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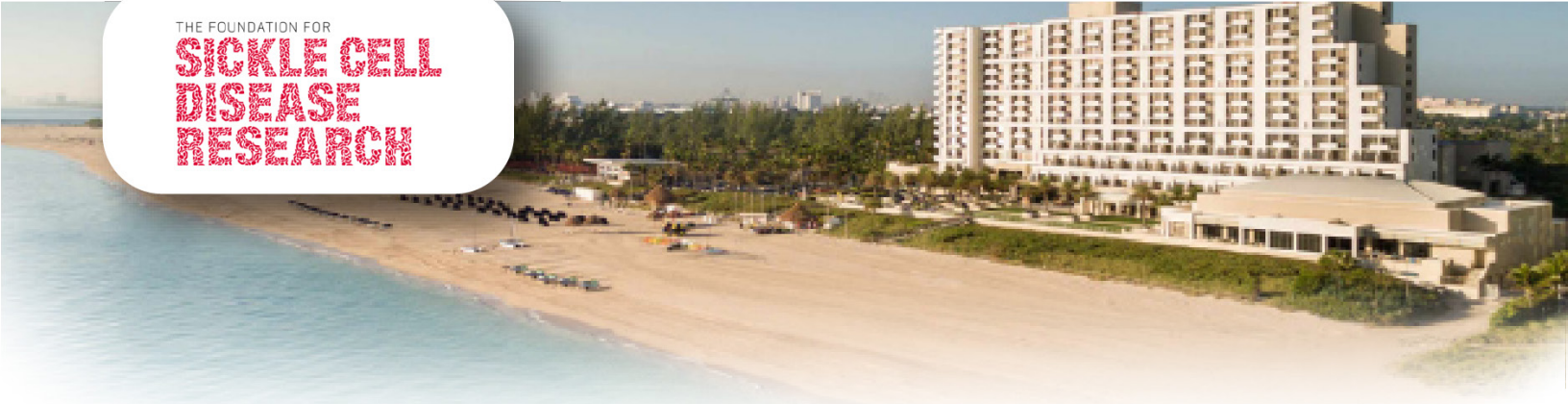

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TOP ABSTRACTS

Presenting: Saturday, June 8, 2019 at 5:45 PM

JSCDH-D-19-00004

OUTCOMES OF OSTEONECROSIS OF THE FEMORAL HEAD IN SICKLE CELL DISEASE AFTER SURGICAL TREATMENT WITH CORE DECOMPRESSION ALONE VS CORE DECOMPRESSION WITH BONE MARROW ASPIRATE CONCENTRATE INJECTION

Authors: Regina Hanstein, Adele Heib, Irene Chern, Ugochi O Ugo, Kerry Morrone, Deepa Manwani, Caterina Minniti, Eric D Fornari, MD

Affiliation: *Children's Hospital at Montefiore*

Background: Osteonecrosis of the femoral head (ONFH) is a common complication of SCD. We set out to describe clinical and radiographic outcomes of SCD patients with ONFH treated with (1) core decompression (CD) or (2) CD plus injection of patients own bone marrow aspirate concentrate (CD+BMAC). CD involves surgical drilling into the femoral head to reduce pressure and allow increased blood flow. The addition of BMAC injection is based on the hypothesis that BMAC contains osteogenic precursors, which will repopulate the osteonecrotic bone.

Methods: 35 hips in 26 SCD patients, 50% female, mean age 24.3years (range, 9.7-50.7years) at surgery were evaluated at average follow-up 3.6years (range 0.5-13years). 30 hips had HbSS/HBSB0 and 5 HBSC/HBSB+. Demographics, surgical parameters, patient self-reported pain and ambulatory status were recorded. Femoral head collapse was assessed on Xrays using the 4-stage Ficat score system (stage1 pre-collapse → stage4 complete collapse+flattened contour+decreased joint space).

Results: 17 hips underwent CD and 18 CD+BMAC based on surgeon preference. All were pre-operatively transfused to a Hb of 10. In each surgical group, 71% used Hydroxyurea at time of surgery; CD+BMAC patients used a higher Hydroxyurea dose compared to CD patients (18.2mg/kg vs. 25.1mg/kg, *p=0.022*). Other demographic and surgical parameters were similar between groups.

Collapse of the femoral head didn't progress in 8/15 CD and 9/13 CD+BMAC (p=0.390). Progression to total hip arthroplasty (THA) was similar between groups: CD 5/17 (29%) vs CD+BMAC 4/18 (22%), p=0.711. Patients progressing to THA were significantly older at surgery, used a lower Hydroxyurea dose, and had more pre-operative femoral head collapse (higher Ficat score) (Table).

Complication rates in the immediate 6 months period post-surgery were low; 2 CD and 3 CD+BMAC were transfused and hospitalization rates for VOC between groups were similar (p=0.103). With either treatment, >90% of patients were pain-free and walked independently at most recent follow-up.

Conclusion: CD and CD+BMAC are safe procedures to prevent progression of ONFH in SCD patients. Older SCD patients using lower dosage of Hydroxyurea and more femoral head collapse were more likely to proceed to THA.

CD and CD+BMAC		No THA	THA	P-value
Age at Surgery in years, Mean±SD		21 ±9.3	33.9 ±12.0	***0.003***
Hydroxyurea dose at Surgery in mg/kg, Mean±SD		24.7±4.9	12.5±8.0	***0.005***
Pre-operative Ficat score, N (%)	1&2	20 (77%)	3 (37.5%)	***0.042***
	3	3 (11.5%)	5 (62.5%)	
	4	3 (11.5%)	0 (0%)	

JSCDH-D-19-00041

BARRIERS TO THE USE OF ENDARI IN AN URBAN ADULT SICKLE CELL DISEASE CENTER

Authors: [1]Ugochi Ogu MD, [1]Merin Thomas NP, [2]Flo Chan Pharm D, [1]Gracy Sebastian NP, and [1]Caterina Minniti MD.

Affiliations: *1 Montefiore Medical Center, 2 Lemed Pharmacy*

Background: In 2017, the US Food and Drug Administration (FDA) approved Endari (L-glutamine oral powder) for patients age five years and older with sickle cell disease (SCD) to reduce disease complications associated with SCD. This was applauded as the first medication approval for SCD in almost 20 years, following Hydroxyurea (HU) in 1998. A phase 3 trial that led to its approval showed that Endari decreased the number of pain crisis in SCD patients. We report our experience with prescribing Endari in an urban adult sickle cell center. To our knowledge, this report is a first of its kind.

Methods: After prospectively establishing guidelines for the use of Endari, adult patients with SCD seen in clinic at a large urban adult SCD center were prescribed Endari via a local specialty pharmacy, over a 10 month period. Upon return to clinic, patients were asked about barriers to obtaining the medication and adherence to the twice a day dosing. Adherence was also evaluated by calculating the mean possession ratio (MPR) utilizing pharmacy's records.

Results: 101 patients with SCD (58% females, 43% males) were prescribed Endari over a 10 month period (Table 1): 82% with severe disease genotypes (Hb SS/Sβ^0), 18% with mild genotypes (Hb SC/Sβ^+). Mean age was 36 years old. 31% of patients were on concomitant HU and 3% on chronic transfusions (>6 months). At the end of the 10 month period, 40 patients (40%) were actively taking Endari, 20 (20%) had discontinued, 35 (35%) never filled the script, and 6 (6%) had received but never started Endari. Barriers to initiating Endari included high deductibles (reported in 7% of patients), denied prior authorizations (11%) and inability of pharmacy to contact patient (11%) (Table 2). Reasons for discontinuing Endari included side effects (46%), poor adherence (22%), no perceived benefit (20%), and pregnancy (1%) (Table 3). Average MPR was 0.74, similar to the Endari study.

Discussion: This is the first study that addresses both acceptance of a new medication by the sickle cell population and the barriers to obtaining it. We identified multiple barriers with the initiation and adherence to Endari in our urban adult SCD patient population. The most common reason that the medication was not initiated was denial from the insurance companies. The most common reason cited for discontinuing Endari was perceived side effects or ineffectiveness by the patients. After 10 months, only 40% of patients prescribed Endari were still taking this medication. As experienced with HU, several years elapsed from initial FDA approval to its being more accepted and widely used. From our report, it is critical to evaluate and eradicate barriers to initiation and adherence to Endari, to ensure it is readily available and accessible to the patient population it gained approval and was intended for.

Tables 1: Demographics

		N = 101
Age (mean, range)		36 (21-68)
Sex	**Female**	57 (57%)
	Male	43 (43%)
Genotype	**Hb SS**	81 (80%)
	Hb SC	12 (12%)
	Hb Sβ^+	6 (6%)
	Hb Sβ^0	2 (2%)
Insurance	**Medicare/Medicaid**	95 (95%)
	Private	6 (6%)
Hydroxyurea	**Yes**	31 (31%)
	No	70 (70%)
Chronic Transfusion		3 (3%)

Table 2: Barriers to initiating Endari

	N = 101
High Deductible	7 (7%)
Prior Authorization Denied	11 (11%)
Unable to contact	10 (10%)

Table 3: Reasons for stopping Endari

	N = 101
Side Effects	46(46%)
Poor Adherence	22(22%)
Pregnant	1 (1%)
No Perceived Benefits	20 (20%)

JSCDH-D-19-00046

THE OXYGENSCAN: A RAPID AND REPRODUCIBLE SOURCE OF CLINICALLY RELEVANT BIOMARKERS IN FOR PATIENTS WITH SICKLE CELL DISEASE

Authors: Celeste K. Kanne[3], Minke A.E. Rab[1,2], Brigitte A. van Oirschot[1], Jennifer Bos[1], Maite E. Houwing[4], Marjon H. Cnossen[4] Roger E.G. Schutgens[2], Gerard Pasterkamp[1], Richard van Wijk[1], Eduard J. van Beers[2] and Vivien A. Sheehan[3]

Affiliations: *[1]Laboratory of Clinical Chemistry & Haematology, University Medical Center Utrecht, [2]Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands, [3]Department of Pediatrics, Division of Hematology/Oncology, Baylor College of Medicine, Houston Texas, USA,[4]Department of Pediatric Hematology, Erasmus Medical Center, Rotterdam, The Netherlands*

Background: In sickle cell disease (SCD), hemoglobin S (HbS) polymerizes upon deoxygenation, reducing red blood cell (RBC) deformability. RBC deformability can be measured over a range of osmolalities and oxygen concentrations using a Laser Optical Rotational Red Cell Analyzer (Lorrca) ektacytometer (RR Mechatronics) with Oxygenscan module (pO2scan). The Oxygenscan measures 3 key parameters: 1) EImax, RBC deformability at normoxia; 2) EImin, deformability upon deoxygenation; and 3) the point of sickling (PoS), the point at which a >5% decrease in EI is observed during deoxygenation, reflecting the patient-specific pO2 at which sickling begins (Figure 1). In this study, we correlated Oxygenscan parameters with various SCD genotypes and treatments.

Methods: We analyzed 53 pediatric SCD patients from Texas Children's Hospital (TCH) and 24 SCD pediatric and adult patients from University Medical Center Utrecht (UMCU). 19 HbSS (median age 5.5 years (y); 10 female (f)), 11 HbSC (median age 8.9y; 6f), and HbSB+ (median age 8.4y; 3f) from TCH were analyzed; 14 HbSS patients without treatment (median age 20.0y; 5f), 6 HbSS patients with alpha-thalassemia trait without treatment (median age 9y; 4f), and 3 HbSC patients (median age 28y; 3f) from UMCU were analyzed. To establish Oxygenscan changes between treatments, we analyzed RBC from 17 HbSS patients from TCH (median age 10.8y; 6f) on HU before and after transfusion. From UMCU, samples from 8 patients before and on HU were analyzed. Tests were performed in duplicate.

Results: In the TCH cohort, PoS differed significantly between HbSS and HbSC ($p<0.01$), HbSS and HbSB+ ($p<0.0002$), and HbSC and HbSB+ ($p<0.02$). HbSB+ patients tolerated lower oxygen concentrations before sickling, PoS (23.5 mmHg) than HbSC patients (31.9 mmHg) and HbSS patients (39.9 mmHg). EImin did not differ between genotypes; EImax did not differ between HbSS and HbSC, but did between HbSS and HbSB+ ($p<0.01$), and HbSC and HbSB+ ($p<0.000003$). In the UMCU cohort, PoS differed between HbSS and HbSS + α-Thal ($p<0.03$) and HbSS and HbSC ($P<0.05$), with the lowest PoS in HbSC (mean 47.5 mmHg). HbSS + α-Thal had a lower PoS (51.1mmHg) compared to HbSS without α-Thal (67.5 (mmHg).

Transfusion significantly improved the EImax, EImin, and PoS ($p<0.0006$, $p<0.00004$, and $p<0.01$ respectively). HU treatment also significantly improved all parameters compared to baseline ($p<0.05$).

Conclusion: The Lorrca with Oxygenscan can fully characterize RBC deformability under a range of oxygen concentrations. Key measurements - PoS, EImin, and EImax – were different between genotypes, and changed significantly with standard of care SCD treatments. We therefore conclude that these are useful biomarkers of clinical severity and treatment response, and may be essential in monitoring novel SCD treatments as part of a clinical trial.

ABSTRACT BREAKOUT SESSION I
BASIC SCIENCE ORAL PRESENTATION

Presenting: Sunday, June 9, 2019 at 1:45 PM

JSCDH-D-19-00047

REGULATION OF FETAL HEMOGLOBIN THROUGH THE INSULIN SIGNALING PATHWAY

Authors: Alireza Paikari, Yankai Zhang, Alicia K. Chang, Ankush Goyal, Evadnie Rampersaud, Jonathan M. Flanagan, Mitchell J. Weiss, Vivien A. Sheehan

Affiliation: *Baylor College of Medicine*

Background: HbF induction is a key therapeutic strategy for sickle cell disease (SCD). Analysis of whole exome sequencing (WES) data from patients with SCD identified variants in two components of the insulin signaling pathway, FOXO3 and its activator, AMPK, to be associated with HbF levels; the association was confirmed by functional studies in hematopoietic stem and progenitor cells (HSPC), and metformin, a FOXO3/AMPK activator, increased HbF in HSPC. Whole genome sequencing (WGS) analysis identified variants in the regulatory region of IGFBP3, another component of the insulin signaling pathway, as associated with HbF levels.

Methods: 658 pediatric SCD patients (>2y, 52% male) underwent WGS; mixed linear regression was used to screen for variants associated with %HbF. Three unique SCD patient-derived HSPC cultures were treated with metformin (100 µM), compound C (1 µM), and exogenous IGFBP3 (1µg/ml); their effect on HbF, gamma-globin, known modifiers of HbF and the FOXO3-AMPK pathway were assessed by HPLC, RT-qPCR and western blot at day 14 and 21 of culture. Erythroid maturation was assessed by morphology and flow cytometry. Plasma levels of IGFBP3 in patients with and without IGFBP3 variants were measured by ELISA.

Results: WGS identified an association between variants in IGFBP3 and baseline HbF levels ($p<1x10^{-6}$). Plasma IGFBP3 levels were higher in patients heterozygous for an IGFBP3 variant (p=0.01). The role of AMPK in HbF regulation was confirmed by pharmacologic blockade of AMPK by compound C, a specific AMPK inhibitor; compound C reduced gamma-globin expression, and prevented gamma globin induction by metformin.

Treatment of HSPCs with recombinant IGFBP3 resulted in a significant increase in %HbF (p=0.008). Adding IGFBP3 to erythroid culture altered the insulin signaling pathway; total protein levels of FOXO3 increased (p=0.01), as well as its activated phosphorylated form (Ser 413) that keeps FOXO3 in the nucleus (p=0.03). AMPK protein levels did not increase, but the phosphorylated form of AMPK (Thr172) that in turn phosphorylates and activates FOXO3 did increase (p=0.01). Neither IGFBP3 nor metformin altered erythroid maturation or expression of known gamma globin regulators; BCL11A, KLF1, and MYB.

Conclusions: Unbiased WES and WGS analysis identified variants in the coding and non-coding region of several insulin signaling pathway effectors (FOXO3/AMPK and IGFBP3) to be associated with HbF levels; this was verified by functional studies in HSPC. We therefore conclude that the insulin signaling pathway plays a significant role in gamma-globin regulation and is an important therapeutic target for HbF induction in SCD patients.

JSCDH-D-19-00009

LENTIGLOBIN GENE THERAPY IN PATIENTS WITH SICKLE CELL DISEASE: UPDATED INTERIM RESULTS FROM HGB-206

Authors: Lakshmanan Krishnamurti, [1]John F. Tisdale, [2]Julie Kanter, [3]Janet L. Kwiatkowski, [4]Markus Y. Mapara, [5]Manfred Schmidt, [6]Alexandra Miller, [6]Francis J. Pierciey, [6]Wenmei Huang, [6]Jean-Antoine Ribeil, [7]Alexis A. Thompson, and [8]Mark C. Walters,

Affiliations: *[1]National Institutes of Health, [2]University of Alabama at Birmingham, [3]Children's Hospital of Philadelphia, [4]Columbia University College of Physicians and Surgeons, [5]GeneWerk GmbH, [6]bluebird bio, Inc., [7]Ann and Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Blood and Marrow Transplant Program, [8]UCSF Benioff Children's Hospital*

Background: β-globin gene transfer into hematopoietic stem cells (HSC) may reduce or eliminate complications of sickle cell disease (SCD). LentiGlobin gene therapy (GT) comprises drug product (DP) made from autologous HSCs transduced with the BB305 lentiviral vector (LVV) encoding β-globin with an anti- sickling T87Q substitution (HbA^{T87Q}). The safety and efficacy of LentiGlobin GT in adults with SCD is being evaluated in a phase 1/2 study, HGB-206 (NCT02140554). Patients were initially treated with DP made from bone marrow harvested (BMH) HSCs (Group-A, fully enrolled), then from DP made from BMH HSCs using a refined manufacturing process (Group-B, fully enrolled), and subsequently from plerixafor-mobilized HSCs (Group-C, currently enrolling).

Methods: Adults with severe SCD (previously described) were enrolled. CD34+ cells, collected by BMH or plerixafor (240 μg/kg) mobilization and apheresis, were transduced with BB305 LVV. After myeloablative busulfan conditioning, patients were infused with DP and monitored for safety and efficacy. Summary statistics are median (min—max).

Results: As of 15 May 2018, 15 patients were treated with LentiGlobin DP. DP and treatment characteristics are shown in Table 1. DP characteristics were improved in Group-B and Group-C vs Group-A. The safety profile post-DP infusion was consistent with myeloablative conditioning and underlying SCD; most common non-hematologic grade ≥3 AEs were stomatitis, febrile neutropenia, and vaso-occlusive pain.

No grade ≥3 DP-related AEs, graft failure, veno-occlusive liver disease, replication-competent lentivirus detection, or clonal dominance were reported.

At last visit (Table 1), HbA^{T87Q} levels were higher in Group-B (3.2 and 7.2 g/dL) vs Group-A 0.8 (0.5—1.2 g/dL). In 4 Group-C patients at 3-months, HbA^{T87Q} (4.1 [3.2—6.0] g/dL) levels were nearly equal to or exceeded HbS levels (3.3 [2.8—3.8] g/dL). In 1 Group-C patient at 6-months, HbA^{T87Q} was 8.8 g/dL and total Hb was 14.2 g/dL.

Conclusions: These data support the safety and feasibility of plerixafor-mediated HSC collection in patients with SCD. HGB-206 protocol changes have improved LentiGlobin DP characteristics, yielding higher HbA^{T87Q} levels. Additional data will determine the clinical effect of increased HbA^{T87Q}/HbS ratios.

Table 1. DP and Treatment Characteristics

	Group-A (N=7)	Group-B (N=2)	Group-C (N=6)
Cell dose (x10^6 CD34+ cells/kg)	2.1 (1.6—5.1)	2.7 (2.2—3.2)	7.1 (3.0—8.0)
DP vector copy number (copies/diploid genome)	0.6 (0.3—1.3)	3.1 (1.4—5.0)	4.0 (2.8—5.6)
Transduced cells (%)	25 (8—42)	87 (46—95)	81 (78—88)
Neutrophil engraftment (days)	22 (17—29)	26 (23—28)	19 (18—20)
Platelet engraftment (days)	56 (29—63)	46 (31—61)	28 (12—64)*
Follow-up (months)	24.2 (22.8—32.9)	11.4 (8.5—14.3)	3.0 (1.2—6.0)

Values are presented as median (min—max); *n=4 Group-C patients; platelet engraftment was pending in 2 Group-C patients as of data cut

JSCDH-D-19-00012

VOXELOTOR TREATMENT OF ADULTS AND ADOLESCENTS WITH SICKLE CELL DISEASE: RESULTS OF THE PHASE 3 HOPE TRIAL

Authors: Elliot Vichinsky[1], Carolyn C. Hoppe[2], Jo Howard[3], Kenneth I. Ataga[4], Videlis Nduba[5], Amal El Beshlawy[6], David L. Diuguid[7], Salam Al Kindi[8], Clark Brown[9], Hoda Hassab[10], Paul Telfer[11], Dimitris A. Tsitsikas[12], Selma Ünal[13], Julie Kanter[14], Miguel R. Abboud[15], Victor R. Gordeuk[16], Joshua Lehrer-Graiwer[2], Margaret Tonda[2], Allison Intondi[2], Russell E. Ware[17]

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Background: Sickle cell disease (SCD) is a genetic disorder caused by a single amino acid substitution in the β-chain of hemoglobin (Hb) resulting in the production of sickle Hb (HbS). When deoxygenated, HbS polymerizes triggering chronic anemia and hemolysis with downstream vaso-occlusive crises and organ damage. Voxelotor is a once-daily oral therapy designed to inhibit hemoglobin (Hb) polymerization, and thereby improve anemia and hemolysis. The randomized phase 3 HOPE study (NCT03036813) evaluates the efficacy and safety of voxelotor in patients with SCD aged 12 to 65 years. Here we report the results of the pre-specified Part A of the HOPE study.

Methods: Eligible patients were randomly assigned to receive voxelotor (900 or 1500 mg/day) or placebo for ≥24 weeks. The primary endpoint was the proportion of patients with a >1g/dL increase in Hb from baseline at week 24. Secondary endpoints included improvement from baseline in measures of hemolysis (eg, reticulocyte counts and unconjugated bilirubin level) and safety.

Results: Part A included 154 patients with a median age of 25 years (range, 12–59); 14% were adolescents, and 42% were male. Most were HbSS/HbSβ^0: 94% (900 mg), 92% (1500 mg), and 90% (placebo). Hydroxyurea use at study entry was 67% (900 mg), 62% (1500 mg), and 64% (placebo), and median baseline Hb was 8.3 g/dL (900 mg; range, 6.3–10.8), 8.6 g/dL (1500 mg; range, 5.9–10.8), and 8.5 g/dL (placebo; range, 6.1–10.4). At week 24, the percentage of patients with a >1 g/dL increase in Hb from baseline was significantly larger for both voxelotor arms, 900 mg (33%; P=0.0159) and 1500 mg (65%; P<0.0001), compared with placebo (10%). Voxelotor also resulted in improvements in measures of hemolysis, consistent with the demonstrated improvement in Hb. Overall, the treatment-emergent adverse events (TEAEs) were grade 1 or 2 in severity and similar across all treatment groups except for diarrhea, which was higher in both voxelotor arms (900 mg, 19%; 1500 mg, 21%) compared to placebo (10%).

Conclusions: Voxelotor treatment demonstrated a dose-dependent increase in Hb, with a large number of patients achieving a >1 g/dL improvement in Hb and decreases in measures of hemolysis. Voxelotor was generally well tolerated. Voxelotor has the potential to be disease modifying by improving anemia and hemolysis leading to the reduction in morbidity of chronic organ damage associated with SCD.

JSCDH-D-19-00048

A NOVEL NEXT-GENERATION SEQUENCING (NGS) BASED ASSAY FOR NON-INVASIVE PRENATAL TESTING OF SICKLE CELL DISEASE WITHOUT PATERNAL DNA

Authors: Vivien Andrea Sheehan, Nelda Itzep, MD, Celeste K Kanne, BS, David Tsao, PhD, Oguzhan Attay, PhD

Affiliation: *Baylor College of Medicine*

Background: Over 300,000 infants are born with sickle cell disease (SCD) every year worldwide, including at least 1,000 in the US. Prenatal diagnosis by amniocentesis or chorionic villus sampling is available; but high cost, invasiveness, and risk of miscarriage limit their use. Recently, non-invasive prenatal testing (NIPT), which operate by genetic analysis of the cell-free fetal DNA (cffDNA) present in maternal blood, has become commonplace for aneuploidies, including Trisomy 21. Yet, no NIPT for SCD or other hemoglobinopathies have been commercialized to date. We have developed and optimized NIPT for SCD by assessing the relative mutation dosage of fetal SCD and beta-thalassemia DNA through a novel molecular counting strategy using NGS.

Objectives: The primary objective of this study is to evaluate the performance of a novel NIPT for sickle cell disease.

Methods: The SCD NIPT assay and associated custom bioinformatics analysis were performed on cfDNA obtained from a training cohort of non-pregnant compound heterozygotes for SCD. The SCD NIPT assay was then performed on a validation cohort of pregnant women with either SCD or sickle cell trait (SCT). The accuracy of the SCD NIPT was evaluated by comparison with newborn screening results.

Results: Non-pregnant individuals aged 2-20 years with genotype HbSE, HbSC, or HbS/beta-thalassemia were included as a training cohort to establish the precision and accuracy of the assay for measuring HbS allele fraction from cfDNA. This cohort had a M:F ratio of 23:17. As expected, the HbS allele fraction in these individuals was 0.500 (standard deviation = 0.011, n = 26), and there was no detectable fetal fraction in these samples. Both training and validation cohort results matched the theoretical limit of detection set by the number of cell-free HBB DNA molecules in plasma. The precision and accuracy of the HBB assay on cfDNA were then used in conjunction with >1000 pre-clinical samples (mixtures of sheared SCT and SCD genomic DNA) to determine analytical sensitivity >98% and specificity >99%, even in the absence of paternal DNA.

Conclusion: We have developed an assay for NIPT of sickle cell disease. The results obtained to date indicate that the assay reliably detects fetal SCD status when the fetal fraction is as low as 5%, the same limit as aneuploidy NIPT. SCD NIPT could be particularly useful for deciding to bank umbilical cord blood as a source of stem cells for future gene-editing cures.

JSCDH-D-19-00049

CLINICAL TRANSFORMATION IN CARE FOR PATIENTS WITH SICKLE CELL DISEASE AT AN URBAN ACADEMIC MEDICAL CENTER

Authors: Sanaa Rizk, MD, David Axelrod, MD, Gaye Riddick-Burden, CRNP, Elisabeth Congdon-Martin, LSW, Steven McKenzie, MD, Carol Haines, John McAna, PhD, Albert G. Crawford, PhD, Lawrence Ward, MD

Affiliation: *Thomas Jefferson University Hospital*

Abstract:

Background: Sickle cell disease (SCD), an inherited red blood cell disorder, is characterized by anemia, end-organ damage, unpredictable episodes of pain, and early mortality. Emergency department (ED) visits and hospitalizations are frequent, leading to increased burden on patients and increased health care costs. We report herein on two clinical transformations at Thomas Jefferson University Hospital in care for patients with SCD over the past 6 years. The first clinical transformation, in November 2013, was a multidisciplinary care team intervention which included monthly team meetings and development of individualized care plans and targeted for management of uncomplicated pain crises. The second clinical transformation, in 2015, involved changing the locus of care from a dedicated Sickle Cell day unit to an approach which "fast-tracks" patients through the ED into an observation unit with 24/7 access.

Methods: This study assessed the two clinical transformations mentioned above. The effects of the first clinical transformation were assessed through quantitative statistical analyses, stratified by high utilizer status (already reported in a manuscript published in the American Journal of Medical Quality[1]). The effects of the second clinical transformation were assessed through both quantitative statistical analysis and qualitative analysis, i.e., five case studies.

Results: Regarding the first clinical transformation, following implementation of the multidisciplinary care team intervention, significant decreases in both ED and inpatient utilization were identified among those individuals with a history of high ED utilization. Regarding the second clinical transformation, quantitative analyses of claims data suggest further decreases in the rates of ED visits and inpatient stays, but these analyses require further refinement. At the same time, five case studies reinforce the overall findings and provide insight into the specific effects of the clinical transformation on the course of patients' SCD and other comorbid conditions, and also their quality of life.

Conclusions: Findings highlight the potential strength of these clinical transformations.

Reference:

[1]Powell RE, Lovett P, Axelrod D, Crawford A, McAna J, Ward L, Pulte E. A multi-disciplinary approach to impact acute care utilization among individuals with sickle cell disease. American Journal of Medical Quality, 2018, 33(2),127-131.

ABSTRACT SESSION I- HEALTH SERVICES ORAL PRESENTATIONS

Presenting: Sunday, June 9, 2019 at 1:45PM

JSCDH-D-19-00014

THE ROLE OF SOCIAL DETERMINANTS OF HEALTH IN AFFILIATION STATUS FOR A COHORT OF SICKLE CELL DISEASE PATIENTS FROM A CHICAGO BASED COMPREHENSIVE SICKLE CELL CENTER

Authors: G.G. Méndez, V. Gordeuk, M. Berbaum, J.M. Nocek, L.L. Hsu.

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Background: Factors associated with clinic attendance are better understood for children with sickle cell disease (SCD) than for adults with SCD. We used a definition for unaffiliated patients developed by the NIH Sickle Cell Disease Implementation Consortium (SCDIC): those who have had no appointments with a SCD expert in the non-acute setting in 2 years. In our previous examination of an administrative dataset, unaffiliated SCD patients (15-45 years of age) were more likely to be uninsured and were lower utilizers of acute care services than affiliated patients, but surprisingly had fewer recorded comorbidities. These findings are consistent with socio-ecological factors exerting an influence on the health of SCD patients. The Distressed Communities Index (DCI) for a zip code is a marker for a community's socio-demographic and socio-economic status (Economic Innovation Group, Washington DC).

Hypothesis: Unaffiliated SCD patients are more likely than affiliated patients to live in zip codes with high DCI.

