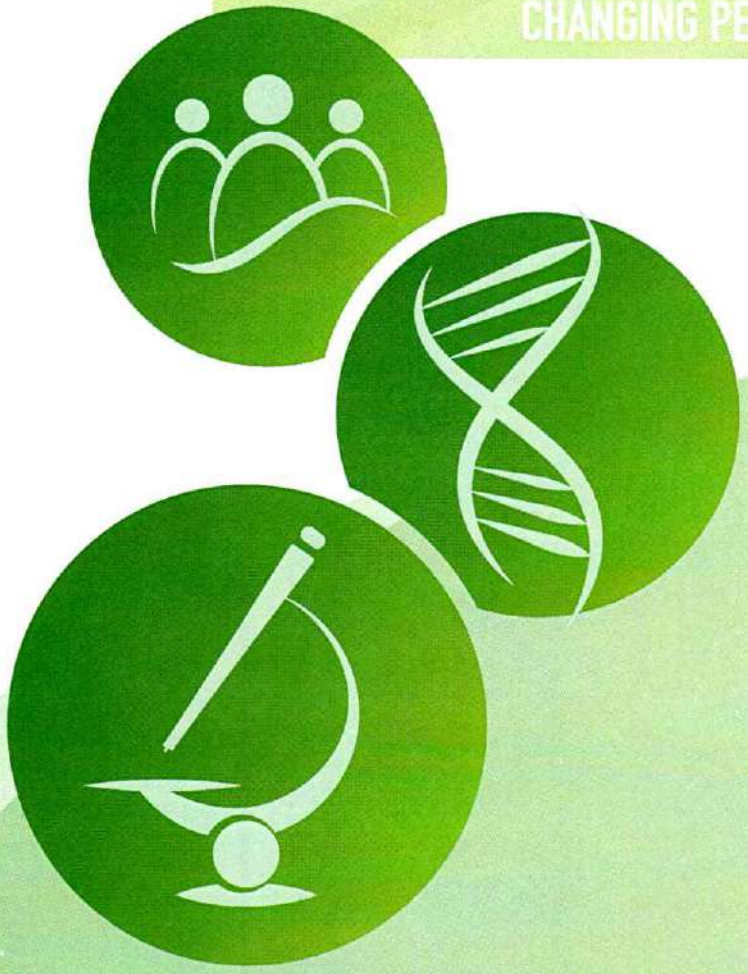
7th Annual Sickle Cell Disease Research and Educational Symposium and **36th** National Sickle Cell Disease Scientific Meeting

SICKLE CELL DISEASE IN THE POST-GENOMIC ERA

CHANGING PERSPECTIVES IN LABORATORY CLINIC & COMMUNITY



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ABSTRACTS

329

VARIATION IN THE TREATMENT OF STROKE IN SICKLE CELL DISEASE: A SURVEY OF PROVIDERS

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Background: The risk of stroke is greatly increased in children and adults with sickle cell disease (SCD). Before the widespread implementation of screening by transcranial Doppler ultrasound, 11% of people with sickle cell anemia (HbSS) and 2% with hemoglobin SC disease (HbSC) had a stroke by 20 years of age.1 Regular transfusion of sickle-negative red blood cells greatly reduces and hydroxyurea moderately reduces the risk of recurrent stroke in children.2 More strokes (~75%) occur in adults than children with SCD,3 but the treatments have not been rigorously evaluated and may vary with the age of first stroke and genotype of SCD.

Objectives: To describe the variation in the treatment of stroke in adults with SCD.

Methods: We invited by e-mail members of the Sickle Cell Adult Provider Network (SCAPN) to complete a 41-question web-based survey (Survey Monkey, Palo Alto, CA). We asked general questions about provider and center characteristics, use of thrombolytics, and knowledge of and agreement with published stroke guidelines in addition to the preferred (>50%) acute management, evaluation, and long term treatment of 4 specific cases. We compared responses among adult hematologists, pediatric hematologists, and other physicians (general internists and Med/Peds, neurologists, transfusion medicine, and emergency medicine) using Student's t-test and the chi-squared statistic.

Results: We surveyed 253 SCAPN members and received 79 responses (31%) including 52 from physicians that care for adults with SCD. This group was 56% female with a mean age of 47 ± 11 years. Most (82%) would always or mostly consult a neurologist/stroke expert to assist in the management of acute stroke in an adult with SCD. Red cell exchange was the preferred therapy (90% of respondents) for acute ischemic stroke in 21 year old with HbSS as well as a 45 year old with HbSC (71%) with simple transfusion considered an acceptable alternative by some providers for stroke in the adult with HbSS, but not HbSC. The acute treatment of ischemic stroke was similar for physicians with different residency training except for less frequent use of intravenous thrombolysis by pediatric and adult hematologists and less frequent use of simple transfusion in HbSS by adult hematologists compared to other specialties. Treatments for the secondary prevention of stroke were similar, except for the less frequent use of simple transfusion by adult hematologists compared to all others and the less frequent use of hydroxyurea by pediatric hematologists compared to adult hematologists and other physicians.

Conclusions: There is substantial agreement on the acute management and secondary prevention of ischemic stroke in adults with SCD despite a paucity of evidence. The greatest variation is in the use of specialized therapies: thrombolysis for the acute treatment of stroke and hydroxyurea for secondary prevention. The lack of evidence and variation in practice present opportunities for prospective study of stroke management in adults with SCD.

Table: Acute Treatment and Secondary Prevention of Ischemic Stroke by Physician Specialty for a 21 year old with HbSS and 45 year old with HbSC

Management	Adult Hematologist N=25		Pediatric Hematologist N=10		Other N=17		P-Value
Acute Treatment	HbSS	HbSC	HbSS	HbSC	HbSS	HbSC	
Neurology Consult	74%	87%	67%	57%	87%	80%	NS
Aspirin	30%	61%	22%	29%	33%	53%	NS
Thrombolysis IV	**0%**	4%	**0%**	14%	**27%**	33%	0.009
Simple Transfusion	13%	0%	33%	0%	20%	0%	NS
Red Cell Exchange	92%	70%	88%	71%	92%	73%	NS
Any Transfusion	100%	100%	100%	100%	93%		NS
Secondary Prevention							
Aspirin	26%	61%	0%	43%	40%	40%	NS
Simple transfusion	**17%**	4%	**56%**	14%	**53%**	13%	0.032
Red Cell Exchange	78%	48%	67%	86%	47%	47%	NS
Any Transfusion	96%	52%	100%	86%	87%	60%	NS
Hydroxyurea	**26%**	9%	**0%**	0%	**47%**	13%	0.046

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383

SPHINGOSINE-1-PHOSPHATE IS AN ALLOSTERIC MODULATOR OF HEMOGLOBIN-OXYGEN AFFINITY AND CONTRIBUTES TO PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a debilitating hemolytic disorder with high morbidity and mortality affecting millions of individuals worldwide. Although SCD was identified a century ago, we still lack effective mechanism-based safe therapies to treat this disease. Thus, identification of specific molecules triggering sickling, the central pathogenic process of the disease, is extremely important to advance the understanding of the molecular basis for the pathogenesis of SCD and develop novel therapeutics.

Methods and Results: Using non-biased metabolomic screening, we found that sphingosine-1-phosphate (S1P) is significantly elevated in the circulation of SCD transgenic (Tg) mice. This finding led us to further discover that the activity of sphingosine kinase 1 (Sphk1) was significantly elevated within erythrocytes of SCD Tg mice. Genetic knockdown of Sphk1 in bone marrow cells of SCD chimeras or chronic treatment of SCD Tg mice with a specific Sphk1 inhibitor significantly attenuated sickling, hemolysis, inflammation and multiple tissue damage by reducing erythrocyte and plasma S1P levels. Erythrocyte S1P levels were further elevated following hypoxia/reoxygenation-induced acute sickle crisis (ASC) in SCD Tg mice and blocking its elevation by a Sphk1 specific inhibitor significantly reduced hallmark features associated with ASC and increased survival rates. Similarly, we found that erythrocyte Sphk1 activity and erythrocyte and plasma S1P levels were significantly elevated in SCD patients compared to normal individuals. Inhibition of Sphk1 in cultured primary human erythrocytes isolated from SCD patients inhibited hypoxia-induced elevation of erythrocyte S1P levels and reduced sickling. Finally, we found that S1P is an endogenous erythrocyte allosteric effector that directly binds Hb, substantially decreases Hb-O2 affinity, promotes deoxygenation and thereby contributes to erythrocyte sickling. Conclusion-Our findings reveal a previously unrecognized important role of S1P in erythrocyte physiology and provide a new paradigm for the pathogenesis of SCD. These findings illuminate novel therapeutic opportunities for the treatment of SCD.

306

PITFALLS OF USING ADMINISTRATIVE DATA SETS TO DESCRIBE CLINICAL CARE IN SICKLE CELL DISEASE

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Background: Sickle Cell Disease (SCD) affects 100,000 individuals in the United States. Advances in care have resulted in a growing population of adults with SCD. Without a parallel increase in the capacity to care for this group of patients, inequities have emerged in access to quality care and health outcomes. Most adult patients are hospitalized outside of SCD centers. Increased mortality in young adults following transition from pediatrics is often due to Acute Chest Syndrome (ACS), a life-threatening pulmonary process usually requiring blood transfusion.(1) Recognition and appropriate treatment of ACS could represent a key indicator of care and promote wellness for adult SCD patients. Our recent query of the California Office of Statewide Health Planning and Development (OSPHD) database found that one-fifth of the hospital inpatient visits associated with the diagnosis of SCD between 2005 and 2008 were for ACS or a related pulmonary process.(2) Despite NIH standard of care guidelines suggesting that transfusion should be used to treat ACS, we found that only 46% of those visits were associated with a transfusion, implying many patients are not receiving appropriate care. Administrative data bases allow researchers to access large populations but their use has not been validated for clinical care in SCD. In light of recognized concerns regarding the relationship of coded diagnoses in administrative data to final clinical diagnoses, we compared OSHPD visit-level discharge data to three hospital databases.

Methods: Hospital billing data from 2009-10 identified 162 patients as having ACS. Equal numbers of cases were reported to OSHPD during the same time period. Chart reviews were then conducted of identified cases which allowed us to verify the diagnoses and assess the true rate of transfusion.

Results: Chart reviews demonstrated that there were a number of cases which were coded as ACS but ultimately proved to have a different final diagnosis. This was due to cases were ACS was investigated but not proven. More transfusions were identified in hospital data than OSHPD. The net effect was a lower transfusion rate in OSHPD (52.3% Hospital 1; 12.9% Hospital 2; 22.7% Hospital 3) than actual transfusion rate (77% Hospital 1; 50% Hospital 2; 50% Hospital 3)(Table 1). Conclusions: Administrative data is widely used to inform health policy, with OSPHD in particular widely used in California. However, these results suggest that using administrative data to assess clinical care for SCD may lead to inaccurate assumptions about quality of care. Future studies may require a different methodology."

Table 2. True rates of ACS and transfusion (Tx) in OSHPD, 2009-2010 (SCD visits with ACS, N=162).

Data Source	Billing Data Cases	Verified ACS Cases	Verified ACS and Tx	OSHPD Tx	True Tx Rate	OSHPD Tx Rate
Hospital 1	110	83	66	57	79.5%	52.3%
Hospital 2	30	26	13	4	50.0%	12.9%
Hospital 3	22	12	6	5	50.0%	22.7%
Total	162	121	85	66	70.2%	40.7%

Table 2

ACS cases found in the billing databases from each hospital are listed in the first column. The second column reports the number of cases with ACS as the final diagnosis. The third column reports those true cases which were transfused and the fourth column reports the number of cases which were associated with a transfusion in OSHPD. The corresponding rates of transfusion are shown in the last two columns.

1

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254

REDUCING 30 DAY READMISSION RATES IN CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Background: Public and private payers increasingly refuse to pay for hospital readmissions within 30 days of discharge for the same problem. In adult care literature, readmissions correlate with an inadequate discharge process. As part of Children's Hospital Association, Nationwide Children's Hospital Comprehensive Sickle Cell Program participated in a 12 month Discharge Quality Improvement collaborative to decrease 30 day readmissions for sickle cell pain.

Objectives: 1) To decrease the rate of 30 day readmissions to the hospital for patients with sickle cell disease (SCD) and pain. 2) To determine preventable causes of 30 day re-admission for patients with SCD and pain. 3) To find which patients with SCD are at highest risk for re-admission within 30 days.

Methods: A multi-disciplinary team was assembled for this 12 month project including the SCD medical director, APN, nurse clinicians, program coordinator, social worker, psychologist, medical director of quality improvement, chief nursing officer, inpatient care coordinator, nighttime inpatient clinical leader, statistician/ data manager, care coordination, and social work administrator. Action steps were developed in a multi-prong approach. 1) The nurse clinicians made follow-up phone calls to patients/parents within 5 days of discharge. Data gathered from these calls included medication reconciliation, whether or not the patient felt involved in his/her care, whether or not discharge instructions were reviewed with the patient prior to discharge, if medications were able to be filled prior to discharge, and if the patient knew his/ her follow-up plan. 2) Pharmacy consult to review outpatient medications prior to discharge. 3) Sickle Cell Action Plans were developed for outpatient pain management. 4) A Peer Mentorship Program was started for the subset of adolescents and young adults with the highest utilization. Data was collected from October 2011 through October 2012, including re-admission rates and the responses to the nurse clinician post-discharge phone calls.

