cell trait, or sickle cell disease (2008-2020; Georgia and 1987-2019; Michigan).

	Normal Hemoglobin			Sickle Cell Trait			Sickle Cell Disease		
	Births	COVID Case		Births	COVID Case		Births	COVID Case	
	N	n	%	n	n	%	n	n	%
Georgia									
Age 0 to 4 years	490,319	18,635	3.80	17,581	711	4.04	659	50	7.59
5 to 12 years	1,154,554	49,315	4.27	36,166	1,586	4.05	1,615	97	6.01
Sex Male	838,298	34,281	4.09	28,720	1,181	4.11	1,109	74	6.67
Female	802,850	33,669	4.19	27,862	1,116	4.01	1,158	73	6.30
Unknown	3,725	0	0.00	165	0	0.00	<10	0	0.00
TOTAL	**1,644,873**	**67,950**	**4.13**	**56,747**	**2,297**	**4.05**	**2,274**	**147**	**6.46**
Hospitalization	-	735	1.08	-	27	1.18	-	35	23.81
Death	-	<10	<1	-	0	0.00	-	0	0.00
Hospitalization odds ratio (OR) compared to Black, normal Hgb					1.04	(0.69, 1.57)		20.79	(24.03, 30.82)
Michigan	n	n		n	n		n	n	
Age 0 to 4 years	424,231	11,544	2.72	6,842	183	2.67	244	14	5.74
5 to 12 years	884,679	35,580	4.02	14,704	503	3.42	472	19	4.03
13 to 17 years	618,379	47,108	7.62	9,301	530	5.70	291	26	8.93
18 to 33 years	2,038,258	136,480	6.70	31,709	1,678	5.29	1,139	111	9.75
Sex Male	2,007,501	113,588	5.66	31,557	1,378	4.37	1,064	59	5.55
Female	1,916,389	114,855	5.99	30,283	1,485	4.90	1,040	75	7.21
TOTAL	**3,965,547**	**230,712**	**5.82**	**62,556**	**2,894**	**4.63**	**2,146**	**170**	**7.92**
Hospitalization	-	1,719	0.75	-	65	2.25	-	32	18.82
Death	-	102	0.04	-	<10	-	-	<10	-
Hospitalization OR compared to Black, normal Hgb					1.17	(0.90, 1.53)		15.21	(10.28, 22.51)
Mortality OR compared to any race normal Hgb					1.52	(0.65, 3.51)		13.53	(4.19, 43.75)

JSCDH-D-22-1236211

PHARMACODYNAMIC EFFECTS OF AG-946, AN ACTIVATOR OF PYRUVATE KINASE IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a monogenetic red blood cell (RBC) disorder that is characterized by hemolytic anemia and vaso-occlusive crises. Among the many factors that contribute to disease pathophysiology is stiffening and sickling of RBC, which is the direct result of the polymerization of abnormal hemoglobin S. Sickling is one of the core factors that cause vaso-occlusion and sickling is modulated by glycolytic intermediates such as 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP). Previously we showed that RBC pyruvate kinase (PKR), the key regulatory enzyme of glycolysis, is impaired in SCD and that ex vivo treatment with mitapivat, an allosteric activator of PKR, increased enzymatic activity and thermostability, reduced 2,3-DPG levels, decreased p50, and subsequently reduced sickling (Rab et al, Blood 2021). Currently, mitapivat is being investigated in phase 1, phase 2, and phase 2/3 trials in patients with SCD (#NCT04000165, EudraCT#2019-003438-18, and NCT05031780).

Recently, AG-946, a novel PK activator, has been developed. Here we investigate the pharmacodynamic effects of AG-946 in ex vivo treatment of RBC from SCD patients in comparison with mitapivat.

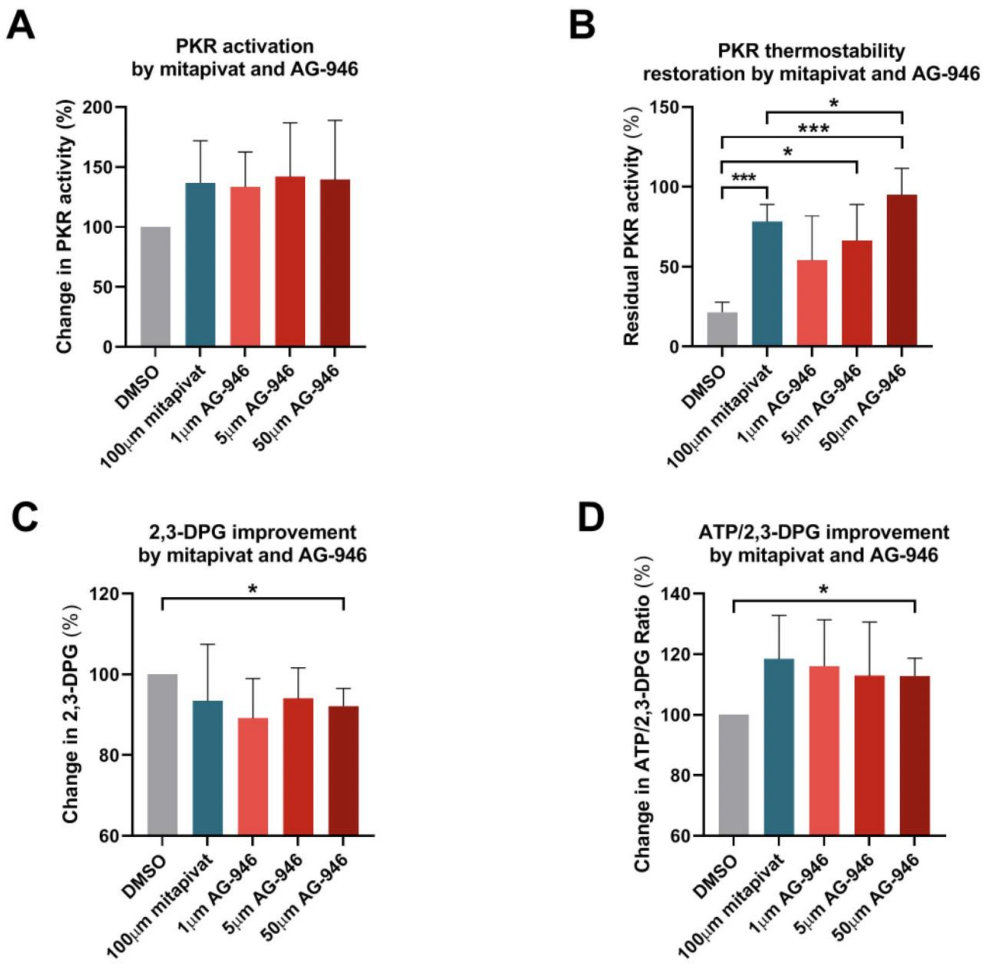
Methods: Buffy coat depleted whole blood obtained from five patients with SCD was incubated for 20-24 hours in absence or presence of mitapivat (100 mM) or AG-946 (1 mM, 5 mM, 50 mM). After ex vivo treatment, enzymatic activities of PKR and PKR thermostability were measured. Glycolytic intermediates ATP and 2,3-DPG were measured using LC-MS/MS. Hemoglobin oxygen affinity (p50) was measured with the Hemox Analyzer. RBC sickling was analyzed with the oxygenscan, a method that characterizes individual sickling behavior by oxygen gradient ektacytometry. Individual tendency to sickle is reflected by Point-of-Sickling (PoS) that indicates the specific pO2 at which RBCs start to sickle during deoxygenation under shear stress.

Results: PKR activity was increased compared to vehicle (DMSO) to a similar extent in the presence of mitapivat or AG-946 (Figure 1A). In addition, PKR thermostability was significantly increased compared to vehicle (mean 22%, SD 6%) in samples treated with mitapivat 100 mM (mean 78%, SD 11%), as well as AG-946 5 mM (mean 66%, SD 23%), and AG-946 50 mM (mean 95%, SD 17%, Figure 1B). After incubation with mitapivat or AG-946, 2,3-DPG decreased (Figure 1C), which was further illustrated by the improved ATP/2,3-DPG ratio (Figure 1D). Accordingly, p50 decreased significantly after incubation with mitapivat 100 mM (mean 95%, SD 2%), as well as AG-946 1 mM (mean 96%, SD 2%), AG-946 5 mM (mean 94%, SD 2%), and AG-946 50 mM (mean 95%, SD 3%, Figure 1E). The improved metabolic status and p50 was accompanied by a decreased PoS compared to vehicle in RBCs treated with mitapivat or AG-946, indicating reduced RBC sickling tendency in vitro (Figure 1F).

Conclusions: Ex vivo treatment of SCD RBCs with the novel PK activator AG-946 activates and stabilizes PKR, decreases 2,3-DPG levels, improves the ATP/2,3-DPG ratio, improves p50 and lowers the PoS. These beneficial effects are similar to ex vivo treatment with mitapivat but, importantly, are obtained at much lower concentrations. Taken together, these results are the first in an ex vivo model to demonstrate that the novel PK activator AG-946 has a similar favorable pharmacodynamic profile to mitapivat with enhanced PKR-stabilizing properties and, hence, might

represent a potential novel therapeutic option in addition to mitapivat for the treatment of SCD.

Figure 1



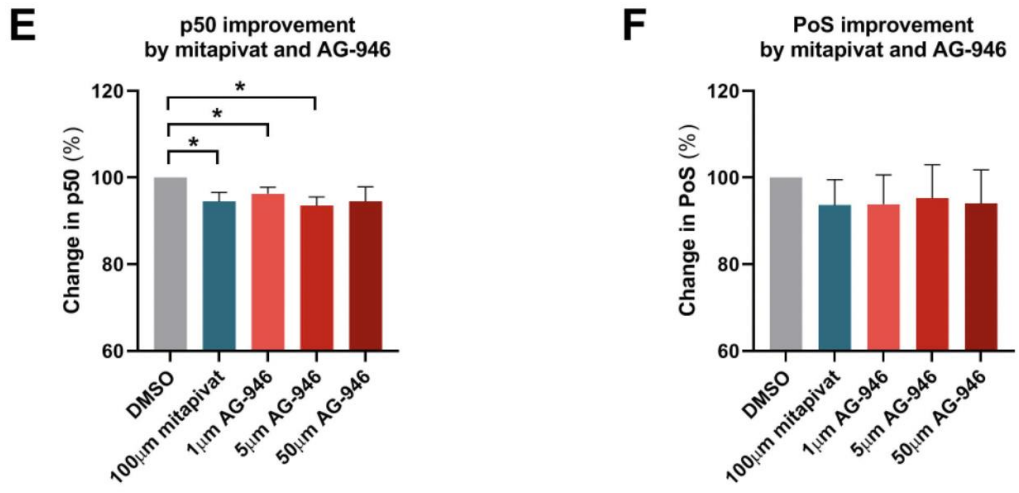


Figure 1. Pharmacodynamic effects of AG-946 in ex vivo treatment of red blood cells (RBC) from sickle cell disease (SCD) patients in comparison with mitapivat. Buffy coat depleted whole blood was incubated for 20-24 hrs in absence or presence of mitapivat (100 µM, blue bar) or AG-946 (1 µM, 5 µM, 50 µM, orange bars) and compared to vehicle control (DMSO, gray bar). Ex vivo treatment increased pyruvate kinase (PKR) activity to a similar extent for both mitapivat and AG-946 (panel A), and significantly increased PKR thermostability (B). This was accompanied by a decrease in the levels of 2,3-DPG (C) and a comparable improvement in the ATP/2,3-DPG ratio for both mitapivat and AG-946 treated samples (D). The metabolic changes were associated with a significant decrease in p50 for both mitapivat and AG-946 treated samples (E), and a comprable decrease in PoS which is indicative of a decreased RBC sickling tendency in vitro (F). Error bars represent standard deviation. ***p<0.001, *p<0.05

JSCDH-D-22-1212753

PHASE 2 SAFETY/EFFICACY OF ETAVOPIVAT IN THALASSEMIA OR SICKLE CELL DISEASE

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Affiliation: *[1]University of California San Francisco, [2]Children's Healthcare of Atlanta, [3]Emory University, [4]University of Southern California Keck School of Medicine, [5]Cincinnati Children's Hospital Medical Center, [6]Children's Hospital of Philadelphia and Perelman School of Medicine, [7]University of Pennsylvania, [8]Forma Therapeutics, Inc., [9]Weill Cornell Medicine*

Background: In sickle cell disease (SCD), a single β-globin gene mutation results in sickle hemoglobin (HbS) that polymerizes upon deoxygenation, causing red blood cells (RBCs) to sickle leading to various complications. In thalassemia, RBCs have an imbalance in the ratio of α/β globin chains and aggregated, unpaired globin chains increase metabolic demands. These stresses result in ineffective erythropoiesis and shorten RBC lifespan, leading to chronic anemia. The resultant anemias, exacerbated by impaired RBC health, are associated with lower ATP levels than in healthy RBCs. Supportive care and agents, eg hydroxyurea, are used most in treating SCD, with some patients on regular transfusions. Regular or episodic transfusions, with their own set of complications, are the mainstay of treatment for thalassemia.

Etavopivat, an investigational, once-daily, selective, erythrocyte pyruvate kinase (PKR) activator increases ATP and decreases 2,3-DPG.1,2 In a Phase 1 study, etavopivat 300-600 mg once daily in patients with SCD not regularly transfused was well-tolerated, improved hematologic markers, decreased hemolysis and improved markers of RBC health.1,2 Etavopivat 200 and 400 mg once daily (doses predicted to provide desired pharmacokinetic response profiles) are being evaluated in a Phase 2/3 study of patients with SCD not on chronic transfusions (The Hibiscus Study, NCT04624659). Here, we describe the design of a Phase 2, open-label, multicenter study (NCT04987489) evaluating the efficacy and safety of etavopivat in patients with SCD on chronic transfusions (Cohort A), transfusion-dependent thalassemia (Cohort B) and non-transfusion-dependent thalassemia (Cohort C).

Methods: Key eligibility criteria and study design are outlined in Figures 1 and 2, respectively. Patients will receive etavopivat 400 mg once daily for 48 wks. Patients will provide written informed consent.

Baseline assessments will include medical, disease, transfusion and medication histories. Transfusions received during the study (every ~3-5 wks) will be recorded and include Hb values before and ≥15 min after transfusion, transfusion dates, number of RBC units, volume of packed RBCs and hematocrit of the transfused unit (if available). If a patient has an increase ≥1.0 g/dL in pre-transfusion Hb vs baseline, the investigator may delay transfusion 1 wk or reduce the number of RBC units transfused. RBC-exchange transfusions may also be performed in patients with SCD.

The primary endpoints are outlined in Figure 2. Secondary and exploratory endpoints include the proportion of patients with a reduction in transfusions ≥33% and ≥50%, respectively, over 12 wks; reduction in transfusions over 12, 24 and 48 wks (Cohorts A/B); and Hb response at Wks 24 and 48 and change from baseline in Hb over 12, 24 and 48 wks (Cohort C). Additional endpoints will be assessed in all cohorts: change from baseline in quality of life (using SF-36 and PROMIS); change from baseline in serum ferritin levels at 12, 24 and 48 wks; liver iron at 48 wks; 2,3-DPG and ATP; pharmacokinetics; and safety. Primary endpoints will be analyzed using a 1-sided test at α=0.025.

Results: Results are not yet available for this trial in progress. Planned enrollment includes ≤20 patients (aged 12-65 y) in each of the 3 cohorts (Figure 2).

Conclusions: Etavopivat is a novel, investigational, once-daily, selective PKR activator with potential to improve RBC health and lifespan. This Phase 2 study will assess the safety of etavopivat and its impact on Hb levels and transfusion burden in patients (aged 12-65 y) with SCD or thalassemia.

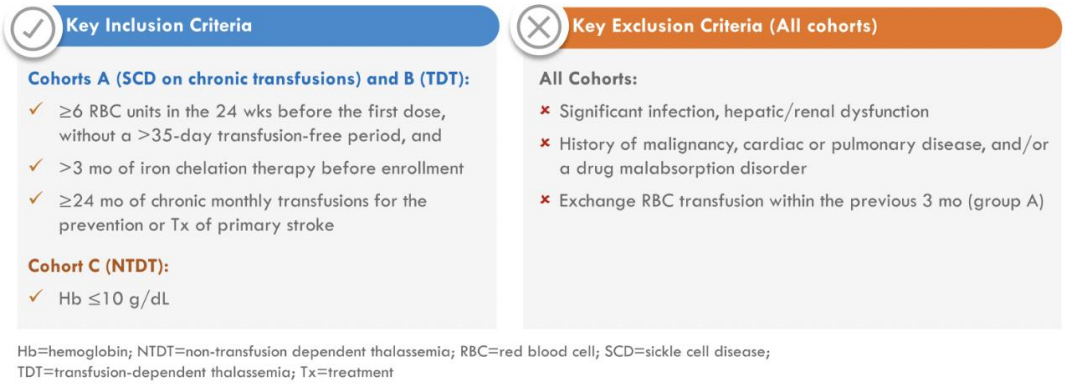

Figure 1: Key eligibility criteria for patients 12–65 y of age

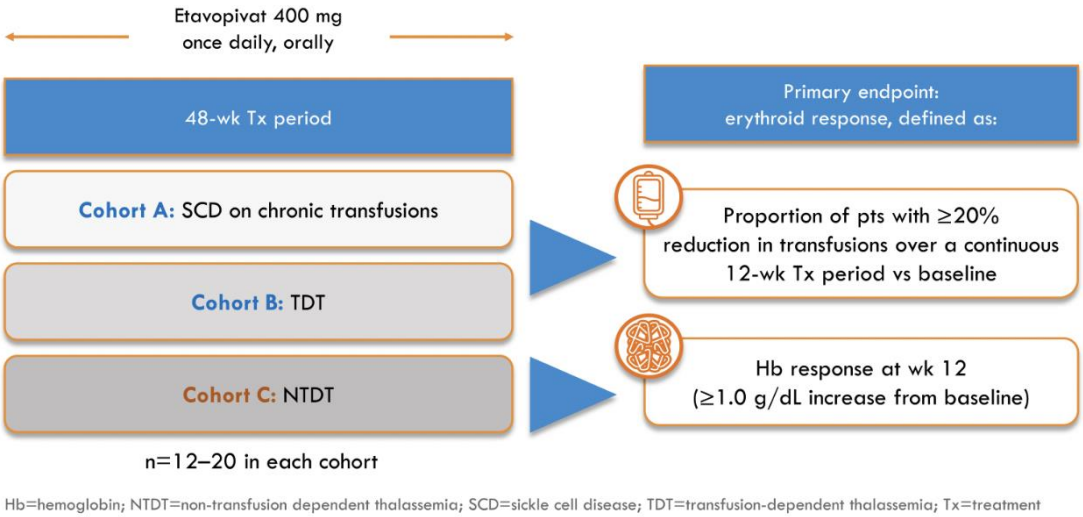

Figure 2: Study design

JSCDH-D-22-1237529

SURVEILLANCE OF SICKLE CELL DISEASE IN PREGNANCY: PRELIMINARY RESULTS OF AN ANGOLAN COHORT

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Background: Sickle Cell Anemia (SCA) is an inherited autosomal and lethal blood disorder caused by a mutation in the HBB gene that promotes hemoglobin (Hb) polymerization and consequent sickling of red blood cells (RBCs) under hypoxia. Regardless of being a monogenic disease, SCA has a remarkably high clinical heterogeneity in its phenotypic expression. Several factors have been shown to modulate the clinical manifestations of SCA, namely genetic markers such as α-thalassemia and β-globin cluster haplotypes, that can modulate biological parameters like the degree of hemolytic anemia or the levels of fetal hemoglobin (HbF). Pregnancy in women with SCA is associated with an increase in adverse outcomes. These outcomes include an increased risk of eclampsia, preeclampsia, maternal mortality, and stroke. This study aims to determine the complications in pregnant women with SCA and study the association between genetic variability and phenotype.

Methods: Pregnant women with SCA are being followed at the Lucrecia Paim Maternity Hospital, located in Luanda, the capital city of Angola. So far, the study has involved 42 patients aged from 18 to 36 years old. The patient's clinical history was registered, namely age at diagnosis, number of hospitalizations, blood transfusions, strokes and other clinical complications. , Biochemical, and hematological data was also collected. Additionally, for genetic analysis peripherical blood samples were used. All samples were genotyped for the HbS mutation by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to confirm the SCA diagnosis. Moreover, four single nucleotide polymorphisms (SNPs) were genotyped in the β-cluster to determine the HbS haplotype by RT-PCR (rs968857, rs10128556) and PCR-RFLP (rs28440105, rs3834466). The presence of the 3.7kb deletion of the α-globin gene was determined by Gap-PCR, allowing the detection of the hybrid fragment that exists with the deletion of 3.7kb, to genotype the samples regarding the 3.7kb α-thalassemia deletion.

Cerebral hemodynamics was assessed using Transcranial Doppler (TCD) mean blood flow velocity (TAMMx) and peak systolic velocity (PSV) measured bilaterally at the middle cerebral arteries (MCA) and basilar artery (BA).

Results: A total of 42 SCA patients have been study until now, with ages ranging from 18 to 36 years old (mean of 25.6±5,0). All the samples were homozygous for the HbS mutation.

The observed frequency of homozygous for 3.7kb α-thalassemia deletion was 16.7%, with an allelic frequency of 34,5% in this sample. The data was consistent with the Hardy-Weinberg equilibrium ($\chi 2=1.852$, $p=0.173$) with the wild-type homozygous genotype being 47.6% and the heterozygous genotype being 35.7%.

The CAR/CAR haplotype was the most prevalent in our population (26 patients, 61.9%), and all patients have at least one CAR allele. There is a considerable number of patients with an unknown haplotype CAR/UKN (9 patients, 21.4%). There is a significant difference in symptoms experienced by SCA patients that co-inherit the α-thalassemia deletion, and in the ones with the homozygous CAR haplotype. We observed an apparent more severe symptomatology in CAR/CAR patients, especially concerning pain crisis, blood transfusions, severe anemia, hospitalizations, premature births, and miscarriages. On the other hand, a significant reduction in these parameters was

evident in patients that co-inherited the 3.7kb α-thalassemia deletion.

At the MCA level, TAMMx reached between 62cm/s and 105cm/s, whereas the PSV was between 96cm/s and 155cm/s. The BA showed TAMMx between 38cm/s and 64cm/s, with the PSV ranging 55cm/s to 93cm/s.

Conclusions: With this project, we seek to support a cohort of SCA pregnant women in Angola to improve their quality of life and reduce problems during pregnancy, but also maternal mortality and neonatal outcomes in Angola. Genetic data showed to be an important marker for follow-up. Moreover, we intend to obtain TCD reference values of cerebral blood flow velocities in pregnant women with SCA as a risk predictor of vascular events.

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POSTERS

JSCDH-D-22-1238877

A COLLECTIVE IMACT PROJECT TO DECREASE THE STIGMA OF SICKLE CELL DISEASE

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Affiliation: *[1]Candice Sickle Cell Fund, [2]Sickle Cell Thalassemia Patient Network, [3]Westchester Sickle Cell Outreach, [4]Lehman College, [5]Rivelis & Associates, [6]William E. Proudford Sickle Cell Fund / SiNERGe, [7]Jacobi Medical Center / NYC Health + Hospital*

Background: One of the most unjust healthcare disparities for individuals living with sickle cell disease (SCD) is the stigma they face seeking care for pain in the Emergency Department (ED). Too often, they are viewed as drug seekers and hear derogatory and depersonalizing terms such as “sickler” or “frequent flyer.” The negative staff attitudes cause many individuals to delay coming to the ED until their pain overwhelms their “dignity,” increasing suffering, hospitalizations, complications, and costs.

As SCD community-based organizations, our members’ care in the ED is a significant and complex problem. We know there are simple, evidence-based interventions that, when implemented, improve staff attitudes towards individuals living with SCD. We also know the ED staff wants to do what is right. The crucial question is how we can help the ED meet our community’s needs. We believe the answer is through the collective impact model. At the heart of the model is:

1) a commitment by a group of different organizations/stakeholders to a common agenda for solving a specific complex problem.
2) support for their actions by shared measurements, mutually reinforcing activities, continuous communication, and support from a “backbone organization.”

Four New York SCD CBOs have committed to work together on a common agenda under the guidance of the SiNERGe CBO leadership (backbone organization). Our goal is for 20% of hospitals with EDs in the NYC/Westchester area to have yearly staff education programs designed to improve staff attitudes towards individuals living with SCD by January 2023.

Methods: We used the Project ECHO model for telementoring to form a learning collaborative. Our monthly telecommunication meetings allowed us to define our shared measurements, reinforcing activities, and learn from each other (all learn/all teach.)

Results: We defined four activities that our “collective” thought was necessary to reach our goal:

1) Outreach to hospital leadership.
2) Developing a clear vision of the intervention we are asking the hospitals to implement.
3) Working with the assigned hospital team to ensure implementation.
4) Establishing our infrastructure to sustain the intervention.

We created a letter using the acronym “CIA” Concern – Impact – Actions to establish relations with hospital leadership. We were pleasantly surprised by the rapid response to the letter (1-2 weeks), though meeting with the designated team ranged from 2-8 weeks.

The minimum educational program we wanted to be implemented was for the staff to hear our stories. Essentially, to understand that individuals with sickle cell disease have a life outside of the hospital, and we want the staff’s help to get back to our lives. This could be done through a video such as “They don’t believe me” or individuals living with sickle cell disease telling their experiences. Most of our CBOs

wanted the hospitals to implement a hybrid of these approaches.

Implementation of the educational program across our programs included:

1) ED staff attending patient support groups.
2) SCD CBOs presenting at staff education conferences and meetings.
3) Use of eLearning module, such as “Sickling is Not Seeking” for staff.

Conclusions: Complex social problems cannot be solved by single organizations working alone. The stigma faced by individuals living with SCD in the ED is a problem that requires diverse organizations to work together on a common agenda – the collective impact model.

JSCDH-D-22-1213101

A PHASE 1 STUDY OF CSL889 (HEMOPEXIN) IN ADULT PATIENTS WITH SICKLE CELL DISEASE

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Affiliation: *CSL Behring*

Background: Episodes of vaso-occlusive crisis (VOC) are the primary reason for hospitalization among patients with sickle cell disease (SCD).

The release of heme from the breakdown of damaged red blood cells is thought to play an important role in contributing to vaso-occlusion in SCD. Free heme promotes activation of endothelium, expression of endothelial cell adhesion molecules and activation of blood cells (neutrophils, monocytes, and platelets) which "stick" to the blood vessel walls. The net result is blockage of blood circulation, resulting in the characteristic pain of VOC.

Hemopexin is a 60 kilodalton (kDa) plasma glycoprotein that is mainly expressed in the liver and belongs to the family of acute-phase proteins whose synthesis is induced after an inflammatory event. Hemopexin binds extracellular heme with the highest known affinity (KD < 1pM) of all plasma proteins. In patients with SCD, hemopexin levels are significantly reduced (approximately 85%) compared to healthy controls due to increased consumption.

CSL889 is human plasma-derived hemopexin. It is hypothesized that pharmacological administration of CSL889 may decrease heme toxicity, restore normal blood circulation and therefore have beneficial effects in the management of acute VOC in SCD patients. Translation to the clinic is supported by studies performed in vitro demonstrating protection of heme-mediated endothelial cell damage and in vivo using the Townes mouse model of SCD, in which hemopexin was shown ameliorate vaso-occlusion following hemoglobin or hypoxia/reperfusion challenges (Gentinetta et al. 2022). Preclinical repeat dose toxicity studies in animals have evidenced favorable tolerability up to the highest dose level tested.