Methods: A retrospective review compared affiliated and unaffiliated Chicago patients in the SCDIC Registry. Each patient's zip code was used to look up the 2016 DCI. DCI ranges from 0 to 100 and the worst quintile is termed "most distressed" (80-100).

Results: Of 299 patients (58% female; mean age 30.0) who met the inclusion criteria, 56 (46.0% female; mean age 30.0) met the definition for unaffiliated. No difference in distress score between affiliated and unaffiliated SCD patients was observed, with 58% of the affiliated and 59% of the unaffiliated residing in the most distressed zip codes (P>.9, by Mann-Whitney U test).

Conclusions: In our Chicago sample, the percentage of patients in the high distress category (DCI 80-100) was the same for affiliated and unaffiliated (58% to 59%). Nationally, (26.9% to 35%) of African-Americans are in distressed communities. The findings reinforce previous reports that SCD is correlated with socioeconomic disadvantage. To overcome the sample bias from a SCD center whose mission is to provide care for the underserved, similar analyses could be conducted in SCD centers that serve a broader population of sickle cell patients. In addition, a limitation of this study is that the unaffiliated SCD patients were identified from a healthcare source and may not be representative of all unaffiliated patients.

Acknowledgements: SCDIC has been supported by US Federal Government cooperative agreements HL133948, HL133964, HL133990, HL133996, HL133994, HL133997, HL134004, HL134007, and HL134042 from the National Heart Lung and Blood Institute and the National Institute on Minority Health and Health Disparities (Bethesda, MD), plus U01 HL134042-3S2 from NHLBI Research Supplements to Promote Diversity in Health-Related Research for Gustavo G. Mendez.

JSCDH-D-19-00020

SYSTEMATIC DESIGN AND REVISION OF A MOBILE APPLICATION FOR ENHANCING ADHERENCE TO PRESCRIBED OPIOIDS IN SICKLE CELL DISEASE

Authors: Daniel Sop[1, 2 *], Wally Smith[1], Azhar Rafiq[3], Abdulkhaliq Alsalman[1], Donna McClish[4], Shirley Johnson[1], Thokozeni Lipato[1], Taylor Elliott[1] and Ding-Yu Fei[2]

Affiliations: [1]Department of General Internal Medicine, [2]Department of Biomedical Engineering, [3]Department of Surgery, and [4]Deptment of Biostatistics, Virginia Commonwealth University, Richmond, VA 23298, USA

Introduction: Sickle cell disease (SCD) is the most common inherited blood disorder that produces a progressively disabling illness with severe clinical consequences. A significant portion of patients with SCD use prescribed opioids regularly. In order to safely start, adjust, taper, and stop opioids clinicians need better tools to follow or trend the opioid use pattern. Thus, the goal of this study was to develop and test the feasibility of a mobile application for adherence to prescribed opioids, and capture context-specific data associated with prescription opioid use.

Methods: The designated OpPill Mobile Application development was carried out to reflect the needs of the SCD community, and allow for information input related to concerns gathered from the focus group.

The overarching software requirements for the app included:

- Easy-to-use and intuitive graphical interface
- Functional parameters to allow documentation of medication adherence and symptomology
- Data transmission and storage capabilities meet HIPAA requirements
- Multi-platform capability to ensure app effectiveness across diverse mobile devices

Each phase of the app development was subjected to continuous expert reviews, and validation of the software through iterations of Low Fidelity Testing. Functional relevance of the software was measured with focus group surveys, which consisted of in-person interviews. The interviews were audio-recorded and transcribed for qualitative analysis.

Results: Approximately 57% (n=12) of the participants were women. Focus group members ranged in age from 18 to 58 years, with more than half (57%) of the participants possessing the SS genotype of SCD. Qualitative thematic analysis from interviews revealed three phenomena: 1) SCD patients exhibited various opioid-consuming behavior patterns including adherence, overuse, underuse, and erratic use; 2) Several biopsychosocial factors hindered or motivated opioid use: severe pain intensity, side effects, stress, family gatherings, unplanned meetings, religious attendance, and anticipatory fear adverse outcomes; 3) Behaviors varied based on the time of day, week, month, or year, and also based on the momentary contexts at times of actual and projected doses.

Conclusion: The presented OpPill app was developed as a specific tool for the documentation of medication adherence by SCD patients. The process and outcome of the study for the development of the app demonstrates a mobile-health model for effective SCD management in alignment with current clinical practice.

JSCDH-D-19-00033

SEVERITY AND BURDEN OF SICKLE-CELL DISEASE IN FRANCE: RESULTS FROM THE NATIONAL HOSPITAL DISCHARGE DATABASE OVER A 7 YEARS FOLLOW-UP.

Authors: Bernard Dauvergne[2], Cheikh Tamberou[1], Valérie Trouillet Poujol[1], Carlosse Keumeugni[2], Maryse Etienne-Julan[3], Frédéric Galacteros[4]

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Background: PMSI is an exhaustive French hospital discharge database covering all overnight or day hospitalizations used by all health facilities. SCD management is mainly linked with admission in intensive care unit (ICU), full or partial hospitalizations.

Objective: The aim of the study was to estimate the number of hospital admissions, to determine the SCD severity and its trend, to analyze the hospital burden in terms of total number of stays, total number of hospital days, and frequencies of readmissions in the database from 2009 to 2016.

Method: A cohort of patients identified in 2009 with the following ICD-10 codes of SCD as primary or associated diagnoses: D57.0 (sickle-cell anemia with crisis), D57.1 (sickle-cell anemia without crisis), and D57.2 (double heterozygous sickling disorders) has been followed over the period 2009 to 2016. All related SCD hospitalizations have been collected. SCD severity for a given patient have been defined by the occurrence of at least one of the following cumulative events occurring since the year of admission and observed over a 12 month-period: (1) at least 3 distinct admissions, (2) 8 or more transfusions, (3) a total of 10 or more days at hospital, regardless of the number of distinct admissions.

Results: 8,695 (46% females and 54% males) SCD patients were hospitalized in 2009, 51% were above 18 of years and 49% below, out of 581 were under 2 years of age (Table 1).

More than 60% of the patients has been re-hospitalized within the first year following inclusion and 80% at least once during the 7 years-follow up.

Patients under 18 years were much more re-hospitalized (90% vs 72% p=0,0001).

Averages of 5 and 21 hospitalizations per patient are observed after respectively one year of follow up and at the end of period.

50% of the admissions were full hospitalizations, 43% were identified with a diagnosis of SCD crisis and nearly 30% of them were first admitted in ICU. (Table 2)

Around 60% of the patients were severe at least once during the follow-up period (Table 3)

Conclusion: Sickle cell patients are young and severe and readmissions are frequent. It is interesting to note that a significant part of the patients presents a period of severity and in this opposite over a 7-years period, 20% of them remain free of hospitalization. Moreover, this study highlights how the French PMSI system can be used for epidemiological analyses.

Table 1: Re-admissions after 12 month-follow up and at the end of the follow up period (2009-2016)

Age	Number of patients	Re-admissions within 365 days	Re-admissions in the follow up period (2009 à 2016)
[00 , 02[	581	61%	80%
[02 , 05[	786	67%	90%
[05 , 10[	1 185	68%	93%
[10 , 18[	1 535	71%	91%
[18 , 30[	2 073	62%	78%
[30 et +[	2 535	46%	68%
Total population	**8 695**	**60%**	**81%**
Age < 18	4 445	53%	72%
Age > 18	4 250	68%	89%

Table 2: Patient care pathway

	Number of stays	Number of stays per patient	% of admission in ICU	% full hospitalizations	% of stays with crisis
After 1 yr-follow up	41 048	5	27,6%	50,3%	43,4%
After 7 yrs-follow up	185 346	21	27,0%	41,2%	43,7%

Table 3: Numbers of severe cases by severity criterion during the follow up period

Age	Number of patients	At least 3 distinct admissions in 12 months	8 or more transfusions in 12 months	10 days of full hospitalizations in 12 months	Severity composite criterion (at least 1 of the 3 criteria)
[00 , 02[	581	53%	14%	51%	62%
[02 , 05[	786	53%	16%	56%	66%
[05 , 10[	1 185	51%	17%	56%	65%
[10 , 18[	1 535	52%	14%	58%	66%
[18 , 30[	2 073	46%	12%	59%	64%
[30 et +[	2 535	29%	11%	48%	52%
Total patients	**8 695**	**44%**	**13%**	**54%**	**61%**
Age < 18	4 250	52%	15%	56%	65%
Age > 18	4 445	36%	11%	53%	57%

JSCDH-D-19-00023

ESSENTIAL FEATURES FOR SICKLE CELL DISEASE PATIENTS AND UTILIZATION OF COMMUNITY HEALTH WORKERS

Authors: Joan Corder-Mabe, RN, MS; Shirley Johnson, BA,LSW; Daniel Sop, MS; Taylor Elliott, MSW; Wally R. Smith, MD

Affiliations: *Virginia Commonwealth University*

Background: Numerous titles are utilized for CHW's that often will misrepresent their similar roles in assisting patients with chronic disease. Therefore, we use an evidence review and consensus to advance a common framework and uniform definition of the functions of CHW's, which identifies differentiated CHW roles and responsibilities. The justification for these roles offers support for certification, credentialing, education, licensure and payment for services performed by CHW's.

Methods: During a recent study funded by the NHLBI" *Start Healing in Patients with Hydroxyurea (SHIP-HU)"*a randomized controlled trial , using synthesized consensus reports and analysis was used to validate the efficacy of CHW's. In order to codify this evidence according to CHW occupational activities, we performed a rapid, narrative and tabular review of the CHW literature, including clinical trials, met an analyses and policy reports summarizing over 200 CHW interventions to improve patient health status or care delivery. We tabulated a numeric frequency count of specific roles, responsibilities, competencies, and behaviors utilized in these interventions, using a predetermined list built from a review of all the included interventions.

Results: (Table) A set of recommendations included content for formal codification of the CHW profession. Our findings suggest that the more frequent CHW behaviors might be more important or generally required of all CHWs, whereas the rarer behaviors might either be more specialized or might be less often required of all CHWs. We propose a common framework or taxonomy consisting of four levels of CHW function: Peer Community Health Worker (PCHW), General Community Health Worker (GCHW), Clinical Community Health Worker (CCHW), and Health Navigator (HN). Throughout the reviews, the CHW's displayed effective culturally competent health education to individuals and groups, as well as health system navigation and care coordination. The literature also did not display strong evidence supporting the efficacy of CHW's in the provision of direct services. Supervision and support were frequently indicated but not universally mentioned.

Core Competencies	Functions (Behaviors/Interventions Demonstrated Competencies)	Total frequency of function by source (n=309)
Health system navigation and care coordination (Service coordination, patient navigation, linkage to resources, information on community resources	Assist patient make physician/medical appointment.	14
	Assist patient understand, obtain or use health insurance.	2
	Arrange child care, transportation, or translation services.	8
	Follow-up on missed health appointments	17
	Link patient with local resource services such as assistance with transportation or meals.	41
	Make appointment telephone calls or send reminders by mail.	55
	Refer to local resources to help meet medical and psychosocial needs.	18
Coaching and social support (Bridging cultural mediation, Building trust, Emotional support, Cultural mediation, Home-based support, Cultural linkage, Cultural liaison, One-on-one counseling, Informal counseling)	Make phone calls to elicit patient concerns or to discuss health status.	4
	Discuss patient's experiences with the health care system.	8
	Refer to or lead support groups.	5
	Model behavior change.	41

	Provide informal counseling and emotional support.	76
	Conduct discussions with patient about their health status, fears or feelings about having a chronic disease or life-threatening event.	12
Culturally competent health education (Health promotion, Peer education, Outreach education)	Provide education about a specific disease or health condition to individuals or groups.	107
	Provide cultural insights to health care team.	4
	Provide information regarding general health maintenance such as diet, exercise and health screening recommendations.	29
Direct service (Serve as member of health care team, Communication with provider and/or health care team, Liaison with health care delivery system, Bridge between health care provider and patient)	Assist in taking prescribed medication or adhere to medical treatment	16
	Monitor patient's vital signs such as blood pressure or blood sugar testing or conduct health screenings.	23
	Assist meeting basic needs such as food, shelter, first aid, and housing.	6
	Assist patient develop health goals and appropriate action steps.	10
	Help patient apply for health insurance or other financial aid.	3
	Encourage patients about health lifestyle changes such as weight management, routine health screenings, or exercise.	12
	Notify and assist in the immunization of children.	4
	Accompany patient to medical	2

	appointments	
	Communicate relevant patient information to the health care team including documentation on medical record.	8
Participation in evaluation and research (Individual or community assessments)	Collect data regarding patient health status for a program or research project.	9
	Engage persons as participatory research partners.	3
	Assist in community needs assessment and assessment of population data.	6
	Conduct environmental assessments.	1
		1
	Provide computerized data entry and conduct web searches.	
Advocacy (Individual and/or community capacity building, Community mobilization, Community organizer)	Advocate for community needs or address specific issues such as living conditions.	20
	Be spokesperson or intermediaries between clients and organized medicine or bureaucracies.	11
	Teach the patient effective communication skills so they can have productive interactions with medical personnel.	3
	Provide translation and/or interpretation services.	7
Outreach and case-finding (Eligibility and enrollment)	Recruit participants into a program or service.	23

Assist patient enroll in program or service	12
Prepare and distribute materials.	14
Promote health literacy	2

Conclusions: The evidence-based CHW taxonomy definitions provides four categories that best describe CHW's in which to place workers and established appropriate guidelines for the level of services that can be provided and if tested, validated and adopted.

JSCDH-D-19-00015

EPIDEMIOLOGY OF SICKLE CELL DISEASE (HBSS) IN US MEDICAID ENROLLEES

Authors: Rishi J. Desai, MS, PhD;[1] Mufaddal Mahesri, MD, MPH;[1] Raisa Levin, MS;[1] Denise Globe, PhD;[2] Krista McKerracher, MBA;[3] Alex Mutebi, PhD;[2] Rhonda Bohn, MPH, ScD;[4] Maureen Achebe, MD, MPH;[5] Sebastian Schneeweiss, MD, ScD[1]

Affiliations: [1] *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA* [2] Vertex Pharmaceuticals Inc, Boston, MA, USA [3] CRISPR Therapeutics, Boston, MA, USA [4] Bohn Epidemiology, Boston, MA, USA [5] Hematology Division, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.

Background: Sickle cell disease (SCD) is a recessive hereditary disease, caused by a mutation in the β-globin gene. Overall, SCD most commonly affects African Americans (AA). A substantial number of SCD patients are covered under the US Medicaid program as the disease can significantly impact functioning and the ability to maintain employment. Because of a paucity of contemporary data, this study was designed to estimate the prevalence of SCD (HbSS) among US Medicaid enrollees.

Methods: Administrative claims data from US Medicaid programs were analyzed (2000 – 2012) to characterize the epidemiology of SCD (HbSS). We assembled annual cohorts of Medicaid enrollees across 13 years to estimate prevalence. Diagnosis codes for HbSS (ICD-9 codes of 282.61 and 282.62) were used to identify patients with SCD in each annual cohort. Crude and age- and race-stratified prevalence estimates with 95% confidence intervals (CI) per 100,000 were generated.

Results: The analysis included annual cohorts ranging from 13,629 cases out of 17.2 million Medicaid enrollees in 2000 to 21,781 cases out of 35.7 million Medicaid enrollees in 2012. There were notable changes in the racial/ethnic distribution of Medicaid enrollees over the years; between 2000 and 2012 the percentage of African American (AA) enrollees decreased from 32.6% to 24.8%, while Hispanics increased from 19.0% in 2000 to 26.5% in 2012. The overall crude prevalence (95%CI) of SCD (HbSS) in the Medicaid program decreased from 79.1/100,000 (77.8-80.4) in 2000 to 61.0/100,000 (60.1-61.8) in 2012. Prevalence (95% CI) in the AA enrollees ranged from 203.2/100,000 (199.5-207.0) in 2000 to 199.2/100,000 (196.2-202.1) in 2012. The highest prevalence was noted in 18-35 year old AAs, which decreased from 421.4/100,000 in 2000 to 317.9/100,000 in 2012. The birth prevalence (among those with age <1 year) was 132.8/100,000 in 2000 and increased to 177.5/100,000 in 2012 among AAs and was substantially lower among Caucasians and Hispanics (3.9 and 9.8 per 100,000 in 2012, respectively).

Conclusion: While the overall prevalence of SCD (HbSS) in Medicaid appeared to decrease over the years, the disease remains majorly prevalent in AAs especially among 18-35-year-olds, suggesting a substantial burden of disease and unmet need. These results provide the most contemporary estimates of the prevalence of SCD (HbSS) in the US. These findings can inform resource allocation and disease-focused initiatives to address this unmet need.

Sponsored by Vertex Pharmaceuticals Incorporated

JSCDH-D-19-00062

USING PROJECT ECHO TO MEET THE NEEDS OF PATIENTS WITH SICKLE CELL DISEASE

Authors: Gail Gutman MD, Megan Rees MD, Toni DeNicola PNP, Jeffrey Gershel MD, Kenneth Rivlin MD

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Background: Sickle cell disease (SCD) is a serious chronic disease affecting approximately 100,000 people in the United States. The American Society of Hematology (ASH) has defined four priorities when addressing SCD healthcare inequities: (1) Access to Care in the United States, (2) Training and Professional Education, (3) Research and Clinical Trials, and (4) Global Issues. We believe that Project ECHO (Extension for Community Healthcare Outcomes) can be an effective model to address these priorities. Project ECHO was developed to improve the treatment of hepatitis C in rural, underserved New Mexico. Employing videoconferencing with specialists, remote primary care providers (PCPs) presented patients, received guidance, and had patient outcomes equal to those who directly saw specialists. This approach of "tele-mentoring" has made significant differences in many complex diseases, from asthma to Zika. Our objective is to review the literature and discuss current and future applications of Project ECHO in the care of patients with SCD.

Methods: The ECHO Institute maintains a database of all peer reviewed papers, editorials, reports, and projects that have used their model of tele-mentoring. We examined these resources and identified applications appropriate for the ASH-defined priorities.

Results: From the start of Project ECHO in 2003, until February 2019, there have been 147 peer-reviewed papers addressing 26 different medical conditions. Most of these studies focused on (1) improving access to care and (2) professional training/education, while some have addressed (3) research through quality improvement/implementation science, and others have demonstrated the (4) model's global potential. Driven by the Health Resources and Services Administration's Sickle Cell Treatment Demonstration Project, the number of SCD ECHOs is increasing. Most address priorities (1) and (2) through mentoring PCPs. Other SCD ECHOs are concerned with eliminating inequities through quality improvement/implementation research (3). These ECHOs establish and support registries, transition of care programs, medical homes, SCD-appropriate emergency care, and community health workers. The World Health Organization has recognized the value of ECHO. Yet, as of February 2019 there were no global SCD ECHOs, despite ECHO's role for other diseases in countries with the highest prevalence of SCD.

Conclusion: SCD is characterized by inequities in healthcare quality, funding, and research. In the United States and elsewhere, Project ECHO is effective for many complex medical conditions. Its application to SCD is just beginning but it has the potential to address all 4 of ASH's priorities for sickle cell disease.

ABSTRACT BREAKOUT SESSION I
PSYCHOSOCIAL ORAL PRESENTATION

Presenting: Sunday, June 9, 2019 at 1:45PM

JSCDH-D-19-00064

HEALTH-RELATED FACTORS PREDICT ADAPTIVE FUNCTIONING PROFILES IN YOUTH WITH SICKLE CELL DISEASE

Authors: Megan Loew, PhD, Mary Keenan, BA, Rebecca Rupff, BA, Jamilla Griffith, MSW, Kathryn Russell, PhD, Jerlym Porter, PhD, MPH

Affiliations: *Virginia Commonwealth University*

Background: Youth living with Sickle Cell Disease (SCD) face health-related and life stressors. These psychosocial factors may impact youth adaptive functioning such as self-esteem and interaction with others. Limited research examines adaptive functioning and related psychosocial, disease, and demographic factors in this population. The purpose of this study is to empirically develop adaptive functioning profiles that describe subgroups among youth living with SCD, and to determine if life stressors, age, gender, hospitalizations, and SCD genotype predict the subgroup membership.

Methods: Participants were 194 youth with SCD aged 8-17 years recruited for a larger study examining SCD (M_{age}=13±2.9 years; 52% female). Youth completed the Behavioral Assessment System for Children (BASC-2), which includes four adaptive functioning subscales (relations with parent, interpersonal relations, self-reliance, and self-esteem), higher scores indicate higher functioning. Youth's age, gender, SCD genotype, and number of hospitalizations were obtained from medical records. Latent profile analyses (LPA) developed profile descriptions based on the BASC-2 subscales. Log of the odds ratio (LogO) with a $p < .05$ was considered significant.

Results: LPA revealed four distinct adaptive functioning profiles: 1) High overall adaptive functioning (n=109; 56.19%) with scores ranged (56.15-58.54); 2) High interpersonal and self-esteem (n=58, 29.90%) with scores ranged (41.94-55.05); 3) High relations with parents and self-esteem (n=11, 5.67%) with scores ranged (29.22-52.01); and 4) High interpersonal (n=16, 8.25%) with scores ranged (32.07-50.12). Experiencing less stress increased the likelihood of being in the High overall (LogO=.314, *p*=.003) or High relations with parents and self-esteem (LogO=.358, *p*=.002) groups compared to the High interpersonal group. Male gender identity increased the likelihood of being in the High interpersonal and self-esteem group (LogO=1.22, *p*=.013) compared to the High overall group. Being hospitalized in the last 3 years increased the likelihood of being in the High interpersonal group (LogO=1.66, *p*=.051) compared to the High overall group. Older age increased the likelihood of being in the High overall adaptive functioning group (LogO=.305, *p*=.020) compared to the High interpersonal strengths group. SCD genotype was not a significant group predictor.

Conclusions: The majority of our sample reported overall high adaptive functioning. Distinct patterns of all four adaptive functioning profiles were predicted by stress in youth with SCD. Age and female gender significantly predicted membership in the High overall adaptive functioning group. Self-esteem, child-parent relations, and interpersonal skills uniquely contribute to adaptive group membership. Findings support examining the impact of stress on adaptive functioning at an early age in this population.

JSCDH-D-19-00057

CARE FOR PHYSICAL ACTIVITY AND SICKLE CELL DISEASE: WHAT IS THE KNOWLEDGE OF TEACHERS IN FITNESS CENTERS AND SCHOOLS IN NORTHEAST BRAZIL?

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Affiliations: *State University of Feira de Santana*

Northeastern Brazil stands out because of the high prevalence of sickle-cell disease, with Bahia, the state with the largest black population in the country and also the highest incidence of SCD, with approximately 5.5% of the population affected the disease. In the period from 2008 to 2014, 8,103 hospitalizations for sickle cell anemia complications were registered in the state health system, proving to be a serious public health problem. Advances in the clinical treatment and improvement of the general physical state of the sick people represented gain in the components of the physical fitness and greater tolerance to physical efforts, providing autonomy for execution of the daily tasks, has allowed the insertion and participation which for children and adolescents in physical activities developed in fitness centers and schools. A cross-sectional, exploratory study was carried out with the objective was to verify the knowledge of physical education teachers about sickle cell disease and care in the gymnasium and elementary school classes in Feira de Santana, a city in the semi-arid region of Bahia, with an average of 4 sickle cell disease cases per 10,000 inhabitants. The data collection was performed using a self-administered questionnaire with multiple choice questions about participants' characteristics and knowledge about sickle cell disease, and a question about the care of these individuals. The data were treated with descriptive statistics and the project was approved by the Research Ethics Committee of the National Health Council. The study was attended by 115 teachers, 80 of whom were linked to 15 fitness centers and 35 linked to the 17 public primary schools in the region. The results showed that most of the teachers knew about the disease, but this knowledge was not sufficient to guarantee safety in the care of the patients who were ill at the sites investigated. Another important finding was that in most schools there was no record of any aspects related to student health. Regarding the care provided in the classes, the teachers reported that they were worried control of the intensity of activities, rest in moments of fatigue, monitoring of the use of prescribed medications and hydration. The physical education teachers demonstrated not know about sickle cell disease and its implications enough. The physical activities so desired by young people always have been avoided because of the insecurity these professionals

.

Table 1. Characteristics of physical education teachers of fitness centers and schools in the Northeast of Brazil, 2016-2018.

Participants	n	%
Total	115	100
Gender		
Female	31	26,9
Male	84	73,0
Formation		
Students	44	38,2

Graduates	39	33,9
Post graduates	32	27,8

Source: Direct search

Table 2. Knowledge of physical education teachers about sickle cell disease in Northeast of Brazil, 2016-2018.

	Yes		No		No answer	
	n	**%**	**n**	**%**	**n**	**%**
Have you ever heard of sickle cell disease?	85	73,9	29	25,2	1	0,8
	35	30,4	73	63,4	7	6,0
Is the information you have about this disease acquired during your undergraduate course?	35	30,4	75	65,2	5	4,3
Dou you make any special arrangements for this student?	3	2,6	46	40	66	57,3
Does the fitness centers have initial physical assessment for your students?	69	86,2	11	13,7	0	0
Does the school have any records on the health aspects of the students?	11	31,4	24	68,5	0	0

Source: Direct search

JSCDH-D-19-00040

STIGMA OF PAIN AND SICKLE CELL DISEASE IN BAHIA – BRAZIL

Authors: [1]Jayanne Moreira Carneiro, [1]Sheila Santa Barbara Cerqueira, [1]Aline Silva Gomes Xavier, [1]Evanilda Souza de Santana Carvalho, [2]Coretta Melissa Jenerette

***Affiliations**: [1]Universidad Estadual de Feira de Santana, [2]College of Nursing University of South Carolina*

Background: Although Bahia is the state with the largest population with sickle cell disease in Brazil, the sick people find barriers to their care that reveal the need for investment in interventions to overcome stigma. This study aiming to understand the stigma experienced by people with sickle cell disease (SCD), in Bahia-Brazil.

Methodology: We developed a qualitative study, 120 people, 52 males and 68 females, with SCD resident in the capital and in the interior of the state of Bahia responded to interviews, which were then submitted to content analysis.

Results: The results show that in the family environment, people with SCD are charged to perform activities that are incompatible with their tolerance, and when they do not, they are criticized and seen as incapable or useless resulting in abandonment by relatives in times of crisis. In the general public they are perceived as lazy and unproductive, incapable of working. In all the scenarios the discredit of the pain reports occurs. And in the health units the experiences of stigma are crossed by institutional racism where professionals nurture the stereotype of the slave and strong black, who supports everything, leading to delays in care, discourteous service or physical and psychological abuse.

Conclusion: It is necessary to overcome the invisibility of the disease, to clarify doubts of the public, to demystify beliefs that put the sick person in a condition of depreciation, as well as to sensitize the family about the physical and psychoemotional limitations that pain produces on the person with SCD. In the context of health services, there is an urgent need to qualify professionals about SCD at different levels of health care so that they recognize pain as one of the complications of the disease and are able to assess and treat the pain episode, understanding that it constitutes a clinical emergency.

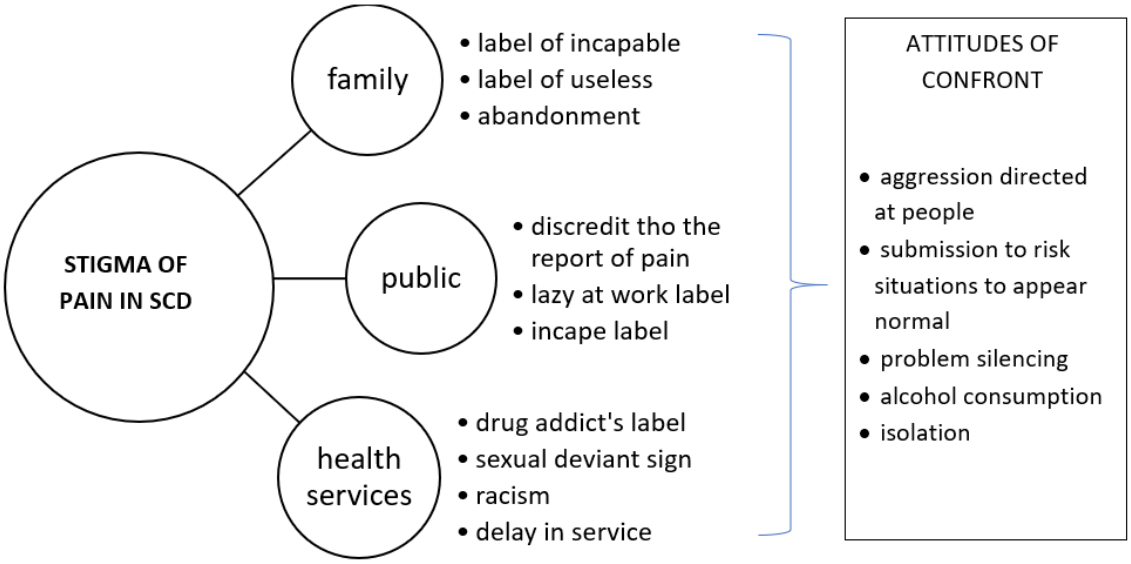


Figure 1 Aspects of stigma of pain and its coping by people with sickle cell disease

JSCDH-D-19-00005

THE ROLE OF DIETARY SELENIUM AND GPX1 IN THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

Authors: Ramasamy Jagadeeswaran[1,], Vinzon Ibanez [2,5], Lenny K. Hong[3], Robert E. Molokie[2,4,5], Alan M. Diamond[3,4], Angela Rivers[1,5]

Affiliations: *[1]Department of Pediatrics, [2]Department of Medicine, [3]Department of Pathology, [4]Cancer Center, [5]Jesse Brown Veterans Affairs (VA) Medical Center, Chicago, IL.*

Background: Sickle cell disease (SCD) affects approximately 100,000 Americans. SCD is a prevalent and devastating illness caused by a mutation in the in the β-globin gene. Despite the cause of the disease being understood for decades, the wide spectrum of disease experienced by patients remains unknown. The major contributory role of reactive oxygen species (ROS) in SCD RBCs is supported by our recent work describing mitochondrial retention in the RBCs of SCD patients and the SCD mouse model. Oxidative stress mediated hemolysis and sickling in the RBCs of SCD patients is possibly exaggerated by lower levels of antioxidants such as selenium-dependent glutathione peroxidase 1 (GPX1). GPX1 was first described as an RBC inhabitant protein and capable of protecting hemoglobin from ROS and has been reported to be lower in SCD. Selenium is an essential component of GPX1 as the amino acid selenocysteine. The levels and activity of GPX1 are particularly sensitive to nutritional selenium availability.