Results: Our 30 day readmission rate for the year leading up to this project was 33%. From October 2011 through October 2012 it ranged from 14% to 56%, with a mean of 38%, an increase of 5%. Two possible preventable causes of readmission were identified. Patients were re-admitted never having filled their prescriptions for pain medications upon discharge, and patients reported that their discharge instructions were not reviewed with them. The most significant finding was that 30 day readmission rates are significantly higher among 19 to 21 year old patients than any other age group. Of 111 unique patients admitted for SCD and pain during the year, 5 patients accounted for almost 70% of the admissions and 50% of 30 day readmissions. Follow-up phone calls by sickle cell nurse clinicians did not decrease readmission rates, but uncovered systems issues including medication reconciliation errors and lack of verbal review of home going instructions at the time of discharge that may contribute to readmissions.

Conclusions: While improvements in systems issues made us feel we are delivering better service, they did not reduce 30 day readmission rates within one year. The highest utilizers are 19 to 21 years of age, with only 5 patients accounting for the majority of admissions. Specific interventions need to be made for this group. We have started a peer mentoring group to pair the highest utilizers with young adult patients who have successfully moved from frequent hospitalizations to rare inpatient stays. We hope that addressing psychosocial needs of these individuals will not only help the current patients, but help us to understand the factors that lead to frequent readmissions for pain.

248

MAST CELL ACTIVITY CONTRIBUTES TO PAIN IN SICKLE CELL ANEMIA

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Background: Chronic and acute pain in sickle cell anemia (SCA) is often difficult to treat. The mechanisms underlying pain in SCA are not clearly understood, limiting therapeutic choices. We found that mast cell (MC) degranulation contributes to neuroinflammation and vascular dysfunction in sickle mice. Together, these processes may stimulate nociceptor sensitization and pain. Therefore, inhibition of MC activity may ameliorate hyperalgesia in SCA.

Objectives: We hypothesize that MC degranulation contributes to nociception and that Imatinib, an inhibitor of mast cell receptor c-kit, will ameliorate hyperalgesia in SCA.

Methods: We used transgenic sickle (HbSS-BERK) and control mice (HbAA-BERK) expressing >99% human sickle or human hemoglobin A, respectively to determine the effect of Imatinib on hyperalgesia in SCA. To assess the contribution of MC activity in hyperalgesia we used MC deficient mice with a mutation in c-kit gene (KitW/KitW-v) and crossbred them with sickle mice to obtain sickle mice deleted for mast cells (HbSS-KitW/KitW-v). Sickle and control mice were treated with Imatinib (100 mg/kg/day, by gavage) or 0.9% saline for 5 days. To examine the contribution of MC in vaso-occlusive crisis (VOC) associated pain, mice were exposed to 3 h of hypoxia at 8% oxygen and 1 h of re-oxygenation at room air (H/R). Pain behaviors were measured as follow: before drug treatment to obtain baseline hyperalgesia, following 5 days of Imatinib, immediately after H/R, and 24 h after H/R. Sensory pain measures included sensitivity to mechanical stimulus evoked by 1.0 g von Frey monofilaments (PWF), paw withdrawal latency (PWL-heat) in response to heat stimulus and deep tissue hyperalgesia by forepaw grip force (GF).

Result: Five days of Imatinib treatment significantly increased grip force, and decreased mechanical and heat hyperalgesia ($p < 0.05$, 0.05 and 0.01 compared to vehicle, respectively), thus ameliorating deep pain, and mechanical- and thermal-sensitivity, respectively in sickle mice. Similar to Imatinib treatment, MC deficiency in sickle mice (HbSS-KitW/KitW-v) resulted in significant reduction in these pain features as compared to sickle mice (HbSS-BERK) ($p < 0.001$ for both mechanical and heat sensitivity). H/R evoked deep, mechanical and thermal hyperalgesia in sickle mice ($p < 0.05$, 0.001 and 0.001 for deep, mechanical and heat sensitivity, respectively, compared to control mice) but not in HbSS-KitW/KitW-v mice for up to 24 h post-H/R.

Pretreatment with Imatinib for 5 days remarkably reduced pain for up to 24 h post-H/R as compared to vehicle ($p < 0.01$, 0.05 and 0.05 for deep, mechanical and heat sensitivity, respectively). Together, these data suggest that MCs contribute to tonic hyperalgesia as well as pain associated with VOC and therefore Imatinib treatment significantly ameliorates chronic pain as well as H/R evoked pain in sickle mice.

Conclusion: MC activity contributes to sickle pathophysiology underlying chronic pain and that associated with VOC. Therefore, inhibition of MC activation by Imatinib may have a therapeutic effect on chronic pain and prevent VOC in SCA.

332 NURSES' ATTITUDES TOWARDS PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) may produce both chronic and acute pain. Because individuals with SCD are often members of minority groups with a history of discrimination, their healthcare encounters embody more than mere presentation of symptoms as individuals with SCD are often perceived as drug-seeking (Strickland et al, 2001). This stigmatization may cause individuals with SCD to avoid the healthcare system. Psychometrically valid surveys of both patients' and healthcare providers' attitudes are needed to provide information on which to base interventions to improve quality of care. Although a valid stigma measure exists to help us understand individuals' with SCD perceptions of stigma, we need to better understand nurses' attitudes towards patients with SCD because nurses are often the first assessors of pain and communicate patient needs to providers.

Objectives: The purposes of this study was to better understand nurses' attitudes towards patients with SCD and compare responses between nurses who work in the emergency departments (ED) or intensive care unit (ICU) and nurses who work on medical-surgical units.

Methods: After IRB approval, a comparative descriptive survey design was used elicit responses from nurses via an online survey at two hospitals located in the Southeast. The survey requested demographic information, responses to the Clinician Attitudes Scale (Haywood et al., 2010), and select adapted questions from the Sickle Cell Disease Health-Related Stigma Scale (Jenerette, Brewer, Crandell, & Ataga, 2012). The Clinician Attitudes Scale is comprised of 4 subscales- Negative Attitudes (NA), Positive Attitudes (PA), Concern Raising Behaviors (CRB), and Red-Flag Behaviors (RFB), which have a potential range of 0-100 each.

Results: A sample 78 nurses responded to the on-line survey. Approximately 90% of the respondents were female with a mean age of 38.6 years (SD 12.2). The majority of the respondents were White (74%), Non-Hispanic (97%), and reported having a BSN degree (61%). Forty-seven percent (47%) described their practice area as ED/ICU while 53% reported medical-surgical nursing. Cronbach's alphas for the 4 subscales of the Clinician Attitudes Scale ranged from .76-.90. Although not statistically significant ED/ICU nurses trended toward reporting more negative attitudes, identifying more concern raising behaviors and more red-flag behaviors. There were statistically significant correlations between NA and PA (r=-.36); NA and CRB (r=.64); PA and CRB (r=-.32); and NA and RFB (r=.40). Ninety-seven percent (97%) of respondents agree that there is a real physical cause for sickle cell pain. Only 64% of respondents reported that patients with sickle cell use pain medication appropriately. Only 31% of respondents reported that patients with sickle cell do not complain about their illness any more than patients with other medical condition.

Conclusion: We know clinicians' attitudes can influence patient outcomes. Nurses play a pivotal role in the provision of care to individuals with SCD. Results support that there is a need to continue to educate nurses about SCD and intervene to improve attitudes. Additionally, it may be important to survey ED and ICU nurses separately to better understand their attitudes towards patients with SCD.

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326

EVALUATION OF THE PEDIATRIC PROMIS HEALTH DOMAINS IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE (SCD)-COMPARISON TO PEDS QL SCALE SCORES

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Health-Related Quality of Life (HRQOL) measures are an important component of evaluating disease management or new therapies. The Patient-Reported Outcomes Measurement Information System (PROMIS) project was developed to advance the science and application of patient-reported outcomes (PRO), and is supported as a trans-NIH initiative. The PROMIS pediatric project has developed generic PROs suitable for comparing a wide variety of health conditions in youths aged 8–17 years across many health domains, including physical function, pain, fatigue, emotional distress, and social function. Parent proxy reporting is also supported. These measures are being validated in a number of pediatric chronic illnesses, including SCD.

Many previous SCD studies have used a similar generic HRQOL PRO, the Peds QL, such as the study conducted by the Comprehensive Sickle Cell Centers (Pediatr Blood Cancer 55:485-494, 2010), which enrolled 1772 subjects (53% boys) with a mean age of 9.6 years (SD 4.7), most with SS or Sβ0 thalassemia (68%). Multiple regression models controlling for age, gender, and hemoglobinopathies suggested that sickle pain, and to a lesser extent asthma, negatively influenced child reports on almost all functioning and fatigue scales.

To establish the sensitivity of the various Peds PROMIS scales, we are currently conducting a longitudinal study of the pediatric PROMIS item banks, as well as the Peds QL, in children with SCD. Children are completing measures at yearly clinic visits, during hospitalizations for pain, and at a follow-up clinic visit after recovery from the acute event. A convenience sample of 101 SCD patients aged 8-17 years followed at our Sickle Cell clinics (Children's Healthcare of Atlanta) has been recruited from routine clinic visits (mean age 12.5 ±3.1 years, 46.5% male, 98% Black/Non-Hispanic, 70% SS). Individuals were eligible to participate if they had an acute care visit for pain in the previous year pain, could speak and read English, and were able to complete a computer administered survey. Children completed the pediatric PROMIS survey over the internet using a computer adapted testing (CAT) protocol on the PROMIS Assessment Center secure website and an electronic version of the Peds QL version 4. Parents also completed a short demographic questionnaire.

At the baseline clinic visit, scores on the age-appropriate child PedsQL Emotional Functioning scale showed a strong correlations with the PROMIS Anxiety (-0.673, $p<0.001$) & Depression (-0.757, $p<0.001$) domain scores. Similarly there were strong correlations between the PROMIS Fatigue domain scores and the PedsQL General Fatigue (-0.804, $p<0.001$) and the Sleep Rest Fatigue (-0.690, $p<0.001$) Scores. The PedsQL Physical Functioning Scores were more strongly correlated with the PROMIS Mobility (0.714, $p<0.001$) then the Upper Extremity domain scores (0.479, $p<0.001$), reflecting the different item content of the two PROMIS scales. Similarly, the correlation between PROMIS Peer Relationships domain scores and the PedsQL Social Functioning Scores, while statistically significant, was relatively weak (0.243, $p=0.033$).

This initial data continues to support the utility of generic HRQOL life measures in evaluating pediatric chronic diseases such as SCD, and highlight the need for carefully examination of item content when comparing scales on various measures. Further information on PROMIS and peds QL scale sensitivities will be reported as that data becomes available.

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376

EVIDENCE OF ALTERED PAIN PROCESSING IN ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Background: Numerous previous functional neuroimaging studies have identified brain regions that show greater activation to painful versus non-painful stimuli. This experiment examined the response of brain regions within this "pain matrix" in patients with sickle cell disease (SCD) to describe possible alterations to neural reactivity that underlies pain sensitization.

Methods: The pain threshold for 12 African American adolescents and adults with SCD (ages 16-31 years) and 12 demographically-matched control participants were determined using a pressure algometer and a calibrated series of weights. Pressure pain sensitivity was evaluated by suprathreshold sensations using an 11 point (0 – 10) patient numerical rating scale following 18 seconds of stimulation. Participants then underwent an fMRI block design pain challenge task using three pre-determined experimental pain levels (none, mild, or moderate) and a standard equal pressure weight (125g) condition. FMRI time series data were realigned, spatially-normalized and smoothed (8mm FWHM) using SPM8 and examined using a finite-impulse-response model to capture any transient or sustained brain activity changes during each stimulation. Mixed-factor SPM8 ANOVA compared groups across pain levels.

Results: There was no statistical difference in the pressure required to produce the predetermined pain levels between SCD subjects and controls. Despite having equivalent pressure requirements at each of the three experimental pain levels, SCD subjects showed reduced hemodynamic response in SII and insular cortex regions-of-interest compared to controls across no pain, equal pain and equal pressure conditions.

Conclusion: We have demonstrated evidence for centrally altered pain processing in patients with SCD. The results indicate that pain-related neural processing is abnormal in SCD patients, involving deficits in brain regions specialized for sensory-discriminative (SII) and somatosensory integration (insula). However, no SCD abnormalities during pain challenge were detected in brain regions thought to represent basic sensation (SI) or cognitive/emotional aspects of nociceptive processing (e.g., anterior cingulate). Although these results stand in contrast to some studies that found pain matrix activation predicted self-reported pain intensity, they make sense within the context of evidence for reduced neural response when pain is delivered in a predictable, fixed context. Therefore, the blunted average SII and insular activation in SCD patients is taken as evidence for even greater-than-usual reduction in repeated pain-induced activation related to pain sensitization. The results also suggest SCD patients pain sensitization might involve abnormal signaling from these brain regions to other cortical areas more directly involved with interpreting and consciously representing the pain experience.

268

CD34-SELECTED, T CELL-DEPLETED ALTERNATIVE DONOR STEM CELL TRANSPLANTATION FOR PEDIATRIC SICKLE CELL DISEASE

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Background: Most patients that could be cured of sickle cell disease (SCD) with stem cell transplantation do not have a matched sibling donor and many do not have a matched unrelated donor. Successful use of alternative donors including mismatched family members could provide a donor for almost all patients.

Objective: The use of a reduced intensity conditioning regimen and a CD34-selected, T cell-depleted peripheral blood stem cell (PBSC) graft will allow engraftment with low incidence of graft-versus-host disease (GVHD).

Methods: Between 2009-2012, six SCD patients underwent CD34-selected, T cell-depleted transplantation from an alternative donor on an IRB-approved protocol. Indications for transplantation included vaso-occlusive pain crisis (n=3), concurrent Kostmann's syndrome and painful crisis (n=1), stroke (n=1) and conditional transcranial Doppler with hypoxia at night (n=1). Five patients had received multiple PRBC transfusions prior to transplantation.