Methods: We describe the design of a Phase 1, first in human, multicenter, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of CSL889 in adult patients with SCD following single intravenous (IV) doses of CSL889 [NCT04285827]. The study will comprise 2 parts. Part A will include patients with SCD in their usual health (not in VOC) who will receive a single dose of CSL889 at one of up to 6 different dose levels. In Part B, patients with SCD who present in VOC requiring intravenous (IV) opioid injections and admission to hospital for further management, will receive a single dose of CSL889 at a level that has been shown to be safe and tolerable in Part A within 36 hours of in-patient admission. All subjects will be followed up for 32 days post-infusion of CSL889. The range of doses to be studied is based on a translational PK model based on data derived from the study of CSL889 in the Townes mouse model of SCD.

Results: The primary objective is to determine the safety and tolerability of single doses of CSL889 given to patients with SCD both without (Part A) and with (Part B) active VOC. The secondary objectives are to determine the PK and immunogenicity of CSL889. Exploratory objectives are to determine changes in biomarkers of target engagement (including changes in cell-free heme) and pharmacodynamic biomarkers related to the mechanism of action. Change in pain scores (as measured by Numeric Rating Scale [NRS]) will be additionally evaluated in Part B.

Conclusions: As of 22 FEB 2022, 8 subjects have received a single dose of CSL889 [N=4 at each of the first 2 planned dose levels]. No serious adverse events considered related to the administration of CSL889 have been reported to date.

JSCDH-D-22-1273566

A RARE CASE OF FAT EMBOLISM SYNDROME IN SICKLE CELL DISEASE

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Background: Fat Embolism Syndrome (FES), first described by Zenker in 1861, is commonly associated with trauma to the long bones [1,4]. The mechanism of action by which fat embolism syndrome happens is not well understood nor how it can be prevented 1. It is a life-threatening condition that can rarely affect sickle cell patients, typically leading to multiple organ failures [2]. The early presentation is very vague and requires a high index of clinical suspicion, a multidisciplinary team approach, and early intervention to prevent mortality and morbidity [3,5]. Therefore, having a broad knowledge and experience about the condition is of paramount importance.

We are presenting a rare case of Fat Embolism Syndrome (FES) in sickle cell to highlight the crucial importance of timely recognition and prompt intervention in preventing mortality and minimizing morbidity of this fatal condition.

Methods: Literature review and retrospective and prospective chart review of electronic medical record EMR from 11/13/2021 to 04/12/2022.

Results: A 27-year-old female with sickle cell disease (HbSC) and migraines presented to King's County Hospital Center for intractable migraine and was admitted to the neurology.

The patient was admitted to neurology for status migrainosus vs. idiopathic intracranial hypertension (IIH). She was started on Prednisone 60 mg daily (Day 3-6) for suspected vasculitis and (LHL), Depakote (Day 3-6), Amitriptyline (Day 6-9), and Topamax (Day 4-13) for status migrainosus: and Diamox 500 mg q12 for possible (IIH). MRI of the brain (Day 2) showed scattered lesions consistent with migraine (what does this mean?). MRA negative or aneurysm/stenosis. Magnetic resonance venography (MRV) was negative for cerebral venous sinus thrombosis.

On day 10, the patient became mentally altered and worsened of hypoxia, requiring a high-flow nasal cannula. The patient was then upgraded to the medical intensive care unit (MICU) for further management and monitoring.

Laboratory results on day 10 showed elevated ammonia levels of 46 umol/L reference range (11 to 32 µmol/L), mildly elevated liver enzymes, and prolonged Prothrombin time (PT). Depakote toxicity was considered as the possible cause of the altered mentation and was subsequently discontinued. Computed tomography (CT) without contrast on day 10 showed a subtle small focus of hypoattenuation in the right corona radiata extending into the basal ganglia, not definitively seen on the prior CT or MRI just 1 week prior. MRI of the brain on day 10 showed interval development of innumerable small foci of low signal throughout the cerebral hemispheres, brainstem, and cerebellum most consistent with microhemorrhages, not present on the MRI of day 2. These findings suggest that the patient's hypoxic respiratory failure and subsequent acute chest syndrome may have been secondary to Fat Embolism Syndrome. The Sickle Cell Team transfused 1 packed red blood cell (PRBC), and 2 units of platelet for low platelets on day 11

On day 15 sickle cell team in collaboration with other teams performed an exchange transfusion of 5 units PRBC was performed after the diagnosis of (FES) was concluded by the sickle cell, neurology, and intensive care teams.

24 hours after exchange transfusion the patient's mentation and clinical condition improved There were also concerns about Hemophagocytic lymphohistiocytosis (HLH) due to the patient's

persistent fever, two-cell line cytopenia, elevated ferritin, and elevated cytokines.

Rheumatology was consulted and the patient was started on high-dose steroids for suspicion of vasculitis and then tapered off rapidly as improvements were seen. The patient began to stabilize with hemolysis parameters down trending, hemoglobin stable >9, and reportedly felt well. The patient was discharged home with instructions for follow-up with the Sickle Cell Clinic.

Prognosis is good if prompt diagnosis and early intervention are warranted.

The patient has full functionality to ambulate, converse, and work, However, as Sequalae, she is complaining of numbness of the lower jaw with shaky chipping lower tooth. Follow up with Oral surgery is recommended no surgical intervention is required

Conclusions: Fat Embolism Syndrome (FES) is a multisystemic clinical condition that carries a high mortality rate, and a high index of clinical suspicion. Prompt treatment can save lives and reduce morbidity and mortality. It should be considered in the differential diagnosis of sickle cell patients with hypoxia, altered mental status, and multiorgan involvement.

FES in Sickle Cell Initial MRI

IMPRESSION:

1. No evidence of acute infarction.

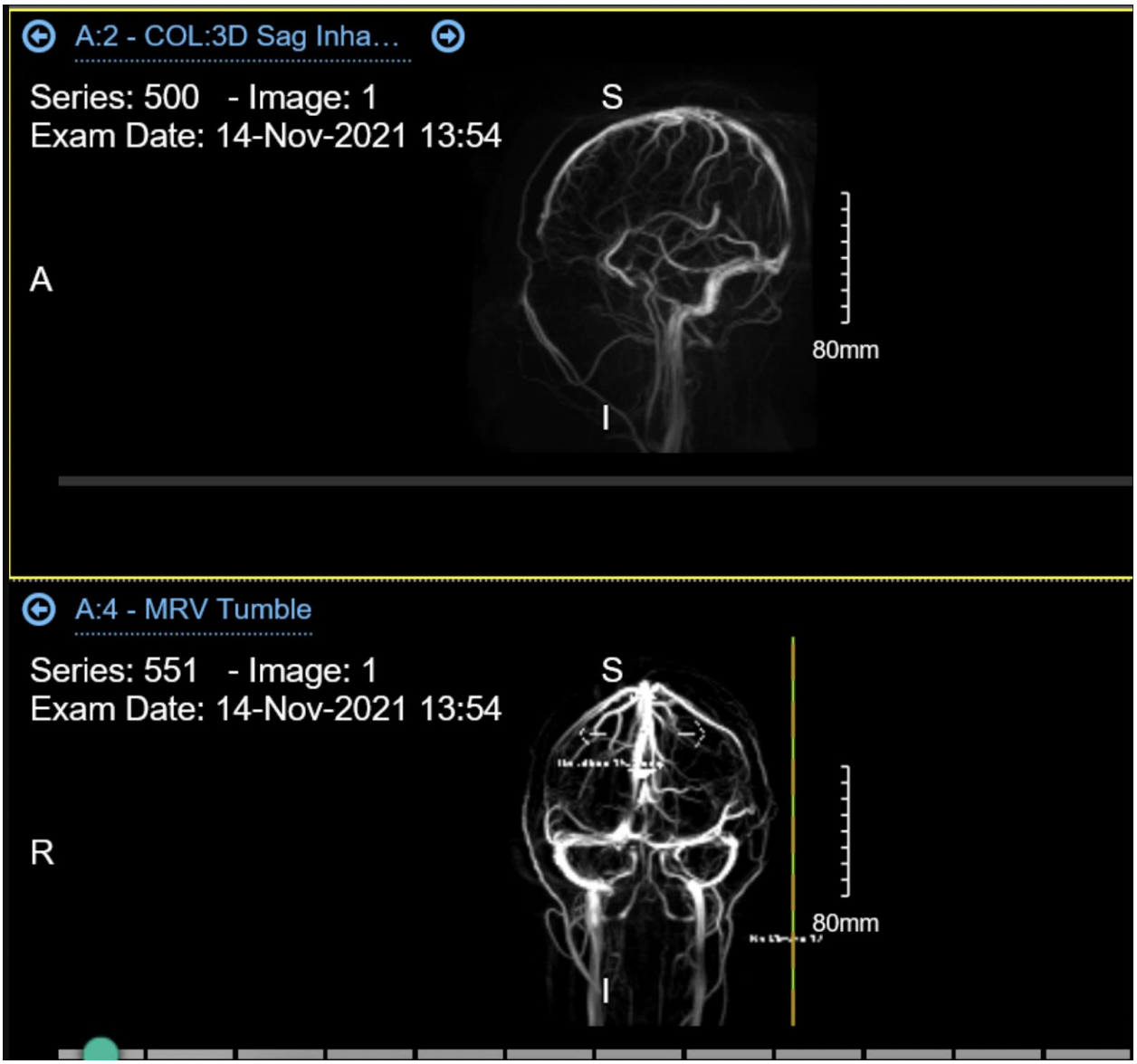
2. Interval development of innumerable small foci of low signal throughout the cerebral hemispheres, brainstem and cerebellum most consistent with microhemorrhages, not present on the recent prior MRI of November 14, 2021. There is no abnormal
intraparenchymal enhancement.

3. Scattered small foci of white matter signal abnormality which may be secondary to the patient's reported migraines versus microvascular changes or a combination of both. Slightly more prominent bilateral signal abnormality adjacent to the frontal horns and the external capsules likely represent small foci of previous ischemia/infarction.

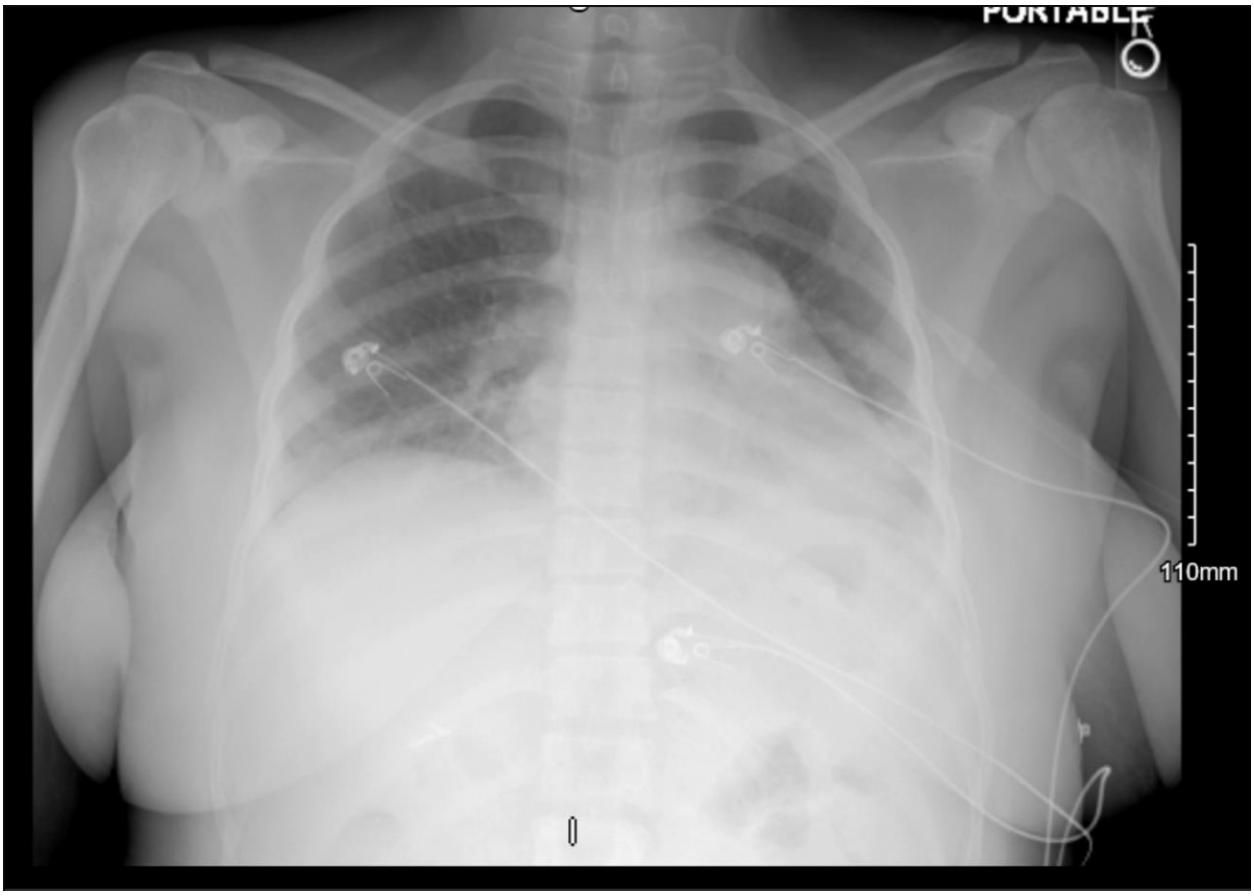
4. Osseous sequelae of known sickle cell disease.

5. Multifocal paranasal sinus disease.

Fat Embolism Syndrome FES in Sickle Cell MRV



FES in Sickle Cell Leading to Acute Chest Syndrome
ACS



JSCDH-D-22-1236680

A SINGLE-SESSION PROBLEM SOLVING INTERVENTION IN PEDIATRIC SICKLE CELL CHRONIC TRANSFUSION

Authors: Dennis Burchette, BA[1], Alecia Nero, MD[1], Jenna Oppenheim, PsyD[2], Julie Germann, PhD[2], Mona Robbins, PhD[1], Paul Nakonezny, PhD[1]

Affiliation: *[1]University of Texas Southwestern Medical Center, [2]Childrens Medical Center,*

Background: Sickle cell disease (SCD) is an autosomal-recessive genetic disorder of hemoglobin that affects millions of individuals worldwide.1 SCD is a chronic disease with devastating complications that can become life-threatening. Chronic red blood cell transfusions (CT) are an effective treatment for severe disease performed about once per month to decrease the percent of circulating abnormal sickle hemoglobin. Chronic disease states such as SCD can exacerbate psychological distress. CT is a burdensome treatment, given the need for ongoing complex care coordination and frequent clinic visits, which can add additional stress to patients and families. Recent research studies in patients and families affected by SCD utilized various mental health assessment tools to gain better understanding of patient outcomes.2 The SSPSI is self-generated and uses the patient's resources/access to care to formulate solutions to the defined problem4. Research utilizing mental health assessment tools that can define and address problems experienced by families affected by SCD on CT is limited.

Objective: This pilot study aims to: (1) Identify problems experienced while navigating CTs to treat SCD. (2) Describe solutions generated through use of a SSPSI to address these defined problems.

Methods: This pilot study was approved by the UT Southwestern Medical Center IRB and conducted at a single institution. Participant pairs (patients and caregivers of patients) receiving CT to treat SCD were enrolled in a study examining quality of life and domains of risk and resiliency. Those in the intervention group participated in a SSPSI where feasibility and acceptability of the intervention were measured. Twenty patients [(age M=13.55, SD=3.52), 55% male; 95% African American/Black (non-Hispanic); 5% Hispanic] and twenty caregivers [(age M=42.45, SD=8.51), 95% female; 95% African American/Black (non-Hispanic); 5% Hispanic] enrolled and completed the Psychological Outcomes Profiles (PSYCHLOPS) measure. PSYCHLOPS is a mental health outcome measures tool used in primary care or community-based setting that is self-completed3. This measure was completed during routinely scheduled transfusion visits: 1 month after baseline assessment (visit 2), 2 months after baseline (visit 3), and six months after baseline for long-term follow-up (visit 4). Participants in the intervention group participated in a SSPSI during visit 2 and generated solutions to address problems identified using the PSYCHLOPS measure.

Results: Families and patients in both the intervention and control groups identified primary and secondary problems they experienced related to managing patient care, navigating medical concerns, and mood-related issues. Patterns in primary and secondary identified problems include: academic performance (15%), advocacy (5%), appointment burden (5%), concentration (10%), COVID-19 (5%), explaining SCD to peers (40%), finances (15%), maintaining health (20%), medical complications (25%), school performance 15%), transportation concerns (5%), treatment adherence (35%), worry of having stroke (5%), and understanding of SCD (10%). Each family in the intervention group (N=10) generated solutions to address the problems identified, which included use of hospital resources (10%), community resources (10%), other family members and friends (10%), and effecting change within themselves (70%).

Conclusions: This SSPSI pilot study explored problems identified and solutions generated by families in a single institution CT program to treat severe SCD. Utilizing PSYCHLOPS to identify areas of concern and

employing solutions generated by the SSPSI should be further studied in families undergoing CT. Medical and psychosocial providers working with these families can consider formal implementation of the strategies within clinical practice to help reduce psychosocial barriers in this patient population. Future studies could include enrolling more participants and extending to SCD patients who may not be in CT programs. This could later inform the use of SSPSIs to broadly address psychosocial needs of patients affected by SCD, particularly those who lack access to mental health expertise.

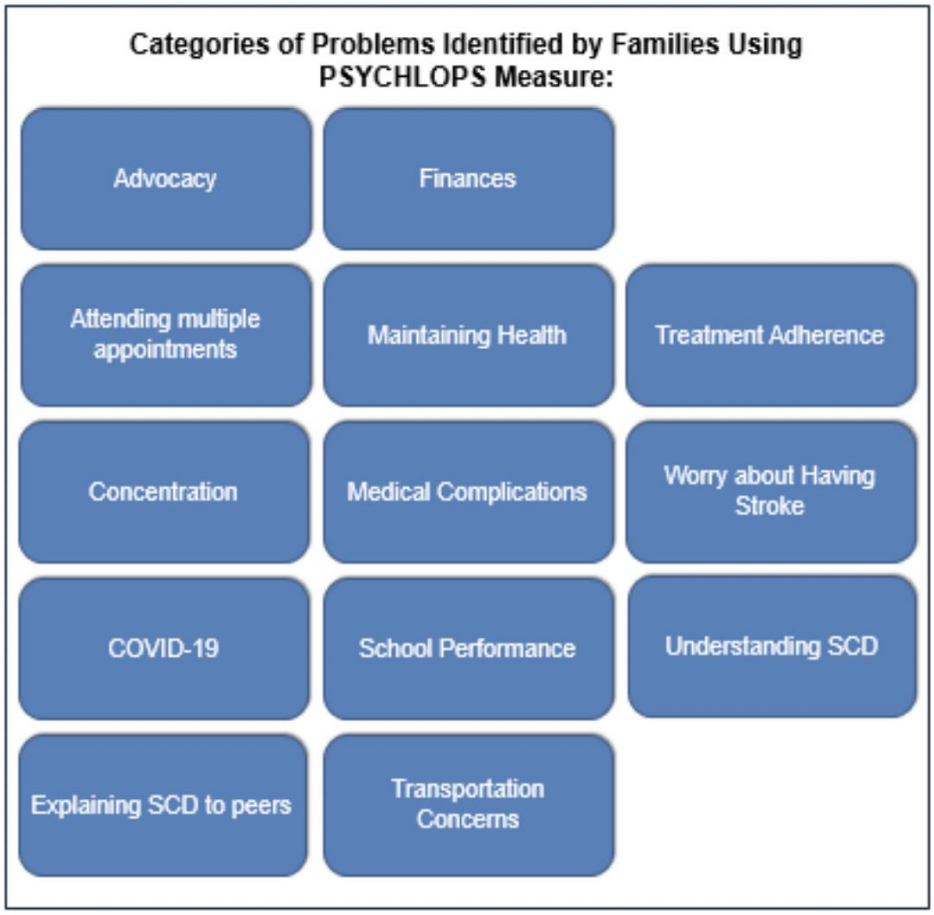


Figure 1. Patterns in primary and secondary identified problems.

JSCDH-D-22-1231535

ASSESSMENT OF FUNCTIONAL BEHAVIORS AND PAIN PHENOTYPES IN BERKELEY SICKLE CELL MICE

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Background: Sickle Cell Disease (SCD) is a family of genetic blood disorders affecting over 20 million people worldwide. It is associated with multiple complications including chronic pain which contributes to significant functional disability in those affected. Berkeley SCD mice (HbSS-BERK) express human sickle hemoglobin, HbS, and display a similar phenotype to SCD patients, thus representing a useful tool to evaluate disease pathophysiology and investigate novel therapeutic strategies. Previous studies with this model have shown that HbSS-BERK mice exhibit mechanical and thermal hypersensitivity, as well as diminished grip strength compared to HbAA-BERK (humanized control) mice. These measures alone may not sufficiently capture and model the functional impairments and disruptions of daily life experienced by SCD patients. Thus, we performed additional experiments in HbSS-BERK mice to evaluate peripheral sensory and functional motor behavior in a variety of assays compared to age- and sex-matched control mice.

Methods: Male and female HbSS-BERK and HbAA-BERK (control) mice from three different age groups (2, 5, 10 months old, + 2 weeks) served as subjects (3-5 mice per sex/genotype/age). Nociceptive behaviors were assessed using the von Frey filaments for mechanical allodynia, hot plate test for thermal hyperalgesia, and acetone assay for cold allodynia. Functional assays were divided into measures of spontaneous and innate behaviors. Spontaneous behaviors included grip strength, inverted screen, and wheel running while innate behaviors involved nesting and burrowing. Data was analyzed using 2- and 3-way ANOVAs followed by Tukey or Sidak post-hoc analysis when appropriate ($p < 0.05$ considered significant).

Results: HbSS-BERK mice displayed mechanical and cold allodynia as well as thermal hyperalgesia compared to control mice with older mice being the most sensitive. HbSS-BERK mice had diminished grip strength and poor performances in both inverted screen and wheel running compared to their controls. HbSS-BERK mice also displayed impaired burrowing and nest building behavior compared to the control mice. Sex differences were significant in the grip strength and wheel running assays.

Conclusions: These findings validate that HbSS-BERK mice display a severe hyperalgesia phenotype that is accompanied by functional behavioral deficits. The characterization of sensory and functional deficits in these Sickle mice will be useful for identifying pharmacological interventions that could then translate to improving the lives of people living with Sickle Cell Disease.

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BOSENTAN ATTENUATES HBS POLYMERIZATION AND IMPAIRED DEFORMABILITY INDUCED BY ENDOTHELIN-1

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Background: Effects of Endothelin-1 (ET-1) on erythrocytes from sickle cell disease (SCD) patients has been described, but lack evidences regarding primary erythrocyte functions. ET-1 is a vasoconstrictor peptide produced by endothelial cells, with expression increased in SCD patients. Thus, our group performed ex vivo experiments with sickle cells patients' erythrocytes, ET-1and bosentan, a dual antagonist of ETA and ETB receptors.

Methods: We performed polymerization of hemoglobin S assay unde hypoxic conditions with three concentrations of ET-1 (10 pg/mL, 20 pg/mL and 50 pg/ mL) and also incubated the same concentrations with bosentan and performed readings in microplate reader at 700 nm for 30 minutes; for deformability assay, RBC was incubated upon Sephacryl column with same concentrations of ET-1 and bosentan and centrifuged at specific speed to separate deformable from non deformable cells that were subsequently lysed for hemoglobin quantification at 540 nm . To observe erythrocyte static adhesion, ET-1 and bosentan were incubated with RBC in a thrombospondin-coated 96 well plate and adherent cells were harvested, lysed and hemoglobin quantifyed at 540 nm. We also assessed ET-1 and bosentan modulating erythrocyte apoptosis by translocated phosphatidylserine binding to annexin V.

Results: In polymerization assay, we observed ET-1increased HbS polymerization in all concentrations used and this effect was blunted by bosentan. During deformability assay, we observed decreased deformability induced by ET-1 in all concentrations, but reversion by bosentan was only seen in two highest ET-1 concentrations. For adhesion to thrombospondin-coated plates, we observed decreased adhesion promoted by ET-1, with this effect deepened by bosentan, with a greater effect promoted by the highest ET-1 concentration. Finally, regarding annexin V binding, we observed decreased eryptosis induced by endothelin treatement in all three concentrations, with reversion by the two higher bosentan concentrations.

Conclusions: In summary, this work provides first-time ex vivo evidence that ET-1 increases HbS polymerization in hypoxic conditions, decreases erythrocyte deformability, static adhesion and phosphatidylserine exposure under normoxic conditions. Besides, bosentan abrogate HbS polymerization, erythrocyte deformability and annexin V binding induced by ET-1 and deepened the static adhesion inhibition. These results point that bosentan possess positive effects for SCD patients and could be of essential importance for increasing SCD drug panel, since there are few pharmacotherapeutic options. These findings may propose a profound discussion on the use of bosentan as principal or combined therapy for SCD.

JSCDH-D-22-1239020

BURDEN OF SICKLE CELL DISEASE AND PATIENTS' UNMET NEEDS: SHAPE SURVEY HCP RESULTS

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Affiliation: *[1]Necker-Enfants Malades Hospital, [2]PRISMA Health Comprehensive SCD Program, [3]University of South Carolina School of Medicine, [4]Haematology and Haemotherapy Centre, School of Medicine, [5]University of Campinas - UNICAMP, [6]King Faisal Specialist Hospital & Research Center, [7]Hopp Children's Cancer Center (KiTZ) Heidelberg, University of Heidelberg, [8]The Hospital for Sick Children (SickKids) and University of Toronto, [9]Global Blood Therapeutics, [10]Ipsos Healthcare, [11]Guy's and St Thomas' Hospital*

Background: Sickle cell disease (SCD) has a substantial emotional and physical burden on patients. Research on the impacts of SCD on patient quality of life (QOL) is limited, but research into treatment options to improve QOL for these patients has increased recently. To complement this drive to improve patient QOL, there needs to be a more detailed understanding of what it means to live with SCD in different communities, especially considering the health inequalities faced by different groups around the world. In addition to surveying patients and caregivers, viewpoints from healthcare professionals (HCPs) should also be considered, as the perspectives of HCPs may impact or reflect patient QOL. The Sickle Cell Health Awareness, Perspectives and Experiences (SHAPE) survey aims to understand the perspectives of HCPs on the patient burden of SCD, the impacts of SCD on patient QOL, and the needs of patients with SCD.

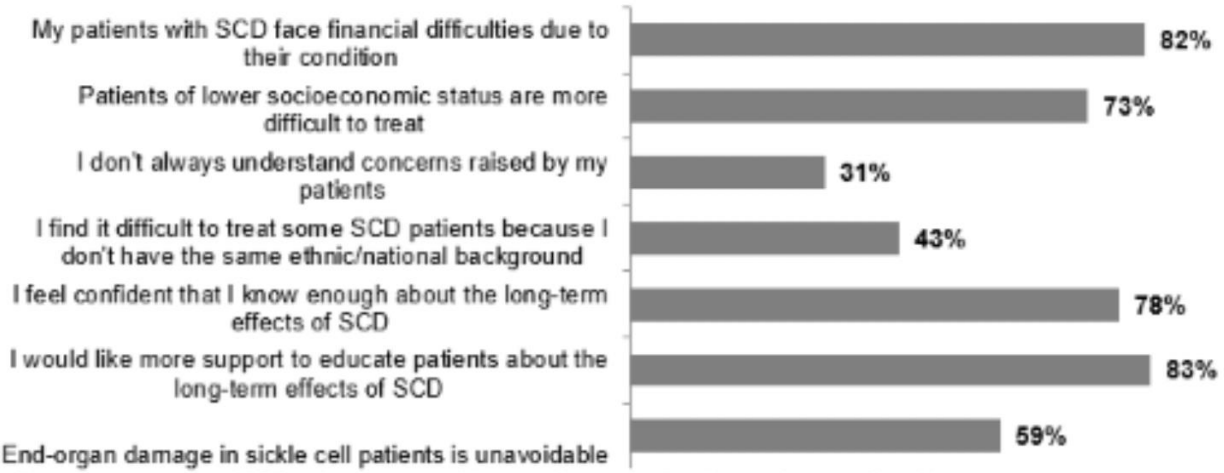
Methods: The SHAPE survey is a multinational study comprising quantitative online surveys of patients, their caregivers, and HCPs. The surveys require participants to answer a range of closed-ended questions about their circumstances and experiences in order to build a robust and reliable dataset on which descriptive statistics were performed. HCPs were included if they had at least 10 patients with SCD under their care and had been practicing for 3 to 35 years. Informed consent was obtained from all participants, and all identifiable information was kept private and secure. The study protocol was reviewed and approved by an independent institutional review board.