Methods: We used the Towns model for the SCD mice experiments. The mitochondrial content and ROS levels in RBCs was investigated by flow cytometry. GPX1 levels were examined by immunoblotting. The energy profile of circulating RBCs and reticulocytes was determined by assessing the rate of oxygen consumption as a marker for mitochondrial respiration and the extracellular acidification rate, as a marker for glycolysis using the Seahorse XF analyzer.

Results: RBCs from HbSS (SCD) mice have significantly lower GPX1 levels as compared to control HbAA mice ($p<0.003$, n=3), indicating that the reduction of GPX1 in SCD may contribute to ROS accumulation. We further investigated the impact of selenium deficiency or adequacy in the HbSS mice. Mice were provided diets either containing 0.02 ppm selenium (deficient) or 0.1 ppm selenium (adequate) for eight weeks, and GPX1 levels, mitochondrial retention, oxygen consumption rate (OCR) and Hb levels were determined. RBCs of HbSS mice provided a selenium deficient diet exhibited very low GPX1 levels as compared to mice maintained on the adequate diet ($p<0.001$, n=4). SCD mice in the selenium-deficient group also exhibited an increase in mitochondria retaining RBCs (Se deficient: 26%±6.9%, n=3 vs. Se adequate: 5 % ± 3.5%, n=3, $p<0.01$), reduced Hb levels (Se deficient 5.7± 0.17 g/dl, n=3 vs. Se adequate 7.0± 0.83 g/dl, n=4 $p<0.05$), and an increased OCR.

Conclusions: SCD mice maintained on selenium deficient diet exhibited reduced GPX1 levels, lower Hb levels and abnormal erythrocyte energy metabolism.

JSCDH-D-19-00044

RENAL MEDULLARY CARCINOMA: THE UNDER-RECOGNIZED AGGRESSIVE SEQUELAE OF SICKLE CELL TRAIT!

Authors: Dianna Hardatt M.D., Rabia Hakim M.D., Isaiah Gonzalez M.D., Revathy Sundaram M.D., Minnie John M.D., Jolanta Kulpa M.D.

Affiliation: *New York Methodist Hospital*

Background: Renal Medullary Carcinoma (RMC) is a rare aggressive form of kidney cancer. RMC has a very poor prognosis, and metastasis is seen in up to 95% of the patients at diagnosis or shortly thereafter. Patients tend to be young black males (2:1 male to female predominance) with sickle cell trait. The most common presenting signs and symptoms include hematuria and abdominal or flank pain. The majority of patients have wide spread metastasis at diagnosis which contributes to a poor prognosis. More awareness can lead to earlier diagnosis and even potential lifesaving therapies.

Case Presentation: We present a case report of a 20-year-old male with sickle cell trait who presented with abdominal pain and significant weight loss. Positive physical findings included a soft abdomen with left upper quadrant tenderness and tenderness over his L4-L5 region. Differential diagnoses that were being considered were infection, tuberculosis, collagen vascular disease, sarcoidosis, HIV and malignancy. Extensive imaging eventually revealed a paraspinal mass that was biopsied and was consistent with renal medullary carcinoma. Our patient's case is unusual in that he did not have a renal mass at the time of diagnosis.

Conclusion: Renal Medullary Carcinoma (RMC) is a rare aggressive form of kidney cancer that is predominantly associated with sickle cell trait. Prognosis is poor and the cause is still currently unknown. Sickle cell trait is often considered a benign condition however, it is associated with several complications including splenic infarction, other renal manifestations and even sudden death associated with exercise-induced rhabdomyolysis.

Awareness of the clinical spectrum of sickle cell trait can aid in earlier diagnosis of associated morbidities. A high index of suspicion in a patient with sickle trait and weight loss should alert us to the possibility of RMC. This case report emphasizes the fact that sickle cell trait is not a benign disorder and should not be taken lightly.

JSCDH-D-19-00034

CRIZANLIZUMAB DOSE CONFIRMATION IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE: SOLACE-KIDS DESIGN

Authors: Matthew M. Heeney,[1] David Rees,[2] Mariane de Montalembert,[3] Isaac Odame,[4] Raquel Merino,[5] Brian Elliott,[6] Shankaranand Bodla,[7] Julie Kanter[8]

Affiliations: *[1]Dana-Farber / Boston Children's Cancer and Blood Disorders Center, Boston, MA, United States; [2]Department of Paediatric Haematology, King's College Hospital, King's College London, London, United Kingdom; [3]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [4]The Hospital for Sick Children (SickKids), Toronto, Canada; University of Toronto, Toronto, Canada; [5]Novartis Pharma AG, Basel, Switzerland; [6]Novartis Pharmaceuticals Co., East Hanover, NJ, United States; [7]Novartis Ireland Ltd, Dublin, Ireland; [8]University of Alabama at Birmingham, Birmingham, AL, United States*

Background: Sickle cell disease (SCD) is the most common serious single-gene disorder in the world with complications including acute pain and acute/chronic organ damage. Episodes of vaso-occlusion are a hallmark of SCD. P-selectin, an adhesion molecule expressed primarily on endothelial cells and platelets, plays a key role in the initiation of leukocyte rolling along the blood vessel wall, contributing to multicellular adhesion and microvascular occlusion. SCD worsens with advancing age as repeated vascular occlusion results in cumulative endothelial damage. Crizanlizumab, a humanized monoclonal antibody, binds to P-selectin, blocking interaction with its ligands. Crizanlizumab significantly decreased vaso-occlusive crises (VOCs) vs placebo and was well-tolerated in SUSTAIN, a phase 2 study in adults with SCD. Here, we report the design of the first crizanlizumab study in pediatric patients with SCD.

Methods: Primary objectives of this phase 2, multicenter, open-label study are to confirm appropriate dosing and safety of crizanlizumab in patients >6mo–<18yrs, using sequential, descending age groups of pediatric SCD patients. Secondary objectives include number of VOCs and number/duration of hospitalizations/emergency room visits. Planned enrollment is ≥100 patients with confirmed SCD diagnosis (all genotypes), who experienced ≥1 VOC within the preceding 12mo, in 3 sequential descending age groups: Group 1 (≥26 patients; 12yr–<18yr), Group 2 (≥26 patients; 6yr–<12yr), and Group 3 (≥8 patients; 2yr–<6yr) and (≥6 patients; 6mo–<2yr). Dose will be confirmed (Part A) by ≥8 patients in Group 1. If unconfirmed, dose will be adjusted based on observed pharmacokinetics/pharmacodynamics, and ≥8 additional patients will be enrolled in Group 1/Part A to confirm the new dose. After dose confirmation, Group 1 will be expanded (Part B), with ≥8 patients enrolled to Group 2 for dose confirmation. This schema will continue until dose confirmed in Group 3, which will be expanded for enrollment of an exploratory group(≥6 patients; 6mo–<24mo). Patients treated with hydroxyurea/hydroxycarbamide must have taken it for ≥6mo prior to enrollment and not plan dose adjustments except for weight changes. Crizanlizumab (5.0 mg/kg intravenously) will be administered on weeks 1, 3 and every 4 weeks thereafter for 2 years.

Results: Trial ongoing (ClinicalTrials.gov: NCT03474965).

Conclusion: This study will address an unmet need in pediatric SCD patients by establishing crizanlizumab pharmacokinetics/pharmacodynamics and confirming dose in different age groups. Safety will be assessed as a primary objective. Additionally, the number of VOCs and number/duration of hospitalizations/emergency room visits will be assessed as a secondary objective.

ABSTRACT SESSION II
CLINICAL EPIDEMIOLOGY ORAL PRESENTATION

Presenting: Sunday, June 9, 2019 at 3:30 PM

JSCDH-D-19-00059

FETAL HEMOGLOBIN AND LEG ULCERS IN ADULTS WITH SICKLE CELL DISEASE

Authors: Seda Tolu, Ugochi Ogu, Andrew Crouch, Giacomo Vinces ,Caterina Minniti

Affiliation: Albert Einstein Medical Center

Background : Sickle cell disease (SCD) is a monogenetic inherited disorder with pleomorphic clinical manifestations. Leg ulcers are a frequent and debilitating complication of sickle cell disease, particularly of the SS genotype. Hemoglobin F (Hb F) concentration is the major genetic modifier of SCD clinical complications, including leg ulcers, and been found to be protective in a previous studies. However, to date, no specific level of hemoglobin F has been identified that results in prevention and/or resolution of leg ulcers. Our aim is to determine a specific threshold of hemoglobin F above which there is low or no occurrence of leg ulcers in patients with SCD.

Methods : After obtaining IRB approval, we queried the Electronic medical records (EMR) of adult SCD patients in our database at Montefiore Medical Center, Bronx, New York. EMRs were reviewed in detail to confirm the documentation of leg ulcers and laboratory values. Lifetime average hemoglobin F values were calculated for each patient using all recorded Hb F values in his or her chart. Patients who were ever prescribed hydroxyurea (HU) and those who were not were included in the study.

Results: Out of 804 adult patients with sickle cell disease, we identified a total of 90 with history of prior or current leg ulcers, most of which were chronic in nature. Twenty seven patients were noted to have a lifetime average Hb F > 8% which included 13 women and 14 men, age range 23 to 72. Four of these patients were never treated with hydroxyurea at any point in time. Patient data is displayed in the table below.

Age, Sex	HbF %	Age, Sex	HbF %	Age, Sex	HbF %
64 M	8.3	36 M	11.8	41 M	17.9
35 M	9.3	51 F	12.1	60 M	18.2
38 F	9.5	40 M	12.1	43 F	18.5*
58 F	9.8	58 F	13.7	65 F	20.7
36 F	10.5	23 M	14.9	50 M	20.9*
33 F	10.6	40 F	15.6	62 M	21.5
22 M	10.7	66 F	15.6	72 F	23.7*
41 M	10.8	47 F	16.7	40 M	29.5*
31 M	11.6	42 M	16.8	40 F	31.9

*Never on Hydroxyurea

Discussion: In a modern cohort of post HU patients, we identified 11 % of SCD patients with leg ulcers, a higher incidence than what was reported in the Cooperative Study of Sickle Cell Disease (5%), which included mostly pediatric patients; but lower than the Bethesda cohort (~18%), which may have been enriched for patients with other vasculopathies, such as high TRV[1,2]. A possible explanation is that, as patients with SCD live longer, the prevalence of leg ulcers increases, which is evident in our cohort with a mean age of 37 years and range up to 72 yrs. Interestingly, we identified 4 patients with hemoglobin F > 20% who had never been on HU and developed leg ulcers. Certainly HU could not be blamed for their occurrence. We conclude that even very high Hb F levels are not universally protective against leg ulcers. Intracellular distribution of HbF is more important than the total HbF, therefore its effect on hemolysis and in protecting from end organ damage cannot be predicted solely by the total HbF level. Patients with hemoglobin F>8 % are still prone to developing leg ulcers and practitioners should have high vigilance when taking care of these patients.

Reference

1. Koshy M, Entsuah R, Koranda A, et al. Leg ulcers in patients with sickle cell disease. Blood 1989;74:1403–1408.
2. Minniti, CP, Taylor JGt Hildesheim M, et al. Laboratory and echocardiography markers in sickle cell patients with leg ulcers. Am J Hematol 2011;86: 705–708.

JSCDH-D-19-00045

CLINICAL TRIAL OF A FETAL GLOBIN INDUCING AGENT WHICH MODULATES REPRESSORS: BALANCING FACTORS FOR OPTIMAL ACTIVITY

Authors: [1]Susan P Perrine, [2]Betty S Pace, MD, [3]Kevin Kuo, MD, [4]Sylvia T. Singer, MD, [3]Rebecca LeRoux, RN, [5]Douglas V. Faller, MD,PhD

Affiliations: *[1]Boston University School of Medicine, [2]Augusta University, [3]Toronto General Hospital, University Health Network, [4]USCF Menioff Children's Hospital at Oakland, [5]Phoenicia BioSciences, Inc*.

Background: Up-regulation of HbF in a majority of red blood cells is clinically proven to reduce anemia and clinical severity in sickle cell disease (SCD) and beta thalassemia (BT). More than 70 small molecules induce fetal globin gene expression *in vitro,* through complimentary molecular mechanisms. The timing of addition of inducing agents relative to stage of erythroid differentiation is important for activity. Exposure of erythroid progenitors to most candidates results in high induction only during a period of EPO sensitivity, while exposure in early or late stages of differentiation often has no or minimal effect.

A repurposed therapeutic, PB-04, which reduces or abolishes mRNA, protein, and/or binding of multiple repressors (*BCL11A, LSD-1*, *HDAC3*) of the fetal globin genes, and promotes appearance of histone activation marks, demonstrates high inducing activity in patients' erythroid progenitors, in anemic baboons with active erythropoiesis, and in transgenic mice undergoing frequent phlebotomy. PB-04 is reported to not induce HbF in subjects without stress erythropoiesis. The magnitude of fetal globin responses *in vitro* differs in progenitors of patients with genomic modifiers associated with variable baseline fetal globin levels. PK parameters of PB-04 in other populations demonstrate brief half-lives, but the drug has been effective for > 40 years in treating an unrelated condition. The design of regimens to optimize these diverse factors may be challenging.

Methods: A trial has been designed to investigate human equivalent doses of PB-04 based on intermittent oral administration in anemic baboons, which produces high-level induction (12-30 fold) of fetal globin mRNA and increases F-reticulocytes 3-fold. Three dose-escalating cohorts will be studied initially. If induction is demonstrated, two expansion cohorts in BT intermedia and SCD will be studied. If induction is not observed, dose and schedule will be adjusted based on PK data. Endpoints include PK parameters, HbF, F-reticulocytes/ F-cells, HbF protein/cell, hemolytic assays, hematology. Seven SNPs which affect basal HbF levels, and *2* SNPs which affect cell proliferation, will be assessed.

Results: An IND is approved for a PK and preliminary activity study of PB-04 in patients with beta hemoglobinopathies.

Conclusions: Intermittent exposure targeting differentiating erythroid progenitors will be investigated with an inducing agent which abolishes BCL11A protein and reduces genomic binding of the transcriptional repressors LSD-1 and HDAC3. Dose equivalents and schedule were effective in anemic baboons and transgenic mice.

JSCDH-D-19-00055

MICROGLIA-LIKE CELLS DERIVED FROM HEMATOPOIETIC STEM AND PROGENITOR CELLS ARE A MODEL SYSTEM TO INVESTIGATE CHRONIC PAIN IN SICKLE CELL DISEASE

Authors: Yankai Zhang[1], Celeste K. Kanne[1], and Vivien A. Sheehan[1]

Affiliations: 1. Division of Hematology/Oncology, Department of Pediatrics, Baylor College of Medicine, Houston TX

Background: Patients with sickle cell disease (SCD) often experience severe chronic pain. In chronic pain, microglia are readily activated, stimulating neurons to send a pain signal. Human microglia are difficult to obtain; we proposed to culture induced microglia-like cells (MLC) from human peripheral blood (PB) to develop a model system to investigate chronic pain in sickle cell disease.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from three individuals from each of the following patient groups: SCD and chronic pain (SCD CP+, defined as pain most days for 3 months), SCD without chronic pain (SCD CP-), and normal donors (WT). PBMCs were cultured with human GM- CSF (10 ng/ml) and human IL-34 (100 ng/ml) to induce peripheral blood derived microglia (PB-MLC). On day 7 of culture, cells were collected and morphology analyzed by phase contrast microscopy, phenotyped by flow cytometry, and indirect immunofluorescence with anti-CX3CR1, TMEM119, CD68, Iba1 antibodies. TNF-alpha, IL-1beta, IL-10 secreted by PB-MLCs were measured with ELISA. Microglia morphology was evaluated by quantitative analysis of cell body roundness and branch length.

Results: When cultured with GM-CSF and IL-34, PBMCs developed microglial morphology, were $CD11b^{high}$ and $CD45^{low}$ by flow cytometry, $CX3CR1^{+}$ and $TMEM119^{+}$ by fluorescence microscopy, consistent with microglia. We treated the PB-MLC with LPS, and found that treated PB-MLC cells had significantly higher CD68 and Iba1 positivity compared to resting microglia cells, indicating activation. PB-MLC differed significantly depending on donor group. SCD CP+ had shorter and fewer branches than WT; branching from SCD CP- were intermediate in number and length. Activated PB-MLC derived from patients with SCD secreted more inflammatory cytokines than PB-MLC derived from normal donors, suggesting that donor characteristics are retained by the PB-MLC. To evaluate the possibility of using this model system to screen compounds, we tested MLC cells with the following drugs: gabapentin, metformin, piceatannol, and resveratrol. All suppressed the release of proinflammatory cytokine from LPS-induced PB-MLC in a dose-dependent manner, and reversed the deramification of activated PB-MLC upon LPS stimulation by quantitative analysis of cell body roundness and branch length with immunostaning of Iba1, with gabapentin exhibiting the smallest effect.

Conclusions: We have established the microglia-like nature of the cultured peripheral blood cells derived from patients with SCD and normal blood donors. We propose to use this model system to derive mechanistic insights into the development of chronic pain in SCD, and to screen pharmacologic agents to treat chronic pain.

Acknowledgments: This work was supported by 1K08 DK110448-01 from the National Institute of Diabetes and Digestive and Kidney Disease

JSCDH-D-19-00003

WEB-BASED TECHNOLOGY AS A LEARNING TOOL TO IMPROVE DISEASE KNOWLEDGE IN ADOLESCENT PATIENTS WITH SICKLE CELL DISEASE

Authors: Anjelica Saulsberry, Jason Hodges, Audrey Cole, Jerlym Porter, Jane Hankins

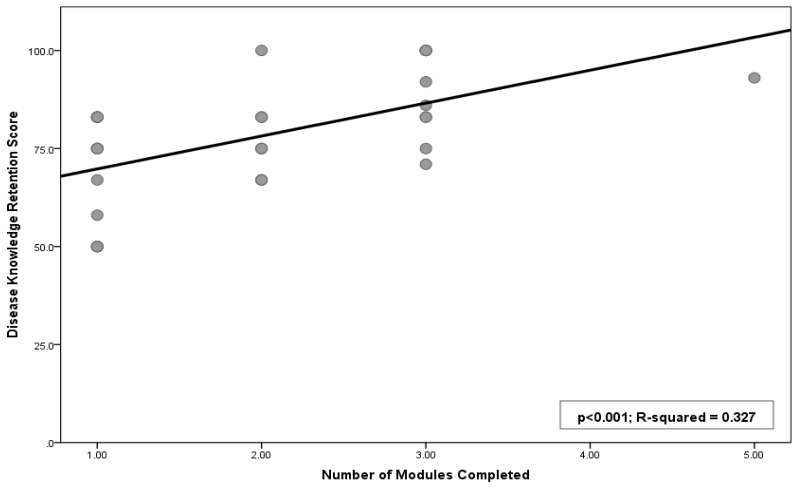
Affiliation: St. Jude Children's Research Hospital

Background: Sickle cell disease (SCD) is a chronic, genetic red blood cell disorder. Advances in SCD treatment have contributed to an increase in survivorship of youth with SCD, prompting the need for "transition readiness" prior to transition into the adult healthcare system. "Transition readiness" encompasses disease specific knowledge and self-management skills and result in improved transition outcomes. The Sickle Cell Transition E-Learning Program (S.T.E.P) is a web-based learning tool aimed at increasing "transition readiness." For the current study, we sought to investigate the use and effectiveness of S.T.E.P. We hypothesize that number of modules completed will be positively correlated to improved disease knowledge retention and confidence in self-management skills.

Methods: The S.T.E.P. program is a public, web-based 6-module tool covering pain, infection, SCD complications, healthy living, genetics, and self-advocacy. Self-management confidence was measured by a self-management skills checklist (SMSC) modified from the validated Transition Readiness Assessment Questionnaire. All patients who participate in the transition program are offered participation in S.T.E.P. in clinic as a complement to education sessions. Disease knowledge retention was measured via an assessment that reflects the entire educational curriculum provided during adolescent education visits. Association of S.T.E.P. modules and disease knowledge retention and self-management scores were evaluated using Pearson correlations.

Results: Thirty-six African-American adolescents with SCD between the ages of 12-15 (25 males; 11 females) participated in the S.T.E.P. The number of modules completed were one (15 participants) two (10 participants) three (10 participants) and five (one participant). The average disease knowledge score for all S.T.E.P. modules was 77 (range of 50-100) for all participants. A positive correlation (r=0.57) was found between number of modules completed and final disease knowledge score ($p<0.001$). No correlation was found between number of modules completed and self-management scores. (Figure 1)

Conclusions: The S.T.E.P. program may serve as a complement to in-clinic disease knowledge sessions for increasing disease knowledge retention prior to transfer to adult care. Further investigation includes replicating our findings in other SCD patient populations and conducting a randomized prospective study to determine the effectiveness of S.T.E.P. as an intervention to increase disease literacy in the SCD youth.



JSCDH-D-19-00058

EXPERIENCES WITH HYDROXYUREA IN AN URBAN ADULT SICKLE CELL DISEASE PATIENT POPULATION

Authors: [1]Christopher Bradford, [1]Hope Miodownik, [2]Gracy Sebastian, NP, [2]Merin Thomas, NP, [2]Ugochi Ogu, MD, and [2]Caterina Minniti, MD

Affiliations: [1]Albert Einstein College of Medicine, [2]Montefiore Medical Center

Background: Hydroxyurea remains the first-line agent for adults with sickle cell disease (SCD), with well- documented improvements in morbidity and mortality. Despite its proven utility, many SCD patients are not prescribed or not taking hydroxyurea. Few studies have evaluated reasons behind this phenomenon among large adult populations.

Methods: Adult patients with SCD at a large urban SCD center completed a survey. Data from 224 outpatients were analyzed. Additional information was collected and confirmed using the electronic medical record.

Results: In total, 173 patients (77.2%) have ever been prescribed hydroxyurea. Among these, 65.3% were taking hydroxyurea when surveyed. For those with severe disease genotypes (HbSS or HbS- BetaThal0), 91.0% have ever been prescribed hydroxyurea, with 68.4% taking it when surveyed. Of those with mild disease genotypes (HbSC or HbS-BetaThal+), 42.1% have ever been prescribed hydroxyurea, with 50% taking it when surveyed.

Among those patients ever been prescribed hydroxyurea, 17.3% endorsed medication side effects, with fatigue, hair loss, and gastrointestinal distress the most common (each 16.7% of those reporting side effects). Other reasons included dizziness, headache, weight gain, cytopenia, and drug reaction (each 6.7%). Hydroxyurea was discontinued at some point by 35.3% of patients, with 24.6% citing side effects as the cause for discontinuation. Other reasons for discontinuation included perceived ineffectiveness (19.7%), physician direction (16.4%), reproductive health, ulcer formation, and general dissatisfaction with hydroxyurea (each 8.2%).

Conclusions: These results suggest that adult patients with severe SCD genotypes are being prescribed hydroxyurea at high rates, with 91.0% having ever been prescribed, and 68.4% taking it at the time of this study. The largest reason for discontinuation among our patients was medication side effects. Some patients reported well-described side effects (weight gain, cytopenias, hair loss).

Others cited side effects that may not be related to hydroxyurea (back pain, depression). Interestingly, 16.4% of patients discontinued hydroxyurea due to perceived ineffectiveness.

By identifying variability in reported side effects and reasons for discontinuation, this descriptive study highlights the need for clinicians to clearly communicate benefits and challenges of hydroxyurea use with their patients to further improve rates of prescribing and adherence.

Patient Demographics (frequency and percentage)

Sex	Male	104	46.4%	**Race**	Black (non-Hispanic)	158	70.5%
	Female	120	53.6%		Hispanic	54	24.1%
Genotype	HbSS/HbS-BetaThal0	167	74.6%		Other/Unreported	12	5.4%
	HbSC/HbS-BetaThal+	57	25.4%	**Age**	37.1 (SD=12.7)	Range 20-86	

TABLE

JSCDH-D-19-00031

SUCCESSOR STUDY: BASELINE DEMOGRAPHICS OF THE RETROSPECTIVE, NONINTERVENTIONAL FOLLOW-UP STUDY IN A SUBSET OF PATIENTS WITH SICKLE CELL PAIN CRISES WHO PREVIOUSLY PARTICIPATED IN SUSTAIN IN THE UNITED STATES

AUTHORS: Nirmish Shah,[1] Ralph Boccia,[2] Walter K. Kraft,[3] Vince Cataldo,[4] Jincy Paulose,[5] Dramane Lainé,[5] Das Purkayastha,[5] Abdullah Kutlar[6]

AFFILIATIONS: [1]Duke University Health System, Durham, NC; [2]Center for Cancer and Blood Disorders, Bethesda, MD; [3]Thomas Jefferson University, Philadelphia, PA; [4]Our Lady of the Lake-Mary Bird Perkins Cancer Center, Baton Rouge, LA; [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [6]Sickle Cell Center, Medical College of Georgia, Augusta University, Augusta, GA

BACKGROUND: SUCCESSOR (*SU*STAIN *C*hart-review of *C*rizanlizumab to *E*valuate *S*ickle-cell *S*tudy *O*ne-year *R*etrospective) reviewed medical records of a subset of patients who completed the SUSTAIN study at US sites to assess subsequent cases of significant pain crisis events and generate real-world data on treatment patterns and health care resource utilization (HCRU) upon completion of crizanlizumab treatment. SUSTAIN was a phase 2, randomized, double-blind, placebo-controlled, 52-week study that compared the effect of crizanlizumab, a P-selectin inhibitor, versus placebo on the frequency of sickle cell pain crises (SCPCs, or vaso-occlusive crises [VOCs] leading to a health care visit) in patients with any genotype of sickle cell disease (SCD).

METHODS: SUCCESSOR is a multicenter, retrospective cohort study of a subset of US patients (≥18 years old) who participated in SUSTAIN to evaluate SCD-related outcomes up to 52 weeks following trial completion. SUCCESSOR included the SUSTAIN population who received at least 12 of the 14 study drug doses, completed a visit at least 14 days after the final dose, and had no major protocol deviations that impacted SUSTAIN efficacy assessments. The post-SUSTAIN study period was from November 2014 to March 2017 and patients' data were obtained from medical records. Crizanlizumab was not administered in the 52 weeks post-SUSTAIN. Patient consent was obtained prior to data collection if required by local and/or central research ethics review.

RESULTS: In SUCCESSOR, baseline demographic data for 48 patients are reported (15, 18, and 15 patients who were previously randomized in SUSTAIN to receive crizanlizumab 5 mg/kg, crizanlizumab 2.5 mg/kg, and placebo, respectively). The median age was 31.5 years (range 19-65 years) and 69% were female. The majority of patients were Black or African American (96%). One patient had HbSβ^{+}, 4 had HbSβ^{0}, 10 had HbSC, 1 had HbS-Lepore disease; all remaining 32 patients had HbSS. The majority of patients live in the Southern US geographic region (63%), followed by the Midwest (18%), Northeast (15%), and West (6%). At 52 weeks post-SUSTAIN, 98% of patients were alive with no bone marrow transplant, no new clinical trial participation, and were not lost to follow-up. No deaths occurred in the 52 weeks post-SUSTAIN. There were high rates of HCRU regardless of the treatment received in SUSTAIN, as more than 60% of patients had at least one hospitalization in the 52 weeks post-SUSTAIN.

CONCLUSION: SUCCESSOR is a real-world study generating evidence on VOC rates, treatment patterns, and HCRU in patients post-SUSTAIN.

ABSTRACT BREAKOUT SESSION II
CLINICAL RESEARCH ORAL PRESENTATION

Presenting: Sunday, June 9, 2019 at 3:30 PM

JSCDH-D-19-00060

A PHASE II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTI-CENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND EFFICACY OF RIOCIGUAT IN PATIENTS WITH SICKLE CELL DISEASE (STERIO-SCD)

Authors: Caterina P. Minniti, Kaleab Z. Abebe, Claudia R. Morris, Victor R. Gordeuk, Mark T. Gladwin, Gregory J. Kato and the STERIO-SCD Investigators

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Background: Systemic hypertension, pulmonary hypertension and proteinuria are each predictive of morbidity and mortality in patients with sickle cell disease (SCD). These complications are associated with more intense hemolytic anemia and decreased nitric oxide bioavailability. Riociguat is a soluble guanyl cyclase stimulator, approved by the FDA to treat patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension.

Methods: STERIO-SCD is an investigator-initiated, industry-funded Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel groups study aimed to evaluate the safety, tolerability and the efficacy of riociguat compared with placebo in patients with SCD. Adult patients are eligible if they have at least one of the following: Systolic blood pressure ≥130 mm Hg, urine albumin to creatinine ratio >300 mg/g, tricuspid regurgitant velocity (TRV) >2.9 m/sec, NT-proBNP level ≥160 pg/mL, or protein 1+ or higher on urinalysis.

This randomized study involves 12 weeks of treatment with riociguat pills or placebo pills, and a follow-up period of 30 days after treatment. The dose is adjusted every 2 weeks based on systolic blood pressure, with a goal to escalate from a starting dose of 1mg TID to 2.5 mg TID. Physical examinations, vital signs, blood tests and questionnaires are performed at 2-week intervals during the double-blinded study treatment. Echocardiogram, urine albumin/creatinine, six-minute walk distance and the Adult Sickle Cell Quality of Life Measure (ASCQ-Me) are assessed at the beginning and end of the treatment phase.

Results: The study is presently open at 11 sites, with 6 more sites in process. Enrollment is underway for a target of 100 patients completing the treatment. Additional sites are being sought.

Conclusions: Although many studies are evaluating efficacy of agents aimed at reducing acute vaso-occlusive complications of SCD, STERIO-SCD addresses an unmet need to control the life-limiting, hemolysis-related chronic vasculopathy associated with death.