Conditioning regimen consisted of melphalan 140mg/m2, thiotepa 5mg/kg x2, fludarabine 40mg/m2 x5, and rabbit-ATG 2.5mg/kg x4 with no post-transplant immunosuppression. Two patients received rituximab during conditioning. Three patients received a planned donor lymphocyte infusion (DLI) between days 33 and 42 with methotrexate IV prophylaxis on a companion study.

Results: Median age at transplantation was 13 years (range 5-17). Four patients had mismatched-related and two had unrelated donors. Median PBSC dose was 17x10^6 CD34/kg (range 11-25) and all patients received 500 at median 13 days (range 10-14). 5/6 patients are alive with follow-up of 40, 28, 4, 3.5, 2 months. One patient had EBV-related post-transplant lymphoproliferative disorder (PTLD), which was cured by DLI but subsequently developed acute GVHD, CMV enteritis and succumbed to aspergillosis. The only other serious viral disease was EBV-related PTLD in one patient which resolved. No acute GVHD developed after transplant alone and no chronic GVHD occurred.

Conclusion: A reduced intensity conditioning regimen followed by CD34-selected, T cell-depleted alternative donor transplantation provided reliable engraftment and a low incidence of GVHD. If this approach is successful in additional patients, it may expand the donor pool for pediatric patients with SCD who do not have a matched sibling donor.

236

UTILIZATION AND OUTCOME OF BONE MARROW TRANSPLANTATION IN CHILDREN WITH SICKLE CELL DISEASE: A PEDIATRIC HEALTH INFORMATION SYSTEM DATABASE ANALYSIS

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Introduction: Bone marrow transplantation (BMT) is curative for hemoglobinopathies but its utilization in sickle cell disease (SCD) is sparse. Though there were 100,000 affected with SCD in the USA, BMT has been utilized in less than 1000 individuals. As SCD has variable clinical course, confusion prevails regarding indication, timing of BMT, benefits and risks for individuals due to morbidity/mortality of the procedure.

Methods: We used the Pediatric Health Information System (PHIS), an electronic database of children's hospitals in the US. Patients under the age of 21 who underwent BMT at one of the 26 PHIS hospitals from 2000-2011 were analyzed. We abstracted data on demographics, hospitalizations, BMT and related complications.

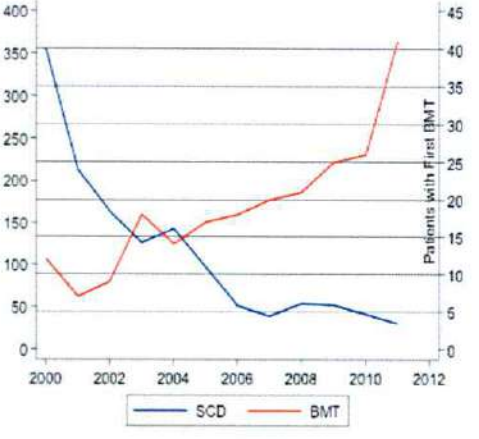
Results: From 2000 to 2011, there were 1365 unique pediatric patients with SCD identified. Among these 228(17%) children underwent BMT and their demographic and baseline characteristics are shown in Figure 1A. Overall, the number of new patients with SCD getting hospitalized has decreased consistently whereas children undergoing BMT has increased (Figure 1B). There was a significant decrease in hospitalizations after BMT compared to pre-BMT state (median hospitalization 2 vs. 4 respectively, n=173, p=<0.0001). After BMT, 6%(13/228) of patients developed stroke, 14%(31/228) had CMV infection, 9%(21/228) developed invasive fungal infections, 2.2%(5/228) had VOD, and 23%(24/102) developed GVHD. Seventeen patients (7.4%) died related to BMT with more deaths occurred when BMT performed at age ^{3}11 years compared to age ^{2}10 years (13/108 vs. 4/120 respectively, p=0.029).

Conclusions: We show an increasing trend of BMT utilization in children with SCD. In this largest BMT cohort of SCD, transplant related mortality is very low especially if BMT is performed before 10 years of age. BMT significantly decreases the overall hospitalizations in these patients. Studies addressing the barriers of BMT and hydroxyurea utilization are needed to decrease the health burden in this chronic disease.

Figure 1A. Baseline characteristics of SCD patients underwent BMT

Total no. of patients (n)	228
Age at BMT (n)	
0-5 years	48
5-10 years	76
11-15 years	56
16-21 years	48
Phenotype (n)	
HbSS	214
HbSβ0 thalassemia	11
HbSC	3
Pre-BMT morbidity (%)	
Vaso-occlusive crises (VOC)	33%
Acute Chest Syndrome (ACS)	27%
Pneumonia	36%
Stroke	13%
Avascular necrosis (AVN)	7%
≥ 2 premorbid conditions	47%
Hydroxyurea use	23%
ICU care	34%
Initial BMT hospitalization	
Median length of stay (days)	31
ICU care (%)	17
Mechanical ventilation (%)	10.5

Figure 1B. Overall trend of new SCD diagnosis and BMT in children and adoloscents



257

EDUCATING PATIENTS AND PHYSICIANS ON HEMATOPOIETIC CELL TRANSPLANTATION AS A VIABLE TREATMENT OPTION FOR SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is the most common inherited disorder in the African-American population. In the US, approximately 100,000 people live with SCD.1 SCD is an inherited sickling blood disorder that can lead to blockage in blood vessels, which in turn can cause progressive and permanent damage to vital organs such as the brain, muscles and lungs, as well as excruciating episodes of pain. 2 The medical and psychosocial costs of supporting patients with this chronic illness and their caregivers is enormous and spans a lifetime.

Although advances in medical care have improved the lives of SCD patients, hematopoietic cell transplantation (HCT) remains the only known cure but is associated with some risks.3 Participation in HCT clinical trials (CTs) by individuals with SCD is critical to improving treatment options. Research suggests that though there is strong interest in HCT and willingness to accept some risk associated with HCT by parents and youth affected by SCD, this therapeutic modality remains underutilized.3 Reasons for this include but are not limited to: 1) lack of information about HCT as a curative therapy including the benefits and risks; 2) uncertainty among clinicians regarding appropriate selection of patients for HCT; and 3) misperceptions about the health impacts of SCD by parents and youth.3 It is essential to educate families and clinicians so they are aware of all treatment options available and can make truly informed decisions about their treatment plan.

Objectives:

1. To increase awareness of HCT as a treatment option for SCD

2. To identify strategies for informed, shared decision-making

Methods: Utilization of HCT is described using 1990-2011 data from the Center for International Blood and Marrow Transplant Research observational registry and the clinicaltrials.gov Website.

The registry contains data for most allogeneic (related or unrelated donor) HCT recipients in the US. A search of clinicaltrials.gov on January 4, and February 13, 2013 included the terms: sickle cell disease, transplant, hematopoietic cell transplantation and non-malignant disorders. Studies not pertaining to both SCD and HCT were excluded.

Nine focus groups of youth (N=10) and adults (N=41) were held at 3 sites each having a substantial population of patients potentially eligible for CTs specific to SCD. The transcriptions were analyzed for themes related to awareness of HCT as a treatment option, willingness to participate in CTs and educational preferences.

Results: Since 1990 more than 680 patients with SCD have received an HCT at 128 transplant centers nationwide. Many of these were allogeneic HCT, utilizing related or unrelated donors.

Among CTs for SCD (N=458) reported to clinicaltrials.gov, 18% were related to allogeneic HCT. More than 3,000 patients have been enrolled in these HCT studies to date. Study status showed 39 CTs currently recruiting; 2 enrolling by invitation only; and 8 not yet recruiting. Study inclusion by age indicated: 65 studies for children and adults, 7 for adults only and 10for children only. Examples of CTs currently enrolling patients with severe SCD are the STRIDE and SCURT studies for young adults and children respectively.

Parents of youth with SCD report low access to information and resources on HCT and CTs. Few are aware of the potential for HCT to cure SCD. Parents and youth alike prefer to learn about SCD and treatment options such as HCT from their physicians and nurses. Strategies for shared decision-making include addressing important questions such as:

§ How is SCD treated with HCT?

§ Who is a candidate for HCT?

§ What are sources of donor cells?

§ What is the recommended timing for an HCT consultation?

§ Where can people go for more information about HCT and CTs?

§ What has been the experience of others who received HCT for SCD?

Conclusion: Now is the time for education on HCT as a potential treatment option for SCD to foster informed decision-making and to empower patients and parents to actively participate in their treatment plan. Shared decision-making between families and physicians to undergo HCT involves discussion of HCT complications versus the shortened lifespan and long-term burden of SCD. Interest and participation in HCT-related CTs is on the rise and critical to improving therapies for those with SCD. Developing education tools for both patients and healthcare professionals will improve access to HCT, currently the only potential cure for severe SCD.

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316

DECISIONS ABOUT TRANSPLANT IN PEDIATRIC SICKLE CELL DISEASE: ARE FAMILIES AND PROVIDERS ON THE SAME PAGE?

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Background: The only cure for sickle cell disease (SCD) is hematopoietic stem cell transplantation (HSCT). The decision to pursue transplant, however, is a difficult one for families of children with SCD, requiring careful consideration of risks and benefits. To our knowledge, no studies have examined medical and psychosocial factors that influence families' decisions about HSCT for children with SCD. Similarly, little is known about providers' perceptions and whether caregivers and providers differ in their beliefs about the relative importance of these factors.

Objective: To compare provider and caregiver reports of factors that impact family decisions about HSCT for SCD

Methods: During a Family Education Symposium about HSCT for SCD that was held at a large urban children's hospital, families completed surveys evaluating the importance of factors thought to affect their decision to pursue HSCT. During their respective team meetings, medical and psychosocial team members completed the same survey, rating their impressions about factors affecting family decisions. Surveys were created with input from members of the SCD, HSCT, and Psychosocial teams at the hospital, were approved by the Institutional Review Board, and were anonymous and optional. Participating family members were entered into a drawing for a small reward. On a scale from 1 ("not important to my decision") to 4 ("very important to my decision"), participants rated the importance of 17 factors that may influence a family's decision to pursue HSCT for their child with SCD.

Results: Sixty-four respondents completed surveys (34 family members; 30 providers). Of the family respondents, 73% were parents/guardians of patients who had not had a transplant (n=25), 15% were parents/guardians of patients who had already had a transplant (n=5), and 12% were "other" family members (n=4). Of provider respondents, 37% were physicians (n=11), 37% were psychosocial team members (n=11), and 23% were nurses/nurse practitioners (n=7). The remaining respondent was a clinical research coordinator (n=1). Compared to providers' ratings, family members rated "emotional strain of transplant on the patient" as significantly more important to their decision, $t(61)=2.32$, $p<.05$, and "religious beliefs" as significantly less important to their decision, $t(62)=-2.54$, $p<.05$. Other factors were rated similarly by providers and family members, with "risk of death", "risk of serious complications", "prevention of SCD risks and complications", and "trust in medical teams" rated as most important to decision-making, and "child losing hair", "child missing school", and "impact of transplant on sibling donor" as least important. See Table 1 for mean importance ratings of survey items.

Conclusions: In general, family members and providers agree on the relative impact of medical and psychosocial factors on decisions to pursue HSCT. Concern for BMT-related risks (e.g., death, serious complications) is appropriate and reflects the importance of open communication about potential outcomes of HSCT so that patients and families can make accurately informed decisions. With trust in medical teams as a high-ranking factor, the role of the patient/family-physician relationship cannot be underestimated. Families also identify concern for the emotional impact of transplant on patients, which highlights the need for ongoing involvement of psychosocial support members throughout the transplant process. Although the current study is limited by a relatively small convenience sample that may not be representative of the larger SCD population, these results offer the first insights into factors that family members and providers view as important when making decisions about HSCT for SCD.

Table 1

Mean Importance Ratings of Factors Impacting Family Decisions to Pursue HSCT for SCD

Survey Item	Mean importance rating (Standard deviation) Family Members (n = 34)	Providers (n = 30)	t
Risk of death	2.91 (0.38)	2.77 (0.43)	1.44
Prevention of sickle cell risks and complications (e.g., pain crises, stroke, acute chest syndrome)	2.82 (0.45)	2.77 (0.43)	0.51
Risk of serious complications, including GVHD	2.70 (0.73)	2.73 (0.52)	-0.23
Trust in the medical teams	2.62 (0.85)	2.43 (0.57)	1.00
Risk of transplant failure (i.e., that it may not cure SCD)	2.50 (0.75)	2.27 (0.74)	1.25
Emotional strain of transplant on patient	2.50 (0.86)	2.00 (0.86)	2.32*
Availability of a donor	2.41 (0.96)	2.30 (0.84)	0.49
Sickle cell doctor's recommendation for or against transplant	2.26 (0.99)	2.40 (0.56)	-0.66
Child's preference (i.e., whether or not child wants transplant)	1.97 (1.09)	1.90 (0.76)	0.30
Risk of infertility	1.82 (1.04)	1.57 (0.68)	1.12
Having friends and family to help you throughout transplant	1.71 (1.19)	1.72 (0.88)	-0.07
Emotional strain of transplant on parent(s)	1.59 (1.05)	1.64 (0.91)	-0.22
Financial strain of transplant process	1.53 (1.33)	1.86 (0.92)	-1.14
Impact of transplant on sibling donor (if applicable)	1.42 (1.23)	1.50 (0.97)	-0.27
Child missing school	1.15 (1.18)	1.37 (0.85)	-0.84
Child losing hair	1.00 (1.06)	0.70 (0.88)	1.22
Religious beliefs	0.68 (1.15)	1.33 (0.88)	-2.54*

Note. * $p < .05$. Mean importance ratings can range between 0 and 3.