Results: Interviewed HCPs (n=219) included 48% hematologists, 37% hematologist-oncologists, 11% pediatric hematologists, 1% pediatricians, 1% internists, and < 1% general or family practitioners. Participating HCPs were from the US (23%), Germany (15%), Brazil (14%), France (14%), UK (14%), Canada (7%), Saudi Arabia (7%), and United Arab Emirates (7%). The mean (range) number of patients under their care was 32 (16-65). Most HCPs (82%) agreed that SCD causes financial difficulties for patients, and many (73%) agreed with the statement that "patients of lower socioeconomic status are more difficult to treat" (Figure). Nearly 1 in 3 HCPs (31%) found it challenging to understand their patients' needs, with more than 2 in 5 (43%) citing difficulties due to having a different ethnic background from their patients. Most HCPs (78%) felt confident in their knowledge of the long-term effects of SCD, but 83% wanted more support in educating their patients on this topic. Almost two-thirds of HCPs (59%) believed that end-organ damage is unavoidable and that SCD greatly impacts patients' long-term health prospects (64% for patients < 18 years; 60% for patients ≥18 years) and their ability to attend and succeed at work or school (53% for < 18 years; 49% for ≥18 years).

Conclusions: Almost one-third of HCPs found it challenging to understand their patients' needs. Based on these findings, additional support for HCPs in terms of their communication with and education of their patients could result in more effective SCD

treatment. HCPs also noted an unmet need for treatments that fully address end-organ damage in SCD. These findings highlight the complex environment that HCPs face when treating patients with SCD, including differences in socioeconomic status and ethnic background, the need for education, and a lack of resources. The patient and caregiver portion of the SHAPE survey will complement the data presented here by providing additional perspectives on the burden of SCD.

Figure: Percentage of HCPs Who Agreed[a] With the Following Statements



[a]Percentages reflect HCPs who answered "somewhat agree" or "strongly agree" to this statement.

HCP, healthcare professional; SCD, sickle cell disease.

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CELEBRITIES WITH SICKLE CELL DISEASE AND THALASSEMIA - A RESOURCE COMMUNITY

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Background: For children who have sickle cell disease or thalassemia, having somebody to identify with who shares the same disease can be very important as role models. Celebrities can be especially inspirational. In the past, early childhood mortality was 50- 90% and few individuals with sickle cell disease survived to adulthood. Career development was probably hampered by the fatigue and medical absences caused by sickle cell disease. Because sickle cell disease disproportionately affects people of color, career options were also limited by racial discrimination. A tiny handful of celebrities are listed in some patient education books and magazine articles about sickle cell disease, and most hid their diagnosis during their lives in order to avoid the stigma that was associated with the disease.

Currently, we have a new era of being able to find adults with sickle cell disease or thalassemia because of the stigma that is slowly disappearing, as well the better survival rates, and global exchange of information like the use of the internet.

Methods:

1) Searched the internet with terms and keywords such as “celebrities”, “sickle cell disease”, “thalassemia” and “famous people”.
2) Used a multilingual angle by searching the same concepts in English, Arabic, French, Italian and Portuguese.
3) Searched personal archives from articles and sickle cell or thalassemia conferences.
4) Conducted the search from the date of September till March 2022.

Results: A total of nineteen celebrities were found. The number of celebrities and other famous people known to have sickle cell disease and thalassemia remains low to this day, despite an increase in survival and knowledge about the disease.

The industries they are in are various and include music (2), fashion (1), sports (5), TV/film (3), medicine/healthcare (2) and social activist (1), for sickle cell disease.

Interestingly, most of the people who were mentioned are listed in celebrity gossip websites of different countries, very few were mentioned on sickle cell disease education or advocacy websites.

As for thalassemia, even fewer people were found, bringing the total number to five, in industries such as sports (2), TV/film (2), and religion (1).

In addition, there were little to no findings for searches made in a language other than in English.

Conclusions: Celebrities, serving as inspiration for youth, can be a helpful source of identification for children and adolescents diagnosed with sickle cell disease or thalassemia. Although the number of known famous people is still low, there is at least one person in each industry that could be acknowledged.

The content of this abstract will be shared through different media such as the ARISE and Sickle Cell Disease Association of America website

The authors will value any additional names to the list, please email lewhsu@uic.edu

JSCDH-D-22-1237933

CHARACTERISTICS OF HIGH HOSPITAL UTILIZERS VS. HIGH CASE MGMT UTILIZERS IN ADULTS WITH SCD

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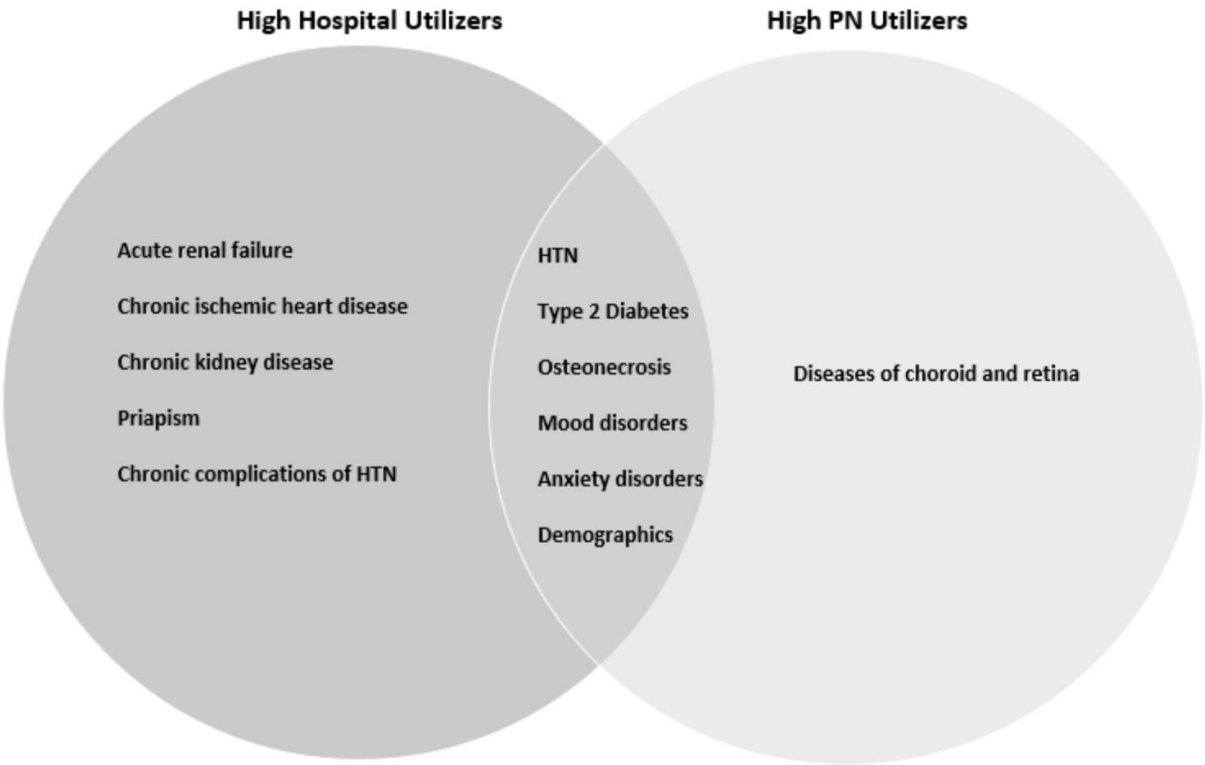
Background: Case management by Community Health Workers (CHW's) and others is instrumental for managing adults with sickle cell disease (SCD). Though case management is often intended to reduce SCD hospital and emergency department utilization by managing social determinants of health, it is unclear how it impacts SCD health care utilization. This raises practical challenges for program managers and CHWs, as well as research questions for SCD implementation science researchers. How should CHW caseloads be assigned? Is there a subset or phenotype of patient who utilizes CHWs more, vs. those who utilize hospitals more? To answer these questions, we compared characteristics of SCD high hospital utilizers versus high case management utilizers.

Methods: We used descriptive statistics to describe subsets or phenotypes of adult patients in our Adult SCD Medical Home (N=522) who were either: a) the top 50 highest ED and/or inpatient utilizers from Jan 2020 to Oct 2021, based on clinical claims; b) the top 50 highest utilizers of Patient Navigators (PNs, our term for CHWs) from Jan 2020 to Oct 2021, based on detailed PN logs of each patient contact, or; c) were the top 50 highest utilizers in both categories. We documented via insurance claims all comorbidities/co-occurring diagnoses. We also documented results of assessments for depression, anxiety, and substance use disorders completed on our patients by our licensed clinical social worker (N=57).

Results: The Figure is a Venn Diagram of groups a, b, and c. Eighty percent of highest PN utilizers (right, category b) were not highest utilizers of the hospital (left, category a). Only 10 patients were both highest PN and highest hospital utilizers (middle, category c). Demographically, the three groups were similar. However, prevalent comorbidities differed by group. Listed in the diagram are all diagnoses in each group with both a prevalence of ³20% and a relative prevalence at least 50% higher than non-high-utilizers.

Limitations: Data came from one medical center. Behavioral assessments were not completed on the majority of the 50 highest utilizers in each category.

Conclusions: The top 50 highest adult utilizers of SCD CHWs (PNs) were not the top 50 highest ED and hospital utilizers, and had far fewer biological complications/SCD comorbidities than the highest hospital utilizers. It is unclear whether these results, particularly the discrepant comorbidity phenotypes, reflect long-term versus early patient navigation, or whether they have been stable over time. Future research should develop a predictive model of these utilization patterns that incorporates biological, psychosocial and environmental factors.


High Hospital Utilizers
High PN Utilizers
Acute renal failure
Chronic ischemic heart disease
Chronic kidney disease
Priapism
Chronic complications of HTN
HTN
Type 2 Diabetes
Osteonecrosis
Mood disorders
Anxiety disorders
Demographics
Diseases of choroid and retina

JSCDH-D-22-1240931

CLINICAL IMPLEMENTATION OF TRANSCRANIAL DOPPLER WITH TRANSFUSION CHANGING TO HYDROXYUREA

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Affiliation: *East Carolina University*

Background: Stroke is one of the most devastating complications of sickle cell disease. The groundbreaking National Institutes of Health (NIH)-funded TWiTCH study established hydroxyurea as an effective non-inferior alternative to chronic red blood cell transfusions for primary stroke prevention in children with sickle cell disease. The study findings, published in 2016, established a protocol for transitioning patients from transfusions to hydroxyurea. It is important to evaluate how well the protocol is being implemented in clinical practice.

Objective: The main objective of this study was to investigate the outcomes of patients who were involved in the TWiTCH study at one academic medical center and the degree of adherence to the transition protocol for patients transitioning from transfusions to hydroxyurea.

Methods: A retrospective chart review of TWiTCH study subjects in one academic medical center. Institutional Review Board (IRB) exemption was obtained. Data were collected for the time from the end of the TWiTCH study (2014) to the most recent (2021). Data collected included: Demographics, Magnetic resonance imaging (MRI), Magnetic resonance angiography (MRA), Ferriscan, TCD, blood chemistries, Ferritin, blood counts, and stroke prevention intervention strategies.

Results: Eight TWiTCH subjects were identified, seven of whom had full evaluable data. All seven patients were stroke-free and had normal TCDs as of their most recent imaging. Four patients transitioned from chronic transfusions during the TWiTCH study to hydroxyurea post-study. One patient who was on hydroxyurea stayed on hydroxyurea while two patients who were on hydroxyurea transitioned to chronic transfusions. The mean current hemoglobin F was 8.3% compared with 27% reported by the TWiTCH study for all centers. Mean current ferritin was 1981ng/mL compared to 2238.6ng/mL at end of the TWiTCH study for subjects who are on hydroxyurea, 5943ng/mL, and 1123ng/mL respectively for patients currently on transfusions. The TWiTCH study reported ferritin of 2624ng/mL and 1226ng/mL for transfusion and hydroxyurea arms, respectively. The mean hydroxyurea dose was 24.5 mg/kg compared to 27mg/kg reported from the TWiTCH study. The mean hemoglobin was 7.9g/dL compared to 8.7g/dL at end of the TWiTCH study.

Conclusions: Most patients from the TWiTCH study have been safely transitioned to hydroxyurea as part of standard clinical care at our institution. Adherence with dosing and laboratory targets was suboptimal likely due to patient noncompliance and a less rigorous follow-up schedule. Suboptimal compliance places patients at risk of not benefiting from all the advantages of transitioning to hydroxyurea identified in the TWiTCH study. Continued monitoring of these patients to identify any complications is warranted. Strategies to improve adherence to the transitioning protocols need to be developed.

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CONCURRENT USE OF HYDROXYUREA AND DEFERASIROX APPEARS SAFE IN CALIFORNIANS WITH SCD

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Affiliation: *[1]OHSU Hospital, [2]California Department of Public Health, [3]Public Health Inst./Calif. Dept. of Public Health*

Abstract: When patients with sickle cell disease have appropriate indications, they can be prescribed hydroxyurea (HU) and deferasirox (DFX) concurrently despite little knowledge about how the two medications interact. Therefore, we analyzed whether there was evidence of adverse interaction between HU and DFX when taken simultaneously by conducting a retrospective cohort investigation of persons with SCD in a statewide, Medicaid-based database who took HU and DFX simultaneously for at least 3 months as compared to those who took either HU or DFX alone or to matched persons who took neither drug. We hypothesized that those who took both drugs together had similar clinical complications when compared to those who took only one or neither drug. Using data from the California Sickle Cell Data Collection Program, a validated database of Californians with SCD, persons who took both HU and DFX concurrently had similar rates of ED and inpatient encounters and had similar rates and distribution of adverse effects compared to those who took either HU or DFX alone or took neither drug. In conclusion, 3 months of concurrent use of DFX and HU appears safe, but further studies are required to better understand the safety and effectiveness of this medication combination.

Introduction: Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder that results in polymerization of hemoglobin, sickle-shaped RBCs, anemia, pain, organ injury, and premature mortality. RBC transfusion is an effective therapy for SCD and many of its complications, but is limited by eventual iron overload. To prevent iron overload and its significant complications, an iron chelator is often necessary in patients with severe SCD. Parenteral deferoxamine was the only iron chelators available until 2005, when enteral deferasirox (DFX) was approved in the United States (US). DFX appears to have equivalent efficacy as deferoxamine but is better tolerated by patients and therefore patients are able to maintain improved adherence.[1, 2]

Intermittent or chronic RBC transfusions were the only widely available treatment until the 1990s, when clinical trials confirmed that pharmacologic induction of fetal hemoglobin (Hb F) reduced complication of sickle cell anemia. Hydroxyurea (HU) was subsequently approved in 1998 in the US for the treatment of adults with SCD to decrease frequency of vaso-occlusive pain episodes, acute chest syndrome, transfusions, and hospitalizations and is routinely recommended for patients with severe SCD.[3, 4]

Therefore, HU and RBC transfusions are the cornerstone of symptom management for SCD. As a result, patients with SCD are often prescribed HU and DFX concurrently despite little knowledge about how the two medications interact. Despite optimizing the use of existing SCD therapies being a top research priority, sufficient concerns exist that clinical trials to date have not allowed study participants to take both drugs simultaneously.[5, 6] Therefore, we wished to investigate whether there is evidence of increased adverse effect or evidence of toxicity between HU and DFX when taken concurrently. We conducted a retrospective, cohort investigation of persons with SCD in a statewide Medicaid-based database who took HU and DFX simultaneously as compared to those with SCD who took either HU or DFX alone or to matched persons who took neither drug. We hypothesized that individuals who took both drugs together had similar adverse effects when compared to those who only took one or neither drug.

Methods:

Cohorts

Included cohorts were validated and followed over time using data from the California Sickle Cell Data Collection Program (CA SCDC) as previously described.[7, 8] In brief, those included in CA SCDC must either have been identified through newborn screening, confirmed by laboratory analysis to have SCD at one of six SCD clinical centers in California, or found in administrative data with three or more SCD-specific International Classification of Diseases – Clinical Modification (ICD-CM) codes over a five year period. People meeting this definition were then linked, using social security numbers and date of birth to (1) the Patient Discharge and (2) Emergency Department Utilization databases from the California Office of Statewide Health Planning and Development, (3) vital records death files, and (4) Medicaid (Medi-Cal) claims. Inclusion criteria and data linking methodologies were previously validated.[9, 10] To be included in this analysis, people must have had at least one prescription claim for one of the drugs of interest in Medi-Cal claims data or had three or more SCD-specific ICD codes in the Medi-Cal claims data for the period of investigation, Figure 1. People without a Social Security number listed in the Medi-Cal claims data were excluded. Data collection and analysis were approved by the California Committee for the Protection of Human Subjects (the state's Institutional Review Board) and by each data steward (OSHPD, the Department of Health Care Services, and the California Center for Health Statistics and Informatics).

We tracked utilization and discharge codes starting on the date of the first pharmacy fill claim of HU (HU Only cohort), DFX (DFX Only cohort), or whichever drug was started second in the Both Drugs cohort. To be included in the HU Only cohort or DFX Only cohort, the person had to be on the drug for at least 90 days. Similarly, to be included in the Both Drugs cohort, a person with SCD had to be on both HU and DFX for at least 90 days. Those in CA SCDC that were on HU or DFX for < 90 days were excluded. People were then tracked until the last day of the last prescription of the qualifying medication or for a maximum of 6 months, whichever was shortest. Using the tracking start and end date and the count of each outcome of interest, we calculated the rate per person year.

Due to the high number of people in the database not on either drug, each subject in the Both Drugs cohort was randomly matched for age category, sex, and tracking start date to four control patients who never filled a prescription for either drug (Neither Drug cohort). Since the aim of this study was to compare outcomes in the Both Drug cohort to the other control cohorts, we did not compare the HU Only and DFX Only cohort to the Neither Drug cohort.

We wished to study whether taking both medications together increased the rate of adverse reactions or toxicity; therefore, known adverse reactions of HU and/or DFX as listed in Lexi-Drugs® (Wolters Kluwer, Alphen aan den Rijn, Netherlands) were converted to International Statistical Classification of Diseases and Related Health Problems version 9 (ICD9) codes, Appendix A. For 2015, when ICD10 was in use, Centers for Medicare and Medicaid Services General Equivalence Mapping was used to map ICD9 to ICD10.[11] Lexi-Drugs categorizes the adverse reactions by body system and these same body systems categorizations are used in Table 2. In order to evaluate whether rates of adverse reactions increased or changed across cohorts, we analyzed all ICD9 or ICD10 discharge codes for individuals from ED and inpatient encounters, regardless of whether they were SCD-related, for a maximum of 6 months after start of tracking. These discharge codes were categorized by body system using their stem code and compared to the ICD9 and ICD10 codes of known adverse reaction.

Statistical analysis

Categorical variables were summarized using frequencies and percentages and compared for statistical significance using chi-square tests. Continuous variables were summarized by means and rates, and analyzed using the Wilcoxon signed rank test for differences between the matched Both Drug

and Neither Drug group and the Wilcoxon-Mann-Whitney test was used to test for differences between the Both Drugs compared to HU Only or DFX only. The analyses were done in SAS version 9.4.

Results: Between 2009 and 2016, we identified 104 subjects in the Both Drugs cohort, 416 matched-controls in the Neither Drug cohort, 877 controls in the HU Only cohort, and 314 controls in the DFX Only cohort, Figure 1. One individual from the Both Drugs cohort and the 4 matched-controls in the Neither Drug cohort were removed because the number of ED and inpatient encounters was greater than 4 standard deviations from the mean and accounted for more than 30% of the encounters. Patient characteristics for the four cohorts are described in Table 1. Of the 103 analyzed patients in the Both Drug cohort, 52 started HU first, while 51 started DFX first, and 97 (94%) filled prescriptions for both medications for the full 6 month analysis period.

When categorized by body system (ICD code stem), the rate of adverse complications captured during ED and inpatient encounters for the Both Drugs cohort was similar, Table 2.

Asthma and pain, especially chest and abdominal pain, were common adverse effects across the cohorts, Table 3. The proportion of diagnosis codes for increased serum creatinine, renal tubular disease, acute renal failure, increased liver function test levels, skin changes, hearing or vision changes, leg ulcers, neutropenia, thrombocytopenia, or sepsis were no higher in the Both Drugs cohort compared to the three control cohorts (Data not shown). During the follow up period, 3 (2.9%), 11 (2.7%), 27 (3.1%), and 10 (3.2%) individuals had a malignant neoplasm diagnosis code in the Both Drugs, Neither Drug, HU Only, and DFX Only cohorts, respectively, which is similar to previous reported prevalence of cancer in those with SCD.[12]

Discussion: Based on this retrospective cohort investigation of a statewide Medicaid-linked database, persons with SCD who took both HU and DFX concurrently did not have higher rates for emergency or inpatient encounters when compared to cohorts who took HU or DFX alone or neither drug. When encountered either in the ED or inpatient setting, those on both HU and DFX had a similar rates and similar distribution of adverse complications compared to most controls. Furthermore, other frequent adverse reactions observed when HU or DFX are used as monotherapy did not appear to be increased when both medications were used concurrently.

Although clinicians prescribe HU and DFX together to patients with SCD, clinical trials have not allowed study subjects to take both concurrently, thereby complicating trial design and slowing progress in our ability to use established therapies optimally. To date, only one study enrolled 28 patients with SCD to a randomized trial of iron chelators and allowed concurrent HU use; this study concluded that ≤2 years of concomitant HU did not influence the efficacy, safety, and pharmacokinetic parameters of DFX.[13] A preclinical study of concurrent HU and DFX in mice also support the safety of the combination and even proposes synergistic iron chelation.[14]

This is the largest analysis to date on the safety of concurrent HU and DFX use in patients with SCD. We had a small but statistically significant difference in mean age across groups that appears to be an artifact of matching within the Both Drug and Neither Drug groups. Although we required only 90 days of combination HU and DFX therapy, 94% filled prescriptions for both drugs for the 6 months analysis. We opted to track cohorts for 6 months with the assumption that many adverse effects would be evident by then given the pharmacokinetic of both medications. Since many high-risk oral medications are prescribed one month at a time, requiring 3 months of refills increased our confidence that the person actually ingested the medication. However, as with all administrative database studies, this cannot be confirmed. Although we may see discharge coding that suggested signs of toxicity, our data would not capture whether either medication was discontinued due to perceived toxicity or intolerance and would

not detect a small difference in adverse effects given our study size. Lastly, this analysis only included patients on Medicaid since we needed prescription data. However, 62% of people tracked through CA SCDC are on Medicaid, therefore the majority of Californians with SCD were captured.

As with any retrospective analysis, this work is susceptible to bias, particularly indication bias, where clinicians may prescribe RBC transfusion (with subsequent DFX) and HU to those with more severe SCD. If this was true, persons in the Both Drugs cohort might be expected to have a higher rate of encounters for ED or inpatient care and a higher rate of adverse events. However, we observe similar rates in Both Drugs cohort compared to controls, which may strengthen our conclusion that concomitant HU and DFX appears safe. Future studies must further interrogate safety and effectiveness of concurrent use of HU and DFX in the short and long-term.

Authorship Contributions: TEW conceived the investigation and wrote the first draft of the manuscript. TEW, JV, SP contributed equally to analysis design and editing the manuscript. SP is Principal Investigator of CA SCDC and oversaw data collection and linkage. Statistical analysis was provided mainly by JV and SP.

Table 1: Baseline patient characteristics

	Both drugs (n=103)	Neither drug, matched (n=412)	*p-value*	HU Only (n=877)	*p-value*	DFX Only (n=314)	*p-value*
Patients with an ED or hospital utilization within 6 months after follow up start, n (%)	58 (56)	214 (52)		506 (58)		112 (36)	
Patients with an ED or hospital utilization resulting in a known adverse reaction within 6 months after follow up start, n (%)	43 (42)	152 (37)		359 (41)		76 (24)	
Mean no. of ED & hospital encounters within 6 months after follow up start	1.89	1.83	0.22*	3.16	0.2606[†]	1.07	*< 0.001*[†]
Mean no. of ED & hospital encounters resulting in an adverse reaction within 6 months after follow up start	1.43	1.71	0.79*	2.17	0.6918[†]	1.05	*0.002*[†]
Female, n (%)	53 (51)	213 (52)	N/A	425 (48)	*0.565*[‡]	172 (55)	*0.56*[‡]
Age, mean, y	26.6	27.2	N/A	27.8	0.3872[†]	25.2	0.39[†]
Age groups, y			N/A		0.2504[‡]		0.17[‡]
< 7	0	0		27 (3)		10 (3)	
7-20.9	39 (38)	156 (38)		289 (33)		121 (39)	
21-40.9	46 (45)	184 (44)		387 (44)		145 (46)	
≥ 41	18 (17)	72 (18)		174 (20)		38 (12)	

*Wilcoxon Signed Rank when compared to Both Drugs; [†]Wilcoxon-Mann-Whitney when compared to Both Drugs; [‡]Chi-Square when compared to Both Drugs; N/A = not applicable due to matching

Table 2: Discharge diagnosis by body system, no. of diagnosis (rate per person per year)

System	Both Drugs (n=103)	Neither Drug, matched (n=412)	*p*-value*	HU Only (n=877)	*p*-value†	DFX Only (n=314)	*p*-value†
Neurology	2 (0.04)	54 (0.26)	**.0063**	115 (0.26)	.3513	13 (0.08)	.7258
Ophthalmology	2 (0.04)	7 (0.03)	.8438	13 (0.03)	.9611	3 (0.02)	.6861
Cardiovascular	10 (0.19)	63 (0.31)	.5947	179 (0.41)	.1290	36 (0.23)	.6421
Pulmonary	32 (0.62)	123 (0.60)	.5849	409 (0.93)	.4036	37 (0.24)	.0589
Gastrointestinal	44 (0.85)	131 (0.64)	.0841	299 (0.68)	.1423	67 (0.43)	**.0040**
Liver	1 (0.02)	8 (0.04)	.5313	28 (0.06)	.6046	6 (0.04)	.6878
Renal	7 (0.13)	36 (0.17)	.8652	91 (0.21)	.9851	6 (0.04)	**.0261**
Hematology	3 (0.06)	41 (0.20)	**.0183**	47 (0.11)	.5299	54 (0.34)	.1900
Oncology	3 (0.06)	15 (0.07)	.5682	57(0.13)	.8636	22 (0.14)	.8515
Endocrine	0	6 (0.03)	.0625	17 (0.04)	.3834	6 (0.04)	.5756
Dermatology	2 (0.04)	12 (0.06)	.9018	31 (0.07)	.8755	13 (0.08)	.8488
Infectious Disease	13 (0.25)	44 (0.21)	.4765	120(0.27)	.9467	46 (0.29)	.5817
Musculoskeletal	27 (0.52)	153 (0.74)	.2404	490 (1.12)	.1420	21 (0.13)	**.0022**

*Wilcoxon Signed Rank when compared to Both Drugs; †Wilcoxon-Mann-Whitney when compared to Both Drugs

Table 3: Top 5 adverse reactions, no of adverse reactions (rate per person year)

Both Drug* (n=122 Adverse reactions)		Neither Drug (n=568 Adverse reactions)		Hu Only (n=948 Adverse reactions)		DFX Only (n=380 Adverse reactions)	
Adverse reaction	no.(rate per py)	Adverse reaction	No.(rate per py)	Adverse reaction	No.(rate per py)	Adverse reaction	No. (rate per py)
Abdominal pain	14 (0.27)	Asthma	47(0.22)	Asthma	139 (0.316)	Aplastic anemia	27 (0.17)
Asthma	13 (0.25)	Chest pain	36 (0.17)	Arthralgia	126 (0.28)	Abdominal pain	19 (0.12)
Constipation	12 (0.23)	Abdominal pain	39 (0.19)	Chest pain	113 (0.26)	Asthma	28 (0.18)
Chest pain	9 (0.17)	Back pain	17 (0.08)	Pain in extremity	68 (0.16)	Malignant neoplasm	20 (0.13)
Back pain	6 (0.11)	Pain in extremity	36 (0.17)	Back pain	70 (0.16)	Chest pain	170 (0.11)

JSCDH-D-22-1236659

COVID-19 OUTCOMES IN PATIENTS WITH SICKLE CELL DISEASE

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Background: In December 2019, The novel coronavirus (SARS-CoV-2) emerged and spread quickly around the globe. Infection from this virus ranges in clinical presentation but often presents with symptoms of fever, cough, shortness of breath, and fatigue. Less common symptoms include gastrointestinal illness and olfactory sensory loss. In more severe cases, especially in those who are immunocompromised, elderly, or living with multiple comorbidities, infection can lead to pneumonia, ARDS, organ damage, or even death. Sickle Cell Disease (SCD) is an inherited hemoglobinopathy, caused by a homozygous beta globin chain mutation resulting in abnormally sickled red blood cells. There is evidence that patients with SCD infected with SARS-COV-2 are at a higher risk of developing acute chest syndrome and painful vaso-occlusive crises. Patients with a heterozygous mutation, are characterized with Sickle Cell Trait (SCT), and often have a less severe presentation with SARS-CoV-2 infection in comparison to those with SCD. This is likely due to the lower proportion of sickled cells and hypercoagulability that contribute to hypoxia and presence of other risk factors. Early studies on SCD and SARS-CoV-2 infection demonstrate evidence that rates of hospitalization and death are higher in patients with SCD compared to the general population; however, it is inconclusive whether outcomes are significantly different when comparing patients with SCD to those with end organ damage or serious comorbidities.