Acknowledgment: Bayer provides funding and study drug for this trial. The University of Pittsburgh is the study sponsor, data coordinating center and central pharmacy. STERIO-SCD investigators: Sophie Lanzkron, Johns Hopkins University; Elizabeth Klings, Boston University Medical Center; James Ford, UNC Chapel Hill; Marilyn Telen, Duke University; Payal Desai, Ohio State University; Laura De Castro, University of Pittsburgh; Temeia Martin, Medical University of South Carolina; Wally Smith, Virginia Commonwealth University; Julie Kanter, University of Alabama at Birmingham; Ken Ataga, University of Tennessee. The core team at University of Pittsburgh includes Carolyn Newkirk, Susan Spillane, Nydia Chien, Nancy Petro, Yingze Zhang and independent statistician Seyed Mehdi Nouraie.

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RESULTS FROM THE DISPLACE CONSORTIUM: PRACTICE PATTERNS ON THE USE OF TRANSCRANIAL DOPPLER SCREENING FOR RISK OF STROKE IN CHILDREN WITH SICKLE CELL ANEMIA

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Background: Stroke is a devastating complication of sickle cell anemia (SCA). The STOP (Stroke Prevention Trial in Sickle Cell Anemia) protocol provides guidelines for stroke screening using transcranial Doppler ultrasound (TCD) and prevention with chronic red cell transfusion therapy (CRCT). The DISPLACE (Dissemination and Implementation Looking at the Care Environment) study consists of 28 sites across the US, designed to identify barriers to implementation of the STOP protocol and test novel methods for overcoming barriers. The study presented in this abstract evaluated current TCD and CRCT measurement and practices at DISPLACE consortia sites.

Methods: An electronic survey was sent to the principal investigator (PI) for each site. PIs were specialty care providers for children with SCA. Items pertaining to TCD included: screening technique; screening frequency; follow-up for abnormal, conditional, and inadequate results; standard value ranges.

Results: Of the 28 PIs, 53.5% were female, 77.8% were White, 11.1% were Asian, 7.4% were Black, and 7.4% were Hispanic/Latino. 57.1% of sites use standard TCD, and 92.9% order TCD annually. To calculate the time-averaged mean of the maximum (TAMM) velocities and characterize TCD results, 96.4% of sites use the middle cerebral artery, but sites also use a variety of other vessels. Table 1 presents the TAMM ranges used to characterize results. Table 2 presents the actions taken/follow up by TCD result.

Table 1: Minimum and maximum TAMM values (cm/sec) reported by sites with among-site means for results characterized as normal, conditional, and high/abnormal by TCD method compared with the STOP protocol

	Normal TCD Low	Normal TCD High	Conditional TCD Low	Conditional TCD High	High/ Abnormal TCD Low	High/ Abnormal TCD High
STOP Protocol		169	170	199	200	
(TCD)						
Standard TCD						
Mean	70	170	170	199	200	234
Min	50	169	170	199	200	200
Max	120	179	171	200	201	300
Imaging TCD (TCDi)						
Mean	83	163	163	188	190	210
Min	0	149	150	174	180	175
Max	170	170	170	199	200	299

Table 2: Action taken or follow-up by TCD result

Action or follow up	Abnormal/high	Low Conditional	High Conditional	Inadequate
(n = 28)	% sites (n)	% sites (n)	% sites (n)	% sites (n)
Initiate HU if not currently on	7.1 (2)	57.1 (16)	67.9 (19)	7.1 (2)
Start CRCT	85.7 (24)	0	3.6 (1)	0
No change	0	0	3.6 (1)	3.6 (1)
Initiate HU and CRCT	3.6 (1)	0	0	0
Obtain MRI/MRA	64.3 (18)	32.3 (11)	46.4 (13)	57.1 (16)
Repeat TCD prior to change	28.6 (8)	71.4 (20)	96.4 (27)	60.7 (17)

Conclusions: Nearly all sites order TCD screening annually, as recommended by guidelines. Variation in practices pertaining to standard TAMM ranges for characterizing results, follow up with MRI/MRA, and initiation of CRCT indicate areas for future study.

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DEVELOPMENT AND EVALUATION OF A SICKLE CELL DISEASE SEVERITY INDEX TO VALIDATE CLINICAL ADHESION BIOMARKERS

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Sickle cell disease (SCD) is a complex multisystem organ condition characterized by vaso-occlusive events and significant phenotypic variability. There is no universally accepted system to objectively define sickle cell disease (SCD) severity, which has hindered attempts to validate the clinical utility of SCD biomarkers. We developed an objective clinical SCD severity index (SCDSI) that reflects an individual's cumulative life-time burden of SCD-related vaso-occlusive pathology. An SCDSI was established by quantifying the total number of objectively documentable vaso-occlusive end-organ events, including acute chest syndrome, stroke, priapism, splenic sequestration, hepatic sequestration, and cholelithiasis indexed over the total years of life. Each objectively documentable "event" is given equal weight in the scoring system for simplicity. These events were selected because they could be objectively verified via retrospective review of medical records within a typical healthcare system or practice. We evaluated the SCDSI in 35 subjects with HbSS disease who were enrolled in a longitudinal SCD study that validated real-time clinical status via a previously described electronic patient reported outcome tool (ePRO)[1]. Daily patient input validated the patient -reported steady state of each individual patient over 6 months. We developed a microfluidic, flow-based adhesion bioassay to measure erythrocyte adhesive properties (previously described[2]) in a CLIA lab environment. Clinical adhesion biomarkers were obtained every 3 weeks at the patient's home during baseline clinical status validated by daily self-report. Baseline adhesion indices showed a strong positive correlation with the SCDSI of the study subjects ($r=0.585$, $p<0.0011$), validating that the cumulative lifetime burden of vaso-occlusive pathology is reflected in the erythrocyte adhesive index during the subjects baseline clinical state. The goal of SCD-modifying therapy is to ultimately reduce the vaso-occlusive pathology by improving the health and survival of the sickle erythrocytes. The results of this study suggest that erythrocyte health, as assessed by a standardized clinical adhesion assay, may be a surrogate for clinical disease severity. The SCDSI provides a simple and accessible scoring system for clinicians to quantify historical disease burden for individuals with SCD. Further studies are needed to validate the utility of the SCDSI in assessing the clinical utility of SCD-specific biomarkers in clinical practice. A prospective study is underway to determine the predictive value of the SCDSI for prospective vaso-occlusive complications in this SCD population.

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SICKLE CELL TRAIT PRESENTING AS SICKLE CELL DISEASE: A CASE REPORT

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Background: Sickle cell disease is a hemolytic anemia with vaso-occlusive complications, including pain, tissue ischemia, splenic infarct, and recurrent infections. It occurs secondary to two abnormal hemoglobin beta globin chains; the glutamic acid is switched with valine at the sixth position. In contrast, children with sickle cell trait have one abnormal allele present, with both hemoglobins A and S. This is clinically protective and explains why these individuals are usually asymptomatic.

An eight year old male, diagnosed with sickle cell trait on newborn screen, was admitted for worsening right calf pain. He was diagnosed with acute osteomyelitis of right distal femur, with myositis, requiring surgical intervention and antibiotics. His hospitalization was then complicated with avascular necrosis of his right femur and stuttering priapism lasting six days.

Objective: To expand focus beyond a patient's newborn screen results, and to understand the complete clinical picture, when caring for a child with sickle cell trait. Understanding the possible sequelae of children with rare hemoglobinopathies and the appropriate evaluation for diagnosis.

Design/Methods: Work up included hemoglobin electrophoresis, DNA sequencing, and mass spectrometry. Thorough past medical history assessment and chart review completed. Family history investigated in detail and hemoglobin evaluation of both parents performed.

Results: Chart review showed failure to thrive, with documented weight of 18.2 kg (1st percentile) and height 107 cm (3rd percentile) at seven years old. Recurrent bone and abdominal pain observed since two years of age. Starting at five years old, electrophoresis was performed multiple times, which revealed both hemoglobin A and S.

On admission, his hemoglobin was 8.2, with 6.5 percent reticulocytes. Hemoglobin fractionation showed Hb S 29.8%, Hb A and Hb Quebec-Chori 61.7%, Hb A2 2.6%, and Hb F 5.8%. This abnormal hemoglobin was confirmed with DNA sequencing and mass spectrometry, which revealed his abnormal beta globin chain. Positive sickle solubility test.

Conclusion: This patient's newborn screen and initial hemoglobin evaluations did not confirm sickle cell disease, although he experienced complications expected with sickle cell disease rather than trait. After many hospitalizations, this patient's diagnosis was confirmed on electrophoresis revealing heterozygous for Hb S and Hb Quebec-Chori. This hemoglobin variant is due to a substitution of the 87 position on the beta chain, from Thr to Ile, indistinguishable from hemoglobin A on electrophoresis. This hemoglobin variant has only been described two times previously and can result in severe sickle cell disease, making it important to detect early, before the patient experiences complications.

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FEASIBILITY AND QUALITY VALIDATION OF A MOBILE APPLICATION FOR ENHANCING ADHERENCE TO OPIOIDS IN SICKLE CELL DISEASE

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Introduction: American health literacy is poor, thereby compromising medication adherence, patient safety, and important health outcomes. Prescription opioid nonadherence, specifically opioid misuse, has likely contributed to the prescription opioid epidemic and opioid-related morality in the US. Popular methods to measure and control opioid adherence have limitations, but mHealth, specifically smartphone applications, offer a potentially useful technology for this purpose.

Methods: We conducted Phase IV feasibility testing of the OpPill application, a mobile monitoring and reporting system intended to enhance health literacy and adherence by collecting data and providing systematic feedback on pain and opioid use. We asked patients with Sickle Cell Disease (SCD) to review, test, and evaluate the OpPill application, all at one sitting. Immediately after OpPill review and use, patients completed the Mobile Applications Rating Scale (MARS), a validated tool for assessing the quality of health mobile apps. The MARS contains 4 scales (range of each scale= 0-4) that rate engagement, functionality, aesthetics, and information quality. It also asks items that rate subjective quality, relevance and overall application impact.

Results: Patients (n=28) all had one of various SCD genotypes; were ages 19 to 59 yrs (mean 36.56); 53.6 % were female, and; 39.3% had completed some college. Patients rated the OpPill application highly on four scales: Engagement, 3.93 ± 0.73; Functionality, 4.54 ± 0.66; Aesthetics, 3.92 ± 0.81; Information, 3.91 ± 0.87. The majority of patients found the application to be relevant for their care. Ninety-six percent of patients reported the information within the app was complete, while 4% estimated the information to be minimal or overwhelming. Patients (91.7%) overwhelmingly reported that the quality of information as it pertained to SCD patients was relevant; only 8.3% found the application to be poorly relevant to SCD. Similarly, patients (91.7%) overwhelmingly rated both the application's performance and ease of use positively. The large majority of participants (85.7%) found the application to be interesting to use, while 74% found it entertaining. All users found the application's navigation to be logical and accurate with consistent and intuitive gestural design.

Conclusion: We conclude that surveyed SCD patients, using a validated rating tool, rated the OpPill application, specifically targeted to monitor opioid use and pain and opioid behavior in patients with Chronic Non-Cancer Pain, as feasible and easy to use

Keywords: Medical Apps, Pain management, Opioids, Chronic Condition, Sickle Cell Disease, mHealth

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CARDIAC INJURY IN SICKLE CELL DISEASE

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Background: Previous study at our institution has shown that 3/22(13%) patients with clinically stable sickle cell disease(SCD) had impaired myocardial perfusion reserve but no epicardial coronary artery disease. The prevalence of this microvascular disease and utility of cardiac troponin in predicting such changes has not been clearly defined. In this study, we evaluated the prevalence of myocardial ischemic injury in SCD. We also examined the sensitivity and specificity of troponin levels to predict microvascular ischemic injury in patients with SCD.

Methods: We conducted a retrospective chart review of patients with SCD seen at OSU Wexner Medical Center from July 2005 to July 2015 to identify patients with troponin-I elevation (normal <0.11 ng/mL) and/or myocardial ischemic changes on cardiac MRI. Clinical and laboratory values related to these events were analyzed. Abnormal cardiac MRI was characterized by impaired subendocardial or myocardial perfusion, myocardial fibrosis or edema, and cardiomyopathy. Fisher's exact test and Wilcoxon rank sum test were used for data analysis for categorical and continuous variables respectively.

Results: Sixty-nine (51% male; genotype Hb SS 75%, SC 16%, and Sβ-thal 9%) of 373 SCD patients had either abnormal troponin and/or had cardiac MRI done. Median age was 34 years (range 19-67 years). Of 230 patients who had troponin-I measured over this period, 18.2% (n=42) had elevated troponin. 26 of 47 patients with cardiac MRI showed abnormalities described above concerning for microvascular disease and myocardial injury. We identified 22 patients with troponin measurement within 30 days before cardiac MRI. Elevated troponin levels predicted MRI abnormalities with sensitivity of 71% (CI 42-92%) and specificity of 65% (CI 24-91%). The degree of troponin elevation did not correlate with the MRI changes. At the time of data review, 31%(n=8) patients with abnormal MRIs and 52%(n=22) patients with elevated troponin levels were deceased.

Conclusion: Over 10-year period, prevalence of cardiac injury as measured by elevated troponin was 18.2%(42/230) in SCD patients with atypical chest pain. The incidence of microvascular cardiac disease was at least 7% as diagnosed by cardiac MRI. In this small cohort, troponin elevation was neither highly sensitive nor highly specific for microvascular cardiac disease. As cardiac complications are known to be related to high frequency of deaths in SCD, there must be high index of suspicion for cardiac disease in patients with SCD and chest pain. More data is needed to accurately predict associated mortality and identify interventions to modify the outcome.

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MODELING INPATIENT OPIOID CONSUMPTION PATTERNS IN TEENAGERS WITH SICKLE CELL DISEASE

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Background: The opioid epidemic continues to be a significant public health issue and involves both legitimate use and illicit drug access. Standard management of patients with sickle cell disease (SCD) includes treatment with opioids amongst other strategies. SCD patients have disease-related obstacles to achieving developmental milestones, and therefore we theorize that these patients are at a higher risk of accelerated trajectories of opioid use. While only 5% of SCD patients account for the majority of inpatient hospitalizations for painful episodes, we sought to develop visual and mathematical models of inpatient opioid consumption between the ages of 12-18, to see if patterns existed that would assist the clinician, the patient, and the patient's family in forecasting the amount and duration of opioid use. We hypothesize that clear visualization of past patterns in acceleration and remittance of opioid consumption in real time could trigger clinical decision support for issues that may contribute to tolerance and addiction.

Methods: A longitudinal study using data from Cerner Health Facts, a database that captures and stores de-identified, longitudinal electronic health record data, and then aggregates and organizes the data into consumable data sets to facilitate analysis. Opioid amount and number of doses per year, along with gender, age, and region of the country were extracted from the database, using ICD 9 and 10 diagnosis codes on patients with SCD between the ages of 12-18. Data was extracted on 451 individual patients across 862 encounters. Simple linear regressions were conducted to examine the relationship between both age and dose, and age and amount.

Results: Of the 451 individual patient encounters, 36 patients with SCD were identified as high utilizers with greater than 5 hospital encounters. Linear regressions conducted on the relationship between age and dose yielded steady increases in the mean dose administered across these 36 patients as age increased. When taking each of these individual SCD patients with greater than 5 hospital admissions, each individual patient had cumulative dose of opioids administered per year graphed at each age between the ages of 12-18.

Conclusions: Attempts to manage opioid consumption in chronic disease will require comprehensive interventions that can be mobilized at the time sharp changes in opioid consumption occur. Graphing opioid consumption across a set age range allows visual identification of opioid trajectory. Practitioners could utilize this tool to isolate trends, recognize previous prescribing patterns and highlight deviations in consumption between painful episodes and baseline that forecast tolerance and addiction.

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A PROSPECTIVE PHASE II, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF SEG101 (CRIZANLIZUMAB) IN SICKLE CELL DISEASE PATIENTS WITH PRIAPISM (SPARTAN)

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Background: Sickle cell disease (SCD) is the most common single-gene disorder in African Americans and can lead to complications, including acute pain and acute/chronic organ damage. Approximately 40% of men with SCD experience priapism, a clinical disorder characterized by prolonged, painful penile erection in the absence of sexual stimulation. Vaso-occlusion-induced ischemia is generally thought to account for SCD-associated priapism. Crizanlizumab, a humanized monoclonal antibody that binds P-selectin and blocks interaction with its ligands (including leukocyte PSGL-1). The antibody significantly decreased vaso-occlusive crises (VOCs) leading to healthcare visit vs placebo, and was well tolerated in SUSTAIN, a phase 2 study in adults with SCD. This study aims to evaluate the clinical efficacy of intravenous (IV) crizanlizumab 5 mg/kg in reducing priapic events in patients with SCD and a history of priapism.

Methods: This is a Phase 2, multicenter, open-label, single arm study of crizanlizumab in male patients aged ≥16 years with SCD-related priapism. The study will consist of 14 weeks prescreening, 12 weeks screening, and 52 weeks of treatment. The primary endpoint is percent reduction from baseline of priapic events frequency (unwanted/painful erection lasting >60 minutes) by 26 weeks. Priapic events will be self-reported via an electronic reporting system. Secondary endpoints include: safety as well as the following outcomes at 26 and 52 weeks: rate of priapic events, percent reduction in ≥4-hour erections requiring an ER visit, rate of VOC at 26 and 52 weeks, and rate of complicated crises. Approximately 56 patients are planned to be enrolled in the study. The baseline period will consist of a 14 week prescreening period and a 12 week screening period. Eligible patients must have ≥4 events during prescreening, ≥3 during screening with 1 event occurring within 4 weeks prior to first treatment. Patients will be treated with IV crizanlizumab 5 mg/kg on the first day of Week 1, Week 3 (loading dose), Week 7, and then every 4 weeks until final treatment at Week 51. Primary analysis will be conducted after patients receive 26 weeks of treatment. Mandatory safety follow-ups will be conducted until 15 weeks after last dose.

Results: Trial ongoing

Conclusions: This study aims to address the unmet treatment need in male patients ≥16 years old with SCD-related priapism.

JSCDH-D-19-00029

IMPACT OF PHYSICIAN EDUCATION ON TIMELY INTRAVENOUS OPIOID DELIVERY AND FLUID BOLUS USE FOR ACUTE PAIN MANAGEMENT IN CHILDREN WITH SICKLE CELL DISEASE IN THE PEDIATRIC EMERGENCY DEPARTMENT

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Background: Pain is the leading cause of pediatric emergency department (PED) visits for children with sickle cell disease (SCD). NHLBI recommends rapid evaluation and treatment of moderate-severe vaso-occlusive pain episodes (VOE) in the acute care setting, including parenteral opioids within 30min of triage or 60min of arrival, frequent pain reassessments, and re-dosing of opioids within 30min. The guidelines also discourage intravenous fluid (IVF) boluses in euvolemic patients with VOE, recommending IV hydration at no more than maintenance rate to avoid over-hydration in patients unable to drink fluids. PED adherence to NHLBI guidelines is variable. We therefore designed a Maintenance of Certification (MOC, part-4) quality improvement (QI) project for physicians in an effort to improve care.

Methods: Thirty physicians enrolled in a MOC/QI initiative where they attended two educational interventions and received monthly performance feedback reports. A retrospective analysis of prospectively collected data from electronic medical records for SCD patients seen by these providers was performed for pre-intervention (7/2017–3/2018) and post-intervention (4/2018–12/2018) phase to evaluate the impact of the intervention. Outcome measures, derived from the 2014 NHLBI VOE guidelines, included: IV opioid administration within 60 minutes of ED arrival, pain reassessment between 10–30 minutes after administration of IV opioids, IV opioid re-administration between 15–60 minutes after administration of first IV opioid, and IV fluid bolus use. 72-hour-return rate was the balancing measure. As a QI project, the data was analyzed as a function of time utilizing run charts.

Results: A total of 354 patient visits in the pre-intervention and 269 patient visits in the post-intervention phase met inclusion criteria. The proportion of patients receiving an IV opioid within 60 minutes of arrival increased significantly from 26% to 36%, p=0.004 with a significant decrease in median time to administration from 87 minutes to 75 minutes, p=0.007.
Improvement in pain reassessment after opioid administration was noted. The proportion of patients receiving an IV fluid bolus decreased from 40% to 11%, p<0.001 (Fig1). No change in the 72-hour-return rate was observed.

Conclusions: Implementation of an educational intervention combined with performance-based feedback reports led to significant improvements in the treatment of VOE, although further efforts are needed to reach goals outlined in the 2014 NHLBI guidelines. The progress made suggests that education combined with performance feedback may be a viable option for future QI initiatives to improve adherence to NHLBI guidelines and improve PED-based care for acute pain in SCD.

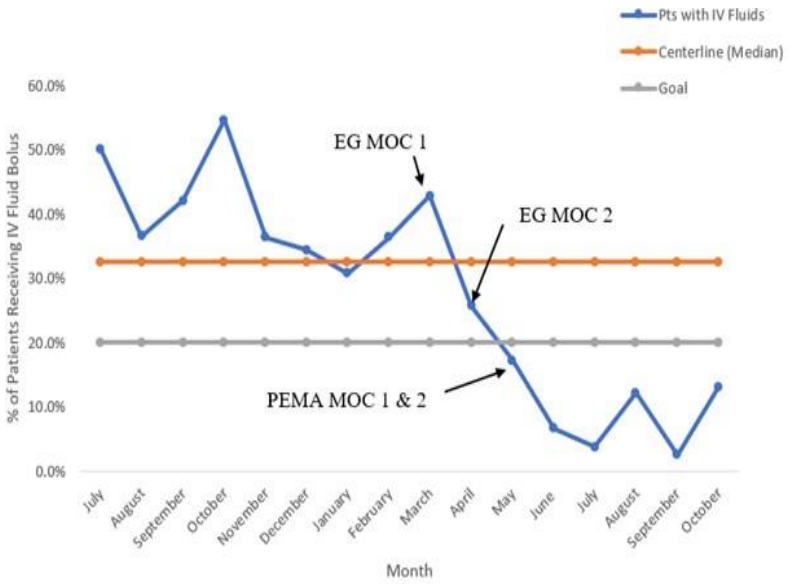

FIGURE 1

JSCDH-D-19-00006

EVALUATION OF THE CLASS I HISTONE DEACETYLASE (HDAC) INHIBITOR CT-101 ON FETAL HEMOGLOBIN (HBF) EXPRESSION IN SICKLE PROGENITORS AND TRANSGENIC MICE

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Background. Up-regulation of HbF is a clinically proven strategy for mitigating the clinical severity and disease phenotype of sickle cell disease patients. HDAC inhibitors including butyrate, phenylbutyrate, and dimethyl butyrate have shown activity in clinical trials. We explored whether the HDAC inhibitor CT-101 would increase HbF over adequately broad concentrations to be useful for therapy, *without* significantly inhibiting erythroid cell growth in sickle erythroid progenitors and in the β-YAC transgenic mouse model. Drug candidates that induce HbF in these mice have demonstrated subsequent *in vivo* γ-globin gene activation in human trials.

Methods. CT-101 (100-200 nM) was evaluated in erythroid progenitors generated *in vitro* from peripheral blood mononuclear cells isolated from 6 patients with sickle cell anemia (HbSS or HbSβ^0thalassemia). *In vivo* studies were conducted in β-YAC mice established with the 248 Kb human β-globin locus, which display normal γ-globin to β-globin switching during development. β-YAC mice were treated with IP CT-101 (5 mg/kg/dose) or vehicle for 3 days/week and hydroxyurea (HU, 100 mg/kg/dose), 5 days/week. F-cell proportions were assayed using anti-γ-globin FITC antibody and HbF/cell quantified using mean fluorescence intensity (MFI) byflow cytometry.

Results. In sickle progenitors**,** CT-101 and HU increased F-cells by 30% and 20% respectively above control cultures from the same subject ($p<0.001$). HbF protein/cell by MFI increased by up to 1.6-fold above vehicle controls. Additive effects were observed with combined CT-101 (100 to 200nM) and HU (75μM) ($p< 0.001$). Erythroid progenitor proliferation did not decrease significantly with CT-101. Treatment with CT-101 in β-YAC mice increased F-cells by 2.5-fold compared to baseline ($p=0.034$) and by 1.6-fold with HU ($p=0.352$). HbF protein by MFI increased1.8-fold, ($p=0.025$) with CT-101 versus 0.9-fold ($p=0.694$) with HU.

Conclusions. The HDAC inhibitor CT-101 demonstrates HbF inducing activity in β-YAC mice and additively induces HbF expression in sickle erythroid progenitors with HU. These findings suggest that CT-101 may be useful in patients who have low or partial responses to HU and merits further investigation as a HbF-inducing agent.

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RISK FACTORS FOR IDENTIFYING CARDIOVASCULAR MORBIDITIES IN SICKLE CELL DISEASE PATIENTS

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Background: Pulmonary hypertension and cardiac dysfunction are complications of sickle cell disease (SCD) that develop independently but have an important additive impact on morbidity, mortality, and quality of life. Although there are numerous studies in the adult population, studies in the pediatric population are less common. Likewise, many studies examine single variables instead of looking at multiple variables to identify patterns for further analysis. Survival in SCD patients has improved with scientific advances in care and management. Cardiac and renal complications as well as vaso-occlusive crisis are being addressed.

Aim: The goal of our study was to evaluate the correlation between BMI, age, hemoglobin, and O2 saturation and parameters of cardiac dysfunction such as left ventricular abnormalities and pulmonary hypertension in SCD patients.

Methods: A retrospective chart review was performed of patients 2-20 years of age with a diagnosis of SCD who had routine hematology and cardiology outpatient visits from January 2017 to March 2019. Patients with HbSS, HbSC, and Hb S-Beta Thal were included in the study. Complete data was available for 47 patients. During cardiology visits patients had echocardiograms performed. BMI and O2 saturation were documented. The parameters reviewed in this study were O2 saturation, BMI, BMI percentile, age, hemoglobin level, and ECHO findings including left ventricular dimensions and tricuspid jet velocity.

Results: A total of 47 pediatric patients with sickle cell disease were included in the study. Age showed a strong positive correlation LV dimension findings (LVPWd 0.65, LVIDd 0.66, IVSd 0.70) and tricuspid jet velocity (0.35). BMI had a positive correlation with LV dimension findings (LVPWd 0.57, LVIDd 0.66, IVSd 0.65), however a weak association with tricuspid jet velocity (-0.06). O2 saturation correlated negatively with echocardiogram variables, however after controlling for other variables was no longer significant. Hemoglobin does not correlate as a univariate, but appears to be significant in the model after controlling for other variables.

Conclusion: This study is intended to be a continuation of previous research that included EKG findings and compared HbSS and HbSC. In this study age and BMI had a strong correlation with increased LV dimensions, however BMI did not correlate with tricuspid jet velocity. O2 saturation did not correlate with ECHO findings. In the model, as hemoglobin decreases echocardiogram findings of IVSd increases. We plan to continue our study to evaluate other parameters of echocardiogram, hydroxyurea use, and acute chest syndrome as predictors of cardiovascular morbidity.

JSCDH-D-19-00054

AP-1 TRANSCRIPTION FACTOR DYSREGULATION MAY CONTRIBUTE TO B CELL DYSFUNCTION AND REDUCED EFFICACY OF PNEUMOCOCCAL VACCINATION WITH PREVNAR-13 IN SICKLE CELL DISEASE MICE

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Background: Patients with Sickle Cell Disease (SCD) are at increased risk of infection with encapsulated bacterial species including *Streptococcus pneumoniae*. Repeated microvascular infarction leads to extensive damage to the spleen, a major immunological site for B lymphocyte development, and functional asplenia in SCD patients is thought to contribute to B cell dysfunction. Prior work in mouse models of SCD has indicated that mice vaccinated with Prevnar-13, mount robust early immune responses to the vaccine, but are incapable of maintaining antibody titers over long time periods. RNA-seq data from vaccinated and unvaccinated SCD and WT murine B cells has identified a dysregulation of AP-1-family transcription factors (TFs) c-Jun and c-Fos, two factors implicated in cell division, differentiation, and suppression of apoptosis. The importance of these three activities in memory B cell formation marked these factors as important candidates for further investigation.

Methods: To establish the role of these AP-1 TFs in B cell responses to vaccination, 8-week-old female C57Bl/6 mice were vaccinated with Prevnar-13 with or without administration of SP600125, a chemical inhibitor of the Jun N-terminal kinase which regulates c-Fos and c-Jun activity. Mice were vaccinated on days 0 and 21, with inhibitor given D-1, D0, and D1 of each vaccine bolus. 5 weeks post-boost, mice were challenged IP with $1x10^5$ CFU *S. pneumoniae* strain A66.1 (Serotype 3, covered by Prevnar-13). An additional unvaccinated group was used as an infection control. Mice were examined for clinical signs, weight loss, and mortality over a 21-day period post infection.

Results: All unvaccinated mice (5/5) succumbed to challenge by 3 d.p.i. Vaccinated but uninhibited mice showed 0% mortality (0/5). In comparison, vaccinated and inhibited mice showed 20% mortality (1/5). Due to concerns of insufficient power, the study was repeated with higher numbers of mice. In a follow-up experiment utilizing the same experimental conditions with larger group sizes, vaccinated but uninhibited mice once again showed 0% mortality, but mortality in the inhibited group dropped to 6% (1/15), for a cumulative mortality between the 2 studies of 10% in mice receiving SP600125.

Conclusions: This data suggests that inhibition of AP-1 TFs in a vaccination and challenge model of pneumococcal infection impairs immune responses to bacterial challenge. Dysregulation of these TFs may partially explain B cell dysfunction in SCD, but further investigation is necessary to solidify this model and thoroughly uncover the roles of AP-1 in B cell function in the context of pneumococcal vaccines.

POSTERS

Presenting: Sunday, June 9, 2019 at 5:15 PM

JSCDH-D-19-00001

PAMIDRONATE USE IN SICKLE CELL DISEASE

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Introduction*:* Avascular necrosis (AVN) of the femur is a serious complication from sickle cell disease (SCD), defined as lack of blood supply leading to death of bone and collapse.[1] Scant literature is available on non-invasive treatment for AVN due to SCD in children. *Methods:* Patient inclusion criteria: HbSS or HbSS B^0Thalassemia, femoral head AVN, 0-18 years, perfusion of the lateral corner, and Pamidronate therapy. Each cycle consisted of labs and 3 consecutive days of Pamidronate, continuing until improvement or a maximum of 2 years. *Results:* Four patients were diagnosed with AVN and treated successfully with Pamidronate. *Conclusion:* Pamidronate prevents resorption of bone, with effects on calcium homeostasis. Our case series demonstrates success of Pamidronate in SCD and our hope is to inspire more in-depth research.