300

NKTT120: A SPECIFIC, SAFE, AND POTENT INVARIANT NATURAL KILLER T CELL (INKT) DEPLETING ANTIBODY FOR THE TREATMENT OF SICKLE CELL DISEASE

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Background: iNKT cells are a small subset of T lymphocytes (ranging from 0.01 – 0.1% of CD3+ T cells) that share surface markers and functional characteristics with T cells and natural killer (NK) cells. Unlike other T cells, they recognize glycolipid antigens and express a unique, highly conserved, semi-invariant TCR-α chain (Vα24-Jα18 in humans), which preferentially pairs with specific TCR-β chains (Vβ11 in humans). Like cells of the innate immune system iNKT cells are rapid-onset cells, but also share properties of T cells and, as such, they serve as a bridge between the innate and adaptive immune systems. iNKT cells have been shown to be involved in mediating tissue injury and inflammation in multiple organ systems. There is a growing recognition that iNKT cells may play a role in the chronic inflammation associated with the pathophysiology of Sickle Cell Disease (SCD). An increased ratio of activated iNKT cells in peripheral blood of patients with SCD compared to normal volunteer has been reported (Blood 114:667, 2009). We have also found that an average of 50.5% of the iNKT cells of the SCD patients are activated as indicated by up regulation of the inflammatory marker CD69. In the healthy controls an average of only 8.9% of iNKT cells expressed CD69. A key role of iNKT cell activation in the pathology of SCD is supported by studies in a mouse model of SCD (Blood 114:667, 2009) that suggest iNKT cell depletion could reduce inflammation in the SCD patient.

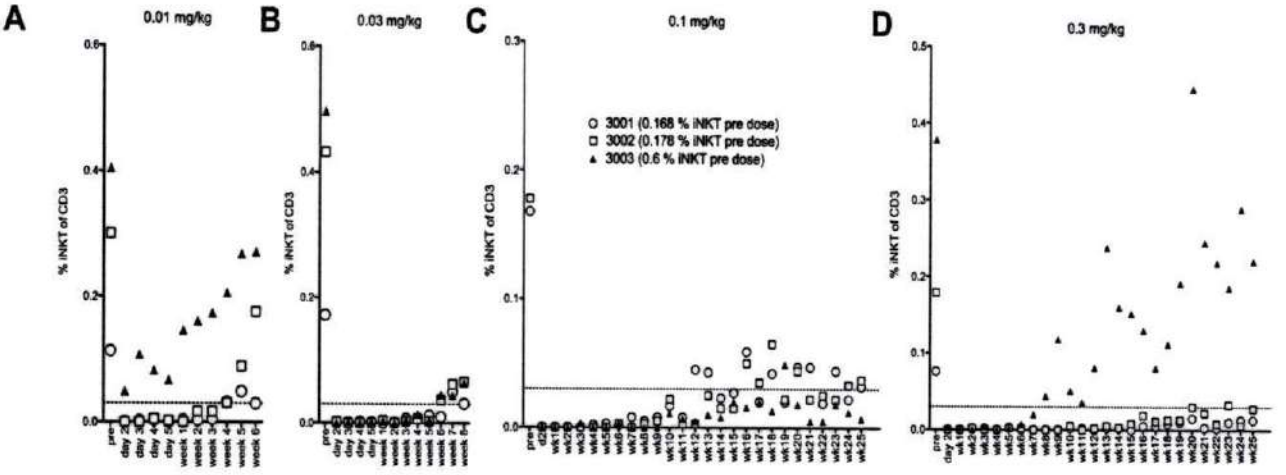
Objectives: We have developed a humanized monoclonal antibody (NKTT120) that binds the CDR3 loop of the human and the old-world non-human primate invariant TCR. NKTT120 depletes iNKT cells in human iTCR transgenic mice and cynomolgus monkeys (Macaca fascicularis). We conducted two studies in cynomolgus monkeys to explore both the safety as well as the relationship between dose and duration of iNKT cell depletion and pharmacokinetics (PK) of NKTT120.

Methods: In study 1, animals (n=3) received a single dose of NKTT120. The dosing groups were 10, 30, 100 and 300 ug/kg respectively. iNKT cells and other lymphocytes were monitored 24, 48, 72, 96 and 168 hours following dosing and weekly thereafter using flow cytometry and ELISA assay for PK. In study 2, animals (n=3 or 6) received 5 repeat doses of NKTT120. The dosing groups were vehicle, 0.3, 3 and 10 mg/kg respectively.

Results: In all dose groups except for vehicle treated animals, iNKT cells were depleted within 24 hours with no significant changes in the other cells of the lymphocytic series. No adverse events have been noted. In study 1, iNKT cells recovered to measureable levels in the 10 ug/kg at week 5, in the 30 ug/kg dose group at week 7, in the 100 ug/kg group at week 15 and in the 300 ug/kg dose group at week 19 (Figure 1). The half-life of NKTT120 was estimated to be ~17.5 days. In study 2, the high exposure to NKTT120 at 10 mg/kg (~3000-fold the planned clinical starting dose) maintained iNKT cells depletion for 3 months with no adverse effects. T cell dependent antibody response to antigen was not inhibited at any dose by iNKT cell depletion.

Conclusions: Overall, our study has shown that we can safely deplete iNKT cells in non-human primates at doses as low as 10 ug/kg without changes in other lymphocytes, with no adverse events, no impact on T cell dependent antibody responses and an iNKT cell recovery that is dose and time dependent. The specificity, safety and long half-life support the evaluation of NKTT120 in the treatment of SCD for the reduction of the chronic thrombo-inflammatory state.

Figure 1 - iNKT Cell Counts following NKTT120 Administration to Cynomolgus Monkeys at 10, 30, 100 and 300 µg/kg IV



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361

STUDIES OF CLINICAL STAGE HBF INDUCERS IN SUB-GENOTYPED SICKLE ERYTHROID PROGENITORS AND PRIMATES

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High-level expression of fetal gamma-globin ameliorates clinical complications in sickle cell disease and is achieved with hydroxyurea (HU) in young children. However, non-cytotoxic high-potency therapeutics, particularly which can be utilized with HU, are needed for many adolescent and adult patients who have continued and serious clinical events. To identify additional compounds which induce gamma-globin gene expression without cytotoxicity, we adapted a gamma-globin promoter construct linked to GFP for robotic high-throughput screening, and screened five diverse chemical libraries, including a library of drugs which are approved for treatment of other medical conditions. A small panel of the approved therapeutics have benign safety profiles and are suitable for long-term use. The most promising three candidates were evaluated in anemic baboons, and these induced gamma-globin mRNA by 15-33-fold over baseline. In erythroid progenitors cultured from sub-genotyped sickle cell patients, 3 novel inducers (BENZ, DLT, RSV) and two clinical stage HDAC inhibitors, MS-275 and SB939, induced 4 to 40-fold higher gamma-globin mRNA above untreated control levels in different subjects' progenitors. The new agents demonstrate activity at nanomolar concentrations. One candidate, BENZ, has been used for decades as an excipient solely to prolong the half-life of an active ingredient, and offers a potentially rapid registration route. In sickle erythroid progenitors sub-genotyped for SNPs in 3 major QTL loci (Bcl-11A, HMIP, Xmn-I), each therapeutic is active in 60-75% of progenitors studied, with differential gamma-globin mRNA responses observed. Progenitors with Xmn-1 SNPs appear associated with higher induction to most agents, eg, BENZ and HDAC inhibitors. Some HDAC inhibitors suppress Bcl-11A expression, and these demonstrate activity in higher proportions of progenitors from subjects who do not have any underlying polymorphism in Bcl-11A. These in vitro and in vivo studies identify a growing pipeline of HbF-inducing therapeutics, both epigenetic and targeted, which are suitable for clinical trials in sickle cell patients, but also suggest that personalized therapeutic combinations may be required to guide and achieve high-level efficacy.

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IMPROVED ANEMIA, ORGANOMEGALY AND SUSTAINED FETAL HEMOGLOBIN INDUCTION WITHIN AGING TR2/TR4 OVEREXPRESSING HUMANIZED SICKLE CELL MICE.

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Introduction: Fetal Hemoglobin (Hgb F) has been shown to improve morbidity and mortality with SCD patients. We recently published t hat forced expression of TR2/TR4 resulted in 2.5 fold induction of Hgb F within adult 2-3m/o humanized SCD mice (PNAS Campbell et al 2011).

Objectives: To determine if the increased Hgb F expression remained durable by HPLC and resulted in improved phenoytpes within > 6m/o mice within SCD:Tg TR2/TR4 UAB SCD Mice when compared t o 2-3 m/o SCD:TgTR2/TR4 UAB Mice and >6m/o UAB-SCD Mice.

Methods: Humanized Homozygous Knock-In UAB-SCD (UAB-Hbahα/hα Hbb hβs/hβs)Mice (Wu et al Blood 2006) was mated to TR2/TR4 Overexpressing Mice(Tg TR2/TR4) to generate SCD-TR2/TR4 compound heterozygotes (UAB-Hba hα/hα Hbb hβs/ hβs TgTR2/TR4). We compared the hemoglobin F levels (HPLC), CBC, and % body weight (liver, spleen, kidney) of 6-8m/o SCD:TgTR2/TR4(n=5) mice t o 2-3m/o SCD:TgTR2/TR4(n=5) mice. We also analyzed 6-8m/o SCD mice t o t he TR2/TR4 SCD Mice.

Results: Fetal Hemoglobin Expression remained elevated in the 6-8 m/o SCD:TR2/TR4 Mice at 16.7% (+/-3.94)compared t o 18.5%(+/-2.91) in 2-3m/oSCD:TR2/TR4 mice. %BW of spleen(3.7% vs 3.4%) liver(7.29% v 7.8%), kidney(0.98% vs1.1%), remained similarly lower. Table 1 shows increased Hgb F, improved anemia, decreased %BW of organs within older SCD:TR2/TR4 SCD Mice. Prot ein expression TR2 and TR4 were 8-11 fold(n=2) and 14-21 fold (n=2)higher wit hin SCD:TgTR2/TR4 mice compared to SCD mice.

Conclusions: TR2/TR4 overexpression wit hin >6m/o humanized SS mouse model result ed in cont inued >3 fold induct ion of fet al hemoglobin compared to control 6-8m/o SCD Mice. Increased TR2/TR4 overexpression improved anemia, organomegaly, within older SCD mice wit h reversion t o the WT phenotype.

Table 1 (m= mean)	6-8 mo(n)	Hgb F (HPLC) (m)	Hct (m)	Plt (m)	% BW Spln (m)	% BW Liver (m)	% BW Kid (m)	% BW Heart (m)	*TR2/4 Fold Protein Expression (by WB)*	
									TR2 (n=2)	TR4 (n=2)
SCD	9	4.88%	21.1	375	4.65	8.1	1.0	0.84	1	1
SCD: TgTR2/TR 4	5	16.7%*	30	332	3.4*	7.29	0.98	0.72*	10*	17*
Wild Type	6	N/A	42	599	0.28	4.84	0.81	0.398	n/a	n/a
*P<0.05 (SCD vs SCD TR2/TR4)										

366

A SIMPLE PAPER-BASED TEST FOR MEASURING BLOOD HEMOGLOBIN CONCENTRATION IN RESOURCE-LIMITED SETTINGS

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Background: In the current medical practice, the measurement of hemoglobin concentration in blood ([Hb]) is performed routinely as a part of the complete blood cell count to evaluate the ability of blood to carry oxygen throughout the body. Devices currently available to physicians and clinical laboratories for measuring [Hb] are accurate, operate on small samples and provide results rapidly, but may be prohibitively expensive for resource-limited settings. The unavailability of diagnostic tools prevents objective diagnosis and thus proper treatment of anemia in low-income developing countries, particularly in the context of sickle cell disease in sub-Saharan Africa.

Objectives: The objective of this study was to develop and validate a simple paper-based assay to enable a low-cost, point-of-care measurement of [Hb] in resource-limited settings.

Methods: Arrays of microfluidic paper-based analytical devices (μPADs) were fabricated on chromatography paper using a solid-ink (wax) printer according to a previously published method. To perform the paper-based Hb assay, a 20 μL droplet of a mixture of blood with the red cell lysis buffer (PBS containing saponin) was deposited onto each μPAD. The resulting blood stain was quantified by scanning the sheets of chromatography paper containing arrays of μPADs with dry blood stains using a portable flatbed scanner, and then analyzing the images with a custom coded algorithm. The average color intensity of the blood stain in a μPAD was used to quantify [Hb] of the blood samples.

Results: We tested the performance of the paper-based Hb assay in comparison with a hematology analyzer (reference standard) using blood samples from 32 subjects (the population average [Hb] was 11.29 ± 3.38 g/dL by the paper-based Hb assay, and 11.39 ± 3.04 g/dL by the hematology analyzer). The values of [Hb] measured using the assay and the reference standard were highly correlated ($r = 0.9593$) and showed a strong linear relationship ($y = 1.066x - 0.8473$, $R2=0.9202$). The standard deviation of the difference between the two measurements was 0.98 g/dL. The assay was accurate within 1 g/dL 81.25% of the time, overestimating [Hb] by ≥1 g/dL in 12.5% of the subjects, and underestimating [Hb] by ≥1 g/dL in 6.3% of the subjects.

Conclusions: This study demonstrated the feasibility of a paper-based Hb assay. This simple, low-cost test represents a major breakthrough towards effective intraoperative care as well as [Hb] testing at the bedside or in urgent care settings where traditional methods of clinical laboratory are unavailable. The paper-based Hb assay will be useful for diagnosing anemia in resource-limited settings of low-income developing countries, particularly in the context of diagnosis and treatment of sickle cell disease patients in sub-Saharan Africa.