Methods: This study reports on 5 cases of patients with Sickle Cell Disease who contracted SARS-CoV-2. These patients had follow up care at a private practice in Southern California following PCR confirmed infection. These cases are used to illustrate the idea that although many with SCD often have cardiopulmonary among other co-morbidities predisposing them to complications of SARS-CoV-2, patients may not experience severe disease following infection.

Results: All but one case was confirmed to be positive for SARS-CoV-2 infection using PCR testing, which was confirmed via Anti-body testing. Baseline demographics demonstrate that patients were between 40-50 years of age, men and women, mostly non-smokers, with SS genotype. One patient was on hydroxyurea. Comorbid risk factors for complications included CKD and the presence of a leg ulcer in 3 of 5 patients. All were negative for a history of CVA. Hospitalization occurred among 3 of the 5 patients. Baseline lab values on admission included Hgb levels between 5.7 - 7.9, lymphocytic leukocytosis in 2 of 3 patients. Chest X-ray Imaging demonstrated infiltrates in all hospitalized patients. Discharge home occurred in ≤24 among 2 of the 3 patients. While hospitalized all patients received antibiotics (levaquin or azithromycin/rocephin) and one patient was administered steroid treatment (dexamethasone). At the time of data collection, no patient was vaccinated or developed re-infection.

Conclusions: Potential reasoning for better recovery/lower mortality rates than expected among these individuals could be that there is some evidence that autoantibodies against IFNs can mute the immune system's response against severe disease. Patients with SCD/SCT are suspected to have elevated levels of IFNa. According to the literature, hospitalization and death due to covid among SCD patients appears to be more related to the presence of comorbidities that occur with “natural progression of SCD.” Additionally, among non-SCD patients with co-morbidities, they appear to have similar outcomes and case fatality rates. We observed that patients with CKD and leg ulcer appeared to have worse outcomes in comparison to those without these

complications. According to the literature, it's been speculated that patients taking hydroxyurea and other SCD modifying therapies (transfusions) have less severe symptoms and better recoveries. This was supported by our data,. We had a single patient on hydroxyurea who presented with critical lab values (reticulocyte count, 23; LDH 249; Hgb 5.7, WBC 19.5 w/ lymphocyte 6.3) but did not have an extended hospital stay. While another patient not on this drug presented with more severe lab values and experienced a longer hospital stay. Early data published on this topic suggest that those with SCD would have worse outcomes, but as the pandemic has worn on, this has not proven to be the case. Further research is needed to compare outcomes among SCD patients and non-SCD patients infected with SARS-CoV-2, and compare the effect of comorbidities on disease severity, morbidity, and mortality rates, especially among vaccinated versus unvaccinated individuals.

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DEPLOYMENT OF RED CELL HEALTH BIOMARKERS AT SICKLE CELL DISEASE PILOT SITES

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Background: Historically, there has been inadequate focus on biomarkers that assess the health of red blood cells (RBCs). As a result, RBC diagnostic technologies are often poorly validated, outdated, lack global standards, and are not routinely used in clinical decision making for people living with sickle cell disease (SCD). In the absence of such biomarkers the approach to SCD care is often reactive, where clinical manifestations of SCD such as vaso-occlusive episodes (VOEs) and organ damage are the accepted indications for therapeutic intervention. The recent surge in the clinical trial pipeline and FDA approval of SCD-modifying therapies has the potential to improve the health trajectory of people living with SCD globally. These first in class therapies represent novel mechanisms of action in SCD, including the increase of hemoglobin oxygen affinity, direct inhibition of p-selectin adhesion, reduction of RBC oxidative stress, induction of fetal hemoglobin, all of which may ultimately improve the health of red blood cells. Most SCD providers have minimal experience prescribing and monitoring multiple SCD-modifying therapies. We hypothesize that broad access to validated biomarkers of RBC health will enable more preventative models for SCD care by making RBC health a measurable target in the clinical setting. The objective of this analysis is to describe our experience in deploying a specialized central lab model that focuses on biomarkers of RBC health.

Methods: Blood samples were received from the following clinical pilot sites between Jan 2020 – Feb 2022: Foundation for Sickle Cell Disease Research, Children's Hospital of Michigan, Detroit Medical Center adult sickle cell clinic, Karmanos Cancer Center, and the Children's National Medical Center. Biomarkers were ordered as standard clinical send-out labs using unique billing (PLA) codes, including: flow adhesion of whole blood to VCAM (0121U), flow adhesion of whole blood to p-selectin (0122U) and mechanical fragility (0123U). Samples were drawn in sodium citrate vacutainers, shipped overnight to our central lab in Detroit, MI in specialized shipping containers validated to maintain internal temperature between 2-8oC for 72 hrs. Turnaround time was defined as the time from lab accessioning to reporting of data to the ordering clinical site. Critical results were reported by phone call or HIPAA compliant text message alert to the ordering provider. We extracted all laboratory metrics from our laboratory management system (Ignite Medical Technologies). A qualitative narrative description of the central lab model is also provided.

Results: A total of 11,550 individual tests were performed during the analysis period on 3,850 individual clinical blood samples from 759 unique individuals with SCD. These individuals were represented across the following age ranges: 0-9yrs (n=233), 11-19yrs (n=266), 20-29yrs (n=122), 30-39yrs (n=66), 40-49yrs (n=52), and 50-59yrs (n=20). Indications for testing included acute crisis (2,291), baseline assessment (809), monitoring therapy (770), therapy start (69), and unspecified (247). The number of individuals on SCD-modifying therapy included hydroxyurea (n=295), adakveo (n=54), voxelotor (n=55), and endari (n=43). Critical values were reported for 19.2% of the individual blood samples received (740 or 3,850 samples). There were 127

occurrences of combination therapy being used, and 45 of these occurrences did not include hydroxyurea. The average turnaround time for reporting results to the clinical site was 2.38 days from the date of sample accessioning.

Conclusions: In this report, we demonstrate that careful coordination with the clinical site can facilitate successful sample acquisition and overnight shipping under the specified conditions to ensure functional RBC health testing can be successfully performed. Weekly interactions with the clinical sites were beneficial in addressing questions about ordering, shipping logistics, and application of biomarker data to clinical management. Feedback from providers confirmed the desire for RBC biomarker data to gain more insight into individual patient cellular phenotype, assess response to therapy, and to give encourage better compliance with chronic SCD-modifying therapies. Our experience validates the feasibility of a specialized central lab model as a strategy to increase clinical access to biomarkers of red blood cell health . Multiple investigator-led collaborations are underway to leverage access to RBC health biomarkers to gain better post-market insight into the response to approved SCD-modifying therapies in the “real world.”

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EXPERIENCE FROM US VOXELOTOR EXPANDED ACCESS PROGRAM FOR CHILDREN WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a life-threatening disorder characterized by sickle hemoglobin (HbS) polymerization and red blood cell (RBC) sickling that causes complications such as hemolytic anemia, episodic vaso-occlusion, and multisystem end-organ damage. A substantial unmet need for novel therapies remains. Early interventions that target the underlying pathology of HbS polymerization can potentially prevent hemolysis and downstream complications.

Voxelotor is a HbS polymerization inhibitor that prevents sickling and improves key measures of RBC health. Voxelotor was approved by the US Food and Drug Administration for treatment of adults and pediatric patients (aged ≥12 years) with SCD in 2019, and the indication was expanded in December 2021 to include children as young as 4 years of age. In February 2021, voxelotor was approved by the European Medicines Agency for the treatment of hemolytic anemia due to SCD in adult and pediatric patients aged ≥12 years as monotherapy or in combination with hydroxycarbamide.

The Expanded Access Program (EAP) is an open-label compassionate-use program providing early access to voxelotor for children with SCD aged 4 to 11 years, hemoglobin ≤10.5 g/dL, and no alternative treatment options to improve hemoglobin other than standard treatment.

Methods: Patients receive a pediatric-friendly formulation of voxelotor as oral dispersible tablets or powder for oral suspension, dosed daily according to their body weight. Clinical assessments of laboratory parameters and health status measures (Patient Global Impression of Change [PGI-C] and Clinician Global Impression of Change [CGI-C]) are performed every 12 weeks. Safety and clinical response with voxelotor are also monitored.

Results: Between January 6 and November 15, 2021, 66 patients from 13 sites were enrolled. Thirty-nine patients have completed the 12-week follow-up visit. Fifty-nine patients are currently still receiving treatment. The mean (SD) age at entry was 7.9 (2.20) years, and the median (range) weight was 26.2 (13-51) kg; 56% (37/66) were male, and 44% (29/66) were female. Eighty-five percent (56/66) of patients received concomitant hydroxyurea. Median (range) treatment exposure was 21.9 (1.4-44.9) weeks. Twelve weeks after starting voxelotor, 72% (28/39) of participants had an improvement in hemoglobin. At 12 weeks, CGI-C scores improved in 59% (23/39) of patients, and PGI-C scores improved in 55% (21/38) of patients. A positive association between reported medication adherence and clinical improvement was observed.

The safety profile of voxelotor among these patients was consistent with previous reports. Three (4.5%)

patients discontinued voxelotor due to treatment-related adverse events.

Conclusions: The preliminary findings of the EAP show that voxelotor treatment was associated with increased hemoglobin levels and reported health improvements in pediatric patients aged 4 to 11 years. Higher reported drug adherence was associated with better clinical outcomes. Further evaluation is needed, with additional data and longer follow-up.

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EXPLORING SLEEP QUALITY IN ADULTS WITH SICKLE CELL DISEASE IN JAMAICA

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Background: Disorders of sleep can negatively affect health outcomes in the general population leading to problems such as decreased daytime function, productivity, and overall quality of life. In the presence of chronic disease, effects of impaired sleep quality are even more severe and may cause poor disease control and higher morbidity and mortality.

There are only a few studies investigating the impact of sleep in persons with sickle cell disease (SCD), but they have demonstrated that poor sleep quality is associated with greater pain events and hospitalizations. In this study we aimed to examine sleep and the predictors of poor sleep quality in Jamaican adults with SCD. We hypothesised that poor sleep quality is common in Jamaicans with SCD, and is associated with disease severity, genotype, sex, and body mass index (BMI).

Methods: A cross-sectional study conducted at the comprehensive sickle cell centre in Jamaica evaluated 177 well adult patients (age ≥ 18 years) with SCD (63.3% females; mean age 34.2± 12.6 years; 75.1% homozygous SS disease) using The Pittsburgh Sleep Quality Index (PSQI) questionnaire. The PSQI measures seven domains of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month, and a global score >5 indicates poor sleep quality. Severe disease was defined as having a medical history score (using the Adult Sickle Cell Quality of Life Measurement Information System) 1 standard deviation greater than the mean score of the study population. Sex specific comparisons were made for sleep quality and its 7 domains using chi squared or fisher's exact tests as appropriate. Multiple linear regression models examined the predictors of poor sleep quality.

Results: The mean global PSQI score was 6.9 (SD 4.2, range 0 - 19) with 56.5% determined as having poor sleep quality. One-fifth (20.3%) of the study participants were overweight or obese. On bivariate analyses 63.4% females versus 44.6% males (p value 0.02) had poor sleep. Overweight or obesity was present in 25.9% females as compared to 10.7% males (p value 0.01) with over 80% of these persons having poor sleep quality(poor sleep quality: 41.3% in underweight; 53.3% in normal weight; p value: 0.005). Genotype and severe disease had no association with poor sleep quality.

Women had significantly higher scores (indicating higher dysfunction) for sleep efficiency (p 0.005), sleep latency (p 0.03) and use of sleeping medications (p 0.02) when compared to men. Subjective sleep quality (p 0.001) and sleep efficiency (p 0.05) was found to be significantly worse in persons who were overweight and obese.

In multivariate regression analysis, overweight individuals had higher prevalence of poor sleep quality (OR: 2.9; 95% Confidence Interval: 1.07, 7.88) than those with normal weight whereas persons who were unemployed and looking for a job had lower prevalence of poor sleep quality (OR 0.2; 95% Confidence Interval: 0.05, 0.77) compared to employed individuals.

Conclusions: More than half of the Jamaican adults with sickle cell disease reported poor sleep quality. Females had significantly worse sleep quality, especially in the domains of daytime functioning, sleep latency and the use of sleep medications. It is imperative that persons with SCD are screened for sleep disturbances at their routine visits, especially those who are at higher risk. Overweight and obesity are an emerging phenomenon in this population. Patient populations as well as healthcare providers will need to manage this appropriately so that the

burden from their chronic illness is not exponentially increased. Further studies will need to examine other possible contributors to sleep dysfunction in this population, including the effects of depression, anxiety and medications being used, among others.

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FOLIC ACID SUPPLEMENTATION AND ITS CORRELATION WITH HEMOGLOBIN LEVELS IN PATIENTS WITH SCD

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Background: Folic acid supplementation is a common element of treatments for patients with sickle disease. It is hypothesized that people with sickle cell disease are at an increased risk for folate deficiency due to increased erythropoiesis. For this reason, children and adults with sickle cell disease, particularly those with sickle cell anemia, commonly take 1 mg of folic acid orally every day on the premise that this will replace depleted folate stores and reduce the symptoms of anemia. Literature review identified one double-blind, placebo-controlled trial on folic acid supplementation in children with sickle cell disease. Overall, the trial presented mixed evidence on the review's outcomes. No trials in adults were identified. With the limited evidence provided, significance of folate supplementation and its relation to clinical events and changes in laboratory parameters is unclear.

The main goal of this study is to evaluate folate supplementation and its impact on markers of anemia, including hemoglobin and clinical complications of sickle cell disease.

Our hypothesis is that patients who have been compliant with folic acid supplementation will have higher levels of hemoglobin in comparison to those who have not been compliant. This research is designed to develop or contribute to generalizable knowledge.

Methods: A retrospective chart review which includes patients with ages ranging from 1 to 26 years having sickle cell disease SS and Sβ0. Data collection included compliance to folic acid (define as taking 1 mg of folic acid for at least 3 months), red blood cell indices, LDH, BMI and other medications. Exclusion criteria included patient who needed blood transfusion and those with hospitalizations due to sickle cell pain. Analysis of variance was used to evaluate mean differences in age, BMI, hemoglobin, LDH and Reticulocytes percentage in folate and non-folate groups.

Results: After reviewing our database we found the following results, 70 out of 382 patients met inclusion criteria. 41.4% of the patients were females and 58.6% were males. 48.6% of the patients were found to be compliant with folic acid supplement and 51.4% of the patients were found not to be compliant with folic acid supplement. Females were more compliant (51.7 %) than males (46.3%). No statistical significance was found between patients taking folic acid and level of hemoglobin, reticulocytes or BMI Incidentally, we did found that patients in the folate group were more likely to be taking penicillin.

Conclusions: Patients with sickle cell disease SS and Sβ0 who were compliant with folic acid supplementation did not have higher levels of hemoglobin when compare with patient who did not take Folic acid.

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HEART RATE VARIABILITY IN PEDIATRIC PATIENTS WITH AND WITHOUT SICKLE CELL DISEASE

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Background: The hallmark of sickle cell disease (SCD) is recurrent episodes of vaso-occlusive pain. Evaluation of pain in pediatric populations is subjective. More objective methods for pain assessment would be useful. A candidate objective method is heart rate variability (HRV)1,4, 5, 6, 7. HRV is cyclical variability that reflects the overall balance of the sympathetic and parasympathetic aspects of the autonomic nervous system (ANS). The indices used to assess the branches of the ANS include time domain and frequency domain indices. This pilot study will evaluate whether HRV is feasible 1) to assess the effect of SCD on the ANS response, 2) as an objective method to assess pain 3) to objectively assess the effect of complementary medicine techniques10 (listening to music) on the management of SCD pain crises.

Methods: Comparison of HRV in pediatric patients aged 2-25 years include SCD (any genotype) vs non-SCD, SCD with uncomplicated vaso-occlusive crisis (VOC) vs. SCD at baseline, SCD at baseline vs. SCD on chronic transfusion. See Figure 1. EliteHRV ®, a previously validated method and technology, non-invasive equipment and software was used to collect de-identified HRV data. Preliminary data was analyzed by comparing groups using log transformed values.

Results: A total of 27 participants were enrolled: 15 non-SCD, 13 SCD at baseline and 4 SCD on chronic transfusions, before and after their transfusion. No patients with SCD VOC were enrolled. Data was collected in clinic exam rooms with participants in their comfortable state (compared to ideal physiological lab settings) - still providing analyzable data. Younger children were observed to have difficulty sitting still for the 15-20 minute protocol and often completed the period moving/actively playing. Preliminary data showed no statistical significance in HRV between SCD vs non-SCD. However, trends in time domain indices (SDNN) and frequency domain indices (HF power) are shown in *Graphs 1 & 2*, respectively.

Conclusions: This pilot study used a simple non-invasive device to examine feasibility of HRV 1) to assess the effect of SCD on the ANS response, 2) as an objective method to assess pain. Preliminary results did not show any statistical significance, though HRV trends in time domain indices of SDNN and frequency domain indices of HF power show decrease in HRV in SCD vs non-SCD and SCD on chronic transfusions. This suggests that the ANS has more parasympathetic response in non-SCD and SCD on chronic transfusions than SCD. The objective value of HRV as an assessment of pain could not be evaluated as no SCD VOC were enrolled. The sample size was underpowered for statistical significance. However, the trends are consistent with published adult HRV data that 1) patients with SCD will have decreased HRV in comparison to those without SCD, 2) disease-modifying interventions make HRV in SCD patients closer to normal. The results also demonstrate the feasibility of measuring HRV in pediatric SCD, and estimates of “effect size” differences between SCD and non-SCD for pediatric and adolescent ages for the first time. Limitations include analysis of HRV could be confounded by the complexities of ANS in SCD3,7,9,11,12, the behavioural limits of cooperation by young children, the high proportion of individuals meeting exclusion criteria, and the logistical difficulty of enrolling SCD VOC. This pilot study demonstrates feasibility and provides preliminary data for future larger-scale studies.

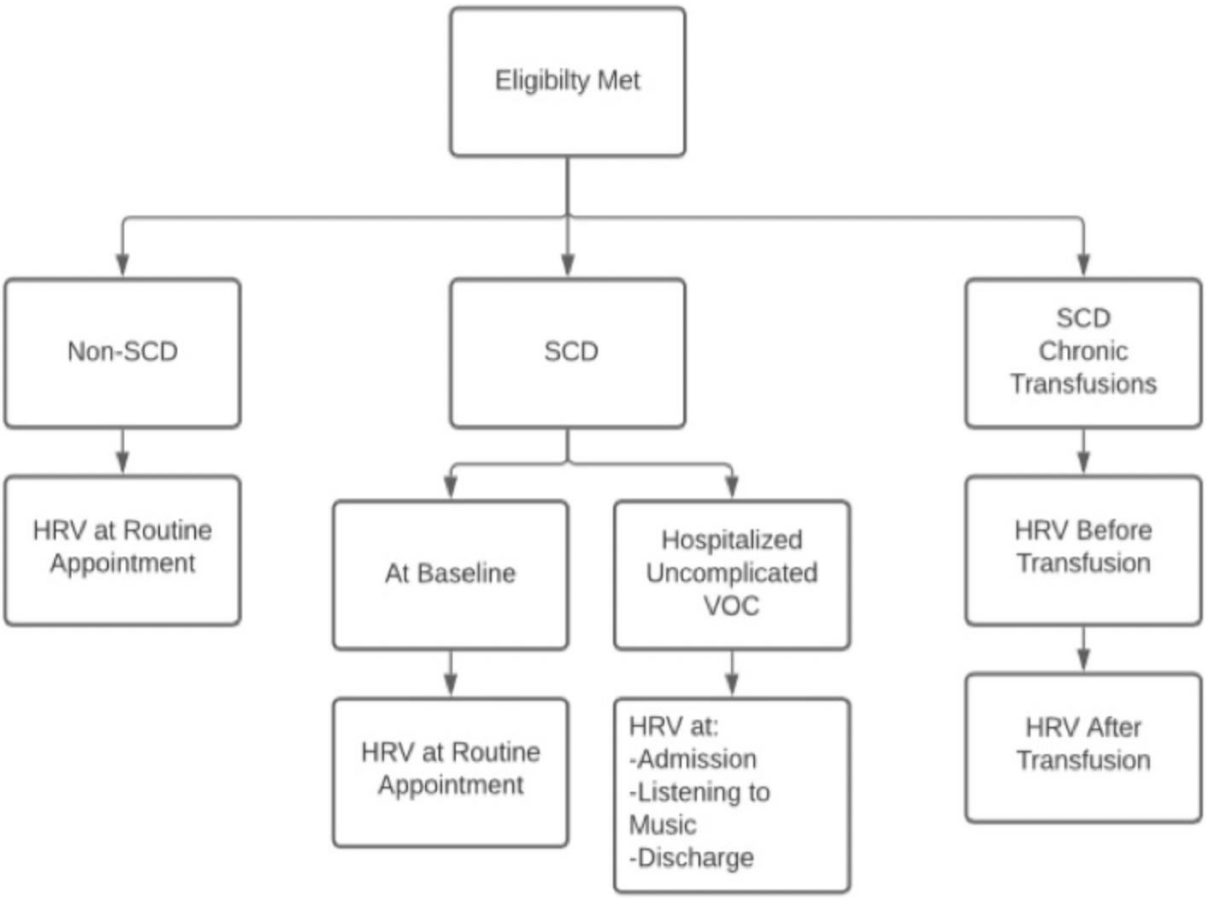
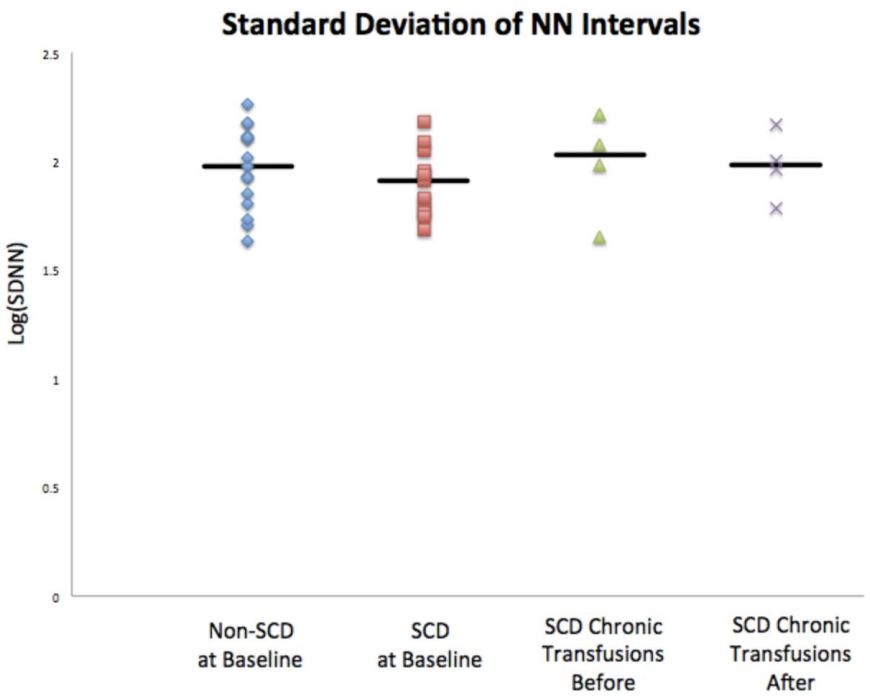
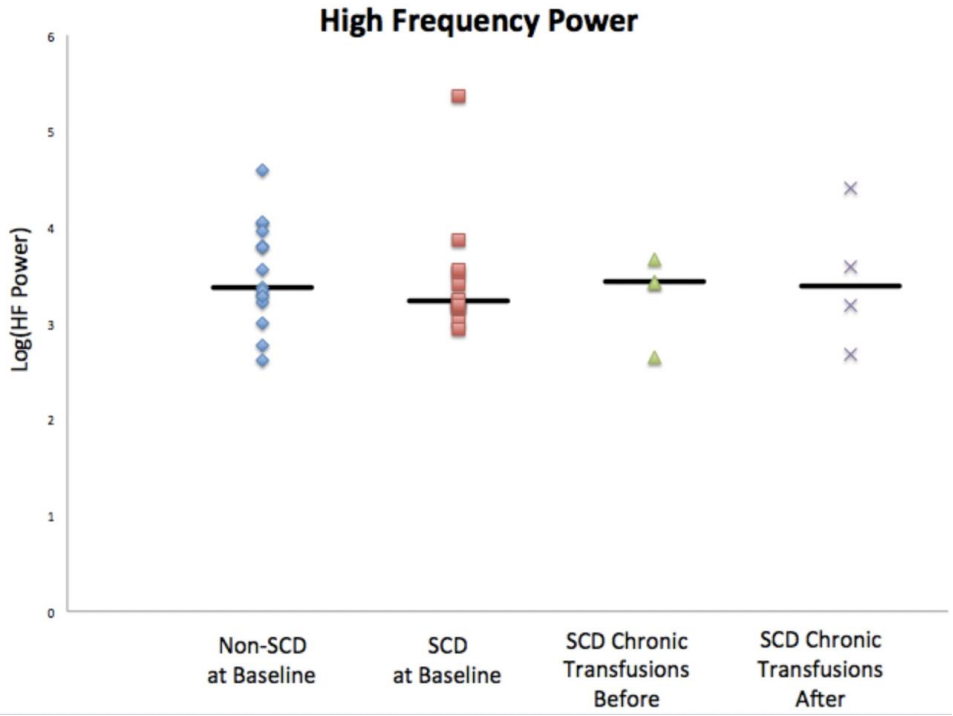


Figure 1
Design Schema



Graph 1
Logarithmic trend of the standard deviation of normal interval beats. The horizontal line depicts the median of each group.



Graph 2
Logarithmic trend high frequency power. The horizontal line depicts the median of each group.