Introduction: Avascular necrosis (AVN), or osteonecrosis, is a terrible complication that can result from sickle cell disease (SCD). Avascular necrosis occurs due to congestion and increase in sickling in the vasculature, resulting in death of bone and collapse.[1] Along with pain, there can be significant destruction. Pamidronate is effective in treatment of AVN only if there is evidence on MRI of healthy bone in the lateral corner. Our aim was to evaluate how to improve non-invasive treatment options. There is little evidence with using non-operative treatments for AVN due to SCD in children. This case series demonstrates the success of Pamidronate as a conservative treatment option for AVN in children with SCD.

Methods

Patients: From our comprehensive sickle cell population of 120 patients, four developed AVN of the femoral head. All patients were boys and were included in the study if they: 1) had HbSS (3 patients) or HbSS B^0 Thalassemia (1 patient), 2) were diagnosed with AVN on MRI (which showed decreased uptake in contrast), 3) had preserved perfusion of the lateral corner of the femoral head, 4) were aged 0-18 years, and 5) were treated with Pamidronate. Exclusion criteria included: 1) sickle cell trait, 2) sickle cell SC disease, 3) those who did not develop AVN, or 4) were not treated with Pamidronate.

Diagnosis: Imaging was performed during pre-treatment to establish AVN, as well as post-treatment to evaluate results of Pamidronate. Imaging modalities were an x-ray or an MRI, either alone or for confirmation.

Treatment: After establishing a diagnosis of AVN, patients were evaluated by orthopedics to determine whether Pamidronate would be appropriate. Candidates for Pamidronate were those who had radiographic evidence of AVN and collapse, but maintained perfusion to the lateral corner of the femoral head. Labs completed prior to initiating each treatment cycle included: complete metabolic panel, complete blood count, and ionized calcium. Dosing and interval were age based (Table 1), and the first-ever dose was half of each of the subsequent doses and given in the pediatric intensive care unit. The first-ever dose was given in the pediatric intensive care unit due to concern for hypersensitivity reaction. Besides this first dose, Pamidronate was given in our outpatient infusion center on days 2 and 3, and thereafter. During infusions, routine vitals were measured. Infusions were given for three consecutive days every 2-4 months, depending on age.

Following each cycle, ionized calcium and complete blood count levels were analyzed. Calcium was monitored closely due to the risk of hypocalcemia with Pamidronate infusions. Physical and occupational therapy needs were also evaluated at

every treatment cycle. X-rays were completed every 3-6 months while on Pamidronate therapy to evaluate for improvement.

Results: Four patients followed at our institution developed AVN with perfusion preserved at the lateral corner of the femoral head. These patients received Pamidronate infusions and monitoring via blood work and x-rays. Each of these patients had labs (CMP, CBC, iCa) drawn prior to each cycle and (iCa and CBC) after each cycle. Only one patient had a drop in his calcium (iCa <1), which necessitated a delay of the administration of Pamidronate by one month, as well as adding calcium carbonate supplements three times per day. Two patients also developed hypovitaminosis D, one prior to starting Pamidronate therapy and one patient 1.5 years after completion, which was corrected.

The full course of Pamidronate therapy is two years, however, it could be stopped earlier if there was evidence of resolution of AVN on imaging (x-ray or MRI). The femoral head shape was round and spherical, and each patient had resolution of AVN radiographically and symptomatically after treatment. As shown in Table 2, there were varying lengths of treatment. Most of the patients had clinical and radiographic resolution of AVN prior to two years, however one patient did require the full treatment course of two years.

Conclusion: Avascular necrosis is an unfortunate complication of SCD. Due to the pathophysiology of the disease, red blood cells have a sickle shape and can cause congestion within vasculature, causing pain crises, stroke, and even necrosis. The femoral head is a common place for avascular necrosis to occur, due to decreased collateral circulation.[3] This complication can lead to long-term effects, such as hip destruction and need for surgical intervention. Thus, detection and treatment of AVN early in its course is important to prevent invasive therapies such as core decompression or hip replacement. Pamidronate is a bisphosphonate that acts by preventing bone reabsorption by blocking hydroxyapatite breakdown, as well as causing osteoclast apoptosis.[4] In other areas of AVN in children such as Perthes disease, it has been shown that if the lateral corner of the femoral head is preserved, outcomes of AVN are much better.[5] It is due to this finding that pamidronate is used to preserve the lateral corner of the femoral head in AVN in SCD. Because there is a decrease in bone breakdown, it is important for vitamin D and calcium to be monitored so that they do not become pathologically low. It is unclear how pamidronate helps resolve AVN of the femoral head in SCD. However, success could be through strengthening of surrounding bone and decreasing further micro-breaks, thereby preserving perfusion to healthy bone. Limitations include: small sample size of our comprehensive sickle cell population, and lack of randomized clinical trials. Strengths include: standardized protocol based on age.

Through our study, we show that Pamidronate is effective in treating AVN of the femoral head, on the condition that the lateral corner has preserved perfusion. By using Pamidronate, one can delay the need for more invasive modalities such as core decompression or hip replacements. At this point, four years is the longest a patient has been removed from Pamidronate therapy and with no surgical intervention. Our hope with this case series is to share our success with using Pamidronate to treat AVN in children with SCD, and for this therapy to be further investigated.

Resources

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Age	Dosage	Interval
<2.0 years	0.37 mg/kg/day for 3 days	2 months
2.1-3.0 years	0.56 mg/kg/day for 3 days	3 months
>3.1 years	0.75 mg/kg/day for 3 days	4 months

Table 1: Dosing chart based on age[2]

Patient	Age at Treatment Start	Length	Cycles
1	27 months	12 months	4
2	6 years	24 months	6
3	9 years	6 months	3
4	15 years	20 months	5

Table 2: Treatment length and number of cycles of each patient

JSCDH-D-19-00002

ARGININE THERAPY IMPROVES MITOCHONDRIAL FUNCTION IN CHILDREN WITH SICKLE CELL DISEASE AND VASO-OCCLUSIVE PAIN

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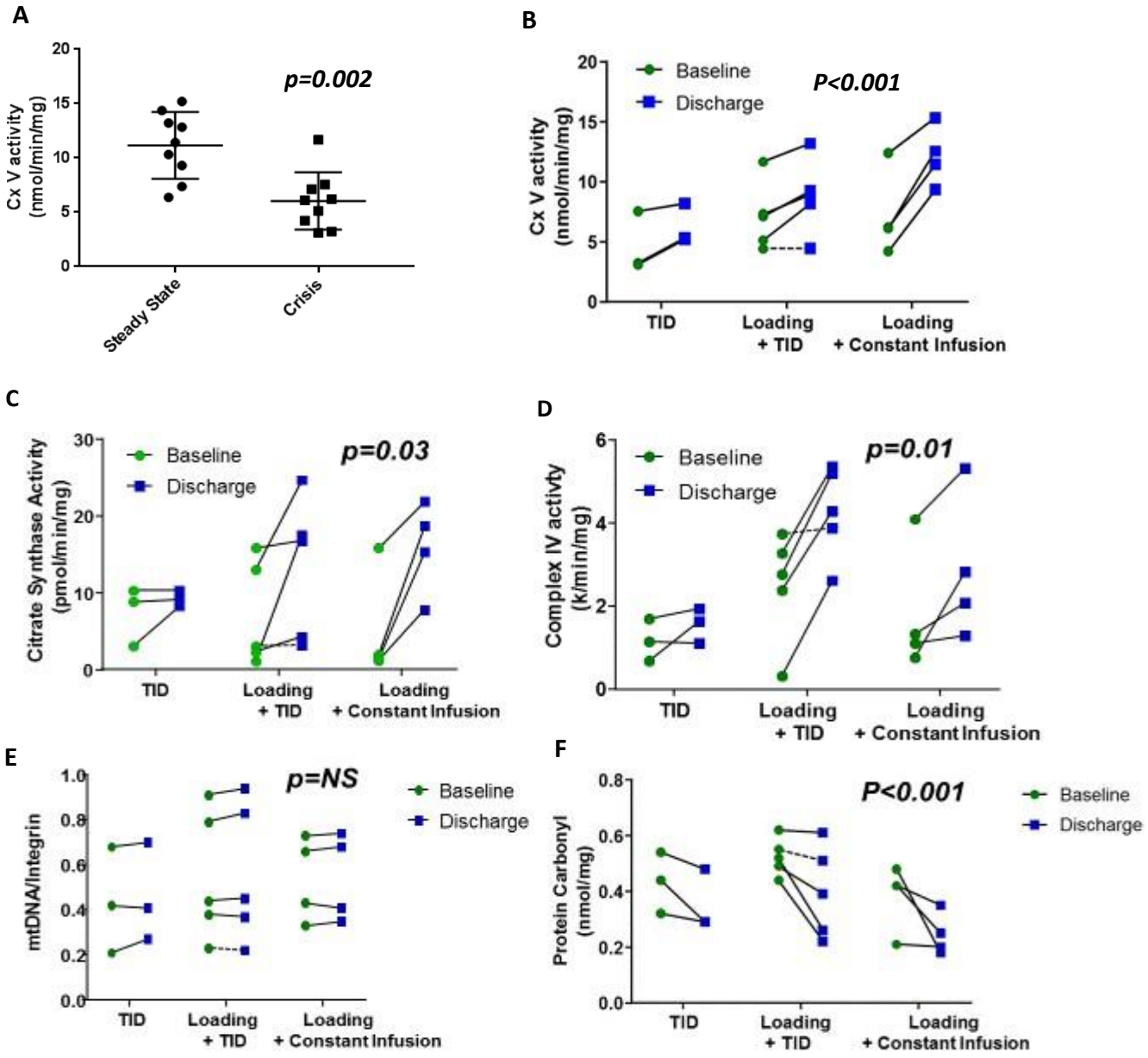
Background: Vaso-occlusive pain episodes (VOE) are the leading cause of emergency department visits and hospitalization in patients with sickle cell disease (SCD). Our prior work has demonstrated that patients in VOE are arginine deficient and that arginine therapy significantly decreases total intravenous (IV) opioid use and improves pain scores in children with SCD during hospitalization. Mechanisms remain unclear, but may be due to stimulation of nitric oxide production. The Shiva lab has reported altered mitochondrial function in SCD patients vs healthy controls; decrease in mitochondrial electron transport Complex V activity leads to decreased respiration and increased detrimental oxidant production. We hypothesized that arginine therapy improves mitochondrial function during VOE.

Methods: Twelve subjects with HbSS or Sβ^0-thalassemia hospitalized for VOE (age 14±3 years, 58% male, 83% HbSS, 92% on Hydroxyurea) were randomized to treatment utilizing one of 3 dosing schemes of Arginine: 1) 100mg/kg IV three times/day (TID,n=3);
2) loading dose (200mg/kg) then 100mg/kg TID (n=5); or 3) loading dose (200mg/kg) followed by continuous infusion (300mg/kg/day) until discharge (n=4). Platelet rich plasma was isolated and stored at baseline presentation to the emergency department for VOE and hospital discharge for each subject and mitochondrial activity, protein expression, as well as protein carbonyls were measured.

Results: Compared to a cohort of SCD patients in steady state, all subjects in VOE had a significantly decreased complex V activity (Fig1A). Notably, complex V activity was increased at discharge in subjects with VOE treated with arginine in all 3 dosing schemes, with greatest increase when utilizing a loading dose. (Fig1B, $p<0.001$). While complex IV and citrate synthase activities were not changed in VOE platelets vs. steady state (data not shown), the activities of these enzymes were significantly increased in VOE subjects after arginine treatment when utilizing a loading dose(Fig1C-D, $p<0.01$). These changes are not due to increased mitochondrial number as quantification of mitochondrial DNA before and after arginine was not different (Fig1E). Complex V protein expression was also unchanged after arginine treatment (data not shown). However, arginine therapy did significantly decrease levels of protein carbonyls in platelet rich plasma across all treatment doses (Fig1F, $p<0.01$), suggesting a decrease in oxidative stress.

Conclusion: These data demonstrate for the 1st time that arginine therapy increases mitochondrial activity and decreases oxidative stress in children with SCD/VOE. This novel mechanism may contribute to decreased pain and ultimately less opioid requirement after IV arginine treatment during VOE.

Figure 1


A
Cx V activity (nmol/min/mg)
p=0.002
Steady State
Crisis
B
Baseline
Discharge
P<0.001
TID
Loading + TID
Loading + Constant Infusion
C
Citrate Synthase Activity (pmol/min/mg)
p=0.03
D
Complex IV activity (k/min/mg)
p=0.01
E
mtDNA/Integrin
p=NS
F
Protein Carbonyl (nmol/mg)
P<0.001

JSCDH-D-19-00007

BEYOND PAIN: THE SYMPTOMS AND IMPACTS OF SICKLE CELL DISEASE ON CHILDREN AND THEIR CAREGIVERS

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Background: Sickle cell disease (SCD) affects approximately 1 in every 400 African American children born in the US and causes chronic anemia, hemolysis, and vaso-occlusive crises (VOCs), resulting in significant morbidity and associated mortality. VOCs have traditionally been the clinical endpoint used in SCD; however, they do not capture the full spectrum of SCD symptoms and the impacts experienced by children and their caregivers, which tend to be underreported in the literature. This study sought to comprehensively summarize the most important symptoms experienced by children with SCD and the impacts on the daily lives of children and their caregivers.

Methods: Qualitative in-person interviews were conducted in children with SCD and their caregivers, recruited from two clinical sites in the US. Children aged 2–11 years diagnosed with SCD with ≥1 VOC in the past year requiring a hospitalization/medical encounter were eligible. Institutional Review Board approval was obtained at each site. Semi-structured interview guides (one for children, one for caregivers) consisting of exploratory open-ended questions were developed using results from a literature review. De-identified interview transcripts were analyzed using a qualitative analysis software. Saturation of concepts was assessed.

Results: Children (N=7, aged 8–11 years, 86% female) were diagnosed with SCD as newborns, with homozygous sickle hemoglobin (HbSS, n=6) or sickle beta 0-thalassemia (HbSβ^0, n=1). Caregivers (N=16) responsible for children (aged 2–11 years) with SCD primarily were mothers (81%) and were employed full time (69%). Concept saturation was reached for both symptoms and impacts among both children and caregivers. Children reported eight symptoms, most commonly bodily pain (7/7), fatigue (6/7), pain crisis (5/7), and difficulty breathing (5/7). Caregivers reported 15 symptoms, most commonly bodily pain (15/16), pain crisis (15/16), fatigue (13/16), fever (13/16), headaches (9/16), acute chest syndrome (8/16), and yellow eyes (7/16). Children reported 23 impacts, including general life with SCD, family, sleep, emotional and physical functioning, school, and recreational activities. The most common impacts reported by children were sadness (6/7), decreased school attendance and performance (5/7), and inability to participate in activities that friends do (5/7). Caregivers reported 29 impacts, with school absences (15/16), caregiver burden (14/16), sadness (11/16), and change in energy level (10/16) the most frequently reported.

Conclusions: This study identified a range of salient SCD symptoms beyond pain (e.g. fatigue) and their substantial impact on children with SCD and their caregivers. Additional treatment and care strategies to address the full symptomatology of SCD are needed.

JSCDH-D-19-00008

STREAMLINING CARE FOR REFUGEE AND IMMIGRANT CHILDREN WITH SICKLE CELL DISEASE AND THALASSEMIA

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Background: Sickle cell disease (SCD) and thalassemia are the most common form of monogenic inherited hemoglobinopathies. Their prevalence is higher in the old world and malaria-endemic areas. Due to immigration, the distribution of SCD and thalassemia has been changing worldwide. For many immigrants and refugees, the following factors can be barriers to health care access:

- Poor economic background
- Prior adverse living conditions
- Lack of education
- Non-English speaking
- Availability of prior health records

We seek to bring attention to the challenges encountered in caring for immigrant children with SCD in Kansas City.

Method: Twenty immigrant/refugee with SCD and thalassemia were followed at Children's Mercy Kansas City.

Results:

- Identified/used consistently a primary/proficient interpreter. Telephone/video services are also used.
- Handouts/instructions in native language
- Encourage participation in research studies
- IRB consent translated to native language
- Utilized local government and community resources
- Donation drives
- Identification of primary care providers, preferably culture competent and qualified bilingual staff (QBS)
- Facilitating medication pick-up or mailing services
- Financial assistance and counseling
- Culturagram psychosocial assessment
- Neurocognitive testing
- Coordination of care with multi-disciplinary teams
- Social-work case management

Conclusions: Health burden of hemoglobinopathies is expected to increase with immigration in the USA. Unfamiliarity with the health care system, underutilization of available services, and lack of understanding of immigrants/refugee health care requirements and clinical complications are major factors to be addressed.

We recommend screening all immigrant children from countries with a high prevalence of hemoglobinopathies using hemoglobin electrophoresis at initial visit. Patients that require continuous health care as transfusions or clinical follow up to be followed by hematologist until a confirmatory electrophoresis is performed.

Immigration from countries with a high hemoglobinopathies prevalence contributes to the addition of S gene and thalassemia genes into the general population. Awareness of the disease prevalence within the patient's country of origin and efficient prevention programs could reduce long-term severe complications in immigrant population

Strategies to better acquaint the immigrant patients with the health care system are required. Effective communication with immigrant patients in their native language using interpreters is essential. Maximizing use of available resources using targeted outreach, combined with financial assistance and counseling, can help improve outcomes among the immigrant population.

Overcoming the linguistic, financial and cultural barriers, will significantly sustain effective communication in the holistic treatment strategy for immigrant population.

JSCDH-D-19-00010

ESTABLISHMENT OF NEUROCOGNITIVE TESTING PROTOCOL IN CHILDREN WITH SICKLE CELL DISEASE

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Background: The neurocognitive sequelae of stroke in children with SCD are characterized by pervasive impairments, including decrements in general intellectual functioning, language and verbal abilities, visual-motor and visual-spatial processing, memory, attention and executive functions, and academic achievement. Impairments in sustained attention and concentration, executive functions, and processing speed are also common in youth who experience silent infarcts. SCD patients are also at increased risk for learning difficulties, particularly in reading and mathematics. Although there is some awareness of these deficits, the most effective and efficient method of referring and evaluating SCD patients for neurocognitive problems has not been well established. The current program aimed to examine patient utilization of testing services and outcomes.

Methods: To accomplish this, the team at University of Illinois Hospital and Health Sciences System distributed flyers about neurocognitive testing in a mass mailing. In addition, 69 families had a practitioner who spoke with patients and families during their regular hematology appointment to explain the goals of neuropsychological testing. The flyers were given again at this time.

Results: Of those 69 patients, 24 patients age 10-24 have received clinical evaluation. Gender was equally distributed. Of the patients tested, 25% had a history of stroke, 41% were physician referred for the suspicion of neuropsychological problems, and the remaining 33% were referred for asymptomatic screening. Across the domains of intellectual functioning, executive functions, and academic skills, patients with a documented history of stroke exhibited the most severe deficits, with an IQ in the impaired range (FSIQ=63, SD=3.3), significant executive deficits, and impairments in reading (SS=59) and math (SS=69). Physician referred patients fared slightly better, with borderline to low average intellectual abilities (FSIQ=79, SD=13.1), fewer executive deficits, and low average reading (SS=89) and math (SS=82). Patients referred for a routine screen fared best, with average intellectual functioning (FSIQ=92, SD=3.4), executive functions, and reading (SS=92) and math skills (SS=97). Of the 45 patients that received flyers but did not go for testing: 8% of patients have a history of stroke, 42% were physician identified and the remaining 46% were referred for asymptomatic screening.

Conclusions: Patients referred for routine screening fared the best on measures of intellectual abilities, executive functions, and academic skills, followed by physician referred patients, and then patients with documented stroke. Children who were asymptomatic were less likely to schedule appointments for testing. Thus it appears that it is more difficult to implement testing for children whose families are asymptomatic.

JSCDH-D-19-00011

TREATMENT OF MODERATE TO SEVERE ANEMIA IN SICKLE CELL DISEASE: RESULTS FROM A 2018 US PATIENT CHART ANALYSIS

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Background: Sickle cell disease (SCD) is a lifelong, debilitating disorder that affects approximately 100,000 patients in the US. SCD is challenging to manage, and there remains a lack of evidence to guide the management of SCD at the community level, where physicians may have limited treatment experience and support. Although there are recommendations for managing patients with SCD with vaso-occlusive crises, there is an unmet need in treating patients with SCD with moderate to severe anemia. This analysis reviewed national treatment patterns of SCD in moderately (hemoglobin [Hb]=7–10.5 g/dL) and severely (Hb <7 g/dL) anemic versus non-anemic (Hb >10.5 g/dL) patients in the academic and community settings.

Methods: Patient charts were obtained from 300 US physicians—primary care practitioners, pediatricians, and adult and pediatric hematologists—64% of whom practiced in the community setting. The 870 charts submitted by physicians responsible for these patients' SCD-related treatment decisions met the following predefined criteria: patients were >2 years of age, followed for ≥1 year, seen in the clinic within the previous year for a routine outpatient visit, and had not received a bone marrow transplant.

Results: Of the 870 patients assessed (74% adult), 52% had the homozygous Hb SCD genotype HbSS, and 28% had the heterozygous Hb genotype HbSC. Most patients had moderate or severe anemia (48% and 12%, respectively), determined by their most recent lab results. Although patients with SCD tend to be anemic, the Hb levels in 12% of patients were not assessed during the previous 2 years. At the time of analysis, more anemic patients (61%, Hb ≤10.5 g/dL) than non-anemic patients (37%) were prescribed hydroxyurea for symptomatic treatment. Similarly, more anemic patients (24%) received chronic transfusions than non-anemic patients (16%). Among both anemic and non-anemic patients, 16% received chronic transfusions for anemia. The most common reasons for chronic transfusions were anemia (79%), prior stroke (9%), and elevated transcranial Doppler scores (11%), a risk factor for stroke in patients with SCD. Finally, 19% of all patients received erythropoietin therapy, of whom 36% received erythropoietin for ≥1 year.

Conclusions: Most patients with SCD in this analysis had moderate to severe anemia, and the observed use of erythropoietin therapy, among other non-disease-modifying treatments, is strong evidence of a clear unmet need to improve anemia in these patients. Even non-anemic SCD patients may benefit from an agent that targets hemolysis and anemia.

JSCDH-D-19-00013

TOBACCO SMOKING AS PROGNOSTIC INDICATOR IN SICKLE CELL DISEASE: A RETROSPECTIVE ANALYSIS OF PROSPECTIVELY COLLECTED DATA

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Background: Sickle cell disease (SCD) is an inherited blood disorder characterized by abnormal sickle-shaped red blood cells. Sickling creates a higher tendency in red blood cells to aggregate and stick to vascular beds, making vascular beds a target organ in SCD. In preliminary screening for a current drug study of high vascular risk SCD patients (characterized by high blood pressure, high estimated pulmonary blood pressure, proteinuria, and early mortality) at UPMC, smokers anecdotally seemed overrepresented. To date, there has not been a broad-based SCD study of smoking and vascular disease outcomes. We hypothesized that smoking could be linked to four important health outcomes that characterize high vascular risk.

Methods: Relevant prospectively-collected data from the walk-PHASST multi-center clinical trial (ClinicalTrials.gov Identifier NCT00492531) were used for this analysis. 672 adult SCD patients (53% female, 47% male; all of age 18-70 years) were separated into three groups: current smokers, former smokers, and non-smokers. In each group, normal distribution for continuous variables were inspected using histograms with addition of a normalized smoothed curve and Shapiro-Wilks test. Parametric or nonparametric analyses were then used for data analysis. P-values were calculated using either ANOVA, or Chi-Squared tests. Additionally, a survival analysis for time to death by smoking status was performed using the Kaplan-Meier and log rank test. Analyses were performed in R and Stata.

Results: About 15% of adults with SCD were active smokers, and 67% had never smoked. In univariate analyses, age, gender, systolic blood pressure, tricuspid regurgitation velocity (TRV, as a noninvasive marker of pulmonary hypertension), and estimated Glomerular Filtration Rate (EGFR), and pack-years show significance or relevant trends. Patients who never smoked are significantly younger, more likely to be female, have a lower systolic blood pressure, and have greater estimated glomerular filtration rate. Upon adjustment for age and gender, current and former smokers had a slightly higher TRV. Despite a very limited duration of follow up, over 20 months the survival analysis shows a trend toward lower mortality in patients who have never smoked, although it is not statistically significant (P=0.37).

Conclusions: SCD smoking status demonstrates statistically significant associations with indicators of hypertension, pulmonary hypertension and renal function; and a non-significant relationship to mortality during follow-up. However, neither causation nor detailed associations can be determined from this limited dataset. The results of this exploratory retrospective analysis are hypothesis-generating, and support a need for further investigation of the consequences of smoking upon SCD outcome.

JSCDH-D-19-00016

PRESENTING ARISE (THE AFRICAN RESEARCH AND INNOVATIVE INITIATIVE FOR SICKLE CELL EDUCATION PROJECT)- "IMPROVING RESEARCH CAPACITY FOR SCD HEATH CARE SERVICE IMPROVEMENT"

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Background: Sickle cell disease (SCD) is among the world's most common serious inherited diseases with more than 300,000 annual births[1], 85% are born in sub-Saharan Africa. SCD accounts for 8-16% of all-cause mortality in childhood in Sub-Saharan Africa even though it represents 2% or less of all births in the region. Increasing migration from high prevalence areas of Africa to European countries like UK, Italy, Greece and Republic of Ireland has grown their SCD population. The outcome of SCD in high-income countries differs markedly with low-middle income countries where less than 50% of affected births will not survive beyond the 10th birthday. Multiple factors account for these disparities including early diagnosis by newborn screening (NBS), prophylactic penicillin and comprehensive follow up. The optimal care for patients with SCD in Africa should incorporate this approach plus laboratory capacity and blood banking services.

The objective of **ARISE** is to establish a multidisciplinary staff exchange program to foster the sharing of best practice in NBS, diagnosis and treatment leading to improvement in overall disease outcome. The purpose is for a sustainable, appropriate health service for those living with SCD.

Methods: This involves research staff exchange between 9 European Union (EU) institutions interacting with non-EU countries including Africa and US. Through work package tasks, staff on exchange visits (secondments) will evaluate the prevalence of SCD among populations; identify SCD specific genotypes and phenotypes; study existing NBS and early infant screening; study engagement with patients, communities especially mothers and policy makers to determine barriers to NBS; establish laboratory diagnosis, quality assurance systems for population screening.

Results: The 4-year project launched in January 2019. Visiting exchanges at University of Illinois at Chicago which focus on NBS and clinical care began in March with the study of Implementation science strategies, community health worker programs and stakeholder engagement observations. A comparison study of USA/UK Community Health Worker (CHW) role will facilitate adaptation and training for settings in Africa to include developing a CHW curriculum.

Conclusions: The multi-directional exchanges will foster new collaborative, institutional partnerships, promote scientific and technological SCD research cooperation between Africa, Europe and USA and build capacity towards sustainable improvement in health-related outcomes. Through ARISE interagency exchange program, interdisciplinary gender balanced teams will work with policy-makers in Africa to examine the effectiveness of a community-based approach to SCD using the tools of implementation science to understand the local context and health systems.

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TRACKING EDUCATIONAL PROGRESS IN OUR SICKLE CELL POPULATION

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Background: An important aspect of improving care in sickle cell disease (SCD) patients is comprehensive patient education regarding disease pathophysiology, symptom management, and resources for treatment. The emergency department (ED) is often the first line resource for management of symptoms such as acute pain crisis, and some patients can develop the perception that they are able to receive all of their necessary sickle cell medical care in the ED setting. As pediatric patients with sickle cell disease grow older, coordinated transition of care and appropriate utilization of care resources are crucial to their long-term success.

Methods: A transition of care program was implemented in our pediatric sickle cell clinic to help assess each patient's readiness to transition to an adult hematology provider. As a part of their readiness for transition of care assessment, a 10-item sickle cell general knowledge quiz is given. The quiz includes questions regarding the genetics of sickle disease, potential triggers for crisis, manifestation of disease in different organ systems, and resources for receiving care. In addition, a retrospective chart review was performed to collect patient disease genotype, number of emergency department visits, and reasons for each visit between 2016-2018.

Results: There were 202 total ED visits with 97 individual patients in 2016 with the following genotype breakdown: hemoglobin SS 64%; hemoglobin SC 24%; hemoglobin SB^0 5%; hemoglobin SB^+ 7%. The numbers for 2017 and 2018 showed a minor decline in yearly visits across all genotypes. The knowledge quiz administered in 2017-2018 to 30 patients aged 13-18 years was revealing in two areas: 1) 50% (15/30) of patients believed that they can receive all of their medical care from the ED and 2) 27% (8/30) patients misidentified complications from their disease.

Conclusions: Although improvements have been made in educating and preparing sickle cell patients for transitioning to adult care, areas in need of improvement remain for example, increasing their baseline knowledge of SCD and management. This study has identified educational gaps that exist as part of the transition process. With this knowledge, we hope to improve current education efforts of sickle cell patients, particularly as they transition from pediatric to adult hematology care.

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IMPACT OF VASO-OCCLUSIVE CRISES ON QUALITY OF LIFE, HEALTHCARE RESOURCE UTILIZATION AND WORK PRODUCTIVITY IN SICKLE CELL DISEASE PATIENTS

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BACKGROUND: Sickle cell vaso-occlusive crises (VOCs) are painful episodes experienced by patients with sickle cell disease (SCD) and triggered by multicellular adhesion that block or reduce blood flow. This study aimed to explore the relationship between VOCs and patients' quality of life (QoL), healthcare resource utilization (HCRU), and work productivity.