381

AGE AND SEX DETERMINANTS OF BONE PHENOTYPE IN A TRANSGENIC MOUSE MODEL OF SICKLE CELL DISEASE

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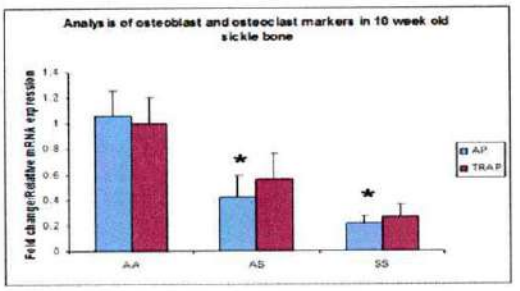
Background: Chronic pain and bone deterioration are the commonest cause of significant morbidity and poor quality of life among adults with sickle cell disease (SCD). The progressive development of low bone mineral density, avascular necrosis, compression spine deformities and degenerative arthritis starts during childhood. Indeed, individuals with SCD develop osteopenia/osteoporosis at a relatively young age compared to the general population. Chronic vaso-occlusion in sickle cell disease patients leads to ischemia and necrotic lesions while bone marrow hyperplasia contributes to the softening of trabecular bone, and overall bone loss. Bone constantly undergoes a self-renewal process and adapts to damage through remodeling. The remodeling process is highly regulated represents a balance between bone formation by osteoblasts and bone resorption by monocyte derived osteoclasts. Although SCD is clearly recognized as a primary cause of secondary osteopenia/osteoporosis, the underlying mechanisms responsible for alterations in bone remodeling that compromises the structure and quality of bone in SCD are not fully elucidated.

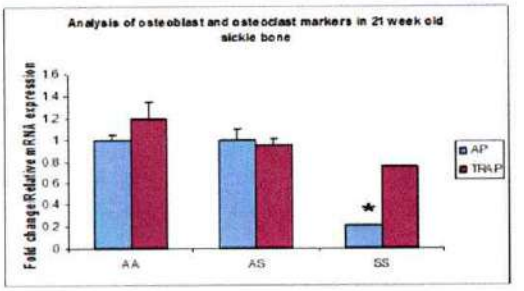
Objectives: To determine the effect of age and gender on the bone phenotype compared to controls using a transgenic sickle mouse model.

Method: To determine the effect of age and gender on the SCD bone phenotype, we used micro-computed tomography (MicroCT), real time PCR and immuno-histochemistry to characterize the bone phenotype in a transgenic mouse model (Townes) of SCD. Femurs and tibia were harvested from 10 and 21 week old sickle mice (SS), heterozygote trait mice (AS), and normal (AA) controls. MicroCT was used to analyze bone parameters (bone volume, cortical and trabecular thickness, trabecular spacing) of the femur and tibia. RNA extracted from harvested bones was reverse transcribed and gene expression assay of tartrate-resistant acidic phosphatase (TRAP) for osteoclast activity, and alkaline phosphatase (AP) for osteoblast activity performed using real time PCR (RT-PCR).

Results: Compared to control mice, sickle (SS) mice demonstrated an age dependent defect in bone morphology of the epiphysis and metaphysic of the tibia and femur. In the 10 week old mice (adolescence) there was a trend towards lower bone volume, as well as cortical and trabecular thickness. At 21-weeks (adulthood), there was general decrease in trabecular number and an increase in trabecular spacing in females with SCD compared to control ($p<0.05$). The relative levels of TRAP and AP at 10-weeks were elevated in controls (AA, AS) compared to SS mice ($p<0.05$, Figure 1a) suggesting reduced bone formation is present in sickle mice. At 21-weeks AP mRNA expression was significantly decreased in sickle mice compared to controls suggesting increased bone loss ($p<0.05$, Figure 1b). The relative expression of TRAP and AP mRNA remained the same at 21-weeks in the control group (AA, AS).

Conclusion: These results suggest an age and gender specific influence on the variability of bone turnover in SCD that needs to be further explored. Females with SCD may be at higher risk for low bone mineral density due to hormonal influences of reduced estrogen that is not present in males. The trend of reduced bone formation in young sickle mice may account for poor peak bone mass accrual in individuals with SCD. Failure to accrue peak bone mass predisposes to early and more severe osteoporosis particularly if it is coupled with the increased bone loss that occurs with age. Future studies looking at larger numbers of mice and at different age groups are currently underway.





Figures 1a; b: Relative mRNA expression of AP and TRAP in normal (AA), trait (AS) and sickle (SS) Townes mice. (a) There was relatively decreased mRNA expression of AP and TRAP in 10-week old SS mice compared to normal and trait mice respectively. Results shown as mean +/-SD (n=3 for each) (b). There was a significant reduction mRNA expression of AP at 21-weeks in SS mice compared to AA and AS. (*) denotes statistical significance.

EVALUATION OF THE IMPACT OF A WEB-BASED EDUCATIONAL TOOL ON AWARENESS OF NEWBORN SCREENING AND CARRIER TESTING

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Background: There is considerable lack of awareness of newborn screening (NBS) among patients in the prenatal setting1. Currently, only 20 states have designed specific educational materials on NBS that are distributed during pregnancy2. Also, previous studies have shown that African American women receiving prenatal care believe that screening for sickle cell disease is beneficial, but they do not personally find themselves at an increased risk to have a child with sickle cell disease3. This suggests that prenatal education on sickle cell and other autosomal recessive conditions is lacking. To increase awareness of newborn screening and carrier screening for sickle cell disease, cystic fibrosis, and the thalassemias, we developed a website called My Baby's Health. This website provides education on NBS and carrier screening that is tailored to the patient's ethnicity. Objectives: The goal of this study is to evaluate this method of educating pregnant women on newborn screening and the genetics of autosomal recessive conditions such as sickle cell disease, cystic fibrosis, and the thalassemias.

Methods: Women in their 1st or 2nd trimester of pregnancy in the waiting room at the prenatal clinic were encouraged to access the My Baby's Health website on a computer kiosk at the clinic. They are encouraged to take brief surveys before and after reading the information on the site. The pre-website survey asked questions on the patient's previous knowledge of sickle cell, cystic fibrosis, and the thalassemias, carrier testing, how these conditions are inherited, and how newborn screening is performed. The follow-up survey asked the same knowledge-based questions on the genetic conditions and newborn screening, as well as questions on the participant's opinion of the site.

Results: Data collection is ongoing. To date, 22 participants have taken the pre-and post-website surveys. Thus far, 81% (17/21) of participants answered more questions correctly on the post-test than the pre-test. Additionally, 100% of participants found the website to be "somewhat helpful" or "very helpful" and would consider recommending it to others. Further statistical analysis will include a paired t-test and data stratification by demographics such as ethnicity and educational background to compare the website's effectiveness between groups.

Conclusion: The website is likely helpful in increasing knowledge of sickle cell disease, and most participants found it useful. However, one of the main challenges is implementing this website into the workflow of a clinic so that it has maximum benefit. Using educational tools like this website may serve to decrease disparities in NBS services across the United States, since lack of awareness can lead to anxiety and failure to comply with recommendations for follow-up.

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303

A NEW PLAY ON AN OLD WAY: SICKLE CELL TRAIT EDUCATION THAT REALLY WORKS

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Background: Educating parents of infants/children with sickle cell trait is a critical aspect of patient care and includes understanding what it is, how it's acquired, how it differs from disease, family planning and possible health outcomes. We propose that developing a standardized education/assessment process, targeting knowledge gaps and using nationally available consumer education materials will aid patient education in a variety of settings. This project was done by Illinois Sickle Cell Action Network (I-SCAN), a collaboration of Federally Qualified Health Centers (FQHCs), sickle cell centers, adult and pediatric hematologists, patients/families, state agencies and a community-based organization, under HRSA's Sickle Cell Disease Treatment Demonstration Program.

Objectives:

1) To develop a simple paper/pencil tool to measure parental knowledge before and after in-person trait education, using standardized materials and pre-/post-tests.

2) To pilot and validate the tool in a pediatric hematology clinic setting, with eventual expansion to primary care medical homes.

Methods: The developed Sickle Cell trait education toolbox contained an education/counseling component and Sickle Cell Trait Test (SCTT).

Education Development: A Sickle Cell educational component was developed using nationally available consumer education materials (NCEC Trait Counseling Tool: 5 Things Parents Want To Know, and All You Wanted to Know About Sickle Cell Trait) and a parent packet (infant's newborn screening result, copies of consumer education materials, SCTT answers and clinic nurse contact information). Education/counseling was provided by healthcare experts in Sickle Cell Disease during a clinic visit.

SCTT Development: A 5-question SCTT was developed with input from the I-SCAN Board. The 5 questions focus on 1) purpose of hemoglobin; 2) problems caused by sickle cell trait; 3) why it's important to know a child has sickle cell trait; 4) autosomal recessive inheritance; 5) testing for sickle cell trait. The SCTT is administered twice during the patient visit, before and after the education/counseling session. To evaluate the content validity of the SCTT, pilot testing (A) was completed with 20 parents, resulting in modifications to 2 questions: "Why it's important to know a child has sickle cell trait" (clarity) and "Autosomal recessive inheritance" (adding a diagram). The modified SCTT was administered to 24 more parents (Pilot B).

Analysis: Comparisons between the percent of questions correctly answered were made between Pilot A (20 parents) and B (24 parents) post-test scores. The clinic educational process (pre-test administration, education to parents, post-test administration) was appraised.

Results: Average post test scores of Pilot A (20 parents) and B (24 parents) were 79.8% and 93.4%, respectively. Comparisons of individual post-test scores for Pilots A and B identified a 9-31% improvement as follows: Q1.Purpose of hemoglobin, 91% improved to 100%; Q2.Problems caused by sickle cell trait,78% improved to 88%; Q3.Why it's important to know a child has sickle cell trait,78% improved to 96%; Q4.Autosomal recessive inheritance, 52% improved to 83%. Q5.Testing for sickle cell trait, 100% (no change). Process evaluation resulted in a detailed process map being developed, constructed, trialed, revised and finalized.

Conclusion: The SCTT is a simple, quick, easy-to-score evaluation tool of Sickle Cell Education designed for use across healthcare settings with accessible education materials. Although initial results indicate systematic clinic processes and education delivery may result in improved patient education, further evaluation is needed. The next step is piloting in primary care medical homes, starting with the I-SCAN FQHCs."

Reference:

1. The project is supported in part through funding from HRSA/MCHB, Grant Number U1EMCO7656.

A FOUR YEAR PERSPECTIVE ON THE ISSUES AND CONCERNS OF MANDATORY SICKLE CELL TRAIT TESTING IN COLLEGE ATHLETES

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Background: The report of sudden death of college athletes has resulted in regulations requiring screening sports for sickle cell trait of student athletes prior to participation in Division I sports. Knowledge of an athlete's trait status and education of the athletic staff is key in ensuring that exertional sickling is not mistaken for cardiac collapse. There is a concern that screening for sickle cell trait may stigmatize those athletes that test positive during the screening process. For the past four years, the Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh of UPMC (CHP) has collaborated with the University of Pittsburgh's Department Of Athletics to facilitate voluntary testing, genetic counseling and education of athletic staff.

Objective: Perform a systematic assessment of the sickle cell trait screening program and to assess the attitudes of athletic staff with regards to sickle cell trait testing following the mandated testing of all Division I athletes.

Methods: Program: The athletic department staff was provided with education regarding sickle cell trait, methods to prevent exercise-related sudden death, and educated on the Genetic Information Nondiscrimination Act. Pre-test counseling, testing within the University's athletic training facilities for each athlete, and post-test counseling, was provided through the program. All testing was performed on-site and samples were transported back to CHP laboratories within 2-6 hours of collection. All samples underwent standard hemoglobinopathy evaluation via electrophoresis and whole red blood cell count. Results were distributed within 24 hours of collection and post-test genetic counseling was provided to those identified with trait and relevant athletic training staff members.

Assessment: A brief survey was distributed to all members of the University of Pittsburgh Athletics Staff. (n=62) The survey addressed questions on a range of topics: the overall opinions of trait testing for student athletes, whether staff members felt that they and their athletes received adequate information about sickle cell trait and consequences, if trait testing should be mandatory, and whether the identification of an athlete affected the dynamics of practice and participation. The results from the surveys were then analyzed to determine how the structure of the current program can be altered to be more effective.

Results: Program: A total of 429 student athletes were screened over the four year period. Six athletes were identified with sickle cell trait and 1 with CC disease. All athletes identified met with their coach, athletic trainer and a genetic counselor for a group counseling session. All athletes identified with trait have continued to play sports through their undergraduate career.

Assessment: Twenty-one individuals responded to the survey, (33.9% response rate) consisting of 11 coaches, 8 athletic trainers and 2 directors of operations. The majority of responders (81%) did not feel that the identification of players with sickle cell trait affected the dynamics of practice. While 71.4% of responders felt that they have a good understanding of the implications of sickle cell trait on the health of athletes and are properly educated, 28.6-38.1% of responders do not feel that they are properly educated on the implications of sickle cell trait or comfortable in recognizing the signs of exertional sickling. Sixty-two percent felt that trait testing should be mandatory for all athletes while 33.3% felt that it should not.

Conclusion: This assessment and evaluation shows that the knowledge has made all individuals within the athletic performance team more aware of potential issues regarding sickle cell trait and how to address them if a situation would arise. Overall, responders described their experience with regards to sickle cell trait testing as positive, affirming the value of the sickle cell trait testing program. The combination of the education and genetic counseling ensures that student athletes and the athletic staff have a solid understanding of sickle cell trait and its impact on exercise and for the continued success of this collaboration and program.