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HOME-BASED STUDY OF VOCs USING A SICKLE CELL DISEASE ELECTRONIC PATIENT REPORTED OUTCOME

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Background: Vasocclusive painful crises (VOC) are a hallmark of sickle cell disease. Historically, the efficacy of drugs intended to reduce frequency of VOC's has been evaluated solely on the frequency of VOC that require a medical intervention, such as a visit to the emergency department, an infusion center and/or hospitalization. Several studies (ELIPSIS, PiSCES) have now demonstrated that the majority of painful events are managed in the home setting.1, 2 Therefore accepted measures to evaluate disease burden do not represent the totality of the patient experience and there remains a significant need to improve on existing clinical trial endpoints. Moreover, participation in clinical trials for patients with SCD faces numerous barriers, such as transportation difficulties, burden to patients/family/work time and recently, involves concerns about Covid-19 exposure. We aim to quantify daily pain episodes, and provide evidence supporting validation of the SCD ePRO, with a home based, remotely run protocol that uses an ePRO device and does not require visits to the hospital.

Methods: This is a prospective study characterizing VOC's in 2 cohorts of patients with HbSS or SB0 Thal >18 years of age. Group 1, "control" consists of up to 150 pts not on disease modifiers, and group 2," Hydroxyurea" includes 50 patients on a stable dose of HU. Patients will complete daily diary entries on an e-PRO device and have two blood draws, performed by phlebotomists that travel to the patient's home for evaluation of biomarkers. Patient's participation is approximately 7 months, all performed by remote procedures. Novel methods of patient centric recruitment include: access to a registry of patients with SCD, Facebook and Google ads, collaboration with community based groups and patients organizations.

Results: As of February 15, 2022, we have reviewed >200 medical records of patients that expressed interest in participating in clinical trials. We have received additional 113 inquiries from our online advertising. Main source of patients' so far recruitment have been private Facebook communities centered on SCD.

Discussion: Classical methods for measuring the rate of VOCs, based solely on utilization of medical resources, vastly underestimates the pain burden in SCD, therefore developing new validated end points that measure the totality of pain episodes, including home VOC is a priority. As enrollment in trials is often burdensome for patients with SCD, the removal of transportation and time barriers may represent a valid alternative to traditional hospital based recruitment.

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HYDROXYUREA REDUCES ADHESION RECEPTOR ACTIVATION ON SICKLE CELL RETICULOCYTES

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Background: Red cell endothelial interactions contribute to vaso-occlusive episodes (VOEs) by participating in a series of adhesive events mediated by cell surface adhesion molecules elevated in the sickle cell disease (SCD) microenvironment. Hydroxyurea (HU) is effective in decreasing the frequency of VOEs however, SCD patients continue to experience VOEs, thus alternative therapies are needed. Despite three recently FDA-approved therapies, efficacy data is limited; thus, HU remains the standard of care for SCD management. HU reduces VOEs, in part, by decreasing adhesion receptor expression and red cell-endothelial interactions however, there are major gaps in our knowledge of mechanisms involved in HU-mediated reduction in vaso-occlusive adhesive events. Lack of our understanding of mechanisms that promote VOEs, yet reduce VOEs in HU-treated patients, and effective drug alternatives, remain critical barriers to improving the care for SCD patients.

Very late antigen-4 (VLA-4, or a4b1 integrin), the best characterized adhesion receptor in SCD, is highly expressed in SCD patients with severe disease phenotypes and decreased in response to SCD-modifying therapy. VLA-4 is a transmembrane receptor that exists in multiple activation states and is functionally regulated by cell signaling pathways to activate binding affinity. Immature red blood cells (reticulocytes) and white blood cells (WBCs) highly express VLA-4 with increased adhesiveness to the vascular endothelium via vascular cell adhesion molecule-1 (VCAM-1). We have previously shown that HU significantly reduces VLA-4-mediated adhesion to VCAM-1 from whole blood (WB) SCD samples and isolated sickle reticulocytes within minutes (although not sickle WBCs) suggesting involvement of rapid, cell signaling pathways. The objective of this study was to determine whether HU reduces VLA-4-mediated adhesion by decreasing the active conformation of VLA-4 on sickle reticulocytes.

Methods: Whole blood (WB) samples were collected from SCD subjects presenting at benign clinic visits. Packed red blood cells (pRBCs) were isolated from WB samples by density-gradient centrifugation using Histopaque-1077 and reticulocytes from packed RBCs using Dynabead magnetic cell separation technology bound to a mouse anti-human CD71 primary antibody (Ab). CD71 is a marker of immature RBCs (reticulocytes) that disappears upon maturation. Isolated reticulocytes we prepared with and without physiologic concentrations of HU (50mcM, 30 minutes at 37°C) and/or 1mM Manganese (Mn+2).

Flow cytometric analyses were performed on a BD LSRII Flow Cytometer to measure VLA-4 activation (CD29+). Reticulocyte samples were also stained with an Ab cocktail consisting of a viability dye, mouse anti-human CD61 (platelets), mouse anti-human CD49d that recognizes the alpha chain of VLA-4, mouse anti-human CD29 that recognizes the β chain of VLA-4 and is involved in VLA-4 binding activity (HUTS-21), mouse anti-human CD45 (exclusive white blood cell marker), and mouse anti-human CD235a (exclusive red cell marker). CD29 expression on reticulocytes (CD61-CD45-CD235a+CD71+CD49d+) was measured as the mean fluorescence intensity (MFI) using CD29 fluorescence minus one (FMO) as a negative control.

Results: VLA-4 activation (CD49d+CD29+) was significantly increased on reticulocytes (CD61-CD235a+CD71+; p=0.03) isolated from pediatric SCD patients at benign (baseline) clinic visits. As we expected, active VLA-4 levels (CD49d+CD29+) were rapidly decreased on sickle reticulocytes (CD61-CD235a+CD71+) in response to in vitro HU treatment (from meanbaseline=0.1550 to meanHU=0.09).

Similarly, HU significantly reduced CD29+ levels on Mn+2-stimulated sickle reticulocytes ($p=0.02$). We are not proposing that Mn+2 and HU modulate VLA-4 through similar mechanisms however our experimental design allowed us to assess the application of using a conformation sensitive anti-CD29 HUTS-21 antibody to detect VLA-4 activation on sickle reticulocytes in an exaggerated environment in which Mn+2 is known to increase VLA-4 activation.

Conclusions: VLA-4-dependent adhesive interactions are rapidly and reversibly modulated by cell signaling pathways that alter VLA-4 binding independent of expression. Clinically, VLA-4 is highly expressed on reticulocytes (immature red cells) from SCD patients with frequent VOEs and decreased in HU-treated patients. The barriers to treating SCD can be addressed with a better understanding of HU mechanisms involved in reducing vaso-occlusive adhesive events. Our ongoing studies aim to elucidate rapid erythroid signaling pathways modulated by HU therapy in sickle reticulocytes using mass spectrometry (MS) to identify VLA-4 post-translational modifications and protein-protein interactions. Understanding these pathways may reveal potential targets for developing new therapies to improve the care for SCD patients.

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HYPOXIA-INDUCED SICKLING TO ASSAY SCD TREATMENTS AFFECTING HEMOGLOBIN POLYMERIZATION

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Affiliation: *Functional Fluidics Inc.*

Background: The clinical presentation of Sickle Cell Disease (SCD) shows wide phenotypic variation, including severe pain (acute and chronic), chronic anemia, acute chest syndrome, stroke, splenic and renal dysfunction with severity varying among patients. The pathology is caused by polymerization of hemoglobin S (HbS) that upon deoxygenation forms fibers within red blood cells (RBCs). The amount of sickling depends on the size of polymerized fraction and polymerization kinetics, which can be significantly affected e.g., by therapeutic fetal hemoglobin induction or hemoglobin-modifying drugs like voxelotor (Oxbryta®). The clinical response to these classes of SCD-modifying therapies may vary between individuals due to variables such as genetic polymorphisms, environmental and lifestyle factors. These therapies also chronically administered over a patient's lifetime to achieve the desired clinical effects, thus more immediate biomarker feedback on the therapeutic response would be beneficial. As a result, there is a need for a reliable and validated test to directly assess dynamic sickling kinetics in response to therapy. The aim of this work is to develop a hypoxia-induced RBC sickling assay as for use in drug development research, and to monitor response to SCD-modifying therapies that impact sickling kinetics (e.g., Hb modifiers, HbF inducers, pyruvate kinase activators, etc.).

Methods: Proprietary approach used protocatechuic acid/protocatechuate 3,4-dioxygenase (PCD) enzymatic oxygen scrubbing system was used for hypoxia induction in both quasi-equilibrium measurements and kinetic sickling assessment. This technology allows for induction of hypoxia of desired severity in a wide range of deoxygenation rates without the need for compressed gas cylinders or regulators. Hypoxia-induced sickling was observed over time in microfluidic channels with fractions of sickled RBC quantified by time-lapse photography. For in-vitro studies, blood samples from SCD subjects recruited under the IRB from Wayne State University. Samples were incubated with voxelotor (Selleckchem.com) when necessary.

Results: HbSS RBC sickling occurred in a single phase as an S-curve function. Treatment with voxelotor resulted in a significant delay in RBC sickling (HbS polymerization) followed by sickling at a much slower rate than for non-treated RBC. Also observed was a small (~10%) fraction of RBCs with sickling similar to that in unmodified RBCs. Increase in deoxygenation rate was linearly associated (r >0.97) with increased rate of RBC sickling for both treated and non-treated RBCs, and with decreased time to sickle (sickling delay). In the 2 to 12 minutes range of oxygen consumption and medium deoxygenation (controlled by PCD concentration; to an est. < 5% oxygen), compared to untreated samples, RBC incubated with voxelotor showed additional delay to sickling between 1 and 5 minutes with the follow up rates being between 35 and 20 percent that of untreated RBC. This observation is consistent with voxelotor-induced delayed sickling (consistent with delay in HbS polymerization) due to slower oxygen release from voxelotor-modified HbS, as opposed to delayed polymerization of deoxygenated HbS. Approximately 100% sickling occurred regardless of whether blood had been supplemented with voxelotor or not, indicating that voxelotor can delay, but not prevent sickling at lower oxygen tension and longer RBC exposure to hypoxia. Clinically, such extended delay and slower sickling rate could significantly reduce the number of sickled RBCs by allowing cells to flow through hypoxic environments before HbS polymerization and resultant sickling would occur.

Conclusions: These data demonstrate high potential of the approach to assess sickling propensity of RBC from SCD subjects with the ability to track drug-induced changes in delay of HbS polymerization and RBC morphology. Assessment of changes in HbS polymerization delay as a function of deoxygenation rates and severity of resultant hypoxia could enable more reliable predictions of clinical benefits of Hb-modifying drug treatments. Ongoing work aims to determine the optimal target pO2 for detection of changes in patient condition including changes due to treatment, ability to measure both equilibrium and kinetic polymerization and RBC morphology changes, detection of RBC subpopulations with different sickling propensity, and future integrating with simultaneous hemoximetry measurements.

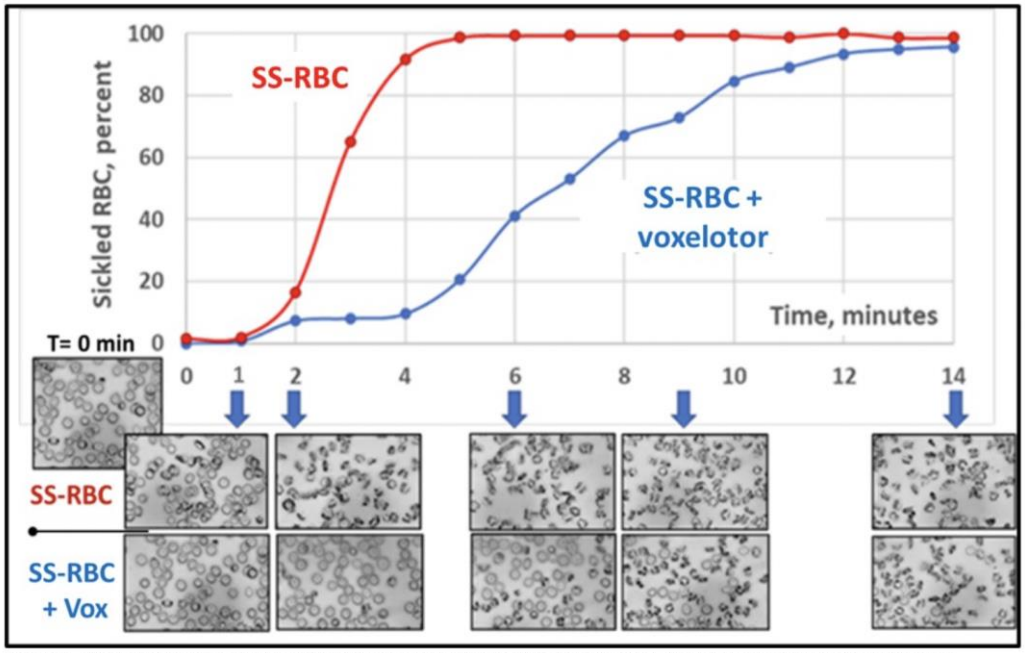

Figure 1. Microfluidic observation of in-vitro sickling for SS-RBC from a non-transfused SCD patient with and without sample incubation with voxelotor at concentration calculated to result in the prescribed 25-30% Hb occupancy. Hypoxia was induced using PCA/PCD system with sample deoxygenation to < 5% oxygen in about 4 minutes.

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IMPACT OF HYDROXYUREA USE ON THE SEVERITY OF SICKLE CELL CRISIS IN A HOSPITAL IN BROOKLYN

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Background: Sickle cell disease (SCD) is an inherited disorder that affects 1 in 365 Black or African American births in the US [1]. The most common challenge is excruciating pain. Hydroxyurea reduces pain crises by 50% and is recommended in infants (6 and 9 months) with symptomatic disease and all older patients. In our practice we have met with significant resistance to the use of hydroxyurea.

Methods: A retrospective review of EMR over a 4-year period was done. Inclusion criteria were SCD patients between the age of 0 to 21 years, followed at the NYP-BMH hematology clinic and on hydroxyurea for at least 6 months. Noncompliant or transfusion program patients within the previous six months of hydroxyurea use were excluded. Information up to 2-year pre and 2-year post initiation of hydroxyurea therapy were assessed. Data collection included frequency of hospital admissions, Length of Stay (LOS), visits to the Emergency Department (ED) for pain, narcotic use and acute chest syndrome (ACS).

Results: Out of 233 patients 44 had been prescribed hydroxyurea. 21 patients had a complete data for the analysis: SCD type (19 SS, 1 SC and 1 SO Arab type), Age (Mean 12.05 [range 3, 20] ± 5.73 SD), Gender (11 (52%) Males and 10 (48%) Females).

Hydroxyurea use decreased the average number of admissions from 2.67 to 1.33 ($p= 0.04$). There was no difference between males and females. Admissions decreased in the 3–5-year age group from 4.33 to 1 ($p= 0.03$). Admissions decreased in the treated 17+ age group from 2.67 to 1.33 ($p=0.03$). The overall average LOS, days on narcotics during admission, and fetal hemoglobin percentage were not statically significant.

There was a significant drop in ED visits for pain in the treated group from 2.15 to 1 ($p< 0.01$). Males showed the greatest difference, 2.8 to 1.3 ($p=0.01$) Females were affected in the 13+ group 1.57 to 0.57($p=0.04$) as were males in the 17+ age group 2.2 to 0.4 ($p=0.01$). The incidence of ACS decreased from 0.43 to 0.33 ($p< 0.01$) mostly in females in the 13+ age group ($p< 0.01$).

Conclusions: Admissions for VOC decreased with hydroxyurea especially in older children. There was a decrease in ED visits for pain and the incidence of ACS decreased with hydroxyurea use, especially in females in the 13+ age group. Overall LOS, fetal hemoglobin, and days on narcotics were not affected. Since this study involved a small sample size the results have to be interpreted with care.

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IMPLEMENTING MEANINGFUL CHANGES FOR SICKLE CELL DISEASE ACROSS A PUBLIC HOSPITAL SYSTEM

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Background: Sickle cell disease (SCD) is a complex chronic disease that affects predominantly racial and ethnic minorities. No other disease better exemplifies systemic racism in health care in the US. As stated by Keith Wailoo, a medical historian, SCD "is a microcosm of how issues of race, ethnicity, and identity come into conflict with issues of health care."

To address this, the Office of Minority Health commissioned the National Academy of Science, Engineering, and Medicine (NASEM) to develop a strategic plan and blueprint for action. Their report (www.nationalacademies.org/our-work/addressing-sickle-cell-disease-a-strategic-plan-and-blueprint-for-action), published in 2020, provides specific guidance on how we as a nation can tackle these disparities. The strategies they developed can also provide a broad framework for action at the local level. The problem for implementation is "priority." Despite the high per capita costs for hospital systems, the low number of SCD individuals makes the financial costs relatively insignificant to more prevalent chronic diseases. For African American and Hispanic communities, this is only a small part of the health disparities they face, and resources for advocacy are limited.

These barriers for implementation also offer opportunities. Given the low number of individuals with SCD, we can leverage the health equity movement to drive quality improvement across hospitals to eliminate disparities in healthcare quality for SCD.

As the nation's largest public hospital system and one of the largest providers of care for individuals living with SCD, what we do to improve the quality of care will make a difference. Through hospital leadership, our Health Equity Council, dedicated providers, and partnerships with SCD community-based organizations, we have prioritized SCD. Our objective is to summarize the specific actions steps we have taken to implement the SCD NASEM's report's eight broad strategies to address the health care inequities for individuals living with sickle cell disease at the local level.

Methods: We used the SCD NASEM report to frame the design and implementation of interventions across our public hospital system that will lead to meaningful improvement in the quality of care we provide.

Results: We summarize our implementation of a local action plan for SCD in the table below.

Conclusions: The SCD NASEM report provides a national strategy to "ensure the SCD population the same high-quality care that every American is entitled to." We used their model to implement a durable and comprehensive action plan for the NYC public hospital system.

Broad NASEM Strategies	Local Actions Implemented	Comments
A. Data	1. Created sickle cell disease registry in the electronic medical record (EMR) 2. Standardize EMR documentation through an SCD toolkit/navigator 3. Share nationally	1. This has been implemented and is critical for measuring improvement. 2. We are sharing our data with ASH, HRSA's Sickle Cell Treatment Demonstration Program, and the National Alliance of Sickle Cell Centers.
B. Organized systems of care assuring both clinical and non-clinical supportive services	1. Development of comprehensive lifespan centers 2. Formalize transitions of care and seamless transfer between our pediatric and adult centers 3. Partner with SCD-CBOs to provide patient support groups and community education 4. Integrate social determinants of health screening into routine care	We have established two comprehensive lifespan centers, documented cost-saving, and are working on expanding to 4 across NYC.
C. Strengthen evidence-based interventions and disease management and implement widespread efforts to monitor the quality of care	1. Implemented an SCD QI Project ECHO across our system to drive QI projects 2. Projects include increasing disease-modifying therapy, the transition of care, use of individualized pain plans in ED, and others	Project ECHO is a model for tele-mentoring that is useful for both clinical care and quality improvement (learning collaborative)
D. Increase the number of qualified providers	1) One year Sickle Cell Fellowship (PGY4) 2) Support for advance practice providers to participate in HRSA funded training (SAPPORT)	1) Our fellowship program was created at KCH with funds from the NYC Council 2) This is part of HRSA's NE region sickle cell treatment demonstration program
E. Improve SCD awareness and strengthen advocacy	1. Partner with SCD-CBOs for patient, staff, and community education 2. Implicit Bias training using SCD as an example 3. Support fundraising for SCD CBO's	This is in line with our mission
F. Address barriers in accessing current and pipeline therapies	1. Participate in clinical trials 2. Participate in the American Society of Hematology SCD-Clinical Network	All patients should have the opportunity to participate in research.
G. Implement efforts to advance understanding of the full impact of sickle cell trait on individuals and society	1. Build SC trait registry 2. Established a QI project to improve newborn screening trait education 3. Partner with CBOs to increase Blood Donation Drives in hospitals and communities of color to expand awareness of challenges in our patients with SCD finding compatible blood and accessing new treatment modalities	Available to researchers
H. Establish and fund a research agenda to inform effective programs and policies across the life span	We created the infrastructure to allow us to participate in research and policy evaluation (standardized documentation of discreet clinical data, registries, national collaboration with ASH)	Useful for grants and advising city and state policy

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INDIVIDUALIZED CARE PLANS: IMPLEMENTATION AND IMPACT ON LENGTH OF STAY

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Background: Sickle cell disease is known to affect approximately 100,000 individuals in the United States. Despite its relatively low incidence, over 1.6 billion dollars are spent per year in the US on the management of sickle cell complications, the majority of which is attributed to inpatient care. Further, patients often report suboptimal pain control and frustration with inconsistent pain management, the causation of which is multifactorial but includes clinician knowledge gaps and bias, discrepancies in provider comfort with analgesia, as well as delays in initiation of care. Numerous strategies to counteract this have been explored, including provider education, dedicated outpatient centers for sickle cell related pain management, and the institution of standardized system-wide algorithms for pain control. While a number of studies have found that patient controlled analgesia (PCA) use may significantly reduce duration of admission, there is as of yet no validated empiric regimen.

Methods: In an attempt to reduce both hospital length of stay and readmission rate, as well as to ensure pain management standardization and equity of care, our institution has piloted a systematic examination of the effectiveness of "Individualized Care Plans" (ICPs), wherein patients and their hematologists formulate specific pain management recommendations utilizing patient controlled analgesia (PCA), based upon each individual's unique needs, to be enacted upon admission for vaso-occlusive crisis. Over the past five months, data from 56 unique patients, over the course of 114 total hospital admissions at our 900 bed hospital has been collected following our initial intervention, which was education of hospitalists and residents on access and use of these ICPs.

At each admission, patients were categorized into those who 1) had an ICP in place and were started on the correct PCA dose; 2) patients who were started on an empiric PCA (either they had no ICP in place or they were started on one other than that recommended in the ICP); and 3) patients who were started on bolus dose pain medicine. Admissions were further stratified into uncomplicated admissions and admissions with severe complications, which included hypoxia requiring advanced ventilation (BiPap, intubation, etc.), exchange transfusion, surgical intervention, ICU admission, and severe sepsis.

Results: The primary outcome measured was the percentage of patients with ICPs who were immediately started on the correct plan upon admission. Secondary outcomes included duration of admission, total hospital days for each unique patient, readmission rate, and patient perceptions and satisfaction. Preliminary data has revealed that following intervention, an increasing proportion of patients have been initiated on their ICPs. At four months post-intervention, 88% of patients with ICPs were initiated on them immediately upon admission. Further, patients with admissions for uncomplicated vaso-occlusive crises initiated on the correct pain plan had an average admission length of 7.8 (SD 4.8) days, while those on empiric PCAs had mean duration 7.02 (SD 4.8) and those on bolus medication stayed for 8.4 (SD 3.09) days on average. Patients with ICPs had a clinically significant decreased readmission rate at 7 days as compared to those without (6.6% vs 20.5%), respectively, as well as fewer total days in hospital throughout the duration of the study (13.3 vs 20.3 days), respectively.

Conclusions: Our data indicates that hospitalist and house-staff education may be an effective way to

promote awareness on the implementation of ICP use. Further we found that patients on PCAs, regardless of ICP use or not, had moderately reduced average admission length, as has been demonstrated in prior studies. However, ICP initiation may confer benefit in reducing early readmission rate and thus, total inpatient days. Surveys gauging patient satisfaction, perception of care, and quality of life are presently being collected.

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KIDNEY TOXICITY OF DEFERASIROX: SOMETHING TO THINK ABOUT

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Background: Deferasirox use may lead to a dose dependent toxicity in certain patients. This is an important and common side effect of the medication. Acute kidney injury (AKI), proximal tubular damage, acute interstitial nephritis and proteinuria are some manifestations of kidney related deferasirox toxicity. We present a unique case of recurrent AKI requiring hemodialysis following deferasirox use.

Methods: 60 year-old African American female with sickle cell disease (Hemoglobin (Hb) -SS), type 2 diabetes mellitus, chronic kidney disease stage III B (baseline creatinine 1.3, glomerular filtration rate (gfr) 43) presented with four days of diarrhea and change in mental status. on admission labs were significant for Hb 6.6gm/dl, severe metabolic acidosis (serum bicarbonate 5mmool/l), elevated anion gap of 16 and oliguic AKI with serum BUN of 160mg/dl and creatinine of 10mg/dl. There was no lab or clinical evidence of Vaso-occlusive episode. Hemodialysis was initiated after no improvement in kidney function with administration of intravenous fluids. The patient's mental status and kidney function improved with 4 sessions of dialysis. At discharge, creatinine was 2.2mg/dl. 3 weeks later she presented with severe diarrhea and AKI (creatinine 6.5mg/dl) again. On further work up looking for a cause of the diarrhea and AKI it was noted that she was started on chelation treatment with deferasirox. This medication was held during her prior admission and the diarrhea had resolved. the had resumed the medication at home after discharge.

Results: On recognizing that deferasirox was the potential cause of the diarrhea and AKIit was promptly stopped with complete resolution of diarrhea. Aki also improved with fluids.

Conclusions: Diarrhea is a common side effect of deferasirox. However, kidney toxicity independent of the diarrhea causing volume depletion and pre-renal AKI is also a very common and serious side effect of deferasirox. Advanced age (>65 years), higher doses (>30 mg/kg per day), comorbidities such as diabetes, kidney disease and liver disease and concomitant use of non-steroidal anti-inflammatory medication are some of the common risk factors for kidney toxicity. Medication discontinuation is the only effective treatment. There is no role for steroids. Our patient had several risk factors for kidney toxicity. Appropriate patient selection and limiting the use in high risk patients is key.This case is a great illustration of a common yet avoidable side effect of deferasirox toxicity.

JSCDH-D-22-1238191

OVERVIEW OF THE VOXELOTOR POST-APPROVAL CLINICAL RESEARCH PROGRAM

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Background: Voxelotor, a sickle hemoglobin–polymerization inhibitor, is approved in the United States for the treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older, and in the European Union for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide. Efficacy and safety data from the randomized, placebo-controlled HOPE trial demonstrated the effectiveness and durability of voxelotor in increasing hemoglobin (Hb) levels and reducing markers of hemolysis in adults and adolescents. Support for the use of voxelotor in children aged 4 to < 12 years was provided by the open-label HOPE-KIDS 1 trial. Due to its mechanism of action, voxelotor has the potential to alter disease pathogenesis and mitigate disease-associated morbidity and mortality. Further research is needed to more clearly understand the role of voxelotor in preventing complications of SCD, reducing healthcare utilization, and improving quality of life. To establish a more thorough understanding of the impact of voxelotor on SCD, a wide-ranging post-approval clinical research program is underway and described herein.

Methods: Seven GBT-sponsored post-approval studies of voxelotor are either currently active or have completed, with results pending. Two observational studies, one retrospective (RETRO) and one prospective (PROSPECT), are evaluating the effect of voxelotor in real-world settings. ActIVe is an interventional, open-label, single-group study evaluating the effect of voxelotor on daily physical activity and sleep quality, as measured by a wrist-worn device, in patients with SCD and chronic, moderate anemia. The four remaining studies are randomized, placebo-controlled studies: the Neurocognitive Function study is assessing the treatment effects of voxelotor on neurocognitive function, as assessed by the National Institutes of Health Toolbox Cognition Module of executive abilities in children and adolescents with SCD; the Cerebral Hemodynamics study is evaluating the impact of voxelotor treatment on cerebral blood flow in adults and adolescents with SCD; HOPE-KIDS 2 is a post-approval confirmatory study evaluating the effect of voxelotor on transcranial Doppler flow velocity in pediatric patients with SCD; and RESOLVE is evaluating the effects of voxelotor on the resolution of leg ulcers in patients with SCD. An overview of patient populations, study arms, and key endpoints for each of the voxelotor post-approval studies is provided in the Table.