METHODS: The analytic sample included adult patients with SCD (N=252) who completed a cross-sectional online survey. QoL and VOC frequency and severity were assessed with the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). Patients answered questions regarding employment impacts and completed the Workplace Productivity and Activity Impairment: Specific Health Problem (WPAI-SHP), which assesses productivity over the past 7 days. Patients also reported the number of times within the past 12 months they used different healthcare services to treat VOCs. Patients were stratified according to the number of VOCs they experienced within the past 12 months and the severity of their VOCs measured by ASCQ-Me pain severity score. Kruskal-Wallis tests were used to evaluate differences in ASCQ-Me and WPAI domains and measures of HCRU according to VOC frequency and severity.

RESULTS: Patients with more frequent VOCs reported greater impacts on all ASCQ-Me domains than patients with less frequent VOCs ($p<.05$ for all). No differences were observed in the number of times patients visited a healthcare provider for VOCs ($p=.087$). Patients with more frequent VOCs reported more ER visits and overnight hospital stays than patients with less frequent VOCs ($p<.05$ for both). Fifty-eight percent of patients reported that SCD negatively impacted their employment status; 73% of patients with ≥4 VOCs in the past year reported negative impacts compared to 45% of patients with 0-3 VOCs. Patients with more frequent VOCs reported greater absenteeism and overall productivity loss than patients with less frequent VOCs ($p<.05$ for both). Presenteeism did not differ according to VOC frequency ($p=.132$). Significant impacts on QoL, HCRU, and work productivity were observed when stratifying by VOC severity; the pattern of results was similar to those found when stratifying by VOC frequency.

CONCLUSION: Patients with more frequent or severe VOCs experience deficits in QoL and utilize costlier healthcare services to treat VOCs. Patients with more frequent or severe VOCs also missed more work in the week preceding survey administration than patients with less frequent or severe VOCs. Future research should examine the impact of SCD-related complications on the relationship between VOCs and QoL, HCRU, and work impairment.

TIERED ORAL THERAPY APPROACH FOR SICKLE CELL DISEASE VASO-OCCLUSIVE CRISIS MANAGEMENT

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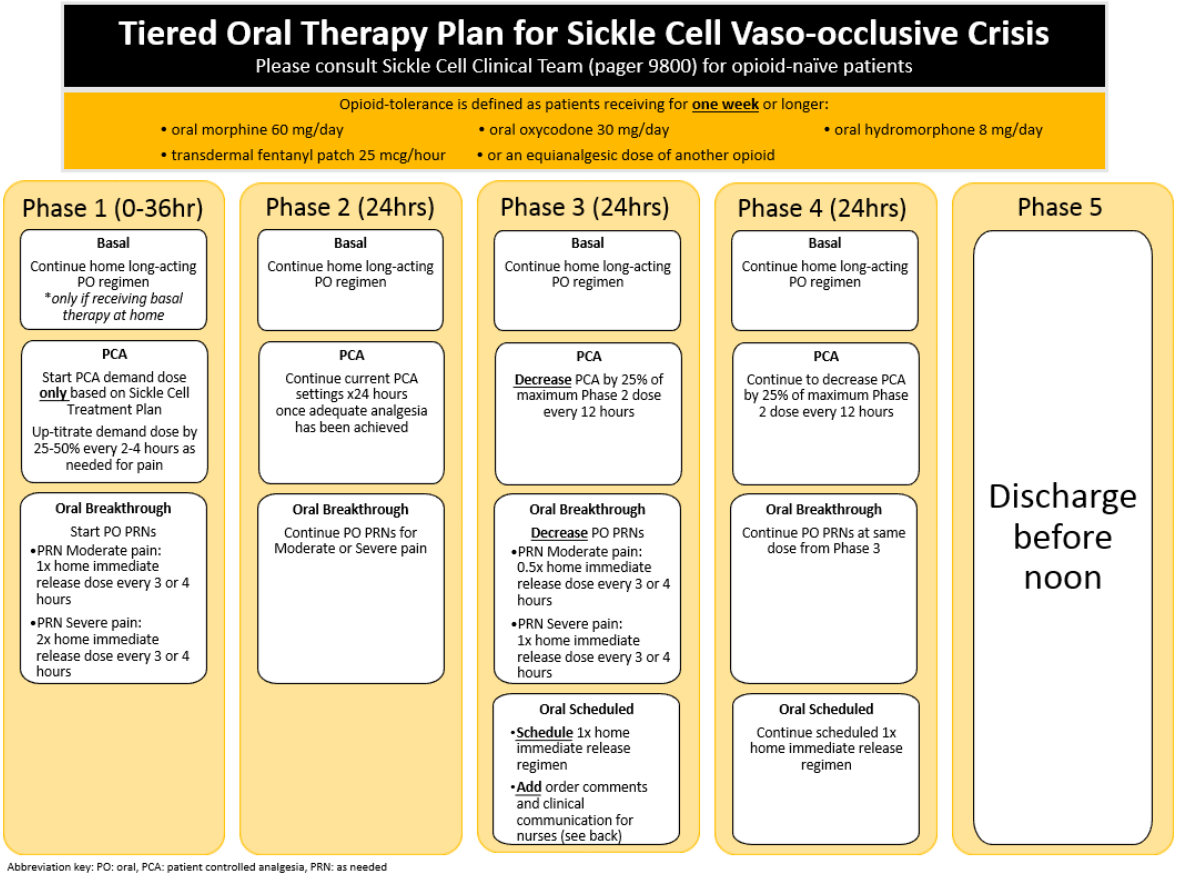
Introduction: Sickle cell disease is responsible for >200,000 ER visits a year most of which are due to pain. Although opioids remain the standard therapy for the treatment of pain, there is little in the literature that has studied opioid therapy in Sickle Cell Patients as a predictor of outcomes; mainly healthcare utilization. To this end, the hospital medicine team of the Virginia Commonwealth University Health System piloted a standardized approach to pain management on one inpatient unit using a Tiered Oral Therapy (TOTP) approach with goals to impact utilization metrics such as the length of stay, 30 day readmission rate while improving quality of care for patients admitted with SCD pain crisis.

Methods: The treatment plan included long-acting oral opioids for basal coverage, patient-controlled analgesia (PCA), and immediate-release oral opioids for breakthrough pain. In phase 1, we rapidly achieved adequate analgesia by up-titrating the PCA every 2 to 4 hours. Patients may receive one to two times their home oral immediate release opioids to aid with breakthrough pain. After adequate analgesia is achieved, we progressed to phase 2 where we **held the course** to allow patients 24 hours of rest and recovery. During phase 3, we decreased the PCA by 25% every 12 hours by initiating the **patient's home oral immediate release opioids scheduled around-the-clock with additional immediate release dosing for breakthrough pain at a dose reduced from the day of admission.** The PCA continued to be tapered by 25% of the maximum dose every 12 hours during phase 4 until the day of discharge which was phase 5. During all phases, patients were continued on their home oral long-acting opioid for basal coverage.



Results: As a result of this implementation, we noted a 3.11 days reduction in LOS from implementation to conclusion on the pilot unit with a mean LOS of 5.589 (SD=0.94, CI=4.909, 6.268). While patient satisfaction was not directly measured as related to the algorithm, when asked whether they noticed changes to their care during their hospital stay patient answered: Yes 72.2%, No 27.8%. When asked if they felt that the team was working together to address their vaso-occlusive crisis pain, patients answered: Yes 94.1%, No 5.9%. 30 day readmission rate was reduced by 6.36% amongst the patients who participated on the TOTP.

Conclusion: The use of TOTP was associated with reduced length of stay and 30 day readmission rate for patients that participated in the tiered oral therapy.

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TRANSITION FROM PEDIATRIC TO ADULT SICKLE CELL DISEASE CARE: A SINGLE-CENTER MODEL FOR TRANSITION IN RURAL POPULATIONS

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Background: Transition to adult care for young adults with sickle cell disease (SCD) in rural populations presents unique challenges. Lack of skilled providers and limited access to subspecialty care hinder successful transition and place these patients at higher risk of morbidity than their peers. The Augusta University (AU) transition program consists of pediatric hematologist, transition coordinator, SCD nurse and social worker, who provide care through the Pediatric Comprehensive Sickle Cell Program. We piloted an off-campus program through bimonthly outreach clinics in rural South Georgia to facilitate successful transition to adult care. Our objective was to evaluate the feasibility and effectiveness of annual in-person transition coordination in this underserved population with limited access to care.

Method: We identified eligible teenage patients scheduled for standard of care at four SCD outreach clinic sites held in Waycross, Dublin, Albany and Valdosta, GA in September 2018. Transition coordinator engaged with patients during wait times and enrolled them in program. She conducted transition readiness assessments, provided educational materials on SCD and transition to adult care, available health insurance plans and information on adult SCD providers. Patients were then transitioned to adult care based on age, high school graduation status and readiness assessment. Patients provided feedback through satisfaction surveys following the visit. Subsequently, the transition coordinator performed telephone follow up 30 and 90 days after the outreach clinic and/or transition to adult care.

Results: Thirty-five teenagers/young adults were scheduled for care, of whom 21 (60%) kept their appointments. All patients were African American with a median age of 15 years (13 – 21 years) and 12 males (57%); the transition coordinator enrolled all patients in the program. Four (4/21) patients aged 18 – 21 years were transitioned to adult sickle cell providers. On satisfaction surveys, all 21 respondents agreed or strongly agreed when asked about ease of understanding of educational materials provided, specificity of information for SCD and whether their questions were addressed appropriately. They reported overall satisfaction with the transition program with no significant changes in wait times or duration of clinic appointments. Three out of four (75%) of transitioned patients had seen or scheduled appointments with adult providers by 90-day follow-up.

Conclusion: For urban pediatric sickle cell programs with rural outreach clinics, focused care on adolescent patients can facilitate successful transition to adult care. In-person transition coordination during outreach clinics represents a cost-effective model for providing transition care when a dedicated transition clinic is unavailable, or limited by existing resources.

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A SMART PHONE BASED INTERVENTION TO IMPROVE OUTCOMES IN SICKLE CELL PATIENTS WITH FREQUENT HEALTH CARE UTILIZATION

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Background: A small group of patients with sickle cell disease (SCD) have frequent ED visits and hospitalizations, mostly with pain episodes, and are responsible for a significant health care costs. These patients comprise 5-10% of the total patient population in many centers, have significant morbidity, poor quality of life, and higher rates of mortality. We recently studied the characteristics of 28 patients with frequent health care utilization (≥6 ED visits/hospitalizations per year) and found that both biologic and behavioral/psycho-social factors contributed to high utilization phenotype (Higher WBC and ANC, higher bilirubin, lower MCV and Hb F, poor adherence to HU, lower educational level, higher anxiety and depression scores, and poorer coping skills compared to patients with low utilization). We studied the efficacy of a smart phone based app, Medisafe, in improving the outcomes in a group of patients with high health care utilization.

Methods: 28 patients (14 males, 14 females, ages 19-60, median 30.5) were enrolled in the study, conducted at the Adult Sickle Cell Clinic, Center for Blood Disorders, Augusta University. Subjects were consented during clinic visits, and downloaded the Medisafe app to their smart phones. This app was used to set medication reminders (primarily HU), but could also be utilized to record and communicate pain scores to the provider's i-pad. The subjects were followed for a minimum of two months, and the preliminary results are reported here.

Results: Compliance with the use of Medisafe was recorded and evaluated in a two month period. Overall, 20/28 patients (71.4%) were compliant to varying degrees and sent status reports, including daily pain scores, via Medisafe weekly. The number of ED visits and hospitalizations and laboratory values at baseline and at the end of intervention were compared. Although positive trends were observed in some parameters (Hb F, hemoglobin, MCV), none reached statistical significance.

Conclusions: Frequent health care utilization in SCD is a significant problem, both from the standpoint of patients (poor outcomes, poor quality of life) and from a medical-economic (increased health care costs) point of view. We previously (Kidwell et al., Blood,…) showed that this is a multifactorial problem, and therefore will likely require a multi-disciplinary approach. The current study shows that a smart phone based approach to improve medication adherence, and to improve patient-provider communications is feasible with 71.4% compliance rate. Its efficacy in improving the outcomes in this patient group should be studied in a longer period of time.

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PATIENT AND PARENT PERCEPTION ON SICKLE CELL TRANSITION OF CARE

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Purpose: To identify the key areas of need during transition and to increase the knowledge base of our Sickle Cell patients and their families in order to improve our transitional program. The goal of this assessment would be to enhance our current transition clinic and increase the educational literacy of our sickle cell population in preparation for transition to adult care.

Background: Transition of care among chronically ill patients is a complex process due to several issues: dependency of the patient on their parents/guardians, cognitive as well as psychosocial difficulties, and the lack of continuity of care. The goal of medical transition is to provide health care that is: uninterrupted, coordinated, developmentally appropriate, and comprehensive.

In response to issues with lack of engagement in transition, we have attempted to understand patients and parents perception on transition by conducting a transitional workshop and support group. Based upon the sickle cell workshop questionnaires during our second transition workshop, it was noted by the teens that attended the workshop that their primary concerns were that they would be lost to care and that the adult providers would not know them once transitioned to adult care facilities. Parents identified on their version of the questionnaire that they felt their children would be successful in transition to adult care from pediatric due to their continued involvement with their child's medical care. Some parents did identify their concern with leaving the pediatric facility due to having spent the majority of their child's medical care with the same providers in the same pediatric system.

The data collected is based upon 20 questionnaires completed by both parents and patients during transitional workshop and support group. The parent and patient were given questionnaires that consisted of open ended and Likert scale questions that were based upon their perception of how prepared they are educationally for adult care.

Conclusion: Based on the data collected from the questionnaires, we discovered that patient and parent have limited understanding of transition of care and the necessary skills needed to transition to adult care. Both patient and parents expressed their concern regarding transition from pediatric to adult care and receiving care from unknown adult providers in an adult facility. The information gathered from the questionnaires will be used in the expansion of our current sickle cell clinic and modification of the structure and curriculum currently being used.

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NEWBORN SCREENING DATA FOR SICKLE CELL DISEASE IN CALIFORNIA AND GEORGIA, 2004-2016: IMPLICATIONS FOR HEALTH INTERVENTIONS

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Background: Most incident sickle cell disease (SCD) cases in the United States are identified through newborn screening (NBS). The Sickle Cell Data Collection (SCDC) program is a population-based, longitudinal surveillance system for SCD that was implemented in California and Georgia to collect information from multiple data sources, including NBS records. SCDC data can be used to identify changes in sickle cell epidemiology and help target public health resources and interventions.

Methods: We analyzed demographic and genotype data for all individuals with SCD who were identified by NBS in California or Georgia with a date of birth during 2004 – 2016. A geographic trends analysis (based on birth county) was conducted to compare the number of SCD births occurring in high-population Metropolitan Statistical Areas (MSAs) (defined for this study as ≥2 million population) to SCD births occurring in other MSAs. Based on 2017 U.S. Census population estimates, there were five high-population MSAs in California and one high-population MSA in Georgia.

Results: An average of 90 (range 68-117) SCD births were identified per year in California and 156 (range 134-223) in Georgia. Forty-seven percent of the newborns with SCD in California and 49% in Georgia were female. The proportion of births by genotype did not differ by state, 56% were Hb S/S or Hb S/β^0 thalassemia, 28% were Hb S/C, 9% were Hb S/β^+ thalassemia; the remaining 7% were other SCD genotypes or the genotype was unknown. Overall, 83% and 58% of SCD births occurred in high-population MSAs in California and Georgia, respectively; these percentages were consistent over time. For specific high-population MSAs, decreases in SCD births were observed from 2005-2009 to 2010-2014 in Los Angeles (213 to 169 births) and San Francisco (67 to 45) and an increase was observed in Riverside-San Bernardino (59 to 84). No significant changes were identified in the other two MSAs in California or the one in Georgia.

Conclusions: There are sizeable numbers of newborns diagnosed with SCD in both California and Georgia. Most SCD births continue to be identified in high-population MSAs; however, decreases in SCD births were observed in select areas, notably Los Angeles and San Francisco, and an increase was noted in Riverside-San Bernardino. Data from SCDC are critical for understanding changes in epidemiology that can identify opportunities for targeted SCD interventions, including workforce development, patient education, and care across the lifespan.

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ESTABLISHING A SICKLE CELL CENTER IN THE NEW YORK CITY (NYC) PUBLIC HOSPITAL SETTING

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Background: Sickle cell patients at Queens Hospital, a public hospital in NYC, historically had a very high readmission rate (defined as occurring less than 30 days from the prior admission). In this hospital the readmission rate for Sickle Cell patients was 63.9% - the highest readmission rate of ANY illness. A Sickle Cell Center was developed with the aim to lower readmission rates.

Methods: The Sickle Cell Center was created to provide comprehensive, individualized, medical and psychosocial services for patients within a public hospital. A designated Hematologist Oncologist was assigned to oversee the program and a Nurse Practitioner (NP) was hired to care for all Sickle Cell patients referred to the Center and seen in the Emergency Room (ER). The NP was also tasked to educate staff in the ER and Inpatient Units on care of the Sickle Cell patient with the latest evidence-based practices on managing pain crisis in a timely manner. A Sickle Cell Support group was formed. Sickle Cell Program leaders also networked with Advocacy programs to provide patients with additional support and education as an outpatient. This Program is designed to promote managing the condition at home to prevent severe crisis. Longitudinal data was collected over a 3 year period and was used to describe patient demographics, needs and services. Results were measured by the percentage of patients readmitted to the inpatient unit at year three.

Results: By year three, 100% of the Sickle Cell patients were seen by Sickle Cell Program leaders directly from the ER or as outpatient referrals. Since its inception, 235 new Sickle Cell patients were served (128 female and 107 male adults). An average of twenty patients attend the support group. Percentage of patients that required readmission to hospital was 63.9% at baseline. By year three, readmission rates decreased to 33.3% - a 48% decrease. This translated to a $1.7 million dollar hospital cost savings.

Conclusions: The Sickle Cell Center has been well integrated and accepted into the public hospital system and can be used as a model for health care delivery for this socio-economically challenged population. The results show that patients are able to live in the community, manage their condition and decrease the need to be readmitted by utilizing the education and support received as an outpatient. The results also show that this translates into significant savings for the hospital which justifies implementation of the program in other facilities.

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SYSTEMATIC REVIEW OF RISK FACTORS ASSOCIATED WITH INCREASED EMERGENCY DEPARTMENT UTILIZATION IN PATIENTS WITH SICKLE CELL DISEASE IN THE UNITED STATES

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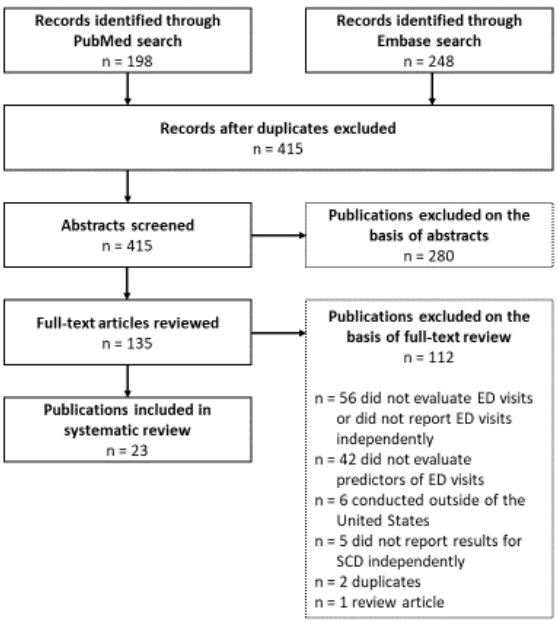
Background: Sickle cell disease (SCD) is a genetic disorder that affects up to 100,000 patients in the United States and affects multiple organ systems. The emergency department (ED) is frequently used by patients with SCD who have severe pain from vaso-occlusive crises. The goal of this systematic review is to identify predictors for ED use among patients with SCD in the United States.

Methods: This systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed and Embase were searched for articles containing the keywords “sickle cell disease” AND (“emergency” OR “acute care”) AND (“utilization” OR “health care”) published between January 1, 2000 and December 14, 2018. Included studies met the following inclusion criteria: report of ED or acute care clinic use; report of health care utilization for SCD; and report of ED visits independent of hospital admission, ED revisits, inpatient care visits, and SCD care unit visits. Articles that were unavailable in English or focused on populations outside of the United States were excluded.

Results: Of the 23 articles included in the review (Figure 1), 4 were prospective, and the remainder were retrospective. Qualitative analysis of the articles revealed a few trends, such as a higher rate of ED utilization among adults relative to children, patients with public insurance relative to private insurance, and patients with more comorbidities, complications, or pain. In one study, ambient temperatures less than 32°F were positively and clinically significantly correlated with ED visits. Overall, gender was not significantly associated with ED usage in most studies.

Conclusions: Age and pain levels were both commonly cited as predictors of ED utilization. Findings from this review highlight the urgent need for prospective evaluations of predictors of ED utilization, as well as assessments of psychosocial issues among patients with SCD that may contribute to greater ED utilization.

Figure 1. Selection of Studies Evaluating Predictors for Emergency Department Utilization Among Patients With SCD



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MAPPING AND IMMUNOLOGICAL PROFILING OF RED BLOOD CELL ALLOIMMUNIZATION AS A GENETIC TRAIT IN ADULTS WITH SICKLE CELL DISEASE

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Background: One of the primary treatments for sickle cell disease (SCD) is red cell transfusion. Its major limiting complication is alloimmunization to minor blood group antigens.
Alloimmunization is rare in the general population, but common in SCD. The underlying mechanism has not been elucidated, but it is proposed that susceptibility is a genetic trait. We hypothesized that the biologic basis for this phenomenon may involve population differences and that admixture mapping could identify susceptibility loci.

Methods
A cohort of 721 SCD adults had allo-antibody status confirmed with the blood bank. Genomic DNA was genotyped for a panel of 1622 ancestry informative SNPs in 359 subjects. Ancestry was estimated from these genetic data assuming an admixture model for 3 ancestral populations. Regression analysis was used to identify variables associated with alloimmunization. Genome wide admixture mapping was performed using a log-additive case control study to identify regions of the genome where ancestry differences between cases and controls suggested an association.

Results
Seventy seven percent of the cohort had a transfusion history with 153 (27.6 %) with allo-antibodies and 65 (11.7 %) with no prior transfusions. Univariate regressions showed association lifetime transfusion history (logistic regression by antibody status, β=0.56, P=6.31 x 10-6). Amerindian ancestry was also associated with alloimmunization (β=4.60, P=0.03), while African and European ancestry were not. These associations remained significant in a multivariable model for alloimmunization status (P=0.09).
Genome wide mapping by admixture linkage disequilibrium compared 91 cases to 210 controls with prior transfusions under 10 different risk models (range 0.25-9.0). The 0.25 risk model showed a significant association (genome log factor 10.96, P<0.001). This scan identified a region of chromosome 5 (5q21.3-5q31.1) defined by 14 snps spanning 21.685 Mb with a peak LOD score of 13.5. This region contains 209 genes and 4 microRNAs, which are implicated in regulating hematopoiesis and immune responses by Genomic Regions Enrichment of Annotations Tool (GREAT) analysis.

Conclusion
Association with Amerindian ancestry suggested admixture mapping is a suitable investigative approach. Genome wide admixture mapping identified a strong association at chromosome 5q21.3-5q31.1. Pathway analysis of this region further suggests involvement in hematopoiesis and the immune response. Ongoing analysis aims to use immunological and gene expression profiling to fine map allo-immunization susceptibility variants within specific genes that underlies this association. Ultimately, mechanistic knowledge of the immune response directed towards minor blood group antigens could lead to potentially novel strategies to disrupt this process.

JSCDH-D-19-00037

SYSTEMIC AND BONE TISSUE IMPACT OF L-GLUTAMINE THERAPY IN SICKLE MOUSE MODEL"

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Background: FDA approval of L-Glutamine (GLN) for patients with sickle cell disease (SCD) is a welcomed advancement, however opposing research has led to uncertainty about it's therapeutic mechanism and long term safety. GLN is vital throughout the body and the benefit experienced by sickle patients may be explained by other means. Sickle bone, which progressively deteriorates with age, may benefit from GLN supplementation due its potential role as an anabolic agent. We aim to determine whether the Townes mouse model recapitulates the clinical observations of GLN therapy and assess tissue level implications via bone quality metrics.

Methods: Sickle mice and littermate controls were evaluated at 4-, 8-, 12-, and 16-weeks of age. GLN supplementation was given ad libitum via drinking water (1g/kg) from weaning (4-weeks) until time of sacrifice. Systemic assessment included plasma GLN concentration, NADH redox potential, lactate dehydrogenase (LDH) activity, hemopexin (HPX), and organ weights. Tissue analysis consisted of femur microCT examination of cortical and trabecular bone morphologies, and microarray of genes related to normal bone physiology.

Results: Plasma GLN of treated mice steadily increased to being higher than untreated (25%) and controls (60%) at 16-weeks. Redox potential of GLN treated mice were significantly higher than untreated groups. LDH activity decreases by 25% in GLN mice at 8-weeks, but returns to untreated levels by 12-weeks. The concentration of HPX in GLN treated sickle mice is comparable to the untreated group at 8-weeks, but becomes significantly higher at 12- and 16-weeks. Organ masses revealed that GLN therapy hinders sickle splenomegaly from 4- to 8-weeks. The 12- and 16-week old time points showed two subgroups in GLN therapy: untreated resembling large spleens (<6% body mass) and wild-type resembling small spleens (<1% body mass). GLN treated mice with small spleens maintained nearly 40% more cortical and trabecular bone, while the large spleen subgroup returned an untreated phenotype by 16-weeks. Gene expression studies showed GLN therapy maintains relatively normal expression levels but significantly decreases FGF23 (~80%) at 8-weeks.

Conclusion: Mouse model recapitulates the reported clinical observations of GLN treated sickle patients, and serves as a viable model to investigate its role in SCD. Subsequent work will discern the inconsistent responsiveness to GLN therapy. Nonetheless, the reduction of organ weights and hemolysis markers suggests GLN supplementation may delay sickle vascular complications. Bone analysis supports GLN therapy maintains healthy tissue as well as highlighting sickle kidney pathophysiology as a pathway of interest.

JSCDH-D-19-00038

STUDY OF EVALUATION OF THE NATIONAL POLICY OF COMPREHENSIVE ATTENTION TO PERSONS WITH SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES IN THE STATE OF BAHIA

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Sickle cell disease is prevalent among the black population and one of the priorities of this social segment in the health policy struggle. In 2005, Brazil instituted the National Policy for Comprehensive Care for Persons with Sickle Cell Disease and Other Hemoglobinopathies (PNAIPDF), estimating the annual occurrence of 3,500 new cases of sickle cell disease and 200,000 people with sickle cell trait. In addition, the state of Bahia, constituted ethnically by blacks (76.26%), has the highest incidence of live births with sickle cell disease (1: 627) and sickle cell trait (1:17) in Brazil. Bahia encompasses a strong social movement and researchers in the search for improvements to people with this aggravation, as well as the support of affirmative policies. However, there are difficulties such as the access of multiprofessional care and the decentralization of specialized services, in which there are only 9 Reference Centers out of 417 municipalities in Bahia. In this sense, the present study aims to verify to what extent the PNAIPDF and other hemoglobinopathies in the state of Bahia can be evaluated. This is an evaluation study of the PNAIPDF with a descriptive and exploratory design, preceding the ex-post evaluation studies of the implantation analysis. The study is organized in three moments that proposes the construction of the logical model, the elaboration of the matrix of analysis and judgment and the validation of the same one. For this, the construction of the indicators plan will follow the dimensions of access to health, management and teaching and research actions and services for PNAIPDF. In this way, the evaluation of health policy aims to contribute to identify limits and possibilities, with greater resolution to services, programs and health systems, as well as elements that help the use of new strategies and decision making, in order to understand the possible significant variables of policy implementation.

Key words: Sickle cell disease, Hemoglobinopathies, Politicy.

JSCDH-D-19-00039

A SECOND LOOK: A CASE OF ORBITAL MANIFESTATION IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is the most common genetic disorder worldwide. Intra-ocular involvement in sickle cell disease is a well-documented clinical presentation though not often discussed by hematologists. Orbital bone infarction in SCD is less well defined[1,2,3]. Prompt diagnosis is required to prevent vision loss[1]. In this report we have a case of a 31 month old female with SCD (hemoglobin SS), presenting with bilateral, symmetric infarctions of the lateral periorbital regions, with sub-periosteal hemorrhage.

Methods: A toddler with hemoglobin SS sickle cell disease, maintained on hydroxyurea, with no previous hospitalizations presented to a local emergency room (ER) with a one-week history of bilateral eye swelling, nasal discharge, malaise, and low-grade temperatures. She was diagnosed with sinusitis and was started on high dose amoxicillin. As the swelling worsened with increased fevers, she returned to the local ER, which prompted blood cultures and initiation of antibiotics and orbital CT scan (Figure1). She was transferred to our hospital for further care and began treatment with Unasyn and Vancomycin. The patient was managed by our team in conjunction with Infectious Disease, ophthalmology and ENT consultations.

Results: Literature review was performed which identified 4 articles with a total of 8 patients with orbital infarction due to SCD with even one with concurrent epidural hematoma[4]. All patients were treated conservatively, with combinations of IV fluids, simple transfusion, exchange transfusion, IV dexamethasone, and IV antibiotics with full recovery[1,2,3].

As our patient's course improved with negative blood, nasal cultures, respiratory pathogen panel and no visual deficits, she was transitioned to oral Clindamycin and Cefdinir on day 3. Additionally, her care was managed with IV hydration, pain medications and antipyretics. Bilateral temporal ultrasound was obtained subsequently (Figure 2). Due to improvement in the patient's clinical course, and the need for sedation, MRI was not obtained. Once improved symptomatically, she was discharged to complete 14 day course of antibiotics while optimizing her dosing in Hydroxyurea and with close follow up.

Conclusion: Given the unusual presentation, as sickle cell providers, we often need to review the presentation of orbital involvement in SCD aside from retinopathy. Orbital involvement of sickle cell disease is a rare occurrence, requiring rapid diagnosis for accurate treatment to avoid long term sequela. There is still more to be understood regarding adequate management for such patients, severity of disease prediction and the role of current disease modifying agents like Hydroxyurea.