237

QUALITATIVE STUDY OF THE APPLICABILITY AND FEASIBILITY OF A WEB-BASED PAIN DIARY FOR ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Background: We have previously demonstrated the feasibility of an electronic pain intensity diary. Participants accessed a web-based diary 3 times a day via smart phone or computer to report real-time pain. Scores above a predetermined baseline prompted contact by a staff member to offer support and intervention. The 22 subjects who participated in the 12 month study submitted 4,931 responses representing 71% of the possible thrice a day responses. Participants received monetary incentive based on the number of responses. This group of patients indicated a high burden of pain at baseline with pain on 66% of the diary days but sought healthcare utilization only for 12% of the diary days. We sought to further explore and understand patient perception, needs, and feedback as a guide to the future development of a multi-dimensional pain diary for long term clinical use.

Objectives: -

1. To analyze participant experiences and attitudes towards real time pain reporting via electronic pain diary.

2. To gather participant opinions regarding health care provider response, felt needs and improvements for user interface of the electronic diary.

Methods: Participants were interviewed in a face-to-face focus group setting with follow up validation of findings via one-to-one telephone interviews of additional participants. All conversations were audio recorded for further data analysis. Conversations were transcribed and analyzed to elucidate common themes.

Results: The first identified theme was a need for an improved tool to report the multi-faceted aspects of pain. This includes the ability to report type/location, precipitating factors, and interventions including medication dosage/frequency. Currently clinic visits only allow snapshots of patient status based on brief discussion and recall. As described by one participant: ". . . because just talking to you guys like once a month, like at clinic, really doesn't show the whole picture of how I've been doing. Like, when you can see it on a day to day basis I think that's really good." A second theme was a desire for clinical application of the diary relating to pain control and home management planning. The ability of medical staff to track pain trends was described as important to improve multi-directional communication and education between patient and provider. Individualization of pain management was stressed and autonomy was demonstrated by a focus on patient/healthcare provider understanding rather than parent/caregiver understanding of current pain trending. Participants did not find the diary intrusive and noted a sense of security from the knowledge that a staff member was immediately aware of their pain status and provided timely intervention. One participant stated: "I think that's really good. So that I'm not just in a lot of pain sitting at home and nobody knows about it."

Participants found direct benefit in using the diary to monitor/manage their own pain trending and to begin to become self-aware of their individual pain course. " . . . like it could help me see what I'm doing, what I'm doing wrong, what I need to change." "I think it's a real benefit to us too . . . I didn't know my pain went like that . . . where did that come from . . .". Participants found the electronic diary easy to use and expressed willingness to participate in a study of a multi-dimensional pain diary even if no financial incentive was offered.

Conclusion These data indicate a need for the development of a more comprehensive system of effectively tracking pain in Sickle Cell patients in real time. A crossover of the pain diary into the clinical setting could potentially facilitate enhanced communication between patients, parents/caregivers, and health care providers. Access to real time data could also potentially improve ER care by providing physicians with access to a continuum of real time pain data that patients may be unable to communicate during a crisis. The availability of smart phones and the internet make the collection of multi-dimensional journaling for chronic disease feasible in real world conditions.

395

ASSESSING HEALTH MAINTENANCE FOR PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE CHART REVIEW OF PEDIATRIC SICKLE CELL PATIENTS AT UNIVERSITY OF ILLINOIS HOSPITAL

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Purpose: To evaluate the current health maintenance status of pediatric sickle cell patient at UI and the impact of a simple reminder in the electronic medical record.

Background: Quality-of-care indicators in sickle cell disease care are emerging at a national level. National Heart, Lung, and Blood Institute (NHLBI) has established Health Objectives to attain by 2015 for care of pediatric and adult sickle cell patients. In addition, a panel of experts using a Delphic consensus approach developed quality-of-care indicators for children with sickle cell (Wang et al. Pediatrics, 2011). No benchmarks exist for these indicators.

Methods:

(A) Five quality indicators were selected for review because they are preventive care tasks that are relatively unique to sickle cell care: (1) pneumococcal vaccination, (2) annual transcranial Doppler ultrasound (3)retina exam, (4) meningococcal vaccination, (5) influenza vaccination.

(B) Retrospective chart review was conducted on 175 Pediatric Sickle cell patients seen at UI pediatric hematology/oncology clinic in 2009 - March 2012. This period spans transition from previous sickle cell team to current sickle cell team.

(C) Intervention to improve quality indicators was implemented - charting a reminder of comprehensive care framework and specific items due prior to each clinic appointment.

(D) Repeat retrospective chart review to determine the change in the quality indicators.

Results: Quality indicators ranged from 40% to 60% of maximim prior to intervention. After the intervention, quality indicators rose, especially immunizations.

Many patients receive primary care elsewhere and documentation of the quality indicators suffers from the fragmentation of medical records. For example, immunization records from PCP are not usually available.

Conclusions: Chart review analysis of UIC pediatric sickle patients shows a relatively low compliance rate to the pediatric sickle cell quality of care indicators and NHLBI health objectives.

Principal limitations: incomplete documentation of immunizations & testing at other facilities

This analysis provides an opportunity for ongoing evaluation of the quality of care provided for the pediatric sickle cell population. Also, provides opportunities to further increase health maintenance compliance and improve the quality of care.

IMPLICATIONS FOR PRACTICE

„[3]Multidisciplinary team approach is needed to ensure that all UIC pediatric sickle cell patients adhere to regular outpatient follow-up visits and required screenings
„[3]Quality of care indicators and NHLBI health objectives are targets to monitor and help improve quality of care for children with sickle cell disease.

„[3]Further research is needed to explore more evidence-based interventions to increase compliance rate among this population group

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427

IMPROVING QUALITY OF CARE FOR SICKLE CELL PATIENTS IN THE PEDIATRIC EMERGENCY DEPARTMENT

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Background: Sickle cell disease (SCD) is the most common genetic disease for individuals of African descent. Episodes of severe pain and hemolysis are the clinical hallmarks of the disease, with more than 70% of ED visits for the treatment of pain. Multiple consensus guidelines recommend that the first dose of parenteral opioid analgesic should be provided within 30 minutes of arrival. The objective of this study is to identify factors associated with delay in treatment of sickle pain crisis in the pediatric emergency department and to discern whether earlier pain management is correlated with better clinical outcome.

Methods: We reviewed the electronic medical charts of pediatric patients treated between January and June 2012 for sickle cell pain crisis. We extracted demographic and clinical characteristics from electronic patient records, as well as date and time of registration, triage, initial pain assessment, medication order, parenteral analgesic administration and pain reassessment. Data were analyzed with the statistical software STATA© version 12. Significance was determined by $P \leq 0.05$ in all statistical tests.

Result: A total of 160 sickle cell pain crises visits by 67 unique patients were identified. Opiates were the most common initial pain medication prescribed and administered. The mean time between registration and triage was 9 minutes, with 63.1% of the study population triaged within 10 minutes. Of the 160 visits, only 3 (1.9%) patients received initial parenteral analgesic medications within the recommended 30 minutes. On average, patients received their initial parenteral analgesic medication in 89 minutes. The mean time to pain reassessment was 60 minutes, and only 37 (23.1%) visits documented pain reassessment within the recommended 30 minutes. Patients who received imaging studies before or during the process of pain assessment and medication administration experienced longer delays in time to initial parenteral analgesic medication (p=0.01).

Pain was assessed on a 10 point scale and higher triage pain score did correlate with shorter time to first dose of pain medication (p=0.012). However, age, gender, and final disposition did not affect time to administration of first parenteral analgesia (p=0.136, p=0.857, and p=0.251, respectively).

Of the 81 (50.6%) visits that resulted in hospital admissions, the median length of hospitalization was 2 days (range: 1 day to 97 days). Earlier pain management resulted in shorter ED LOS (p=0.003) for all patients regardless of disposition. The mean ED LOS for patients discharged to home was 289 minutes, and 495 minutes for those who were admitted. However, earlier pain management did not affect total length of hospitalization for admitted patients (p=0.472).

Conclusion: The longest delays in the treatment of pain were from medical assessment to administration of parenteral analgesic. Delays in ordering parenteral analgesia were, in part, caused by time spent obtaining imaging studies. Nursing staff also identified the time spent reviewing previous ED records and verifying whether patients were under contracts as two components that delayed administration of analgesics. Individualized pain management plans and medications with alternative delivery routes, such as intranasal fentanyl, may help us in achieving our goal of medication administration within 30 minutes.

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Background: The growing number of adult patients with sickle cell disease(SCD)experience significant disparity in healthcare contributed by a lack of access to quality healthcare and a lack of trained hematologists experienced or interested in the care of these patients. Patients aging out of pediatric care often need to rely on the Emergency Department for treatment (1). Furthermore, use of evidence-based interventions, such as hydroxyurea therapy is sub-optimal (2). Increased availability of medical homes for patients with SCD has been proposed by the US Department of Health and Human Services to improve access and quality of care (3). Effectiveness of the medical home for SCD needs to be evaluated.

Objectives: To implement a medical home in primary care settings in two Southern Georgia communities that have underserved adult SCD patients and to evaluate the impact of this approach on patient outcomes.

Methods: The medical home has been designed to address challenges of adult SCD patients who lack access to sickle cell specialty care on an ongoing basis. The comprehensive study team, led by a hematologist with sickle cell expertise, is comprised of family medicine physicians and residents, general internists, adult and pediatric hematologists/oncologists, emergency medicine physicians, and a medical anthropologist. Principal research sites include primary care practices aligned with family medicine residency programs and a federally qualified health center serving six rural counties. The model utilizes education of involved physicians on the management of SCD patients tailored to the practice setting and medical specialty, healthcare provider survey instruments, and evidence based treatment protocols. A unique feature is the availability of individualized consultations provided by a SCD expert hematologist from a university based, comprehensive sickle cell center, in the setting of a combined outreach clinic experience with primary care providers.

Results: The development of these medical homes have been facilitated by support from the healthcare systems, willingness of primary care physicians to serve as principle care providers in concert with sickle cell consultative services, participation of physicians from multiple specialties, and an ongoing educational program. As a part of the continuum of care, management of acute exacerbations of SCD are coordinated between the emergency and primary care physicians using an Observation Unit based treatment program.

Conclusion: Primary care medical homes for adolescents and adults with SCD have been developed in two communities. Co-management with hematologists, use of guidelines for ambulatory and inpatient care settings, a fast track Emergency Department pathway, and ongoing support from SCD experts have been incorporated into the model. Project leadership is shared with local physician champions from each medical specialty. Family Medicine residents are participating in all aspects of program development and research. In the future the impact of the program will be evaluated including assessment of patient health related quality of life, provider satisfaction, and cost effectiveness.

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386

MATERNAL AND PERINATAL OUTCOME IN PREGNANT WOMEN WITH SICKLE CELL DISEASE AND RISK ASSESSMENT OF NEAR MISS OR MATERNAL DEATH: PROSPECTIVE STUDY OF PROJECT ANINHA IN MINAS GERAIS, BRAZIL.

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INTRODUCTION: Sickle cell disease during pregnancy is associated with increased complications due to the disease itself and with a higher maternal and perinatal mortality.1-3 The aim of the study was to analyze the clinical complications of pregnant women with sickle cell disease, with primary focus on those potentially serious and life-threatening ("near miss") or leading to actual maternal death. We sought to identify predictors of "near miss" or maternal death in order to provide information to reduce complications and improve maternal and perinatal prognosis.

METHODS: The 104 patients were enrolled in the Blood Center of Belo Horizonte (Hemominas Foundation) and were treated at several institutions that provide high-risk prenatal care. The study was a prospective cohort. As for the genotypes of sickle cell disease, patients were divided into two groups: Group I (n=54), consisting of sickle cell anemia (HbSS, n=51) or Sβ0-talassemia (n=3) and Group II (n=50), SC hemoglobinopathy (n=49) or Sβ+-talassemia (n=1). The median age of both groups was 25 and 26 years, respectively. Predictive factors for "near miss" or maternal death with alpha error probability $p \leq 0,25$ in univariate analysis were included in a multivariate logistic regression model and then those with $p \leq 0.05$ were considered significant..

RESULTS: Women in Group I showed, compared to Group II, higher number of episodes of vaso-occlusive crises during pregnancy, higher number of blood transfusions in both antepartum and postpartum and a higher percentage of preterm births. The frequency of infections and pain crises during the postpartum period was similar in both groups. Urinary infections were equally common in both groups. The overall mortality rate was 4.8%, three deaths in the sickle cell anemia group and two in the SC group. One third of the women in each group had severe complications classified as indicative of "near miss". The most frequent complication was pneumonia/acute chest syndrome. The co-inheritance of alpha thalassemia and beta globin gene haplotypes (CAR/CAR, BeninBenin or CAR/Benin) were not significantly associated with "near miss" or maternal death. Significant predictive factors for "near miss" or maternal death in both groups together were mother parity >1 and basal red cell macrocytosis. In Group I, baseline hypoxemia (oxygen saturation below 94%) was also predictive of "near miss" or maternal death. Multivariate analysis showed that painful crises during pregnancy and SS genotype were factors that significantly contributed to a higher prevalence of preterm delivery (Table).

CONCLUSIONS: Pregnant women with sickle cell disease had several complications during pregnancy and postpartum. One third of the women suffered "near miss" and almost 5% died. SS and SC pregnant women had the same risk of severe complications and maternal deaths, especially in the third trimester and postpartum period. Pulmonary events were the most frequent complications and deserve special care, including performing partial exchange blood transfusion. Higher rate of premature delivery was significantly associated with SS genotype and with pain crises during pregnancy. Specialized training in high-risk prenatal care for several complications of sickle cell disease and early identification of risk factors for "near miss" or maternal death are fundamental to improving care for pregnant women with sickle cell disease.