Results: RETRO recently completed data collection, and analyses are currently underway. Enrollment is ongoing for all other trials, with results expected to be released in late 2022 through 2029.

Conclusions: The current post-approval clinical research plan for voxelotor represents a methodologically diverse set of studies, mixing real-world evidence with randomized, controlled trials. The data generated from these studies are expected to further guide clinicians and patients regarding the clinical use of voxelotor for people with SCD.

Table. Overview of the Post-Approval Clinical Research Plan for Voxelotor

Clinical study	Patient population	Study arms	Key endpoints
Observational studies			
RETRO (NCT04930328) Location: United States Status: Completed Primary completion: Jan 2022	All patients with a documented SCD diagnosis (all genotypes) treated with voxelotor for ≥2 weeks	Voxelotor prescribed according to the USPI	• Hb level • Hemolysis measures • Significant SCD-related clinical events • HRU • HRQOL • Adverse events
PROSPECT (NCT04930445) Location: United States Status: Recruiting Est. primary completion: Dec 2028	All patients with a documented SCD diagnosis (all genotypes) treated with voxelotor	Voxelotor prescribed according to the USPI	• Hb level • Hemolysis measures • Significant SCD-related clinical events • HRU • HRQOL • Adverse events
Interventional studies			
ActIVe (NCT04400487) Location: United States Status: Active, not recruiting Est. primary completion: Nov 2022	• Aged 12-55 years • Confirmed SCD (HbSS, HbSβ^0) • Hb ≤8.0 g/dL at screening	Voxelotor 1500 mg	• Daily physical activity • Sleep quality (time, interruption, efficiency) • Nocturnal Hb oxygen saturation (%, dips >3% per hour) • Hb response (defined as the proportion of patients with a >1 g/dL increase in Hb)
Neurocognitive Function (NCT05228834) Location: United States and Europe Status: Recruiting Est. primary completion: Oct 2023	• Aged 8-17 years • Confirmed SCD (all genotypes)	• Voxelotor 1500 mg or weight-adjusted equivalent dose for patients aged <12 years + SOC • Matching placebo + SOC	**Primary** • Executive abilities composite score **Secondary** • Processing speed • Nonexecutive cognitive abilities • Hb level • Hemolysis measures
Cerebral Hemodynamics (NCT05228821) Location: United States Status: Recruiting Est. primary completion: Nov 2024	• Aged 12-30 years • Confirmed SCD (HbSS, HbSβ^0)	• Voxelotor 1500 mg + SOC • Matching placebo + SOC	**Primary** • CBF **Secondary** • Global OEF • Hb level • Regional CBF (gray and white matter) • Hemolysis measures
HOPE-KIDS 2[a] (NCT04218084) Location: International Status: Recruiting Est. primary completion: Mar 2026	• Aged 2-14 years • Confirmed SCD (HbSS, HbSβ^0) • TCD TAMMV arterial cerebral blood flow ≥170 to <200 cm/s during screening	• Voxelotor 1500 mg or weight-adjusted equivalent dose for patients aged <12 years • Matching placebo	**Primary** • Change in TCD FV (24 weeks) **Secondary** • Change in TCD FV (48 and 96 weeks) • Conversion to abnormal TCD FV • Reversion to normal TCD FV • TCD FV reduction ≥15 cm/s • Hb level • Hemolysis measures
RESOLVE (PACTR202102669041711) Location: Nigeria, Kenya, Brazil Status: Start-up Est. primary completion: Q1 2024	• Aged ≥12 years • Confirmed SCD (HbSS, HbSβ^0) • ≥1 cutaneous leg ulcer on the lower extremity meeting inclusion criteria	• Voxelotor 1500 mg + SOC • Matching placebo + SOC	**Primary** • Resolution of target ulcer(s) **Secondary** • Hb level • Hemolysis measures

[a]Post-approval confirmatory study.

CBF, cerebral blood flow; FV, flow velocity; Hb, hemoglobin; HbSβ^0, sickle cell beta zero thalassemia; HbSS, homozygous for SCD; HRQOL, health-related quality of life; HRU, healthcare resource utilization; OEF, oxygen extraction fraction; SCA, sickle cell anemia; SCD, sickle cell disease; SOC, standard of care; TAMMV, time-averaged maximum of the mean velocity; TCD, transcranial Doppler ultrasound; USPI, United States prescribing information.

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PROMOTING HEALTH EQUITY IN THE PUBLISHING INDUSTRY: 2 DECADES OF INVESTMENT IN SICKLE CELL

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Background: In a novel approach to health equity, HPC International, Inc. (HPC) was founded with a mission to fill a gap in the publishing industry: partnering with academic authors, medical experts, providers and community advocates for dissemination of high-quality health information for people suffering health disparities to live better lives. Initial subjects aimed primarily at African Americans, Hispanics and children included heart disease, sickle cell disease (SCD), cancer, and diabetes. SCD is an inherited blood disorder with multisystem complications that requires acute and chronic medical care plus extensive lifestyle accommodation – a topic that clearly benefits from public-private sector collaboration. SCD disproportionately affects people of color and is known for racial disparities in care and outcomes. SCD is classified as a rare disease in the USA and Europe, so the small market creates a challenging business model and limited funding for research.

Methods: Narrative description of social entrepreneurship and practicing conscious capitalism to advance health equity.

Results: HPC has experienced both success and challenges. Books were selected as the initial way to overcome the "digital divide" for underserved populations. Multiple editions of 6 SCD books were produced and distributed in the last two decades to non-profit associations, children's hospitals, clinics, universities, and health systems and are among the best-selling SCD education available today. Research and customer feedback led to more engaging formats that weave personal stories and pictures amidst the health facts, simplify complex terminology, and interactive workbooks and booklets. New revised editions are crucial for keeping the material accurate and trustworthy in the fast pace of medical progress.

HPC, in partnership with Klein Buendel, parents and medical experts, then began developing an app for teenagers with SCD. Using gaming technology, the app provides a safe, convenient tool for learning, tracking, and sharing information about SCD pain with medical providers and parents. NIH Small Business grants facilitated this effort in a classic form of public-private partnership. Market research, focus groups, surveys and interviews with teens, parents and clinical specialists were part of study recruitment. Challenges arose, however, with matching recruitment infrastructure to audience needs and were exacerbated by the COVID-19 pandemic.

Conclusions: HPC's mission to serve health equity has been proven successful for distributing educational print media to underserved and minority communities through public-private sector partnerships. In the newer market of distributing electronic apps to teens in these communities, HPC still faces challenges but looks to the success of its past book distribution model for how to overcome them. Overall, the experience of two decades shows that supporting health equity while staying in business is possible.

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REGIONAL ANESTHESIA DOES NOT REDUCE OPIOID REQUIREMENTS OR PAIN FOR SICKLE CELL PATIENTS

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Background: Sickle cell disease (SCD) is the most common congenital hemoglobinopathy in the United States and is associated with a high incidence of hip and knee osteonecrosis requiring total joint arthroplasty. We aimed to examine if regional anesthesia (neuraxial or peripheral) is associated with better postoperative pain control and lower opioid consumption in these patients.

Methods: Non-experimental retrospective chart reviews were conducted for all adult patients with a diagnosis of sickle cell disease who underwent hip arthroplasty procedures between 2014 and 2019 at one large, urban, academic hospital. Age, gender- and race- matched control patients, who did not have a sickle cell disease or trait diagnosis were also included. Perioperative pain scores and all administered analgesics were extracted from the electronic medical records, including the anesthesia record and post-operative reports.

Results: The final cohort of SCD patients consisted of 17 patients representing 23 procedures. The control cohort consisted of 45 age-, gender-, and race-matched patients who underwent hip arthroplasty procedures during the same period. The use of regional anesthesia was not associated with lower pain scores or MME requirements for either cohort of patients, except at 24-48 hours for control patients who demonstrated a higher post-op high pain NRS score with the use of regional anesthesia.

Conclusions: SCD patients require high doses of opioids for pain control after hip arthroplasty. Regional anesthesia does not improve pain scores or opioid requirements for patients with SCD or control counterparts.

Introduction: Over 30 million people worldwide have sickle cell disease (SCD), an inherited hematological disorder characterized by a missense mutation on the beta-globin gene (HbS). Deformed red blood cells can cause vaso-occlusion that may lead to acute or chronic pain, tissue ischemia, and infarction. Many individuals with SCD suffer from avascular necrosis (AVN) of their femoral and humeral heads, femoral condyles, and distal tibia. AVN of the femoral head is most common, with an incidence of 22%.[1] These patients may require hip replacement surgery at a young age (median 36 years).[2]

Chronic pain among SCD patients is common and primarily caused by vaso-occlusive crises (VOC), blockage of blood vessels by sickled red blood cells.[3] The mainstay of treatment for chronic and VOC pain in SCD patients is opioid therapy. Therefore, it is not uncommon that these patients develop significant opioid tolerance, which complicates their perioperative pain management. In addition, perioperative anxiety, stress from surgery with release of cytokines and inflammatory mediators, and perioperative respiratory complications including desaturation can promote sickling of erythrocytes and trigger VOC. These factors can lead to suboptimal analgesia. [4]

The approach for anesthetic management during orthopedic surgical procedures for SCD patients must include consideration for these complications and should minimize hypoxemia, hypercapnia, hypovolemia. Both regional and general anesthesia are options with varying degrees of safety and efficacy.[5] Despite extensive studies on the effects of different anesthetic modalities, nevertheless, the relative safety and benefits of general compared to regional anesthesia in SCD patients remains unclear.

Spinal anesthesia is suggested to be associated with lower complication rates in hip and knee surgeries in the general population.[6] A study comparing spinal to general anesthesia (GA) for patients undergoing total knee arthroplasties suggests that the use of spinal anesthesia demonstrated reduced risk of post-operative complications including reduced wound infections, blood transfusions, and overall complications.[7] In contrast, the Cooperative Study of Sickle Cell Disease showed that complications, such as acute chest syndrome, bleeding, and thrombosis were more common in patients receiving regional anesthesia.[8] There is significant controversy in the literature, indicating the need for further studies of the perioperative course in this population.

In this study, we aim to examine the prevalence, severity, and dynamics of postoperative pain as well as opioid requirements after total hip replacement in patients with SCD. Moreover, we aim to determine if regional anesthesia is associated with better analgesia and shorter hospital length of stay. We hypothesize that patients with SCD have significantly higher pain scores and opioid requirements than controls and, therefore, benefit from regional anesthesia.

Methods: The study was conducted at Boston Medical Center, a safety-net hospital with the largest population of patients with sickle cell disease in New England. The study protocol was approved by the Institutional Review Board. The requirement for written informed consent was waived given the retrospective nature of the study. There was no external funding for this study.

Patient Selection: All adult patients, between the ages of 18 and 89 years, with a confirmed diagnosis of SCD who underwent total hip arthroplasty (THA) procedures between 1/1/2014 and 1/1/2020 were enrolled. The control cohort consisted of age-, gender-, and race- matched patients who underwent the same procedure during the above period but did not have a diagnosis of SCD or trait. Exclusion criteria included age < 18 years or incomplete information or perioperative data.

Data Collection and outcome parameters: Demographic data, medical history, pre-admission medications, and diagnoses were extracted from each patient's electronic medical record. Vitals sings, including heart rate, blood pressure, oxygen saturation, respiratory rate, and laboratory values were collected. Clinical data were also extracted from electronic medical records, including the documented pain score on a numeric rating scale (NRS) from 0 (no pain) to 10 (worst pain). The highest recorded and average pain scores were recorded for the initial 8 hours after surgery, and between 8-16, 16-24, 24-48 and 48-72 hours postoperatively. The type of anesthesia (general or monitored anesthesia care) and use of regional anesthesia (neuraxial anesthesia and/or peripheral nerve block) were documented. As single-shot regional anesthesia is expected to mitigate pain primarily during the early postoperative period, we categorized the pain scores into two groups to create dichotomous variables for early (initial 24 hr) versus late (24-72 hr) postoperative time intervals.

The type and dose of opioids and other analgesics administered were documented. For comparability, Morphine Milligram Equivalents (MME) were calculated for each patient using the following conversion factors: morphine 1, fentanyl 100, hydromorphone 7, meperidine 0.15, sufentanil 1000, tramadol 0.1, nalbuphine 0.8, hydrocodone 0.12, buprenorphine 30, and codeine 0.1.

The primary outcomes were pain scores and MME administered post-operatively for patients with sickle cell disease and controls, with or without regional anesthesia. Other calculated variables include Charlson Comorbidity Index (CCI), duration of surgery, post-anesthesia care unit (PACU) length of stay (LOS), and hospital LOS. De-identified data were entered into a secure cloud-based database (RedCap) and used for analysis.

Statistical Analysis: Continuous variables are presented as mean ± SD if normally distributed or median with interquartile range (IQR). Categorical variables are presented as counts and percentages. Chi-square test was used for comparison of relative frequencies between the groups. For continuous

variables, repeated measures ANOVA was conducted if data was normally distributed, followed by Bonferroni correction for multiple comparisons. For all non-normally distributed variables, non-parametric multiple comparisons were performed using Friedman test followed by post-hoc analysis with Wilcoxon signed rank test. Statistical analyses were completed using SPSS Statistics 26 (IBM Corporation, Chicago, Ill.) and a two-sided significance level of < 0.05 was used for statistical inference.

Results: During the period of this study, 1260 total hip arthroplasty procedures were performed. Of these procedures, a total of 62 patients representing 68 procedures were included in the study. Seventeen of these patients had a diagnosis of sickle cell disease, representing 23 distinct procedures. The control cohort consisted of 45 age-, gender-, and race-matched patients (Figure 1). Average age of patients in the sickle cell cohort was 35.4 (+11.9) years and in the control cohort was 39 (+6.4) years. Males represented 43.5% (10/23) of the sickle cell cohort and 55.6% (25/45) of the control cohort. Other demographic characteristics and clinical data for each group of patients is summarized in Table 1.

Postoperative pain scores

Postoperative pain scores were not significantly different between SCD and control groups at any examined period (Tables 2(a) and 2(b)). MME requirements were significantly higher for patients with sickle cell disease at every time range (Table 2(c)).

Effect of Regional Anesthesia

Of the 23 surgeries for patients with sickle cell disease, 15 received general anesthesia (with no regional anesthesia) whereas 8 patients received regional with general or monitored anesthesia care (MAC). Similarly, of the 45 control patients, 29 received general anesthesia and 16 received regional anesthesia with or without general anesthesia. When comparing the effect of regional anesthesia on pain score outcome for control patients, only high NRS scores were significantly lower at 24-48 hours ($p < 0.038$)(Table 3 (a)). For patients with sickle cell disease, high VAS scores did not differ significantly at any time points with or without regional anesthesia (Table 3 (b)).

Morphine requirements did not significantly differ with the application of regional versus general anesthesia for patients with sickle cell disease for any time points, despite numerically lower MME requirements for patients that received regional anesthesia in both group of patients. For control patients, median morphine equivalent requirements were 0 at every time range for those patients who received regional anesthesia, except from 0-8 hours.

PACU and Hospital Length of Stay

While mean PACU length of stay was similar for both groups, 4.5 (+4.5) hours for SCD patients and 3.8 (+1.6) for controls, SCD patient's total hospital length of stay was more than twice as high as control counterparts (332 +331.6 hours vs 131 +184 hours) and was significantly higher ($p< 0.001$) (Table 4(a)). As demonstrated in Table 4 (b), regional anesthesia did not lead to a reduction in hospital or PACU length of stay in either SCD or control patients.

Discussion: The findings reported herein reveal that pain scores (both average and high) after THA do not significantly differ for patients with sickle cell disease compared to controls. However, post-operative opioid requirements are significantly higher for patients with SCD compared to the general population. Furthermore, regional anesthesia significantly improve pain scores for either group at any time point, except for high NRS scores from 24-48 hours in control patients. Post-operative MME requirements did not differ between groups with the use of regional anesthesia. While SCD patients and their control counterparts did not differ in their PACU length of stay, total hospital length of stay was twice as long for SCD patients. The use of regional anesthesia did not lead to decreased PACU or hospital length of stay in either groups.

Effective analgesia is salient in the perioperative management of sickle cell disease. Pain increases the risk of complications and may hinder early

mobilization, a requisite for good outcome after THA.[9] These findings can be explained by an inherent difference in the sensitivity to painful (thermal and/or mechanical) stimuli in patients with SCD.[10] Other studies identify differences in functional MRI in patients with SCD, which is suggestive of peripheral and central nervous system abnormalities. [11, 12]

High Morphine Requirements in Sickle Cell Disease Patients

Our finding that MME requirements were significantly higher for patients with SCD, is consistent with earlier report by Darbari et al., who demonstrated that patients with SCD show evidence of central sensitization to pain. [13, 14] In addition, due to their chronic pain and opioid requirements some patients may have developed a relative tolerance to opioids. Consequently, these patients require significantly higher opioid dose to control their postoperative pain. Pharmacokinetic parameters of most medications in patients with SCD are thought to be similar to those observed in the general population. However, as a result of increased hepatic and renal blood flow and an elevated glomerular filtration rate secondary to increased cardiac output, the clearance of morphine is almost three folds higher than patients without SCD.[15] Consequently, the half-life of morphine is reduced 3-10 fold in patients with SCD while the volume of distribution remains the same as patients without SCD.[15] The shorter half-life may also contribute to the higher morphine requirements in these patients.

The Effect of Regional Anesthesia on Post-operative Outcomes

In this study, we found that while regional anesthesia was associated with numerically reduced MME requirement in patients with SCD and controls, they did not reach statistical significance. These findings are in contrast to those reported by Min et al., who suggested significant advantages of regional over general anesthesia with regards to perioperative pain management in the general population.[16] Donauer et al. also reported decreased opioid requirements during the first 24 hours postoperatively in non-SCD patients who received regional anesthesia for THA requiring.[17] Although our study was not powered to explore the etiology of this difference in response to regional anesthesia in the SCD patients, we suspect that their sustained opioid needs despite regional anesthesia may be related to their increased pain sensitivity and relative opioid tolerance, as described above.

Studies report chronic pain occurs in 7-23% of patients following THA. Since high perioperative, pain is associated with the risk of developing chronic postoperative pain [18-20], appropriate and timely pain control is of particular importance in the SCD population, many of whom are at risk for debilitating chronic pain syndromes.

Another important finding in our study was the significantly longer postoperative length of stay following THA in patients with SCD, when compared to controls. This is consistent with the findings by Kamble et al., who reported patients with SCD had significantly longer LOS following joint replacement and incurred higher cost when compared to controls.[21] In general, regional anesthesia is associated with reduced LOS compared to general anesthesia following THA. [22, 23] However, our study was unable to validate these findings in sickle cell patients as PACU and hospital length of stay were independent of regional anesthesia use.

In summary, patients with SCD who were admitted for THA and total knee replacement experienced required significantly higher MME for perioperative pain control. Despite other studies having presented evidence for regional anesthesia use in patients with sickle cell disease; our study did not show an increased benefit.

A potential consideration of our finding that regional anesthesia does not provide any additional benefits for sickle cell patients is that all patients in our study (both sickle cell and control patients) were treated with single shot nerve blocks or spinal anesthesia that lacked prolonged pain control effects. A longer acting nerve block using liposomal bupivacaine may be more effective in lowering post-operative pain scores and opioid requirements in this population.[24]

However, the therapeutic impact of epidurals for reduction in morphine requirements is still ambiguous with one large study of over 6000 opioid-naïve patients showing that peri-operative epidural use is not protective against long-term opioid usage in patients undergoing abdominal surgery. [25]

Limitations of this study include the relatively small sample size of the population, i.e. patients with sickle cell disease who underwent total hip arthroplasty procedures, which may not have the statistical power to expose small differences resulting in a type II error. Secondly, the outcomes are based on retrospective observational data. Given the lack of randomization of anesthetic groups, results are subject to biases and confounders that may have influenced the results. Further large-scale multi-center randomized trials are needed to further explore the effect of anesthesia on perioperative pain scores, pain management, and surgical outcomes.

Conclusion: Patients with SCD require significantly higher opioid doses following total hip arthroplasties. Regional anesthesia did not demonstrate superior outcomes as it relates to post-operative pain scores and the MME requirements in this population. Secondary outcomes such as PACU and hospital length of stay were also unaffected by the type of anesthetic used.

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Variables	SCD (N= 23)	Control (N = 45)	P-value
Age	35.4 (11.9)	39 (6.4)	0.20
Biological Sex			0.30
Male	10	25	
Female	13	19	
BMI	25.8 (6)	31.2 (9.8)	0.01
Race			0.04
Black/ African American	21	45	
Unknown	2	0	
Ethnicity			0.20
Hispanic /Latino	3	2	
Not Hispanic	20	43	
Comorbs			
ADHD	0	2	0.30
Depression	6	16	0.43
Anxiety	6	12	0.96
Asthma	6	6	0.19
HIV	1	3	0.68
Intra Op			0.03
General	17	33	
MAC	2	11	
Fentanyl Administered	395	219.26	0.12
TXA (Yes or No)	16	41	0.01
TXA (Dosage in mg)	739.1 (540.8)	1122 (331.3)	0.004
HgB pre op (g/dL)	9.9 (1.2)	12.1 (1.7)	< 0.001
HgB post op (g/dL)	8.2 (1)	10.3 (1.6)	< 0.001
Blood loss (mL)	510.5 (235.3)	416 (366.2)	0.23
Pre-op Transfusion (mL)	403.3 (385.7)	15.56 (104.3)	< 0.001
Post-op Transfusion (mL)	517.4 (470.4)	70 (231.2)	< 0.001

Table 1: Baseline Characteristics represented as count or mean (SD).

	Mean Values (SD)		P values
Post-op High NRS	SCD	Control	
0- 8 hrs	7.25 (2.70)	7.00 (0.85)	1
8- 16 hrs	8.00 (2.86)	6.40 (1.37)	0.831
16- 24 hrs	7.65 (1.69)	6.20 (1.57)	0.071
24- 48 hrs	7.70 (1.91)	6.25 (1.44)	0.074
48- 72 hrs	6.29 (2.81)	6.64 (1.21)	1

Table 2 (a): Mean (SD) post-op High NRS Scores for SCD and control patients.

	Mean Values (SD)		P values
Post-op Average NRS	SCD	Control	
0- 8 hrs	7.25 (2.70)	6.89 (0.85)	1
8- 16 hrs	7.94 (2.86)	5.66 (1.37)	0.145
16- 24 hrs	7.62 (1.69)	6.33 (1.57)	0.149
24- 48 hrs	7.58 (1.91)	6.55 (1.44)	0.399
48- 72 hrs	6.24 (1.81)	6.06 (1.21)	1

Table 2 (b): Mean (SD) post-op Average NRS Scores for SCD and control patients.

	Mean Values (SD)		P values
MME	SCD	Control	
0- 8 hrs	641 (4- 4935)	100 (0- 606)	*< 0.001
8- 16 hrs	416 (0- 3615)	12.5 (0- 96)	*0.0005
16- 24 hrs	646 2 (0-4668)	12.7 (0- 160)	*0.0006
24- 48 hrs	2121 (0- 14640)	74.2 (0- 1690)	0.0002
48- 72 hrs	1933 (0- 14520)	48.3 (0- 875)	**< 0.0001

Table 2 (c): Mean (SD) post-op MME requirements for SCD and control patients.

SCD	Mean Values (SD)		P values
Post-op High NRS	Regional Anesthesia	General Anesthesia Only	
0- 8 hrs	8.00 (1.16)	6.88 (3.22)	0.794
8- 16 hrs	7.00 (5.20)	8.23 (2.28)	0.888
16- 24 hrs	7.33 (1.21)	7.79 (1.93)	0.476
24- 48 hrs	6.50 (1.87)	8.21 (1.53)	0.054
48- 72 hrs	5.43 (2.57)	6.71 (2.79)	0.228
Post-op Average NRS			
0- 8 hrs	8.00 (1.16)	6.88 (3.22)	0.794
8- 16 hrs	7.00 (5.20)	8.15 (2.34)	0.888
16- 24 hrs	7.33 (1.21)	7.75 (1.89)	0.476
24- 48 hrs	6.25 (2.02)	8.14 (1.61)	0.060
48- 72 hrs	5.29 (2.81)	6.71 (1.79)	0.228

Table 3 (a): Mean (SD) high and average NRS scores for sickle cell patients who either received regional anesthetics and those who did not.

Controls	Mean Values (SD)		P values
Post-op High NRS	Regional Anesthesia	General Anesthesia Only	
0- 8 hrs	8.25 (2.36)	5.75 (2.36)	0.189
8- 16 hrs	6.00 (1.83)	8.00 (.)	0.468
16- 24 hrs	6.57 (2.34)	6.00 (2.86)	0.658
24- 48 hrs	7.27 (2.20)	5.59 (1.94)	*0.038
48- 72 hrs	7.00 (1.58)	6.34 (0.82)	0.508
Post-op Average NRS			
0- 8 hrs	6.96 (0.90)	6.78 (1.11)	0.800
8- 16 hrs	5.54 (1.55)	6.16 (.)	0.800
16- 24 hrs	6.63 (1.85)	5.94 (1.16)	0.510
24- 48 hrs	6.93 (1.54)	6.12 (1.28)	0.351
48- 72 hrs	6.50 (1.29)	5.60 (1.11)	0.378

Table 3 (b): Mean (SD) high and average NRS scores for control patients who either received regional anesthetics and those who did not.

	Median Values (Range)		P values
SCD MME	Regional Anesthesia	General Anesthesia Only	
0- 8 hrs	196 (4-1148)	240 (55-4935)	0.680
8- 16 hrs	18 (4- 159)	97.5 (0-3615)	0.758
16- 24 hrs	48 (0- 110)	60 (0- 4668)	0.462
24- 48 hrs	53 (7.5- 8520)	163 (0- 14640)	0.338
48- 72 hrs	45 (0-8550)	134 (21- 14520)	0.185
Controls MME			
0- 8 hrs	17 (0- 323)	26.2 (0- 606)	0.972
8- 16 hrs	0 (0- 45)	0 (0- 96)	0.583
16- 24 hrs	0 (0- 45)	5.6 (0- 160)	0.974
24- 48 hrs	0 (0-1690)	15 (0- 320)	0.605
48- 72 hrs	0 (0-875)	0 (0- 400)	0.331

Table 3 (c): Median MME Values for SCD and control patients who either received regional anesthetics and those who did not.

Fig 1: Consort diagram detailing selection of sickle cell disease and control groups.