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Figure 1: CT scan. Left image showing bilateral orbital and temporal hemorrhages. Right image showing temporal fluid collection, greater on left.

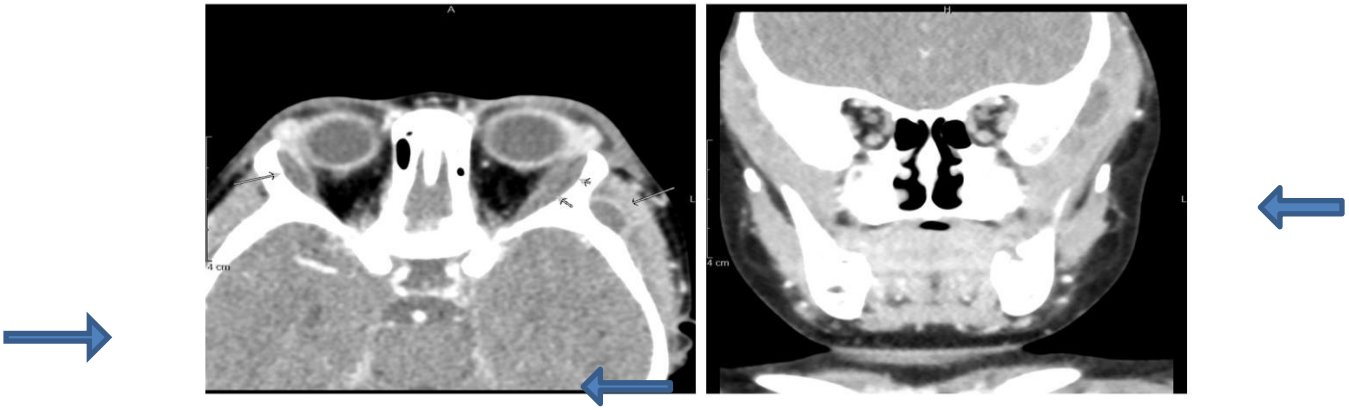
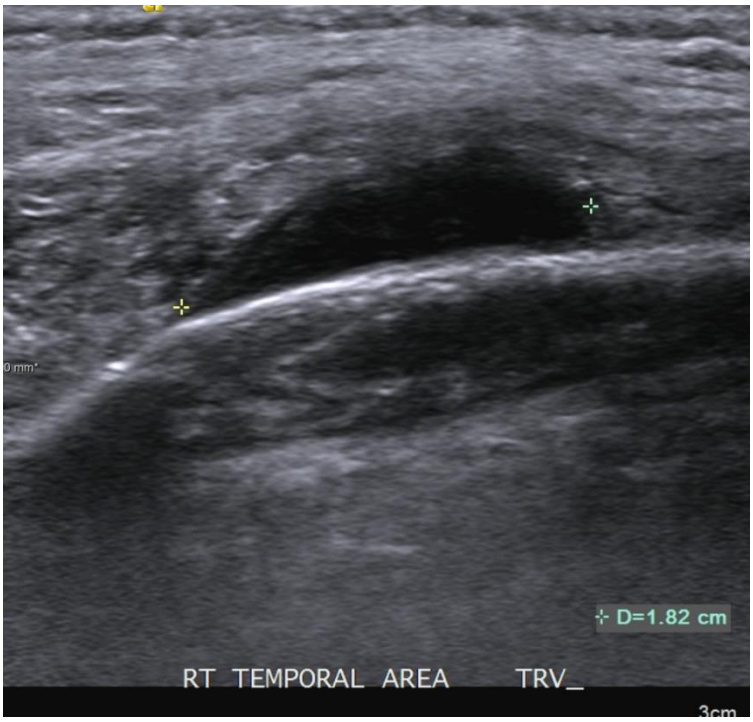


Figure 2: Ultrasound: Right temporal sub-periosteal hematoma



JSCDH-D-19-00050

BENEFITS OF A COORDINATED TRANSFUSION MEDICINE AND HEMATOLOGY SICKLE CELL DISEASE QUALITY PROGRAM

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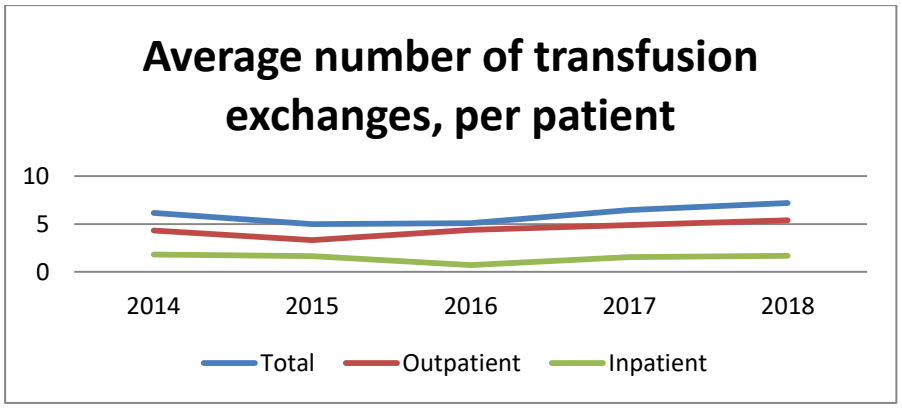
Background: Red cell exchange (RCE) is a mainstay of treatment of sickle cell disease (SCD) complications. Compared to simple transfusions, exchanges have the benefit of decreasing iron overload. Indications for chronic RCEs include secondary prevention of stroke, prevention of future episodes of Acute Chest Syndrome if already on hydroxyurea, refractory pain despite hydroxyurea, persistent stuttering priapism, and pulmonary hypertension. Given the multiple indications for transfusions in SCD patients, we sought to have a collaborative quality program to establish standards of care and improve adherence to RCEs.

Methods: In 2016, hematology and transfusion medicine at the OSUCCC—James began a combined quality program in which they reviewed SCD patients quarterly. During these meetings, patients were reviewed to ensure they were undergoing evidence-based treatments and psychosocial barriers to RCE were addressed. We sought to evaluate the impact of the program on patient outcomes.

Results:

Year	Number of patients on chronic exchange	Male (total)	Female (total)	Inpatient and outpatient exchanges (average, per patient)	RBC units exchanged (average, per patient)	Outpatient exchanges (average, per patient)	Percent of patients receiving ≥4 outpatient exchanges per year	Inpatient exchanges (average, per patient)	Inpatient admissions (average, per patient)	Mortality	Average ferritin
2014	6	5	1	6.17	44.33	4.33	66.67	1.83	9	0%	1663.75
2015	6	6	0	5	38.17	3.33	33.33	1.67	5.33	0%	3652.44
2016	10	8	2	5.1	39.8	4.4	60	0.7	3.2	0%	2735.04
2017	18	9	9	6.45	48.89	4.89	61.11	1.56	5.06	5.55%	1650.1
2018	20	9	11	7.2	53.85	5.4	70	1.7	5.2	0%	1980.44



107 unique patients with SCD underwent RCE during this time. Data regarding 27 patients who were on chronic RCEs was analyzed. In total, the patients on chronic exchanges underwent 378 RCEs, of which 286 were outpatient.

Conclusions: Since the quality program began in 2016, the average number of total (inpatient/outpatient) and outpatient exchanges increased. Furthermore, the total number of patients on chronic exchanges as well as the percentage of patients who underwent at least 4 outpatient exchanges per year increased yearly since 2016. While currently we did not see a decrease in the number of inpatient exchanges, there is likely a false elevation caused by patients who undergo non-emergent exchanges when admitted for convenience. Closer monitoring also led to an overall downtrend in ferritin levels. We conclude that a structured quality program between hematology and transfusion medicine leads to improved care for patients with SCD on chronic transfusions.

JSCDH-D-19-00051

IT IS NOT JUST ABOUT THE OPIOID PRESCRIPTION: THE PATIENT PERSPECTIVE ON THE USE OF OPIOIDS TO MANAGE SCD PAIN.

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Background: The hallmark of SCD is vaso-occlusive pain, which may be acute and episodic but may progress to chronic persistent pain with unpredictable and disabling exacerbations. Gaps in practice in the management of SCD related pain are well established with little data regarding the patient perspective on opioids and their use in the management of SCD related pain. This qualitative study sought to understand the perspective of the adult patient with SCD in the use of opioids in the management of SCD related pain.

Methods: We conducted qualitative interviews of adult SCD patients from a geographically diverse population recruited from national conferences and local clinics. A semi-structured open-ended interview guide was used to collect data. Audio recordings were transcribed verbatim. Transcripts were coded using descriptive qualitative analysis using NVivo 11.

Results: We interviewed 26 adults (19 females) all African American of age ranging from 21 to 52 years old, ten employed full-time or part-time and 16 receiving social security disability benefits. All participants self-reported that their genotype was either HbSS, HbSC, and or HbS-Beta thalassemia. Participants were interviewed in-person and over phone. All participants reported pain on three or more days a week and had a current prescription for opioids to treat their pain. We developed three themes to address our research objective.

"You know, we're just hurting and we're trying to get people to hear us." First, participants felt physicians only focus on prescribing opioids and do not try to evaluate the underlying cause of pain. Patients want to feel listened to and included in the discussion of understanding their pain.

"It eases the pain, it doesn't take it away." Second, participants reported they prefer not to rely on opioid therapy to manage their acute and chronic pain as opioids only temporarily ease their pain without eliminating the cause of the pain.

"Granted it helped but now what?" Third, participants are concerned about the adverse side effects of long-term opioid therapy, and are worried about becoming physically dependent on opioids.

Conclusion: Adult SCD patients would like their physicians to focus on evaluation of underlying causes of pain in discussion with them rather than merely focus on prescribing opioids. Patients are dissatisfied with opioids which they see as temporary fix to their problem and are worried about adverse effects and physical dependence.

JSCDH-D-19-00052

GAZELLE: A PORTABLE, AFFORDABLE POINT-OF-CARE DIAGNOSTIC TECHNOLOGY FOR DETECTING HAEMOGLOBIN DISORDERS IN INDIA

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Affiliations: *[1]Indian Council of Medical Research (ICMR)-National Institute of Research in Tribal Health, Jabalpur, India [2]Hemex Health, Portland, OR, [3]Case Western Reserve University, Cleveland, OH*

Background: Sickle haemoglobin (HbS) and thalassaemias are the most common inherited disorders of blood resulting in anaemia and associated complications. Sickle Cell Disease (SCD) is particularly common among natives of sub-Saharan Africa, India and Mediterranean countries. Screening in India involves solubility and sickling slide test followed by confirmation by High-performance liquid chromatography (HPLC) or haemoglobin electrophoresis. Lack of public health diagnostic facilities contribute to vast majority of hitherto undetected patients resulting in increased morbidity and mortality. Here, we describe the field performance of microchip based cellulose acetate electrophoresis "Gazelle™". The study was conducted in tribal-dominated Madhya Pradesh and Chhattisgarhstates in India, regions where HbS prevalence varies from 3% to 35%. Gazelle™ is a rapid (<10 minutes) and easy-to-use test which can be performed by minimally trained personnel using only a finger-prick volume of blood.

Methods: Blood samples were collected from 300 patients who were enrolled in a pilot study in a high prevalence setting (ICMR-NIRTH, India). Each sample was tested with Gazelle™, and the results were compared to electrophoresis and HPLC. Overall, 295 patient samples were included in the analysis (3 samples were excluded due to incomplete runs; sequencing results pending for 2 samples).

Results: Gazelle yielded a high accuracy (100%) compared to standard laboratory tests (Table 1).

Table 1. Overall accuracy of Gazelle in comparison to clinical standard tests.

Category	Hemoglobin Type	Correct	Incorrect	Accuracy
Sickle Cell Disease and sickle β-Thalassemia	HbSS, HbSβ-thal	12	0	100%
Sickle Cell Trait	HbAS	62	0	100%
Normal	HbAA	221	0	100%
All categories	-	**295**	**0**	**100%**

Gazelle™ demonstrated high sensitivity and high specificity for identifying SCD (HbSS) and β- Thalassemia, sickle cell trait (HbAS) (Table 2).

Table 2. Sensitivity and specificity of Gazelle in comparison to clinical standard tests.

Category	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	PPV	NPV
Sickle Cell Disease HbSS/HbSβ-thal vs. HbAA	12	221	0	0	100	100	100	100
Sickle Cell Disease HbSS/HbSβ-thal vs. HbAS	12	62	0	0	100	100	100	100
Sickle Cell Trait HbAS vs. HbAA	62	221	0	0	100	100	100	100

Conclusions: Microchip electrophoresis technology offers a low-cost ($2 per test), rapid, and accurate method for detecting hemoglobin disorders such as SCD. Gazelle can be a potential clinical tool for rapid diagnosis of SCD and other hemoglobin disorders in resource-limited settings.

JSCDH-D-19-00065

TIME-TREND OF MORTALITY OF BLACK WOMEN AND MEN BY SICKLE CELL DISEASE IN THE STATES OF BAHIA - BRAZIL, NORTH CAROLINA AND SOUTH CAROLINA - UNITED STATES, 1999-2016.

Authors: Aline Silva Gomes – Universidade Estadual de Feira de Santana – Brasil, José Roberto Santos Silva – Universidade Federal da Bahia – Brasil, Carlos Alberto Lima da Silva - Universidade Estadual de Feira de Santana – Brasil, Evanilda S. de Santana Carvalho - Universidade Estadual de Feira de Santana – Brasil, Coretta Melissa Jenerette – University of North Carolina and University of South Carolina – Estados Unidos, Abbas Tavakoli - University of South Carolina – Estados Unidos

OBJECTIVE: To analyze the time-trend of mortality of black men and women from sickle cell disease (SCD) in the states of Bahia - Brazil, North Carolina and South Carolina - United States, from 1999 to 2016.

METHODS: Ecological study of time series that considered the deaths due to SCD of black women and men (ICD 11-D57), residing in the states of Bahia, North Carolina and South Carolina, from 1999 to 2016. The data from the state of Bahia were accessed at the Department of Information System of the Unified Health System in November 2018, and the data from the US states were obtained through the Platform for Disease Control and Prevention in December 2018. The Trend of mortality rates by SCD was analyzed by the adjusted regression model of *Prais-Winsten*, $(Rate)t = \alpha + \beta\ (time)t + \epsilon t$ (95% confidence interval), to compile data, we used the Microsoft program, Office Excel 2010, and to analyze the trends we adopted the statistical program R, version 3.5.0.

RESULTS: We observed a growing trend in the mortality rate of black women and men by SCD in Bahia, with emphasis on the ages 0-9 and 10-19. In South Carolina, we observed a decreasing trend in the age group 10 to 19 years, while in the state of North Carolina, there is a steady trend of mortality among black women and men in all age groups.

CONCLUSION: This study highlights the need for priority actions for the health of children and teenagers with SCD in the Brazilian state. We recommend to know the successful experiences of the State of North Carolina seeking to overcome the limitations to reduce mortality due to SCD in the state with increasing tendency of mortality due to SCD.

Keywords: Mortality; Mortality Registries, Sickle Cell disease; Epidemiology; Time Series Studies

Table 1: Results of the trend analysis of the mortality rates series by sickle cell disease, by State, women and black men and age group, 1999-2016.

Variável	Beta	t-valor	p-valor	Tendência
ESTADOS				
Total - BA	0,02	7,83	**<0,001**	**Crescente**
Total- NC	-0,0039	-1,88	**0,078**	**Estável**
Total - SC	0,0004	0,1	**0,921**	**Estável**
SEXO/NÃO BRANCOS				
Homem - BA	0,024	7,968	**<0,001**	**Crescente**
Homem - NC	-0,0172	-1,323	**0,204**	**Estável**
Homem - SC	-0,012	-0,523	**0,608**	**Estável**
Mulher - BA	0,023	6,429	**<0,001**	**Crescente**
Mulher - NC	-0,015	-1,345	**0,198**	**Estável**
Mulher - SC	0,017	1,138	**0,272**	**Estável**
GRUPO ETÁRIO				
1 a 9 - BA	0,014	2,696	**<0,01**	**Crescente**
1 a 9 - NC	-0,003	-0,004	**0,501**	**Estável**
1 a 9 - SC	0,0007	0,106	**0,917**	**Estável**
10 a 19 - BA	0,015	3,526	**<0,001**	**Crescente**
10 a 19 - NC	0,00088	0,003	**0,795**	**Estável**
10 a 19 - SC	-0,015	-2,148	**<0,05**	**Decrescente**
20 a 64 - BA	0,031	7,627	**<0,001**	**Crescente**
20 a 64 - NC	-0,0082	0,0042	**-1,96**	**Estável**
20 a 64 - SC	0,005	0,821	**0,424**	**Estável**
65+ - BA	0,006	1,082	**0,295**	**Estável**
65+ - NC	0,0018	0,795	**0,438**	**Estável**
65+ - SC	0,0007	0,118	**0,908**	**Estável**

JSCDH-D-19-00066

SUPPRESSION OF HBF REPRESSORS BY SMALL MOLECULES AND RESPONSES IN DIFFERING SNP PROFILES: POTENTIAL RELEVANCE FOR TAILORING GENE MODULATING THERAPIES

Authors: Yan Dai, Betty Pace, David Chui, S.P. Perrine

Affiliations: *Phoenicia BioSciences Inc, Augusta University, and Boston University School of Medicine*

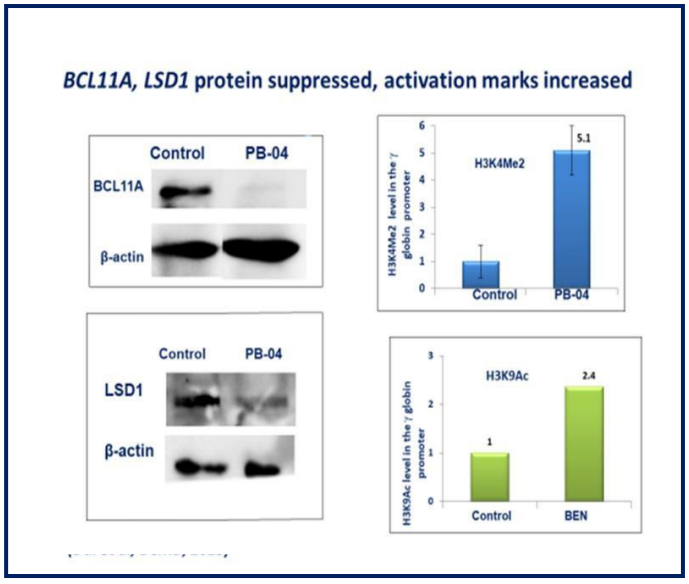
Background: Up-regulation of HbF in a majority of red blood cells is clinically proven to reduce anemia and clinical severity in sickle cell disease (SCD) and beta thalassemia (BT). More than 70 small molecules induce fetal globin gene expression *in vitro,* through diverse, potentially complimentary molecular mechanisms with exposure during a specific period of EPO sensitivity. Small molecule therapeutics can be pulsed or given sequentially to promote efficacy, reduce off- target effects on other lineages. Genetic modifiers relevant to baseline HbF could influence the magnitude of induction by targeted gene editing or small molecule therapeutics.

Methods: Three HDAC inhibitors, ST20 (which displaces *HDAC2)*, and a therapeutic with multiple actions, PB-04, which displaces or suppresses transcriptional repressors *HDAC2 and HDAC3, LSD-1, and BCL11A* were evaluated in erythroid progenitors cultured from >100 sickle cell and thalassemia patients. Fetal globin mRNA, F-reticulocytes, and F protein/cell were assayed. ChIP assays and Western blots were performed to assess drug effects on repressor components. Comparative induction was preliminarily assessed in the progenitors by SNPs related to basal HbF levels or cell survival.

Results: All HDAC inhibitors and ST20 significantly reduced or abolished *BCL11A* protein in erythroid progenitors. Addition of PB-04 once during erythroid differentiation resulted in loss of BCL11A protein and reduced binding of *BCL11A, LSD-1*, and *HDAC3* to the γ globin promoter; histone activation marks appeared at the same time. The relative fold-increase in γ globin mRNA above untreated controls was highest (5-9 fold) in progenitors from patients with SNP profiles associated with *lower* baseline fetal globin levels in *BCL11A* (*766432 and 1427407), ZBTB7A, OR51B4, Xmn-I (7482144)* and rs 4601817. Induction was 4 to 9-fold in progenitors from GG and GA patterns in AKAP12, (rs10872670 associated with cell senescence) and G/G in SNX29P2 (rs 1872670), but was 1.3- to 3-fold in other SNP profiles.

Conclusions: Multiple HbF inducers suppress LSD-1 and BCL11A protein binding to the promoter. Responses in erythroid progenitors with differing SNP profiles suggest that genetic modifiers relevant to baseline HbF or F-cells may offer a means to guide modulating therapies.

Figure 1. Western blot and ChIP assays show loss of BCL11A, LSD-1 and new histone activation marks with PB-04 exposure in erythroid progenitors.



FEATURED MANUSCRIPT

JSCDH-D-18-00076R1

THE PATTERN OF BLOOD PRESSURE AND RENAL FUNCTION AMONG CHILDREN WITH SICKLE CELL ANAEMIA PRESENTING IN A TERTIARY HEALTH INSTITUTION IN NIGERIA.

Type of Manuscript: A cross-sectional study (original research)

Authors: Adebukola Ajite[1], Ezra Ogundare[1], Oludare Oluwayemi[1], Oladele Olatunya[1], Oluwasola Oke[1], Kayode Tolorunju[2],Evelyn Omoniyi[1],

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ABSTRACT

Background: In sickle cell anemia (SCA), compromise of the renal vasculature due to sickled red cells has been recognized.

Objectives: To assess the renal function and blood pressure pattern in children with sickle cell anemia (SCA) presenting in a tertiary institution

Method: A cross-sectional study of patients with sickle cell anemia (SCA) over six months involving the use of questionnaires, general physical examination, blood pressure, investigations for hemoglobin genotype, urinalysis, serum creatinine, screening for hepatitis B and HIV.

Results: 51 children with SCA were seen. The prevalence of impaired renal function as defined by reduced eGFR <90mL/min/1.73m^2 in this study was 27.5%, previous hospital admission and blood transfusion were associated with reduction in eGFR but blood pressure did not have significant correlation with the eGFR. The overall mean age at diagnosis of SCA was 4.09 ± 3.33 (years).

Conclusion: Impaired renal function is a major comorbid condition in children with SCA. In countries/locations where there is no newborn screening for sickle cell disease, diagnosis is delayed, thus detecting impaired renal function may be delayed, therefore the need for early detection and management is imperative.

Introduction: Sickle cell disease (SCD) is a clinical condition in which an individual inherits two abnormal hemoglobin (Hb) genes following mutation and at least one of which is Hemoglobin S (HbS)[1]. HbS is the result of a single base pair change, thymine for adenine, at the 6th codon of the β-globin gene[1]. This change encodes valine instead of glutamine in the 6th position[1, 2]. Consequently, there is production of an unstable isoform which when slowly deoxygenated can polymerize leading to the production of sickle cell[3]. The most severe type is HbSS, otherwise called sickle cell anemia (SCA) which occurs when both β-globin genes have the sickle cell mutation [1,2]. Sickle cells lack the fluidity of the normal erythrocytes and can impede capillary flow thereby leading to tissue ischaemia[3,4]. The kidney, being a highly vascular organ, is vulnerable to vaso-occlusive events. The hemodynamic changes that occur with chronic anemia, renal hypoxia from recurrent vaso-occlusion and hemolysis-related endothelial dysfunction can lead to functional and structural changes presenting as hematuria, proteinuria, concentrating defect, renal insufficiency and hypertension which may progress to chronic kidney disease (CKD) [5-8].

Renal disease in patients with sickle cell anemia is a major comorbid condition that is seen in 15-18 % of all SCD patients, and is a cause of early death[5, 9]. The presence of renal failure in sickle cell disease (SCD) ranges from 5 to 18% of the total population of SCD patients[9].

Blood pressure has been found to be lower in SCD patients when compared with their healthy counterparts with normal hemoglobin genotype and this has been attributed to the low systemic vascular resistance seen in them[10-15]. For the same reason, hypertension is uncommon in sickle cell disease patient, hypertension in them predisposes to greater risk of vaso-occlusive crisis and death[16]. Compromise of the renal vasculature due to sickled red cells has been associated with glomerular hypertrophy, glomerular hyperfiltration and consequent proteinuria[16]. Hemolysis in SCA may also contribute to the development of kidney disease due to the increase in levels of plasma free hemoglobin and subsequent hemoglobinuria. The free heme filtered through the glomerulus is directly cytotoxic to renal tubular epithelial cells and induces damaging inflammatory responses[17].

Objectives: This study was conducted to contribute to existing data on the pattern of blood pressure and renal function among children with sickle cell anemia.

Study design and location: A cross-sectional study of patients diagnosed to have sickle cell anemia who were attending the pediatric hematology clinic of Ekiti State University Teaching Hospital Ado Ekiti was done over a period of six months from June 2016 to December 2016 after obtaining an ethical clearance from the Ethical and research committee of the institution.

Data collection and sampling technique: Patients presenting at the pediatric hematology clinic during the duration of the study (six months) were serially recruited provided they met the inclusion criteria and after obtaining informed parental consent as well as assent from the patients, where applicable. Inclusion criteria included patients aged two to sixteen years who were diagnosed by hemoglobin electrophoresis to have sickle cell anemia and presenting at the pediatric hematology clinic over a period of six months. Exclusion criteria included patients who had crises or were admitted at least two weeks prior to their scheduled clinic visit, patients on blood pressure lowering medication and those on steroids. Questionnaires were administered to consenting parents and subjects. Information requested for included the age, gender, age at diagnosis, regularity of clinic attendance, compliance with routine medication, number of hospital admissions in a year, common crisis noticed and previous blood transfusion. General physical examination, weight, height and blood pressure of the subjects were done alongside investigations such as hemoglobin genotype, urinalysis, serum creatinine , hepatitis B and HIV screening.

Blood pressure measurement: Blood pressure was determined using standard procedure according to the recommendation of the task force on high blood pressure in children and adolescent[17]. This was done by auscultation in the right arm after a 10-minute resting period using the mercury gravity sphygmomanometer with appropriate bladder cuff sizes. The onset of the first tapping sound (Korotkoff sound 1) was taken to indicate the systolic blood pressure (SBP) while the point of complete disappearance of the sound (Korotkoff sound 5) was taken to indicate the diastolic blood pressure (DBP). For each subject two measurements were taken after an initial blood pressure trial run to achieve subject's confidence and composure. The average reading was then determined[18].

Urinalysis: Freshly voided urine was collected from every subject into a plain universal bottle and the UriScreen Combi 10 dipstick was used to assess urine protein semi-quantitatively, specific gravity of the urine as well as the presence of erythrocyte were also assessed. The test strip was dipped into the freshly voided urine for approximately 1 second, and then drawn across the edge of the container to remove the excess urine. After 30 seconds, the test strip was compared with the colour scale and the result was recorded immediately. Colour changes taking place after 2 minutes was regarded as of no significance. The amount of protein in the urine was assessed as negative, trace, 1+ (30 mg /dL), 2+ (100 mg/ dL), 3+ (500 mg/dL).

Patients with proteinuria had repeat urinalysis on three consecutive occasions over three months to ascertain those at risk of chronic kidney disease.

Estimated glomerular filtration rate: This was calculated by using the Schwartz formula [19], where the estimated glomerular filtration rate = kh/ serum creatinine in mg/dl (k is a constant 0.55 in children and adolescent girls and 0.77 in adolescent male, h is the height in cm) and serum creatinine was assessed using modified Jaffe's method, type is endpoint, wavelength 520nm and the instrument is Spectioscan 60 DV, Biotech Engineering co.uk

Data analysis: Data analysis was performed using both descriptive and comparative statistics. Descriptive statistics comprising of mean, standard deviation, percentages and proportions were used for the age, anthropometry, estimated glomerular filtration rate and blood pressure profile of the subjects.

The comparative statistics comprised of Chi-square test for categorical data, independent samples t-test and analysis of variance (ANOVA) for comparison of the mean of continuous dependent variables for categorical variables with three or more categories. Pearson's correlation was also done

RESULTS: Fifty one children with sickle cell anaemia were studied over a period of six months with the age range of two to sixteen years. Thirty nine (76.5%) of them were male while twelve (23.5%) of them were female. All the subjects had homozygous haemoglobin SS. Serology test for hepatitis B, C and HIV were negative in all of them.

THE BIODATA AND ANTHROPOMETRIC CHARACTERISTICS OF THE SUBJECTS

Age and sex distribution: The male to female ratio was 3.25:1 Out of the 51 subjects, 19 (37.3%) were aged 2-5years, 16 (84.2%) of them were males and 3 (15.8%) were females. Those aged 6-9years were 13 (25.5%), 10 (76.9%) of them were males and 3 (23.1%) were females. Those whose ages were ≥ 10 years were 19 (37.2%) and 13 (68.4%) of them were males and the remaining 6 (31.6%) were females.

Table I shows a comparison of the mean age at the time of the study, mean age at diagnosis of the disease condition, mean anthropometry and blood pressure profile based on the gender. There were no statistically significant differences in these parameters between genders. The overall mean age at diagnosis was 4.09 ± 3.33 (years), however, the mean age at diagnosis was earlier in male as compared to female. The mean values for blood pressure, mean arterial pressure and estimated glomerular filtration rate were all within normal range for each gender and there were no statistically significant difference between them.

Parents level of formal education, clinic attendance and routine medication: Among the subjects, 37 (72.5%) of the fathers had at least tertiary level of education, while 33 (64.5%) of the mothers had same. Majority of the patients 35 (69%) attended hematology clinic regularly, at least once in two months, however, the teenagers rarely came for follow up. The routine medication used by these subjects included; folic acid, multivitamin and Proguanil.