TABLE – Final logistic model for premature delivery in pregnant women with sickle cell disease (Hb SS and SC)

	Coefficient	Risk of premature delivery	95% CI	p value
Genotype (Hb SS)	2.622	13.76	3.28-57.64	< 0.001
Painful crises	2.137	8.48	1.39-51.57	0.020
Constant	- 3.373	0.034	—	0.001

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388

ISCHEMIC STROKE PREVENTION IN SICKLE CELL DISEASE: DATA FROM BELO HORIZONTE BLOOD CENTER, BRAZIL

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Background: Minas Gerais is a Brazilian state where the incidence for sickle cell disease (SCD) is 1:1,400 newborns. Newborn screening for SCD started in 1998 within the Brazilian public health system. Patients diagnosed with SCD are referred for treatment in the blood centers throughout the state, the one in the city of Belo Horizonte (BHBC) being the largest of them. Ischemic stroke (IS) risk is 11% up to the age of 20 years among patients with SCD [1]. IS incidence in BHBC is 0.77/100 children-year [2]. Time-average mean of the maximum (TAMM) velocities of blood flow in the brain arteries ≥200 cm/s using transcranial doppler (TCD) is the best risk predictor, and regular blood transfusions reduced risk up to 90% [3]. TCD was introduced at BHBC in 2007 to track the disorder in all Hb SS or Sβ0-thal children from age of 2 years onwards: every year up to age of 16 if their TAMM< 170 cm/s; every 6 months if TAMM is 170-184; or every 3 months if TAMM is 185-199 cm/s. Magnetic resonance angiography (MRA) is performed if TCD is inconclusive or TAMM ≥170 in the anterior cerebral or ≥130 in the basilar arteries. High-risk children are sent to regular exchange transfusion using deleucotized red cell concentrates screened for Hb S and phenotyped for CDE and Kell groups. Serum ferritin tests are carried out periodically.

Objectives: To describe the impact of implanting TCD on the prevention of IS, as well as the associated complications.

Methods: The study revised the medical files of all children that underwent TCD from Jan 2007 to Nov 2012 and were on regular exchange transfusion because of high-risk for IS.

Results: High-risk was detected in 39 children; 35 with TAMM ≥ 200 cm/sec in middle cerebral or internal carotid arteries, and 4 with abnormal MRA after inconclusive TCD. Females predominated (56.4 %). A child with an abnormal TCD did not come back for test confirmation and had a IS; for another one, family did not accept regular transfusions and hydroxyurea (HU) was started. The families of 37 children (average age 6.8±2.5 years) accepted regular transfusions. One of them eventually underwent bone marrow transplant, one was transferred to another blood center, and another complied irregularly with the program, thus migrating to HU treatment. The observation time was 89.9 children-year, getting exchange transfusion for 2.34 years on average. Pre-transfusion Hb S mean concentration was 41.2±8.3%. Mean ferritin (last test) was 917±820 µg/L for 34 children currently undertaking regular transfusions. Iron chelation has been used by 13 children. Concomitant use of HU was initiated for 13 children because of no reduction to low-risk on TCD. Follow-up TCD(s) were performed in 28 of the 33 children that initiated treatment because of TAMM ≥ 200 cm/sec in the aforementioned arteries (Figure). The resulting risk groups at the end of the study were: high conditional in 6 and low conditional in 5 (39.3 % in total); low risk in 11 children (39.3 %). For the remaining, 3 continued with high-risk and TCD was inconclusive in 3. No significant statistic differences (t test) for pre-transfusion Hb S concentration, age at transfusion beginning, or time span under exchange transfusion treatment were detected. No death, IS, or transfusion-associated infections were observed, but 10 children (27%) were alloimmunized: 4 anti-C; 3 anti-E; 3 anti-Kell; 2 anti-Di^a; 1 anti-D (partial D); 1 anti-V, and 1 anti-Lu^a; 4 children had alloantibodies to more than one antigen.

Conclusion: 1. TCD is useful to track high-risk cases and blood transfusions are effective in preventing IS; 2. Over half of the children had their risks reduced to low or conditional; 3. Iron overload can be controlled with chelation; 4. Alloimmunization is of major concern.

A SIMPLE, RAPID, LOW-COST DIAGNOSTIC TEST FOR SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is the most common inherited blood disorder caused by a point mutation in hemoglobin (Hb) and associated with significant lifetime morbidity and premature mortality. Nearly 700 children are born with SCD in Africa every day (75% of all affected births worldwide) – more than 50% of them will die before reaching adulthood due to lack of diagnosis and early intervention. For comparison, most children born with SCD in the U.S. are able to survive into adulthood primarily because the universal SCD screening enables timely management of symptoms and complications associated with SCD. Current technology for diagnosing SCD (hemoglobin electrophoresis, isoelectric focusing and high performance liquid chromatography) remains prohibitively expensive and largely unavailable in low-income developing countries where SCD is most prevalent. The urgent need to develop a low-cost diagnostic test for SCD has been recently recognized as a priority by the World Health Organization.

Objectives: The objective of this study was to develop and validate a paper-based Hb solubility assay as a simple, low-cost and rapid test for definitive diagnosis of SCD.

Methods: Normal blood (HbAA) was collected and compared to blood from patients with SCD (HbSS) and sickle cell trait (HbAS). To perform the test, a 20uL droplet of blood mixed with the components of the Hb solubility assay (SickleDex™, Streck) was deposited onto a paper-fluidic device fabricated using a previously published method. Polymerized deoxy-HbS remained in the center of the blood stain entrapped by the paper substrate, while other forms of Hb remained soluble and were transported laterally to the periphery of the stain by capillary action. The resulting blood stain was digitized with a portable scanner and analyzed automatically. The red color intensity profiles were normalized by the total area under the curve to account for the differences in hematocrit among subjects. The SCD index was defined as the normalized color intensity 5 mm from the center of the blood stain. The values of the SCD index for samples from each Hb genotype were compared using a paired two-tailed t-test.

Results: The entanglement of polymerized deoxy-HbS by the fibers of the paper substrate resulted in the formation of a dark red spot in the center of the blood stain, while the wicking of the soluble forms of Hb from the center produced a pink ring on the periphery of the stain. The patterns of the blood stains produced on paper by normal (HbAA), SCT (HbAS) and SCD (HbSS) samples were significantly different. The tight clustering of the normalized color intensity profiles for different subjects with the same Hb genotype enabled the use of the SCD index as a quantitative metric for distinguishing between the three types of samples. The difference between the SCD index measured for HbAA, HbAS and HbSS samples was highly significant, with $p<0.001$. Unlike the conventional, commercially available Hb solubility tests (e.g. SickleDex), the paper-based Hb solubility assay can conclusively differentiate between SCT and SCD samples using the characteristic blood stain patterns produced by each sample on the paper substrate.

Conclusions: This study demonstrated the feasibility of using the paper-based Hb solubility assay as a simple, low-cost, point-of-care diagnostic test for SCD. The ability to diagnose SCD quickly and inexpensively will be particularly useful for universal SCD screening in resource-limited settings, such as Africa. This test will also be useful in the emergency room setting in high-income countries to enable healthcare professionals to objectively confirm suspected SCD at the bedside.

376

EVIDENCE OF ALTERED PAIN PROCESSING IN ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Background: Numerous previous functional neuroimaging studies have identified brain regions that show greater activation to painful versus non-painful stimuli. This experiment examined the response of brain regions within this "pain matrix" in patients with sickle cell disease (SCD) to describe possible alterations to neural reactivity that underlies pain sensitization.

Methods: The pain threshold for 12 African American adolescents and adults with SCD (ages 16-31 years) and 12 demographically-matched control participants were determined using a pressure algometer and a calibrated series of weights. Pressure pain sensitivity was evaluated by suprathreshold sensations using an 11 point (0 – 10) patient numerical rating scale following 18 seconds of stimulation. Participants then underwent an fMRI block design pain challenge task using three pre-determined experimental pain levels (none, mild, or moderate) and a standard equal pressure weight (125g) condition. FMRI time series data were realigned, spatially-normalized and smoothed (8mm FWHM) using SPM8 and examined using a finite-impulse-response model to capture any transient or sustained brain activity changes during each stimulation. Mixed-factor SPM8 ANOVA compared groups across pain levels.

Results: There was no statistical difference in the pressure required to produce the predetermined pain levels between SCD subjects and controls. Despite having equivalent pressure requirements at each of the three experimental pain levels, SCD subjects showed reduced hemodynamic response in SII and insular cortex regions-of-interest compared to controls across no pain, equal pain and equal pressure conditions.

Conclusion: We have demonstrated evidence for centrally altered pain processing in patients with SCD. The results indicate that pain-related neural processing is abnormal in SCD patients, involving deficits in brain regions specialized for sensory-discriminative (SII) and somatosensory integration (insula). However, no SCD abnormalities during pain challenge were detected in brain regions thought to represent basic sensation (SI) or cognitive/emotional aspects of nociceptive processing (e.g., anterior cingulate). Although these results stand in contrast to some studies that found pain matrix activation predicted self-reported pain intensity, they make sense within the context of evidence for reduced neural response when pain is delivered in a predictable, fixed context. Therefore, the blunted average SII and insular activation in SCD patients is taken as evidence for even greater-than-usual reduction in repeated pain-induced activation related to pain sensitization. The results also suggest SCD patients pain sensitization might involve abnormal signaling from these brain regions to other cortical areas more directly involved with interpreting and consciously representing the pain experience.

318

CHOOSING OPIOID MANAGEMENT FOR PAIN AND ANALYZING ACS RATES EQUALLY (COMPARE)

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Background: Painful episodes are the most common cause of morbidity and hospitalization for patients with sickle cell disease (SCD). Acute Chest Syndrome (ACS) has become the most prominent complication associated with painful episodes, it is the leading cause of death, and contributes to increased morbidity and prolonged hospitalization.1 Primary and secondary ACS prevention would prolong life, improve clinical outcomes, and reduce healthcare costs. Morphine is the most frequently used opioid for the treatment of pain, but has been associated with the development of ACS during sickle cell pain events.2 The mechanisms underlying this association have not been fully elucidated. The development of pulmonary disease during painful events maybe associated with morphine's Mμ receptor properties, linked to histamine release, endothelial activation, and possibly also exacerbated by respiratory depression. Nalbuphine is a mixed opioid agonist/antagonist and is equi-analgesic to morphine in doses up to 30 mg. Treatment with nalbuphine has reportedly fewer untoward side effects compared to morphine. Most importantly, it has not been linked to or associated with the development of ACS. Nalbuphine is not routinely used in the treatment of sickle cell pain.

We have previously found differences in the development of ACS when children with SCD were treated with either morphine or nalbuphine.3 Of the 186 pediatric sickle cell patients, there were 37 (21%) acute chest events; 26 (29%) in morphine treated group and 11 (12%) in those who received nalbuphine. However, the findings were confounded by differences in route of administration between the two different opioids. Morphine was more likely to be administered via continuous infusion with accompanying patient controlled administration (PCA), while nalbuphine was usually administered intermittently. Nalbuphine therapy was more often changed to an alternate medication. There was no clear pattern in the choice of opioid administration, and changing medication in the nalbuphine group was complicated by sub-therapeutic dosing prior to the change.

Objective: To better understand whether opioid analgesic choice may be associated with the development of ACS in children with SCD, we conducted a prospective double-blinded randomized trial comparing morphine or nalbuphine administered via PCA in the treatment of acute pain episodes, measuring outcomes of the development of ACS and effectiveness of pain control.

Method: After IRB approval, children 6 - 18 years with SCD were recruited when they presented in the emergency room(s) for acute treatment of pain at Children's Healthcare of Atlanta and Children's Mercy Hospital, in Kansas City, Missouri. Subjects were randomized (1:1) to receive either morphine or nalbuphine, once the decision was made to admit the subjects for continued pain control. Study subjects were treated with both opioids administered via continuous infusion with patient controlled administration. Study subjects were visited twice daily by the research team, to document pain control and side effects, utilizing a multidimensional pain meter calculation. Laboratory measurements of C-reactive protein, LDH, and cytokines were obtained on day one and three. Mμ receptor genetic analysis was conducted to determine whether polymorphisms may account for differences in opioid response.

Results/Conclusion: Forty subjects successfully completed the trial. Four subjects developed ACS, three in the morphine group and one in the nalbuphine group. Five subjects, in the nalbuphine group, changed to an alternate opioid for pain relief. There was no statistical difference in patient hospital days between the two groups (morphine

4.9 vs. nalbuphine 3.5 days). However on day 1, after the study medication began, the two groups differed in C - reactive protein levels (morphine 5.9 vs. nalbuphine 2.1) $p < 0.05$. Not surprisingly, there were statistical differences in hospital days and CRP in those who developed ACS compared to those who did not. Nine eligible candidates refused participation. Recruitment for our study in an emergency room was feasible. We found a lower rate of ACS complicating acute pain admissions than in our original study. Differences observed in this prospective trial may be due to universal screening chest x-rays to rule-out ACS at the time of admission and standardized aggressive preventive respiratory care for all inpatients treated for pain episodes.

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391

CLINICALLY MEANINGFUL MEASUREMENT OF PAIN IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Pain, the hallmark of sickle cell disease (SCD), is associated with significant morbidity from infancy throughout life. Guidelines for pain management in SCD recommend that pain be assessed routinely to guide treatment. Interpretation of self-reported pain scores remains a barrier to optimal treatment. Specifically, there is a lack of knowledge regarding the amount of change in pain scores over time indicating clinically significant pain relief and the degree of pain score signifying the need for treatment and how much improvement leads to treatment satisfaction.