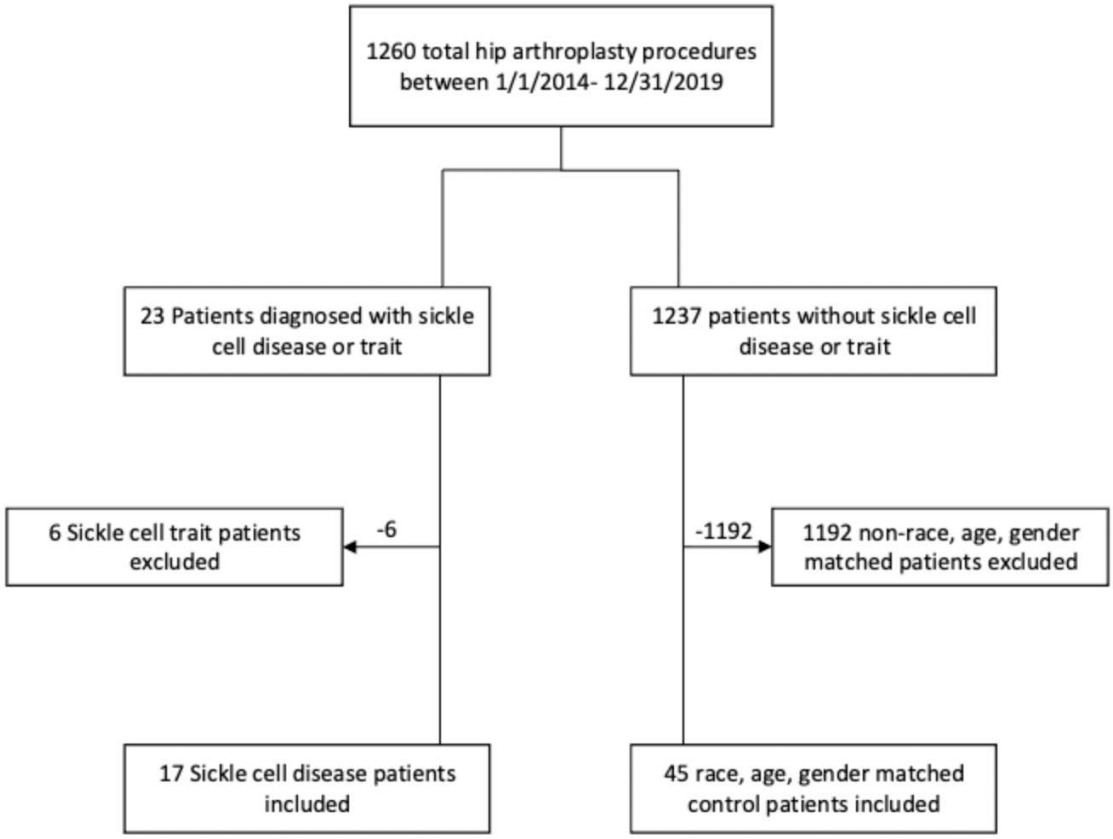
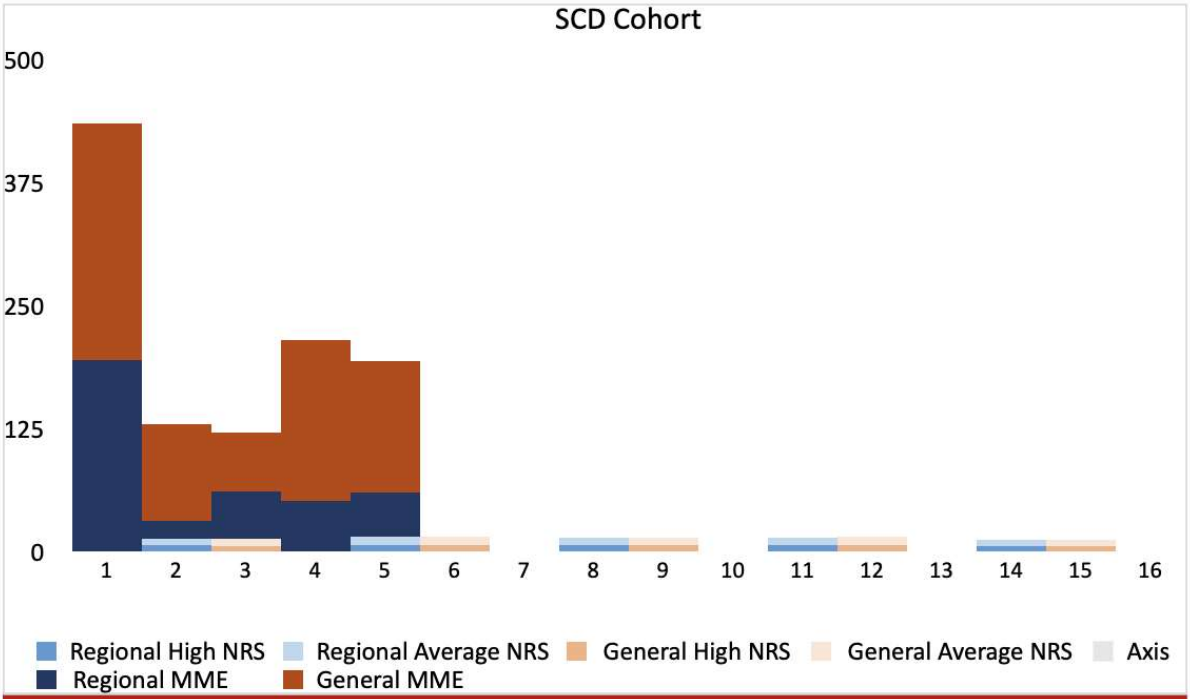
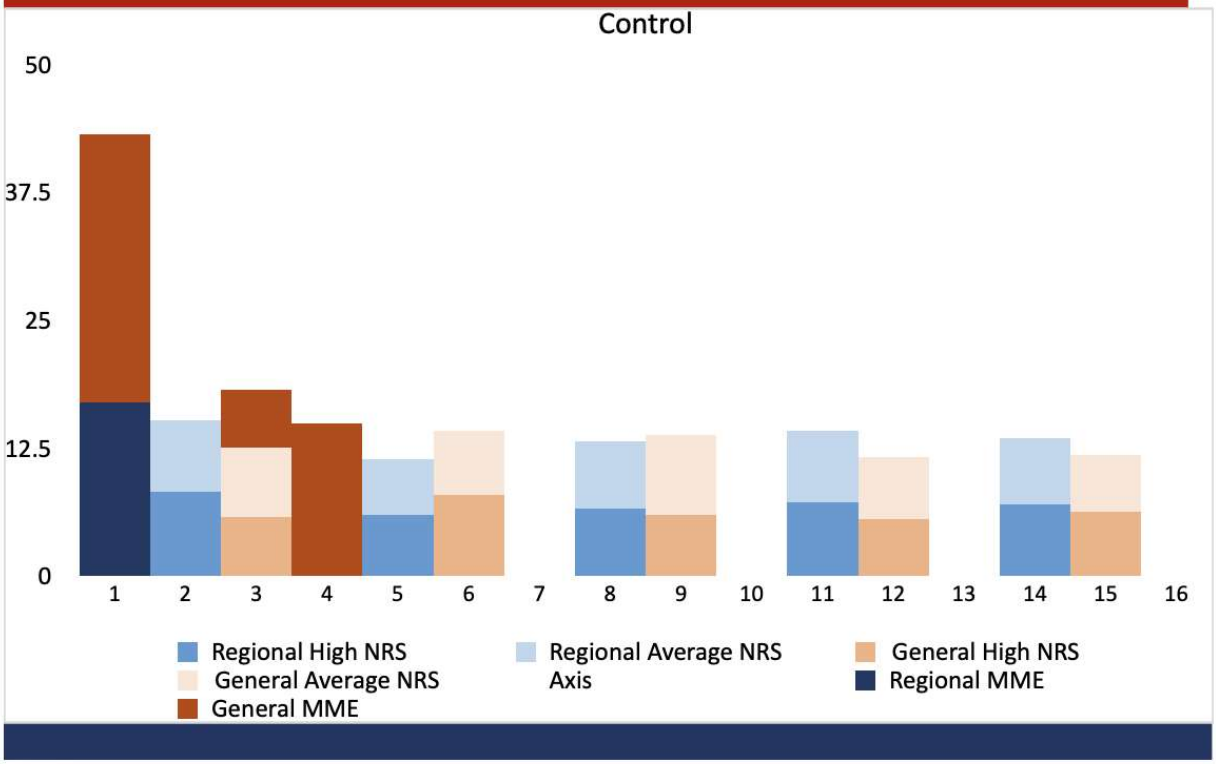


Fig 2(a) and 2(b): Mean high NRS and average NRS scores (bar graphs) along with MME requirements for both SCD (Fig 2 (a)) and control patients (Fig 2 (b)).





JSCDH-D-22-1274229

SILENT CEREBRAL ISCHEMIA IN ADULT PATIENTS WITH SICKLE CELL DISEASE: A RETROSPECTIVE STUDY

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Background: Sickle cell disease (SCD) can lead to complications including stroke, acute chest syndrome, pulmonary hypertension, priapism and blindness. Central Nervous system complications of SCD can include Silent cerebral infarcts (SCI), strokes, seizures and Moyamoya syndrome. SCI is defined as abnormal magnetic resonance imaging (MRI) of the brain in the setting of a normal neurologic examination without a history or physical findings associated with an overt stroke. SCI occur more often in patients with Hb SS and HBS beta-zero thalassemia genotype. In Silent Cerebral Infarct Multi-Center Clinical trial (SIT), lower baseline hemoglobin concentration, higher baseline systolic blood pressure and male sex were significantly associated with increased risk of SCI. Neurological complications in SCD is under-diagnosed and our study is investigating the incidence of incidental cerebral ischemic or hemorrhagic findings based on brain imaging in adult SCD patients without stroke diagnosis.

Methods: In this retrospective study we reviewed 200 adult patients at our Comprehensive Sickle Cell Center. We looked at the incidence of documented stroke and other complications in SCD patients. We reviewed the hospital records of SCD patients for any incidental brain imaging (MRI brain or Computed Tomography brain) findings, done as inpatient or in the emergency room as part of hospital visits.

Results: Out of the 200 patients, 31 patients had documented stroke. On the review of other 169 patients, 36 patients had Computed Tomography (CT) brain, 4 patients had MRI brain and 15 patients had both MRI and CT of brain. Out of the 55 patients with brain imaging, 17 patients had incidental neurological finding- 15 patients with ischemic changes, 1 patient with petechial hemorrhage and 1 patient with both ischemic and hemorrhagic findings. 12 out of 19 patients with MRI brain had significant incidental neurological findings and 10 out of 46 patients with CT head had incidental findings. So, in our study 63% of MRI brain had significant incidental neurological finding when compared to 19% of CT brain. 114 SCD patients have no brain imaging, and incidence of SCI could be much higher if they also had brain imaging.

Conclusions: This study shows that the true burden of neurological complications in SCD patients is under-diagnosed and MRI brain is superior to CT brain in detecting neurological complications in SCD patients. In our study, out of 17 patients with incidental neurological finding, 13 patients had HBSS genotype, 3 patients had HBSC genotype and 1 patient had HBS beta-zero thalassemia genotype. 10 patients were male and 7 were female. Among patients with SCI, there is risk of new SCI or overt strokes when compared to patients without SCI. SCI is associated with decreased intellectual abilities and poor academic achievement. SIT showed that regular blood-transfusion significantly reduced the recurrence of cerebral infarct in children with SCI. Finding of SCI in adults also warrants consideration for follow up brain imaging, neurology consultation and discussion of treatment modalities like chronic blood transfusion regimen. Because of high incidence of neurological complications in SCD patients, routine screening with MRI brain should be considered in SCD patients.

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SUBSTANCE USE DISORDERS IN A POPULATION-BASED SAMPLE OF ADULTS WITH SICKLE CELL DISEASE

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Background: Pain is the clinical hallmark of sickle cell disease (SCD), both acute pain resulting from vaso-occlusive crises and chronic pain. Treatment guidelines outlined by the NHLBI include prescribing opioid drugs for mild-to-severe pain, which raises the question of whether substance abuse, either drug or alcohol, is an issue in the SCD population. This study examined substance use in Black patients with SCD compared to Blacks with other health conditions or without health conditions. A secondary goal of this study was to evaluate whether risk factors such as socioeconomic status (SES) and mental health were associated with substance use in SCD.

Methods: Data from a population representative sample of Blacks with SCD, with other conditions, and without health conditions were obtained from the National Survey of American Life (NSAL) database. Two-sample t-tests, Wilcoxon Rank Sum, and Fisher Exact Tests, were conducted to assess differences between study groups. One-Way ANOVA, Kruskal Wallis, and Chi-square tests examined the relationship between groups and substance use diagnoses. Finally, hierarchical models were created controlling for covariate groups that were determined a priori based on prior literature. Alpha level was set at $p< 0.05$.

Results: This study included 4,846 participants, 63.5% female, with a mean age of 42.3 years (±16 years). They were categorized into one of the following, mutually exclusive groups: “SCD” (n=85), conditions other than SCD (“other condition”; n=3,024) or those without a health condition (“no condition”; n=1737). Controlling for age and sex, the odds of a substance abuse disorder among individuals with SCD is 2.165 times greater odds (95% CI 1.2-3.906; p=0.01) compared to black adults with other conditions and 4.39 times greater (95% CI 2.387-8.065; $p< 0.001$) compared to black adults with no condition. These differences in substance abuse were primarily accounted for by a higher prevalence of alcohol abuse among Blacks with SCD compared to those with other conditions or no conditions. Prevalence of drug abuse, however, did not differ between those with SCD and those with other conditions.

Conclusions: Risk for opioid and other drug abuse is not significantly higher among adults with SCD compared to other black adults living with a health condition. Further research is needed to determine whether increased risk for alcohol abuse among adults with SCD is related to inadequate pain management. More large scale, population-based studies of this kind will be needed to understand factors that increase substance use in chronic illness and provide the necessary data to fully address medical providers hesitancy to prescribe opioids to patients with SCD related pain.

Measure	Sickle Cell (n=85)	Other Conditions (n=3024)	No Condition (n=1737)	Total (n=4846)	P-Value
Age, mean (SD)	40 ± 13.9	46.9 ± 16.3	34.5 ± 12.1	42.3 ± 16	<0.001
Household Income, Median [IQR]	17000 (10000, 37000)	25000 (12163.8, 44348)	30000 (17500, 48176)	27000 (14000, 45000)	<0.001
Education > 11 years	60 (70.6%)	2200 (72.8%)	1436 (82.7%)	3817 (76.2%)	<0.001
Married/Cohabiting	26 (30.6%)	1106 (36.6%)	653 (37.6%)	1834 (36.7%)	0.382
Divorced/Separated/Widowed	25 (29.4%)	1093 (36.2%)	323 (18.6%)	1501 (30%)	<0.001
Never Married	34 (40%)	823 (27.2%)	761 (43.8%)	1665 (33.3%)	<0.001
Employed	51 (60%)	1887 (62.4%)	1364 (78.5%)	3401 (68%)	<0.001
Unemployed	10 (11.8%)	273 (9%)	204 (11.7%)	499 (10%)	0.01
Not in Labor Force	24 (28.2%)	862 (28.5%)	169 (9.7%)	1098 (22%)	<0.001
Children, Median [IQR]	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	<0.001
Poverty Index, Median [IQR]	1 (1, 3)	2 (1, 3)	2 (1, 4)	2 (1, 4)	<0.001
Overall Health, Median [IQR]	3 (2, 4)	3 (2, 4)	4 (3, 5)	4 (3, 4)	<0.001
Substance Use (Drug or Alcohol)	15 (17.6%)	300 (10%)	132 (7.6%)	447 (9.3%)	<0.001
Drug Abuse	6 (7.1%)	157 (5.2%)	87 (5%)	250 (5.2%)	0.708
Alcohol Abuse	14 (16.5%)	262 (8.7%)	104 (6%)	380 (7.9%)	<0.001
Prescription Abuse	7 (8.2%)	176 (5.8%)	76 (4.4%)	259 (5.4%)	0.052

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Background: Approximately 100,000 people in the US are living with Sickle Cell Disease (SCD). SCD is a debilitating condition that leads to acute pain from vaso-occlusive crisis (VOC) that is severe as childbirth, postoperative and terminal cancer pain. Clinical guidelines recommend rapid treatment of pain for patients with VOC. Adherence to pain management guidelines are low among healthcare providers (HCPs) treating patients with SCD and delays in treatment are impacted by implicit biases. The literature shows that patients with SCD experiencing acute pain wait 70-75 minutes longer on average than the guidelines recommend. Additionally, patients with SCD wait 50% longer to see an emergency room(ED) physician than patients with long bone fractures after adjusting for race and triage priority. Training HCPs on cultural humility has been identified as a potential solution in addressing implicit biases.

Methods: A one group posttest quasi-experimental design was used to evaluate a live, virtual 2-hour certified nurse education (CNE) program that was hosted by Advancing Sickle Advocacy Project (ASAP), a community based organization (CBO) dedicated to raising awareness and providing social services for people with SCD and their caregivers in South Florida. The CNE program used a combined lecture and panel format. The lecture was used to deliver didactic material on SCD pathophysiology, complications, treatment and clinical guidelines. It was also used to share information on how implicit biases affect health outcomes and results in health disparities among people with SCD trying to obtain treatment for acute pain. The panel presentation consisted of healthcare providers, caregivers and patients with SCD sharing their experiences on cultural humility, best clinical practices and instances of discriminatory practices in the healthcare setting. HCP's and pre-licensure healthcare professionals were recruited from healthcare organizations, professional nursing organizations and colleges and universities around South Florida. The event was also shared with non-healthcare professionals, patients and caregivers of people with SCD. There were a total of 201 participants who attended the live event.

Results: A total of 68 participants completed the post evaluation survey, the profession type ranged from 35% registered nurses, 21% healthcare professionals in training, 15% licensed practical nurses, 12% certified nursing assistants, 10% advanced practice registered nurses and 7% other or non-healthcare related professionals. On average, participants scored 83% on questions related to SCD epidemiology, pathophysiology, treatment, health disparities and implicit biases. An average of 91% of participants reported that learning and educational outcomes were met, 94% agreed the information presented improved knowledge and skills, 91% responded that information presented new ideas expected to use in practice and 94% agreed the teaching strategies used were appropriate.

Conclusions: SCD is a debilitating, severe disorder that results in acute pain that is as severe as childbirth, postoperative and terminal cancer pain. However, when patients with SCD try to obtain treatment for acute pain and VOC they often experience delays in pain medication and inadequate treatment. People with SCD wait an average of 70-75 minutes longer than the guidelines recommend to receive analgesia. They also wait 50% longer to see an ED provider than other acute conditions that result in severe pain. These healthcare disparities are driven by implicit biases. A live virtual CNE program is effective in teaching concepts on SCD and implicit biases. These programs can be used to address implicit biases that impact health outcomes and cause the health disparities seen in people with SCD

with acute pain in outpatient and inpatient healthcare settings. Therefore, educators in healthcare and academia should include implicit bias training in their curriculum and continuing education programs relating to SCD. Healthcare administrators should incorporate policies mandating training for HCP's who care for patients with SCD and develop outcome measures to evaluate healthcare quality and equity for patients with SCD. Finally, given the limitations of our study related to the small sample size and the use of a posttest design without a comparison group, additional research should focus on more rigorous evaluation of educational interventions that would make the results more generalizable. Researchers could validate our findings on the best teaching strategies to develop cultural humility in HCP's caring for patients with SCD.

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THE PREFERRED PATIENT PROFILE: WHAT SICKLE CELL PATIENTS WANT PROVIDERS TO KNOW ABOUT THEM

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Background: Pain is a hallmark of sickle cell disease (SCD). Similar to an Asthma Action Plan, we created an individualized action plan for pain in the electronic medical record. This form allows the hematologist and the patient to develop a patient-specific management care plan for mild, moderate, and severe pain for patient reference at home. The plan also serves as a reference for Emergency Department (ED) providers when the patient presents with a vaso-occlusive crisis not manageable at home.

We believe that an SCD patient in pain needs a kind and gentle, humanistic approach and included a section called the patient's preferred profile as part of the severe pain plan. This is a small blurb about the patient, written in their own words, to help the ED care team to approach the patient as an individual with some familiarity of their interests.

Also, believing "nothing about me, without me," we reached out to an SCD community-based organization to see what their members thought about the patient's preferred profile and what types of personal information they wanted the ED care team to know about them.

Methods: The SCD CBO did a phone survey of 20 members with SCD. In addition, two members were selected for a 1-hour focus group via WebEx using questions approved by our IRB. The first and last authors analyzed the transcript for common themes.

Results: When asked about the preferred patient profile, all thought it was important to include. As to what to include in the profile: family (e.g., "father of 2"), job/vocation (e.g. "high school senior" "church organist" "community advocate," hobbies/sports (e.g., "guitarist" "dance team in college"), and personality traits (e.g., "good friend, very funny, a little sarcastic"), self-identified descriptors of their person, were seen as important.

The focus group gave similar answers but with more clarifying insight. During the discussion participants discussed their experience of bias and categorization, "you don't look sick" and "they see me as trouble and drug seeking." In response to using the profile, they agreed it should be included. At first the concept was approached with skepticism, "they know I am a doctor" and "many know me from the community," but the categorization and bias in treatment still occurred. As the conversation proceeded and questions answered, a recognition that their person and voice were missing from their medical chart grew, "I hope this can help" and "now I am bought in." They thought it will be prescriptive for the future and "change young minds."

As for the type of information to share they discussed jobs, family, interests, and personality. At the end of the interview, they concluded that what they wanted the providers to know is "they have a life outside the ED," and they are coming to the ED to get help so they can get "back to their life."

Conclusions: Including a preferred patient profile and individualized pain action plan in the EMR offers an opportunity for personalized and humanistic documentation. The key information patients want the ED care team to know is they have a life outside of sickle cell disease.

JSCDH-D-22-1224816

TXA DOES NOT CONFER ADDITIONAL RISKS TO PATIENTS WITH SCD UNDERGOING ARTHROPLASTY

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Background: Perioperative management of patients with sickle cell disease (SCD), particularly for surgical procedures with high bleeding risk, can be challenging given both their chronic anemia and increased risk for venous thromboemboli. SCD is caused by a point mutation that leads to production of abnormal hemoglobin, which causes irregular shape and rigidity of red blood cells. This can result in red blood cell precipitation, difficulty passing through capillaries, and occlusion of blood flow to vascular beds throughout the body; which increases risk for VTE and VOC.[2] SCD also leads chronic activation of the coagulation cascade with increased levels of tissue factor, phosphatidylserine exposure, thrombin generation, and fibrinolysis.[2] SCD patients also have an increase in baseline platelet activity and reduced levels of anticoagulant proteins C and S, which also contribute to a hypercoagulable state.3 In addition, the abnormal red blood cells are more prone to hemolysis with a reduced lifespan of 10-20 days, resulting in a state of chronic hemolytic anemia.[4]

Given the risks for blood loss and transfusion complications, prophylactic measures to reduce blood loss hold value, but must be balanced with the increased risk of venous thromboemboli in an already vulnerable group. Guidelines for pre-operative transfusion of SCD patients currently propose maintaining hemoglobin between 9 and 11 g/dl.[5]

In surgical procedures with high potential for blood loss such as complex spinal surgery and joint replacement surgery, tranexamic acid (TXA), a synthetic lysine analog, has been shown to effectively reduce bleeding and need for blood transfusion by promoting clot stability.[6] TXA works as an antifibrinolytic agent by sequestering plasminogen, effectively reducing fibrin binding and thereby inhibiting plasmin formation.[1] Due to concerns for VTE promotion based on this mechanism, many institutions have developed criteria to avoid TXA use in patients at increased risk for thromboembolic complications such as patients with active VTE or pre-existing coagulopathic disease.[7] The American Association of Hip and Knee Surgeons (AAHKS) and The American Academy of Orthopaedic Surgeons (AAOS) collaborated to develop evidence-based guidelines on the use of TXA in primary total joint arthroplasty (TJA) of the knee or hip, all promoting its use as a safe and effective prophylactic treatment.[8] Poeran et al. also looked into the safety of TXA in hip and knee arthroplasties in high-risk patients, specifically patients with a history of venous thromboembolism, myocardial infarction, seizures, ischemic stroke/transient ischemic attack, renal disease, and atrial fibrillation.[9] Over 400,000 patients who received TXA were evaluated and ultimately no significantly increased risk of complications were noted, even among the highest-risk groups which included over 118,000 patients.[9]

However, there remains a lack of literature on the safety of TXA use in SCD patients, despite their baseline hypercoagulability. Though the overall prevalence of SCD remains low among the general U.S. population, given the inherent risks for VOC and VTE in SCD, research into the safety and potential benefits of TXA is important to better estimate perioperative risk. Therefore, this study sought to investigate whether TXA affects the perioperative incidence of VTE in SCD patients after hip or knee arthroplasty.

Methods: This study was conducted at Boston Medical Center, a level 1 trauma safety-net hospital

with the largest sickle cell population in New England. The Boston University School of Medicine Institutional Review Board approved the study protocol. The requirement for written informed consent was waived given the retrospective nature of the study.

Patient Selection

All adult patients, between the ages of 18 and 89 years, with confirmed sickle cell disease diagnosis who underwent knee or hip arthroplasty procedures between 1/1/2014 and 1/1/2020 were included in the study. Control cohort consisted of age, gender, and race-matched patients who underwent the same procedures during the above period but did not have a SCD diagnosis. Exclusion criteria included age less than 18 years; or missing information or perioperative data.

Data Collection and outcome parameters

Demographic data, medical history, pre-admission medications, and diagnoses were extracted from each enrolled patient's electronic medical record. Vital signs (including heart rate, blood pressure, oxygen saturation and respiratory rate) and laboratory values (e.g. hemoglobin) were documented. Patient charts were reviewed for time periods pre, intra, and post procedure for TXA dose administered, vaso-occlusive crises, thromboembolic events, and estimated blood loss and transfusion of blood products.

Statistical Analysis

Categorical data are presented as frequencies; normally distributed numeric data are presented as means and standard deviations (SD). Baseline characteristics of the SCD cohort and controls were compared using the Chi-squared analysis for categorical variables, and analysis of variance (ANOVA) for continuous variables. Among the SCD cohort, a multivariable logistic regression model using the R command glm logistic was performed to examine demographic and clinical factors associated with vaso-occlusive crisis (Post). Multivariate logistic regression analyses for independent parameters were used to assess for group-differences in the incidence of VTE, VOC, estimated blood loss and volume of transfused packed red cells, with other covariates included to control for their effects. All statistical analyses were performed using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). All tests were two tailed, and a P value < 0.05 was considered statistically significant.

Results: Our analysis included 19 patients with SCD who underwent 26 distinct procedures (figure 1). The control cohort consisted of 63 age, gender, and race matched patients. The average age of patients in the SCD cohort was 36.7 years and in the control cohort was 40.3 years (Table 1). Males represented 46% (12/26) of the SCD cohort and 50.8% (32/63) of the control cohort. The average BMI was 25.8 and 31.2 in the SCD and control cohorts, respectively. Other demographic characteristics and clinical data for each group of patients are summarized in Table 1.

In the SCD cohort, 50% had a preoperative history of DVT; 42.3% had a history of at least one episode of VOC. The average preoperative hemoglobin was 9.6 g/dl, emphasizing the presence of baseline anemia within this group. Pre-operative packed red blood cell transfusions were administered in 73% of cases (19/26). Among the SCD cohort who received transfusions pre-operatively, TXA was administered in fourteen cases. Within the control cohort, 9.5% of patients had a prior history of DVT; and the average preoperative hemoglobin was 12.3 g/dl. Only one patient (1.5%) was transfused preoperatively and also received TXA.

Rates of regional anesthesia utilization between cohorts were also evaluated. In the SCD cohort, 42.3% (11/26) received some type of regional anesthesia (spinal anesthesia, lumbar epidural, femoral nerve block, or adductor canal block), of which 54.5% (6/11) received spinal anesthesia. The one patient who experienced a postoperative DVT in the SCD cohort received spinal anesthesia, but did not receive TXA perioperatively. In the control group, 52.3% (33/63) of the patients received some type of regional anesthesia, of which 81.8% (27/33) received spinal anesthesia. TXA was administered in 90.9%

(30/33) of those who received regional anesthesia. The patient who experienced a DVT did have spinal anesthesia performed and received TXA intra-operatively.

Intraoperatively, among the SCD cohort, TXA was administered in 73.1% (19/26) of cases, of which none experienced a DVT postoperatively. Among patients with SCD who did not receive TXA, one patient experienced a postoperative DVT. Of note, this patient had a history of prior DVT and VOC. Within the SCD cohort with a prior history of DVT (13/26), TXA was administered in 6/13 of cases and held in 7/13 of cases. Within the control cohort, TXA was administered in 90.5% (57/63) of cases. Only one patient experienced a DVT postoperatively and had received TXA. In the 6 cases where TXA administration was held, two patients had a history of prior DVT. A history of DVT was noted in 9.5% (6/63) of patients and TXA was administered in four of these patients.

SCD patients had an average of 476 ml blood loss; and 69.2% (18/26) of cases were transfused postoperatively. The incidence of VOC in the 6 months following the procedure was 26.9% (7/26) among those who received TXA and 19.2% (5/26) among those who did not receive TXA. The average blood loss in the control group was 416 ml and 6.3% (4/63) were transfused postoperatively.