Blood pressure percentiles: Among the male subjects the systolic blood pressure percentiles recorded were; less 50^{th} percentile [21(53.8%)], 50^{th} percentile [2(5.1%)], $>50^{th}$ percentile to $<90^{th}$ percentile [13(33.3%)] and 90^{th} percentile [3(7.7%)]. The diastolic blood pressure percentile recorded were; $<50^{th}$ percentile [19(48.7%)], 50^{th} percentile [2(5.1%)], $>50^{th}$ -$<90^{th}$ percentile [17(43.6%)] and 90^{th} percentile [1(2.6%)]. Among the female subjects 10(83.3%) had the systolic blood pressure percentiles less than 50^{th} percentile while 2(16.7%) had theirs between $>50^{th}$ percentile to $<90^{th}$ percentile. The diastolic blood pressure percentiles recorded were; $<50^{th}$ percentile [9(75.0%)], 50^{th} percentile [2(16.7%)] and $>50^{th}$ percentile to $<90^{th}$ percentile [1(8.3%)]. Majority of all the subjects had both diastolic and systolic blood pressure less than the 50^{th} percentile and none of the subjects had blood pressure percentile above the 90^{th} percentile for age and gender.

Serum Creatinine and estimated glomerular filtration rate (eGFR): As seen in figure 1, the serum Creatinine levels were majorly less than 1mg/dl. The eGFR value for the subjects ranged from 32.2mL/min/1.73m^2 to 197.0mL/min/1.73m^2. The mean eGFR for the subjects was 105.75±35.66. In figure 2, the eGFR for the male subjects were divided into classes of normal eGFR (90-120ml/min/1.73m^2), mildly reduced eGFR(60-89 ml/min/1.73m^2), moderately reduced eGFR (30-59 ml/min/1.73m^2), severely reduced eGFR (29-15 ml/min/1.73m^2), end stage kidney disease(<15 ml/min/1.73m^2), elevated eGFR (>120-139 ml/min/1.73m^2) and glomerular hyperfiltration (>140 ml/min/1.73m^2). Eight (20.5%) male subjects had mildly reduced eGFR while 5(12.8%) had moderately reduced eGFR. Majority of the female subjects had eGFR above 90 ml/min/1.73m^2 as seen in figure 3, only one female subject had mildly reduced eGFR (60- 89mL/min/1.73m^2). The prevalence of reduced eGFR (<90ml/min/1.73m2) among the study population was 27.5% (14 subjects). These patients with reduced glomerular filtration cut across age 2-13years; more than half of them had previous hospital admission and blood transfusion as seen in figure 4 and 5 respectively. None of the subjects had eGFR <15mL/min/1.73m^2. However, in Figure 6, all the subjects with age ≥ 14 years had estimated glomerular filtration suggestive of glomerular hyperfiltration (eGFR ≥ 140mL/min/1.73m^2).

Proteinuria and haematuria: The prevalence of dipstick proteinuria among the subjects was 11.8% (6subjects), the proteinuria was in the range of 30mg/dl -100mg/dl. The age range of these subjects with persistent proteinuria was 2-13years and 4(67%) of them had previous blood transfusion and all were male. The eGFR range of subjects with proteinuria was 94.8-169.0mL/min/1.73m^2. Three of these subjects had eGFR ≥ 140mL/min/1.73m^2. One subject (12year old male) had dipstick detected blood in the urine; the eGFR was also above 90mL/min/1.73m^2

Correlation of age at diagnosis, anthropometry, blood pressure and estimated glomerular filtration rate.

Using Pearson's correlation, there was a significant positive correlation of the age at diagnosis of the disease condition with the height and the weight of the patients, the correlation was 0.678 and 0.536 respectively and both were significant at 0.01level with 99%degree of confidence. The estimated glomerular filtration rate was also shown to have a significant positive correlation with the weight and height, the correlation was 0.678 and 0.536 respectively and both were significant at 0.01level. Blood pressure parameters had no significant correlation with the estimated glomerular filtration rate.

DISCUSSION: In the study, there was a male preponderance with M:F of 3.25:1. The age range of the subjects was 2-16 years, it was noticed that the population of the subjects was like a pyramid with a decline in the population as the age increased. This could be explained by the increase in mortality and poor survival of children with haemoglobinopathy in resource poor setting [20] such as the location of this study. The increase in mortality and poor survival may be attributed to ignorance of the disease

condition, poverty, environmental factors like the malaria endemicity and delay in presentation in the hospital. The overall mean of age of the subjects at first diagnosis was 4.09 ± 3.33 years which depicted delay in diagnosis when compared with developed countries with the facility for newborn screening. This also suggests that the haplotype of sickle cell in these patients may be of less severity, making the patients to present to the hospital with symptoms at older age since facility for newborn screening is not widely available yet. There is also the possibility that the most severe cases had died before presenting at the hospital for routine care.

The blood pressure pattern showed that both systolic and diastolic blood pressure were below 50th percentile for most of the patients across genders. This is in agreement with the documentation of low blood pressure in sickle cell disease patients which has been attributed to low systemic vascular resistance seen in them[3]. The serum creatinine levels were majorly less than 1mg/dl in the recruited subjects. Reduced muscle mass as compared with normal healthy individuals may be one of the contributing factors. Similar finding was reported in a study among adults with sickle cell disease[21].

The prevalence of dipstick positive proteinuria in this study was 11.8%, this is lower than the prevalence of 20.0% recorded in adult Nigerian patients with SCA by Aneke *et al*[22]. This disparity can be explained by the difference in the ages of the study population. Out of the six subjects with persistent proteinuria, 5(83.3%) of them were above the age of 5years, the tendency to have persistent proteinuria seemed to increase with age. Age has been described as the most potent modifying factor of sickle nephropathy of which persistent proteinuria is a feature and progression to overt CKD has been noticed in early adulthood[23].

In this study, the six patients with proteinuria had their eGFR in the range of 94.8-169.0mL/min/1.73m^{2}and half of them had eGFR above 140ml/min/1.73m^2 suggestive of glomerular hyperfiltration. A previous study [24] reported similar finding that higher rates for developing microalbuminuria were seen in SCA patients with glomerular hyperfiltration and the same study also noted that the prevalence of hyperfiltration decreased with age[24]. These subjects may be in the early phase of kidney damage with compensatory increase in glomerular filtration which may be responsible for the enhanced glomerular passage of albumin and larger proteins that has been previously described in SCD [3]. Age related progression to chronic kidney disease and decrease in renal function may be implicated in the reduction of the prevalence of hyperfiltration with age as seen in the study of adults with SCA[21].

The prevalence of impaired renal function as defined by reduced estimated glomerular filtration rate <90mL/min/1.73m^2 in this study was 27.5%. The subjects with reduced glomerular filtration rate cut across ages 2-13years and had at least an episode of previous hospital admission and blood transfusion. This suggests that renal impairment is common in sickle cell anaemia and that sickle cell crisis which is severe enough to warrant hospital admission and blood transfusion may be a contributing factor. Ongoing hemolysis and vaso-occlusive injury have been reported to likely contribute to continuing renal injury [17, 23]. Among patients with sickle cell disease, decreased kidney function has been reported in 5 to 30 percent [21, 25, 26] which is close to our finding in this study. A higher prevalence of 67.6% was recorded by Yusuf et al[27] in his study of adults with SCA in Zaria, Nigeria using similar cut off point of eGFR of <90 ml/min/1.73m^2. Previous scholars have suggested that as more individuals with SCD are reaching the fourth to sixth decade of life, the prevalence and risk of CKD is likely to increase as well[23] , this may explain the higher prevalence of decrease kidney function seen in adults with SCD.

The range of eGFR in normal children aged 2-12years was put at 89-165mL/min/1.73m^2 by Heilben et al[28] in 1991, however in this study among children with sickle cell anaemia, the range was 32.2mL/min/1.73m^2 -197.0mL/min/1.73m ^{2}. Worthy of note is the fact that all subjects above the age of 14years had the estimated glomerular rate above 140ml/min/1.73m^2. An earlier study by Olowu et al[29] among children with sickle cell disease patient aged 5-13years showed that Nigerian children with homozygous sickle cell anaemia who are in steady states have normal glomerular filtration rate while studies in adult SCD showed reduced glomerular filtration rate[19,20]. The disparity in the outcome of these various studies may be due to the fact that the changes in the glomerular filtration rate could be a spectrum; with the earlier ages 5-13years having predominantly normal glomerular filtration rate [23], ages > 14years having glomerular hyperfiltration as a feature of compensation in early kidney disease as seen in this study and the adults SCD patients having reduced glomerular filtration rate due to age related renal decompensation[21, 25]. A similar continuum of hyposthenuria in children to progression to end-stage renal disease (ESRD) in adults has been described by other authors[23]. Although in the early ages the eGFR values were predominantly normal in this study, evidence of glomerular hyperfiltration as suggested by eGFR >140ml/min/1.73m^2 was seen across all the ages from 2-16 years. Similarly, hyperfiltration has been seen as early as 9–19 months of age according to the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) study[30]. The compromise of the renal vasculature due to sickled red cells has been associated with glomerular hyperfiltration, proteinuria and glomerular hypertrophy. However, there is need for further elaborative study to unravel factors implicated in the outset of glomerular hyperfiltration in sickle cell anaemia.

There was no correlation between the estimated glomerular filtration rate and the blood pressure of the subjects in this study; this is similar to previous observation that in contrast to other glomerulopathies, the development of systemic

hypertension is uncommon in HbSS subjects with renal insufficiency[21].

CONCLUSION: The prevalence of renal insufficiency as demonstrated by estimated glomerular filtration rate of <90mL/min/1.73m^2 was 27.5%. Previous hospital admission and blood transfusion were associated with reduction in eGFR but blood pressure did not have significant correlation with the eGFR. There is delay in diagnosis of SCA and the prevalence of persistent proteinuria and glomerular hyperfiltration was noticed to increase with the age of the subjects. Therefore, there is a need for early detection and management of SCD to forestall recurrent vasoocclusive crises and end organ (kidney) damage. However, in the absence of newborn screening for SCD in some countries/locations leading to delay in diagnosis, early detection of renal function is critical. Routinely, renal function in sickle cell disease patients should be monitored as some might actually have impaired renal function with a need to adjust dose of medication, ensure prompt intervention and follow up.

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TABLE 1: Age, anthropometric, estimated glomerular filtration rate and blood pressure profile of the subjects.

Age, anthropometric and blood pressure characteristics	Overall mean ± Standard deviation N = 51	Male N = 39	Female N=12	p value
Age at onset of the study(years)	7.92 ± 4.18	7.72 ± 4.32	8.58 ± 3.78	0.536
Age at diagnosis (years)	4.09 ± 3.33	3.75 ± 5.23	5.19 ± 3.56	0.193
Height (cm)	117.24 ± 22.56	116.56 ± 24.10	119.47 ± 17.34	0.700
Weight (kg)	23.37 ± 9.43	23.13 ± 9.66	24.12 ± 9.00	0.753
Systolic blood pressure (mmHg)	93.21 ± 10.96	94.51 ± 10.86	89.00 ± 10.67	0.129

Diastolic blood pressure (mmHg)	52.08 ± 7.55	52.56 ± 7.21	50.50 ± 8.70	0.413
Mean arterial blood pressure (mmHg)	65.79 ± 7.59	66.56 ± 7.17	63.33 ± 8.67	0.200
Estimated glomerular filtration rate (ml/min/1.73m^2)	105.75 ± 35.66	105.12 ± 37.87	107.81 ± 28.61	0.822

TABLE II; ESTIMATED GLOMERULAR FILTRATION RATE OF PATIENTS AND THE PRESENCE OF PROTEINURIA

		PROTEINURIA		
		NEGATIVE	30MG/DL	100MG/DL
ESTIMATED GFR VALUE	> 90mL/min/1.73m2	32	5	1
	60-89mL/min/1.73m2	8	0	0
	30-59mL/min/1.73m2	5	0	0
Total		45	5	1

TABLE III; ESTIMATED GLOMERULAR FILTRATION RATE AND THE PRESENCE OF BLOOD IN THE URINE

		BLOOD IN THE URINE	
		NEGATIVE	POSITIVE
ESTIMATED GFR VALUE	> 90mL/min/1.73m2	37	1
	60-89mL/min/1.73m2	8	0
	30-59mL/min/1.73m2	5	0
Total		50	1

FIGURE 1

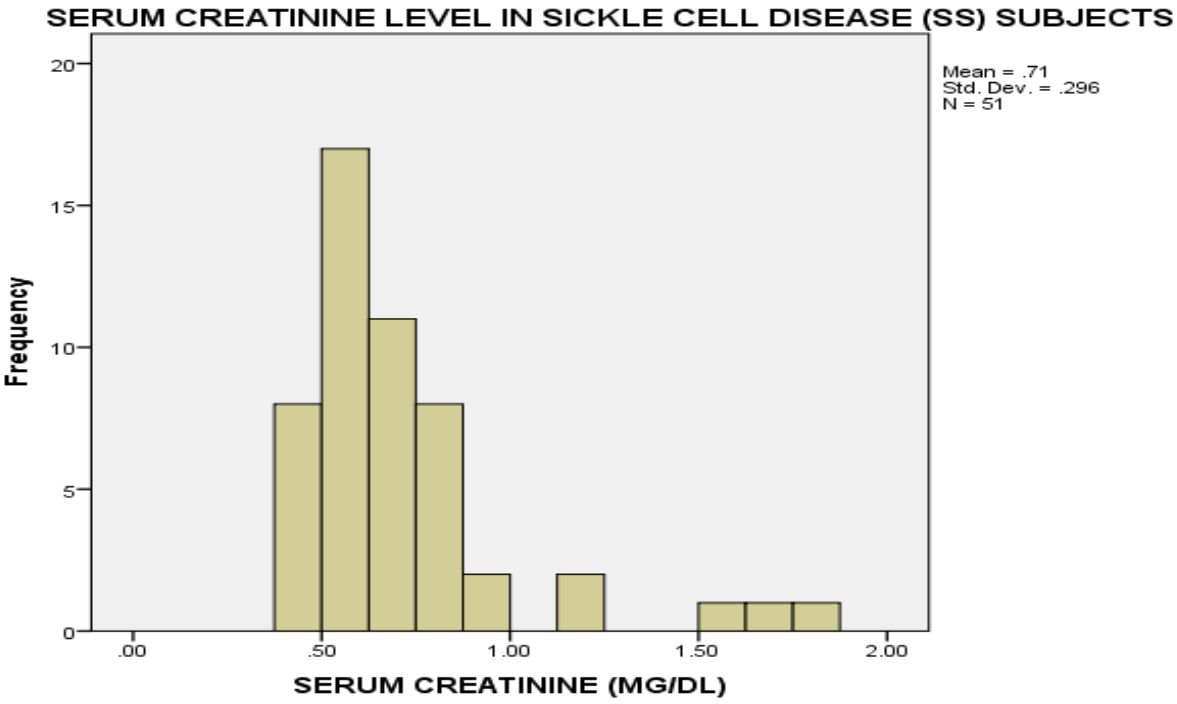

FIGURE 2

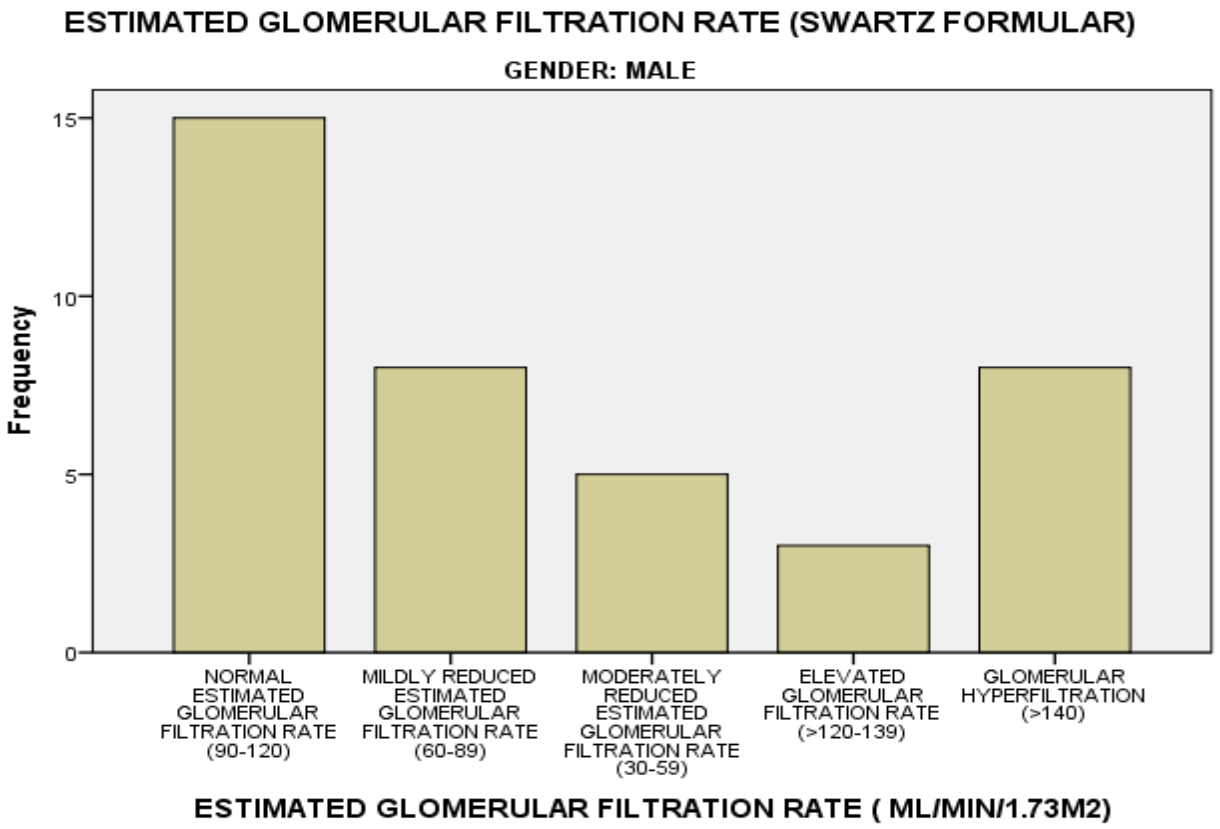
ESTIMATED GLOMERULAR FILTRATION RATE (SWARTZ FORMULAR)
GENDER: MALE
Frequency
15
10
5
0
NORMAL ESTIMATED GLOMERULAR FILTRATION RATE (90-120)
MILDLY REDUCED ESTIMATED GLOMERULAR FILTRATION RATE (60-89)
MODERATELY REDUCED ESTIMATED GLOMERULAR FILTRATION RATE (30-59)
ELEVATED GLOMERULAR FILTRATION RATE (>120-139)
GLOMERULAR HYPERFILTRATION (>140)
ESTIMATED GLOMERULAR FILTRATION RATE (ML/MIN/1.73M2)

FIGURE 3

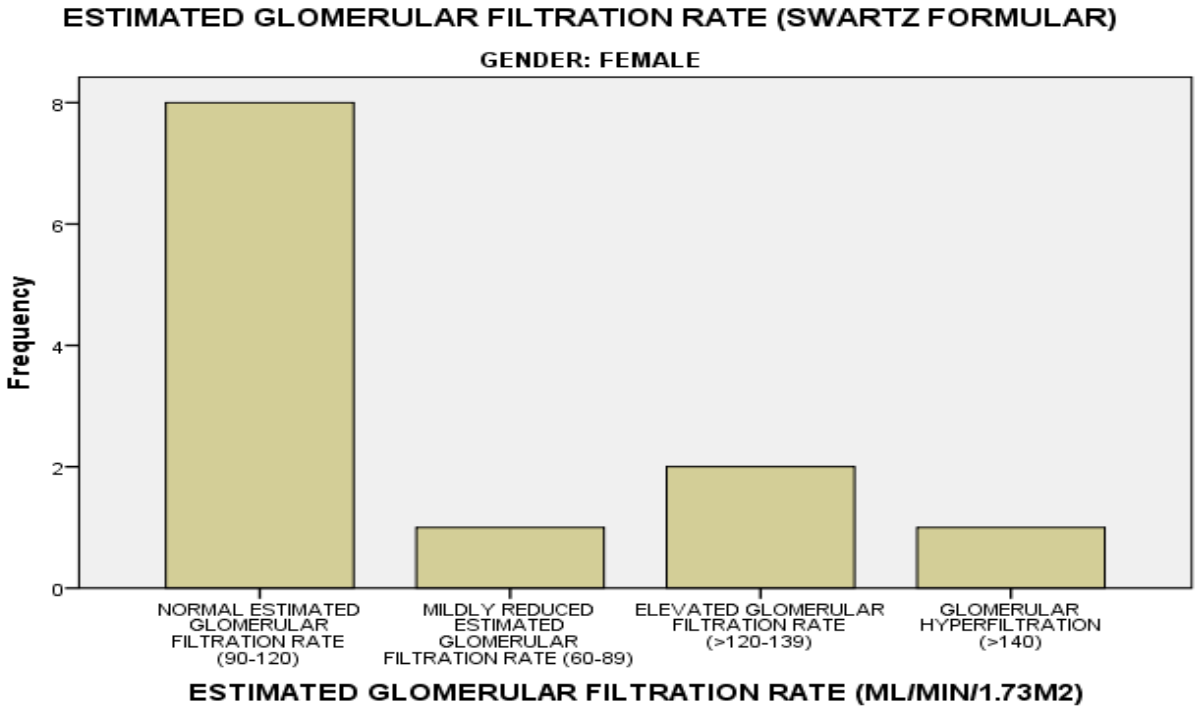
ESTIMATED GLOMERULAR FILTRATION RATE (SWARTZ FORMULAR)
GENDER: FEMALE
Frequency
8
6
4
2
0
NORMAL ESTIMATED GLOMERULAR FILTRATION RATE (90-120)
MILDLY REDUCED ESTIMATED GLOMERULAR FILTRATION RATE (60-89)
ELEVATED GLOMERULAR FILTRATION RATE (>120-139)
GLOMERULAR HYPERFILTRATION (>140)
ESTIMATED GLOMERULAR FILTRATION RATE (ML/MIN/1.73M2)

FIGURE 4

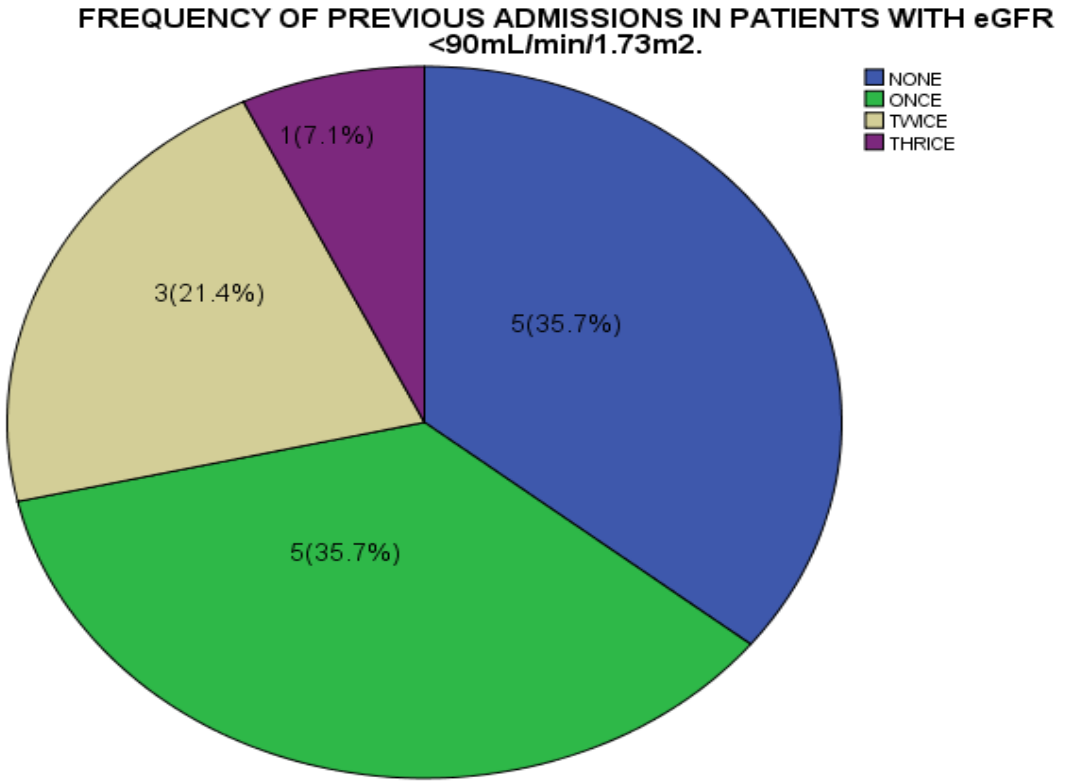

FIGURE 5

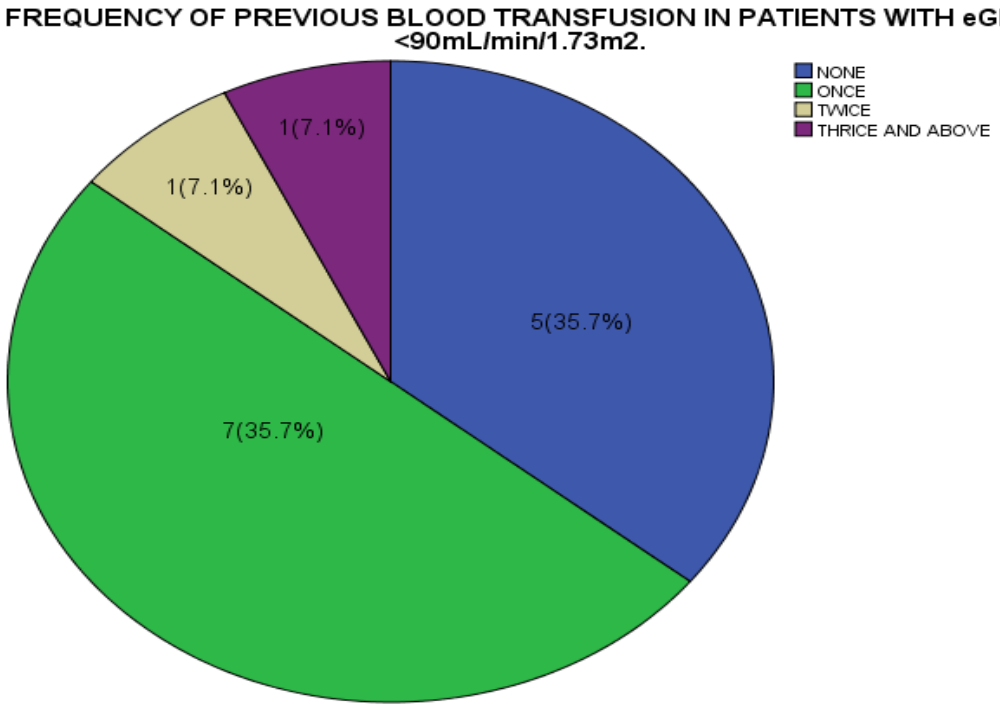
FREQUENCY OF PREVIOUS BLOOD TRANSFUSION IN PATIENTS WITH eGFR <90mL/min/1.73m2.
NONE
ONCE
TWICE
THRICE AND ABOVE
1(7.1%)
1(7.1%)
5(35.7%)
7(35.7%)

FIGURE 6

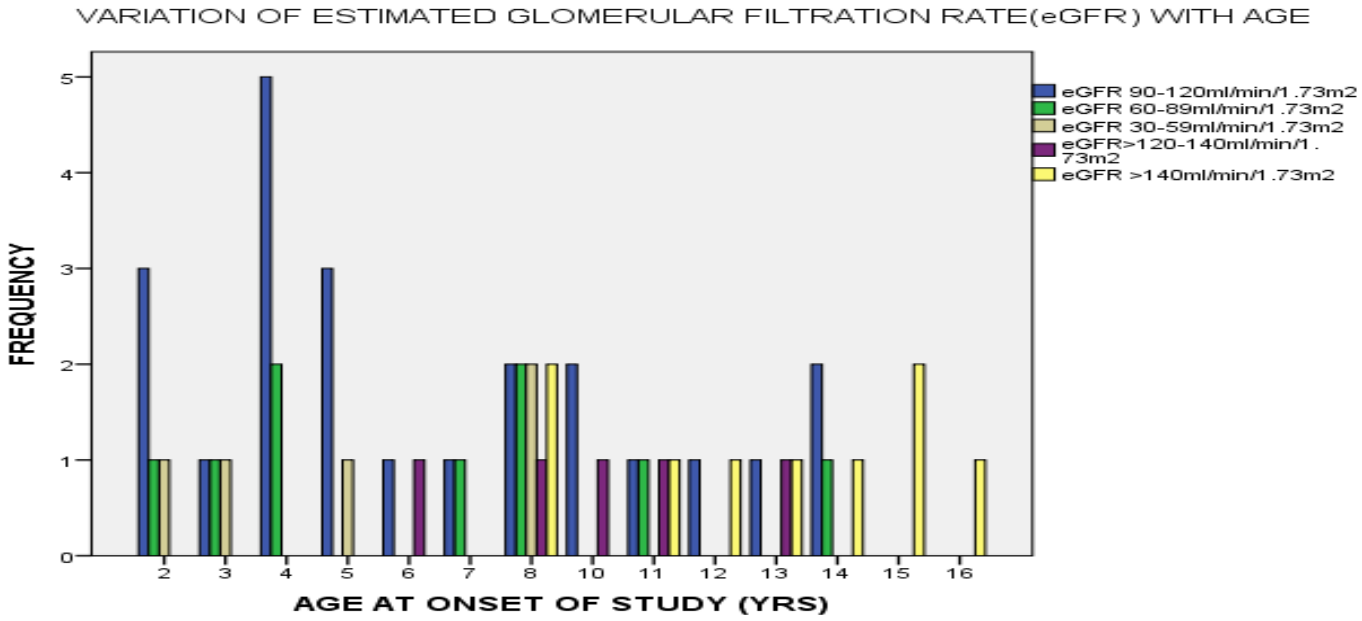
VARIATION OF ESTIMATED GLOMERULAR FILTRATION RATE(eGFR) WITH AGE
eGFR 90-120ml/min/1.73m2
eGFR 60-89ml/min/1.73m2
eGFR 30-59ml/min/1.73m2
eGFR>120-140ml/min/1.73m2
eGFR >140ml/min/1.73m2
FREQUENCY
AGE AT ONSET OF STUDY (YRS)

TABLE OF AUTHORS


GENES NO PARENT WANTS TO PASS ALONG
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