Postoperatively, the hours spent in the post anesthesia care unit (PACU) and total hospital length of stay were also evaluated among the cohorts. Of the data recorded, the SCD cohort spent an average of 4.3 hours in the PACU and 14.4 days in the hospital. The control cohort spent an average of 3.8 hours in the PACU and 5.5 days in the hospital (Table 1). The increased times spent in PACU (p=0.58) and the hospital (p=0.01) in the SCD cohort highlight the greater medical complexity and burden of comorbidities often noted in this patient group.

In our final analysis, no significant difference in perioperative venous thromboembolism between our study groups was noted. Additionally, TXA administration and transfusion (pre or post operatively) showed no effect on the post-operative incidence of VOC (Tables 2(a) and (b))

Discussion: As no statistically significant difference in the incidence of DVT was noted between the SCD and control cohorts, our data supports the notion that perioperative use of TXA is likely safe in this population. However, the benefits of TXA use with regards to perioperative blood loss and transfusion requirements were questionable.

Part of perioperative management of SCD patients includes the decision whether to proceed with pre-operative transfusions, especially when anticipating large surgical blood loss. Transfusion of RBCs pre-operatively offers the benefit of reduced sickling and improved oxygen delivery given a reduced level of HgbS, but poses the risks inherent to any blood transfusion as well as the danger posed by increased viscosity.[3] To maximize the benefit/risk ratio, many institutions target a Hgb of 10g/dl or higher.[3] As previously noted, the average preoperative hemoglobin in our SCD cohort was 9.6 g/dl, with 73% of cases (19/26) receiving pre-operative packed red blood cell transfusions, likely in accordance with these recommendations.

Many postoperative factors may increase the risk of VTE and VOC in SCD patients. Poorly controlled pain can lead to splinting and result in inadequate ventilation. This increases the risk for hypercapnia or hypoxemia, both of which are triggers for VOC. Limited mobilization can increase risks for acute chest syndrome and thromboembolic events such as pulmonary embolism (PE) and deep venous thrombosis (DVT). In a study by Naik et al, hospitalized SCD patients less than 40 years of age were found to be at 3.5 times greater risk of PE compared with non sickle cell African-American controls. [10] This was despite the SCD group having a median age of 28 years vs. 57 years for the control group. Vichinsky et al. reported the most frequent complications in SCD patients undergoing orthopedic procedures included excessive intraoperative blood loss (greater than 10% of blood volume), acute chest syndrome, VOCs, and transfusion complications.[5]

Post-operative management currently emphasizes aggressive pain control and oxygen supplementation to prevent sickling crisis; while incentive spirometry and early mobilization may help reduce incidence of acute chest syndrome and venous thrombosis.[11] Postoperative DVT prophylaxis is also critical, especially in surgeries where patients experience delayed return to independent ambulation, such as knee and hip arthroplasties.[3] In our study, while the SCD cohort had notably longer PACU and hospital stays compared to the control cohort, this did not lead to a higher incidence of VTE. However, larger trials may demonstrate a correlation as longer stays suggest longer periods of limited mobilization. This may confound interpretation of data when assessing the safety of TXA use.

We considered various limitations of our study. Most notable is the small sample size for the SCD cohort, which limits the generalization of our results. Only one patient in the SCD cohort experienced a DVT during the post operative hospital course and this patient did not receive TXA. We also consider the potential exclusion of SCD patients suffering from more severe disease and significant comorbidities to be a major source of bias. If those patients had been given TXA and their outcomes measured, it stands to reason that our measured results for the SCD group may have had a higher incidence of thromboembolic events.

In the SCD cohort, the use of regional anesthesia appears reduced compared with the control cohort, complicating analysis of the effects of TXA with regional vs general anesthesia; and the incidence of perioperative complications such as VTE or VOC. Though the reasons providers chose to proceed with a specific mode of anesthesia was not a subject of our investigation, comorbidities and functional status likely played a role. Overall, the superiority of regional versus general anesthesia in patients with SCD has not been firmly established. The Cooperative Study of Sickle Cell Disease by Koshy M et al. did note an increased incidence of complications, such as fever, infection, and VOC in patients who received regional anesthesia compared with general anesthesia.[12] However, this study failed to control for several confounding factors, such as inclusion of pregnant patients with SCD who received epidural analgesia. Generally, pregnant patients are already at increased risk for these complications compared to patients undergoing different surgical procedures. Other studies advocate for the use of epidural anesthesia as a mode of analgesia for prevention of VOCs, arguing that effective pain control is key in improving oxygenation.[13] Whether regional vs PO and IV narcotics in the postoperative period provides superior analgesia and affects incidence of VOC or VTE remains to be investigated further.

Other limitations include the variable dosages of TXA administration. In the SCD cohort, in 7/26 cases TXA was not administered, 1/26 received 2000 mg of TXA, while the remaining 18/26 received 1000 mg of TXA. In our control group, 6/63 did not receive TXA, 9/63 received 2000 mg of TXA, and 48/63 received 1000 mg of TXA. TXA may have been withheld in patients of both groups who were deemed at higher risk of hypercoagulability based on comorbidities. The variability in administration further reduces the strength of the study with an already small SCD cohort. It may also be presumed that a larger dose of TXA might significantly alter perioperative blood loss, the need for transfusion, or thromboembolic risks. Overall, these different dosages may confound a direct comparison of the effects of TXA in patients with and without SCD.

In conclusion, our data showed no increased risk for venous thromboembolism in patients with sickle cell disease who received tranexamic acid (TXA) for hip and knee arthroplasties despite their baseline abnormalities in hemoglobin and hypercoagulability. This supports the safety of using TXA in patients with SCD to help reduce blood loss. Though TXA use did not appear to cause any harm, it did not significantly reduce blood loss, transfusion requirements, or incidence of VOC within the SCD cohort. This is in spite of current evidence establishing the benefits of reduced blood loss and transfusion requirements in larger studies.[9] Given that our institution does have the largest single-site (single hospital) cohorts of patients with sickle cell disease in New England, our

results do help provide an initial look into the potential risks and safety profiles for intraoperative TXA administration in SCD patients undergoing surgery. Further studies are warranted before conclusions can be drawn.

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Fig. 1 Consort Diagram

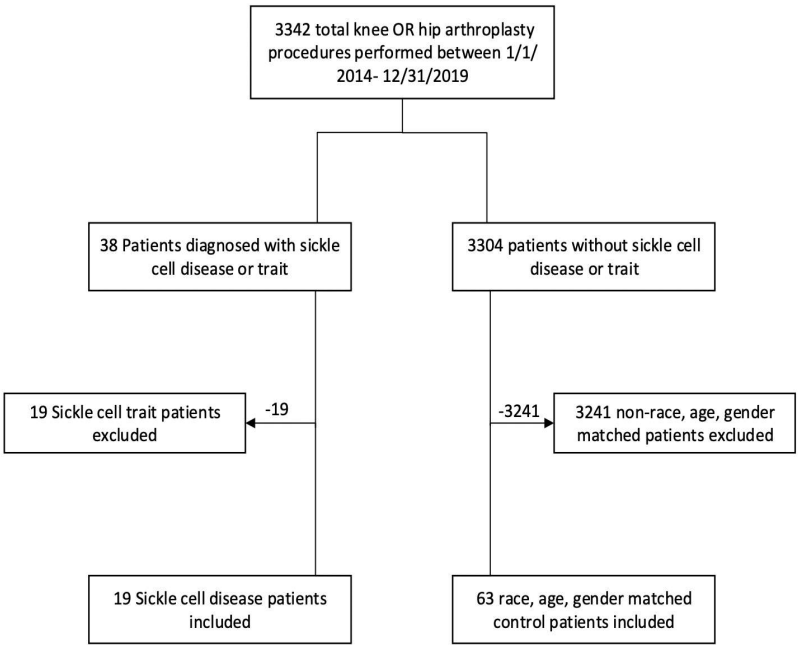

Table 1: Baseline Characteristics of SCD cohort patients and age-, gender-, race- matched controls.

Variables	SCD (N= 26)	Control (N = 44)	P-value
Age	36.77 (11.85)	38.96 (6.42)	0.39
Biological Sex			0.39
Male	12	25	
Female	14	19	
BMI	25.81 (5.63)	31.20 (9.79)	0.0044
Race			0.020
Black/ African American	23	45	
Unknown	3	0	
Ethnicity			0.11
Hispanic /Latino	4	2	
Not Hispanic	22	43	
Type of Procedure			
Knee	1.0	25.0	
Hip			
Comorbs			
ADHD	0	2	0.28
Depression	8	16	0.68
Anxiety	8	12	0.71
Asthma	6	6	0.29
HIV	1	3	0.60
Intra Op			0.037
General	20	33	
MAC	2	11	
Fentanyl Administered (count)	19	41	
Fentanyl Administered (dosage)	371.84 (410.67)	219.27 (180.77)	0.14
TXA (Yes or No)	19	41	0.037
TXA (Dosage)	769.23 (514.41)	**1121.95 (331.29)**	**0.0035**
HgB post op	8.26 (1.01)	**10.31 (1.63)**	**<0.0001**
Blood loss	476.23 (246.24)	416.07 (366.22)	0.43
Pre Transfusion	424.04 (370.98)	15.56 (104.35)	<0.0001
Post Transfusion	**484.62 (454.48)**	70.00 (231.20)	0.00013
Post Op			
LOS (hours)	**344.60 (355.72)**	131.50 (184.01)	0.01
PACU LOS (hours)	4.31 (4.28)	3.78 (1.60)	0.58

Variables	Unadjusted OR (95% CI)	P-value (unadj)	Multivariate OR (95% CI)	P-value (adj)
Age	0.96 (0.89, 1.04)	0.33	1.10 (0.94, 1.37)	0.28
Biological Sex (male=0)	1.00 (0.18, 5.5)	1.00	0.46 (0.02, 6.11)	0.56
BMI	0.98 (0.84, 1.13)	0.79	0.88 (0.68, 1.07)	0.24
Pre-op Hgb	0.40 (0.13, 0.95)	0.064	0.21 (0.02, 0.82)	0.071
Pre-operative vaso-occlusive crisis	7.11 (1.20, 55.24)	0.041	37.61 (1.44, 6562,9)	0.076
Anes transfusion difference	1.00 (1.00, 1.00)	0.87	1.00 (1.00, 1.00)	0.39

Table 2(a):Unadjusted and multivariate adjusted odds ratio of post-operative vaso-occlusive crisis

	Unadjusted OR (95% CI)	P-value (unadj)	Multivariate OR (95% CI)	P-value (adj)
Age	1.01 (1.00, 1.03)	0.10	1.02 (1.00, 1.03)	0.49
Biological Sex (male=0)	0.99 (0.65, 1.51)	0.97	1.07 (0.71, 1.62)	0.09
BMI	0.97 (0.94, 1.01)	0.11	0.98 (0.94, 1.01)	0.72
TXA Administered	0.97 (0.62, 1.53)	0.90	0.86 (0.55, 1.35)	0.49

Table 2(b): Unadjusted and multivariate adjusted odds ratio of transfusion requirements

	Unadjusted OR (95% CI)	P-value (unadj)	Multivariate OR (95% CI)	P-value (adj)
Age	1.01 (0.99, 1.02)	0.31	1.00 (0.99, 1.02)	0.67
Biological Sex (male=0)	0.85 (0.63, 1.13)	0.25	0.85 (0.61, 1.20)	0.34
BMI	1.01 (0.98, 1.05)	0.38	1.02 (0.98, 1.05)	0.34
TXA Administered	1.21 (0.84, 1.73)	0.29	1.14 (0.78, 1.67)	0.47

Table 2(c): Unadjusted and multivariate adjusted odds ratio of blood loss during procedure

JSCDH-D-22-1269140

USING VIRTUAL PATIENTS TO ASSESS PROVIDER IMPLICIT BIAS IN PEDIATRIC SICKLE CELL DISEASE

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Background: Provider implicit bias has been identified as a source of health inequities for youth with sickle cell disease (SCD). However, few studies have examined the impact of provider bias on pediatric SCD pain care. Study objectives were to 1) assess implicit racial bias among pediatric providers and 2) use virtual patient vignettes to determine the impact of implicit racial bias on clinical decision-making in pediatric SCD pain care. We hypothesized that: 1) providers' implicit racial bias would be consistent with the general population and 2) providers' decision-making for Black virtual patients with SCD would be less consistent with best practices compared to White virtual patients with leukemia.

Methods: This web-based study was conducted at a mid-sized, freestanding children's hospital in the northeast as part of a larger project evaluating provider-focused interventions targeting implicit bias in pediatric SCD pain care. Baseline data were collected from pediatric hematology/oncology and emergency medicine providers who completed a demographic questionnaire, the Race Implicit Association Test (IAT) with adult and child faces, and an explicit bias measure (5-point Likert scale). Providers also made clinical decisions for four virtual patient vignettes depicting youth in the emergency department (ED) with either SCD or cancer pain. Frequency tables were calculated.

Results: Participants (N = 52) were pediatric providers (50% hematology/oncology providers, 87% cisgender female, 90% White, M age = 38.78), including physicians (n = 15), advanced practice providers (n = 10), nurses (n = 19), and medical trainees (n = 8). On the Race IAT, providers demonstrated a pro-White bias with both adult (81%) and child (89%) faces. Responses to the explicit bias measure reflected low levels of agreement with negative stereotypes of SCD patients (33% agreed youth with SCD are more challenging to treat, 10% agreed they are less treatment compliant, and 2% agreed they present with less urgent issues). No significant differences emerged in the quality of providers' pain treatment decisions for White vs. Black or SCD vs. cancer virtual patients (all p-values > 0.05).

Conclusions: Findings are consistent with previous research indicating pediatric providers exhibit implicit racial bias similar to the general population. Providers were more likely to endorse treatment decisions consistent with best practices for all virtual patient vignettes, and no differences based on race or diagnosis were observed. Although allowing for greater experimental control over patient variables (i.e., race and pain type), virtual patient vignettes may not have fully captured key characteristics of real-life ED settings (e.g., time pressure, cognitive and emotional demands) known to activate implicit racial biases. Future research is needed to develop interventions to address high rates of implicit racial bias among pediatric providers and promote health equity in pediatric SCD.

Table 1. Race Implicit Association Test with Adult Faces

Interpretation	Frequency	Percentage
Slight Pro-White Bias	9	17.3
Moderate Pro-White Bias	16	30.8
Strong Pro-White Bias	17	32.7
No Bias	8	15.4
Slight Pro-Black Bias	2	3.8
Total Pro-White Bias	42	80.8

Table 2. Race Implicit Association Test with Child Faces

Interpretation	Frequency	Percentage
Slight Pro-White Bias	11	21.2
Moderate Pro-White Bias	22	42.3
Strong Pro-White Bias	13	25.0
No Bias	5	9.6
Slight Pro-Black Bias	1	1.9
Total Pro-White Bias	46	88.5

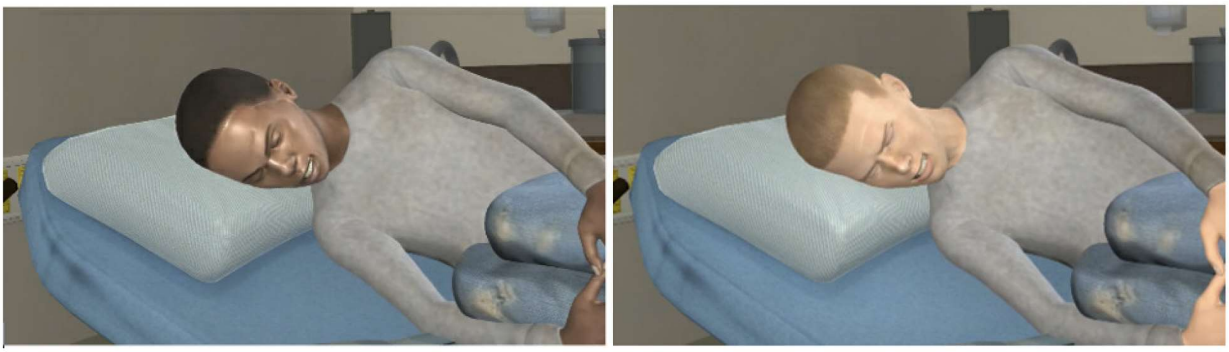

Figure 1. Still-Frames of Black Virtual Patient with Sickle Cell Disease and White Virtual Patient with Leukemia.

JSCDH-D-22-1242869

VASCULAR ISCHEMIA WITH MULTIPLE AMPUTATION: A RARE SEQUELA TO SICKLE CELL DISEASE

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Background: Vascular ischemia is a condition in which the blood flow is decreased in an organ or part of the body. Ischemia and reperfusion (I/R) injury is a phenomenon associated with microvascular dysfunction and occurs in several pathological conditions including sickle cell disease (SCD). The cellular mechanism is of ATP depletion leading to increase anaerobic metabolism. As a result, lactic acid production drastically increases. This prolonged process eventually leads to necrosis. In sickle cell disease, there is the phenomenon of recurrent Vaso-occlusion leading to ischemia and transient reperfusion. This leads to oxygen-free radical production and further cell injury. Furthermore, there is underlying inflammation and increased prothrombotic state that could contribute to ischemia and overall necrosis.

Sickle cell disease is an inherited autosomal recessive disease. It is the most common genetic disorder in the United States affecting 1 in 500 African Americans. The hemoglobin formed in SCD has the propensity to polymerize, altering the erythrocyte shape and its overall ability to deform. This polymerization occurs in various situation some of which includes hypoxic and acidotic states, dehydration, and cold temperatures. The decreased deformability and adhesion of sickle erythrocytes to endothelial cells leads to Vaso-occlusion and eventual recurrent ischemia/reperfusion injury in both large and small vessels. Sickle cell anemia is different from other Vaso-occlusive diseases as occlusion typically involves microvasculature. One form of this microvascular disease in sickle cell is ischemia/reperfusion injury of the femoral head eventually leading to avascular necrosis. Macrovascular occlusion is not typically seen in sickle cell disease. There is more of a mismatch as occlusion of the microvascular re-directs blood flows into the macrovascular leading to increase blood flow through them.

We aim to report on a case of homozygous sickle cell disease with a complication of multiple amputations. Our primary objective is to evaluate the possibility of ischemia playing a larger role in leading to necrosis of multiple digits in sickle cell disease.

Methods: We report a case of homozygous sickle cell disease (HbSS) with a history of multiple digital amputations. A systematic search (March 2022) of PubMed, Scopus, Cochrane, and EMBASE databases was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for literature “vascular ischemia” or “gangrene” and “sickle cell disease”. Included studies were peer-reviewed articles or academic society Full-Text publications. Papers with non-English language, and not fitting the search criteria were excluded.

Results: A 25-year-old female diagnosed with HbSS presented to our clinic with a history of multiple digit amputations of the left hand and bilateral transmetatarsal amputation of the feet that occurred at 10 years old (2007). Historically the patient was admitted to the hospital for painful crises for 4 months and 10 days. During the hospitalization period, she developed end-organ failure and subsequently entered a comatose state. The patient remained in a state of coma for the first 2 months. During this period patient developed avascular necrosis of the right femoral head with subsequent removal.

Post comma patient was noted to have seizures and distal digital ischemia to both her upper and lower limbs. She subsequently underwent amputations of

the left-hand 2nd-5th distal digit and all distal digits of her bilateral lower limbs at the trans-metatarsal region. Patient was discharged after a total of four months and ten days in the hospital. Of note, the patient received physical therapy post-discharge.

Patient's seizures continued for one year treated with Keppra.

A total of 115 articles were found further filters for English, Full Text articles yield a result of articles. Two articles fulfilled the criteria. Patients' ages were 7-months and 16 years old.

Conclusions: The sequelae of sickle cell disease are far-reaching, affecting multiple organ systems. Ischemia of the distal digits may be one of those sequelae. As we know thrombosis in sickle cell disease typically occurs in the venous system. By combining our case and two other cases from our search of the literature, we believe that arterial occlusion is possible. This could lead to ischemia and later gangrene in the digits. We believe that this may be attributed to the baseline pro-thrombotic state in sickle cell disease that when superimposed with another prothrombotic chronic disease increase the risk of arterial occlusion.

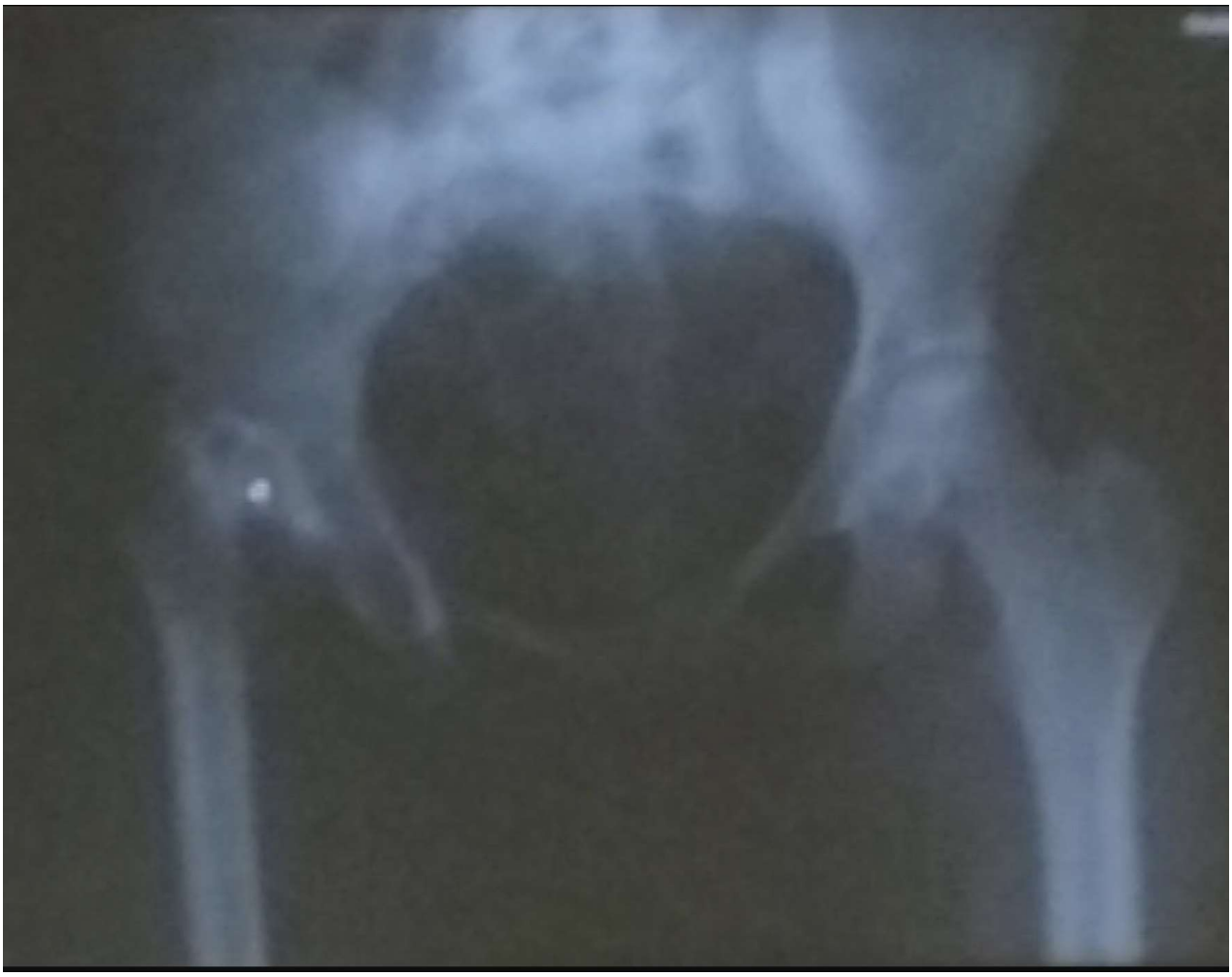

Figure 1
AVN of the Right Hip with Femoral Head Removal

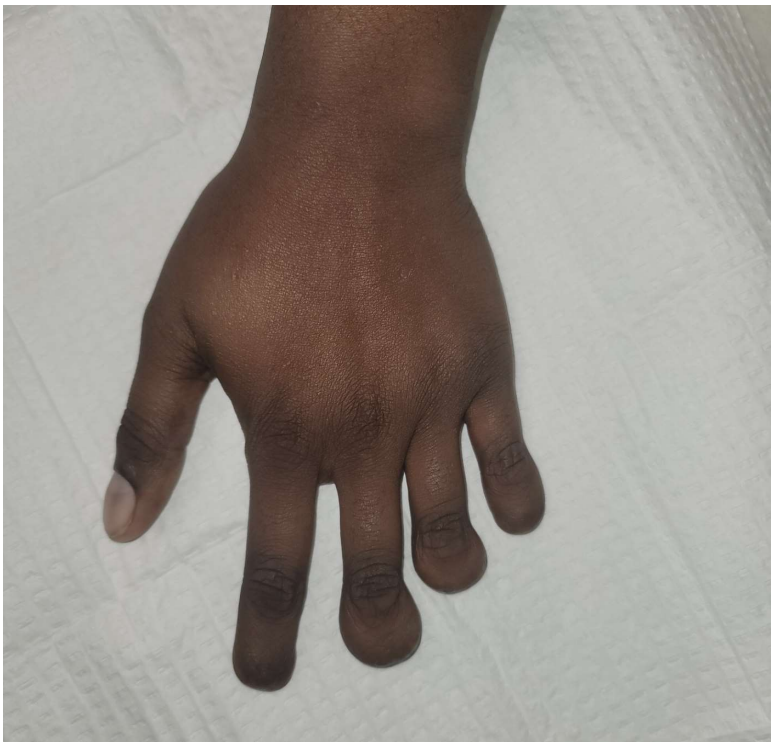

Figure 2
Amputation of Distal Phalanx 2-5 digit

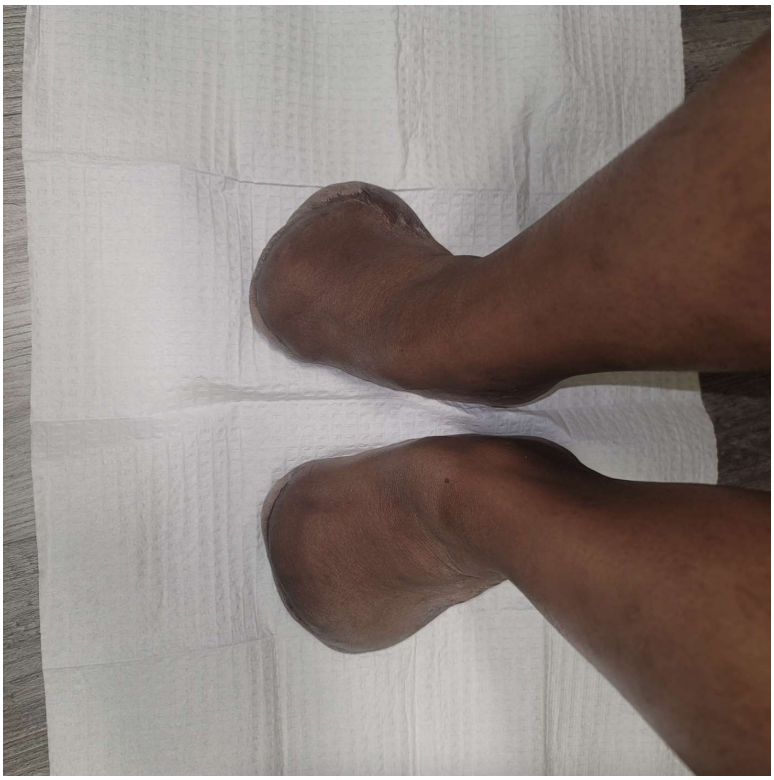

Figure 3
Bilateral Trans Metatarsal Amputation

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