Objectives: To determine the minimum clinically significant difference in pain scores using the Numeric Rating Scale (NRS) and to describe the pain score threshold associated with the need for pain medication and treatment satisfaction.

Methods: A sample of children with SCD, aged 8 to 18 years, treated within the emergency department and inpatient unit for uncomplicated pain events were recruited for this prospective study. Children completed initial ratings of pain severity using the NRS upon arrival to the emergency department followed by serial assessments every 30 minutes while in the ED and three times daily upon admission until discharge. The NRS is an 11-point scale for self-report pain ranging from "no pain (0)" to "the worst pain possible (10)." At the same time intervals, children also reported pain relief (i.e., much worse, a little worse, the same, a little better, or much better), need for medication (i.e., yes or no), and treatment satisfaction (i.e., not at all satisfied, somewhat satisfied, or very satisfied). The minimum clinically significant difference in NRS pain score that resulted in patient-reported pain relief was calculated. Receiver operator characteristics curves were developed to examine NRS thresholds for patient-reported need for medication and treatment satisfaction.

Results: Three hundred and five assessments were collected from 28 children. The minimal clinically significant difference identified as pain reported as being "a little better" was +0.93 (SE = 0.24) on the NRS. Changes in NRS scores greater than +0.5 had good sensitivity (0.66) and specificity (0.84) to discriminate self-reported improvements in pain as being "a little better." An NRS score >7.5 had good sensitivity (0.82) and specificity (0.59) to discriminate a patient's need for medication. A NRS score <8.5 had sensitivity of 0.72 and specificity of 0.81 in discriminating satisfaction with treatment, (i.e., "somewhat satisfied" or "very satisfied" with treatment).

Conclusion: This study provides important information regarding the clinical interpretation of NRS pain scores in children with SCD receiving treatment for acute pain. Specifically, we identified NRS pain scores signifying the minimal clinically significant difference in pain relief, perceived need for medication, and perceived treatment satisfaction within this population. These data can be utilized to guide medical decision-making in acute pain management and provide treatment outcome scores useful in future pain research.

434

THE DEVELOPMENT AND VALIDATION OF THE CHILDREN'S ACUTE PAIN-FUNCTIONAL ABILITY QUESTIONNAIRE

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Background: Numerous previous functional neuroimaging studies have identified brain regions that show greater activation to painful versus non-painful stimuli. This experiment examined the response of brain regions within this "pain matrix" in patients with sickle cell disease (SCD) to describe possible alterations to neural reactivity that underlies pain sensitization.

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Conclusion: We have demonstrated evidence for centrally altered pain processing in patients with SCD. The results indicate that pain-related neural processing is abnormal in SCD patients, involving deficits in brain regions specialized for sensory-discriminative (SII) and somatosensory integration (insula). However, no SCD abnormalities during pain challenge were detected in brain regions thought to represent basic sensation (SI) or cognitive/emotional aspects of nociceptive processing (e.g., anterior cingulate). Although these results stand in contrast to some studies that found pain matrix activation predicted self-reported pain intensity, they make sense within the context of evidence for reduced neural response when pain is delivered in a predictable, fixed context. Therefore, the blunted average SII and insular activation in SCD patients is taken as evidence for even greater-than-usual reduction in repeated pain-induced activation related to pain sensitization. The results also suggest SCD patients pain sensitization might involve abnormal signaling from these brain regions to other cortical areas more directly involved with interpreting and consciously representing the pain experience

INDIVIDUALIZED PAIN MANAGEMENT AND USE OF PATIENT CONTROLLED ANALGESIA CAN LEAD TO HIGH QUALITY CARE AND HIGH PATIENT SATISFACTION IN THE PEDIATRIC EMERGENCY DEPARTMENT

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Background: Vasocclusive pain crisis is the most commom morbidity associated with sickle cell disease and the most common reason for presentation to the emergency department (ED). We have successfully implemented the use of individualized pain management for more than a decade. These individualized pain plans are now part of the electronic medical record and regularly updated. A prior survey of physicians and nursing staff revealed that while physicians were aware and used the individualized pain plans in the electronic medical record, nurses were generally unaware of them. Further, we also observed that inpatient pain medication orders and initiation of PCA were delayed for patients who failed ED pain management and were admitted to the floor.

Objective: We sought to further improve the quality of pain management by adding the use of patient controlled analgesia (PCA) and intensive nurse education to the emergency department care of our patients with sickle cell disease (SCD) and pain crisis.

Methods: Children's Hospital of Pittsburgh of UPMC (CHP) provides comprehensive care for more than 255 pediatric patients with sickle cell disease. For this quality improvement initiative, we streamlined processes for the initiation of the PCA in the ED, accompanied by extensive education for the ED nurses and physicians regarding sickle cell disease, pain management and the use of the PCA. We then analyzed workflow and processes in the ED from the initiation of the project in November 2012 through the present. We also administered a six question survey to evaluate patient satisfaction with quality of care and patient experience in the ED. We asked patients: (1) "During the ED visit did the doctors and nurses seem to know about sickle cell disease?" (2) "Did the doctors and nurses believe that your child had bad SCD pain?" (3) "Did they re-check your child as often as you would have liked?" (4) "Were they able to relieve your child's pain?" and (5) "Did previous negative experiences in an emergency department influence your decision about when to come to the ED for care?" Families rated each item on a 5-point Likert scale (except question 5), as: not at all, a little bit, somewhat, quite a bit, or very much. They were then asked to rate their care on a scale of 0-10 (0 as "poor," 10 as "excellent." This work was supported in part by Health Resources & Services Administration Grant 6H46MC 00255-01-0

Results to Date: Of the 58 patients who presented to our Emergency Department with vasocclusive pain crisis during the period December 1, 2012 and February 6, 2013, 35 patients were contacted and surveys completed (60% response rate). The median time for placement into a room after arrival in the emergency department was 5 minutes. Median time until an order for a narcotic being placed was 41 minutes. Median time to the administration of the first narcotic after arrival was 76 minutes. The median time for PCA being ordered after arrival was 54 minutes. The median time for the PCA being started after arrival was 232 minutes. The patients who completed the survey rated doctors and nurses knowledge of sickle cell and their belief their child had severe pain as "quite a bit", and their satisfaction with how often the nurses re-checked the child and how much they were able to relieve the pain as "somewhat". Patients rated the care as a median of 7 on a scale of 10.

Conclusion: Individualized pain plans, use of PCA in the ED, and intensive staff education can result in high quality care with high levels of patient satisfaction with quality of care and the ED experience.

397

MEASURES OF CLINICAL OUTCOMES IN VASO-OCCLUSIVE CRISIS OF SICKLE CELL DISEASE- GRADING THE LITERATURE

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Background: Various measures have been used to assess clinical outcomes in vaso-occlusive crisis (VOC) due to sickle cell disease (SCD). Data comparing the use of various measures for assessing clinical outcomes in VOC are limited. Such information would be valuable to clinicians evaluating and interpreting VOC treatment studies and may also inform clinicians' evaluation of outcomes in their VOC patients.

Objectives:

1) Identify clinical outcome measures used in published studies assessing VOC clinical outcomes and;

2) Evaluate and compare the quality of evidence across studies by type of measure used for assessing VOC clinical outcome measures.

Methods: PubMed, COCHRANE and CINAHL databases (1966 to August 2012) were searched. Reference lists from identified articles were also used to identify additional studies. Studies that employed any measure to assess clinical outcomes for VOC were selected. Articles not written in English or non-human studies were excluded. The 'Grading of Recommendations Assessment, Development and Evaluation Working Group' (GRADE) recommendations were utilized to assess evidence quality for each measure. Four domains were assessed: risk of bias (coded '1 ' for a randomized controlled trial that had no serious limitations, else '0'), consistency (coded '1' for demonstrated clinical and methodological homogeneity, else '0'), directness (coded '1' for use of a non-surrogate endpoint, else '0') and precision (coded '1' if total number of cases across all studies of a measure was greater than 400, else '0'). Overall strength of evidence was calculated by summation of each domain score. Overall strength of evidence score was denoted '4' ('high'), '3' ('moderate'), '2' ('low') and a score less than or equal to '1' denoted 'very low' strength of evidence.

Results: 1,917 potentially relevant studies were identified and reviewed. Of those, 71 studies (42 randomized controlled trials and 29 observational studies) passed selection criteria and were retained for review. The most common clinical outcome measures employed in studies were 'length of hospital stay' (24 studies), 'decrease in pain' as from baseline measure (19 studies), 'total dose of analgesia required' (converted into morphine equivalent units) until the end of crisis (23 studies) and 'number of re-hospitalizations' within 15 and 30 day period (12 studies). 'High' degree of evidence was observed for 'decrease in pain' and 'total dose of analgesia required' (converted into morphine equivalent units) until the end of crisis. However, the degree of evidence in studies using 'length of hospital stay' was 'moderate' and the evidence quality was 'low' in studies using 'number of re-hospitalizations' within 15 and 30 day period as outcome measures.

Conclusion: Studies with higher quality design tended to use 'decrease in pain' or 'total dose of analgesic required' to assess VOC outcomes compared to those that used 'length of hospital stay' or 'number of re-hospitalizations.

264

PULMONARY FUNCTION TESTING IN INFANTS WITH SICKLE CELL DISEASE

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Background: Children with sickle cell disease (SCD) and asthma have an increased incidence of acute chest syndrome (ACS), stroke, hospitalization for pain, and premature death relative to children with SCD who do not have asthma. Pulmonary function tests (PFTs) have been performed safely on infants without SCD for over 15 years and yield the same information as conventional spirometry and plethysmography.

Objectives: 1) To determine the safety and feasibility of enrolling 6-18 month old infants with SCD in a study requiring sedation for PFTs. 2) To determine whether infants with SCD have impaired lung function relative to a historical control group of Afro-American (AA) infants. 3) To determine whether infants with SCD have increased albuterol responsiveness prior to the onset of clinical asthma and 4) To examine correlations between PFTs and exposure to smoking, family history of asthma, personal history of wheeze, and relevant laboratory studies.

Methods: Infants with SCD were approached at their regular SCD visit at a single institution. Following a clearance history and physical exam, patients were sedated orally with chloral hydrate (100 mg/kg). Once asleep, functional residual capacity (FRC) was measured plethysmographically, followed by spirometry using the raised volume rapid thoracic compression method. Albuterol was then given in a dose of 2 puffs every 2 minutes until an increase in heart rate of 10% was observed. PFTs were repeated between 15 and 35 minutes following albuterol. Clinical blood tests were obtained while the infant remained drowsy. The infant was monitored until alert and able to feed by bottle. Follow-up calls were made 24-48 hours after the study to document the child's clinical status, feeding, and sleep/wake cycle.

Results: Of 47 eligible patients, 19 enrolled (40%), of which 15 had Hgb SS, 2 Hgb SC, and 2 Hgb S Beta+Thal. One patient developed splenic sequestration requiring transfusion 5 days after the PFTs. Hyperactivity was noted in 4 of 19 patients (21%) the day following the test. There were no other adverse events. When compared to AA historical controls, infants with SCD had lower forced vital capacity (FVC), forced expiratory volume in 0.5 seconds (FEV0.5), forced expiratory flow between 25 and 75% of expired FVC (FEF25-75), FEV 0.5/FVC and higher residual volume (RV)/total lung capacity (TLC) and FRC/TLC ratios in z-scores($p<0.01$). No significant changes in mean measures of lung function were observed following albuterol. There was an inverse correlation between FEV0.5 z-score and percentage of hemoglobin S ($p<0.05$). FEF25-75 z-score was inversely correlated with patient history of wheeze ($p<0.03$). No relationships were found between PFTs and family history of asthma, smoke exposure, absolute hemoglobin level or other routine clinical blood tests.

Conclusions: PFTs on infants with SCD age 6 to 18 months, using oral chloral hydrate as a sedative, was safe. Even with small numbers of patients, there were statistically significant differences in the PFTs of infants with SCD compared to AA historical controls. A longitudinal multi-center study is necessary to determine whether smaller lung volumes and impaired airway function in infancy predispose to asthma in childhood, and ultimately to pulmonary hypertension in young adulthood.

321

ABNORMAL RENAL TUBULAR HANDLING OF PHOSPHORUS IN SICKLE CELL DISEASE

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Background: Persistent or intermittent elevation of serum phosphorus has been reported in adults and in some pediatric studies in patients with sickle cell disease(SCD) . Elevated phosphorus levels have been correlated with reduced life expectancy and cardiovascular mortality even in the normal population.

Objectives: As there is limited pediatric data we decided to evaluate factors that contribute to phosphorus homeostasis in children with sickle cell anemia, including tubular maximum reabsorption of phosphorus (TMP/GFR), a good indicator of phosphorus reabsorption in the proximal tubules, and the novel biomarker Fibroblast Growth Factor 23(FGF23) which is considered one of the main factors involved in phosphorus excretion by the kidneys.

Methods: We conducted a cross-sectional study evaluating renal tubular handling of phosphorus in 24 subjects (mean age 15.5± 2.4 yr) with SS disease and normal or elevated GFR. Blood and urine samples were collected at the same time. Patients with acute painful crisis or recent infectious process were excluded from the study. Serum creatinine, cystatin C, mineral biochemical data including 25-(OH)vitamin D,PTH and FGF23 were measured. Intact FGF23 levels were measured by ELISA kit (Millipore, MA; normal range 22-60 pg/mL) and C-terminal FGF23 by immunotopics (up to 220 RU/ml). The tubular re-absorption of phosphorus (TRP) and TMP/GFR were calculated. GFR was estimated by serum creatinine using modified Schwartz and by cystatin C.

Results: Of the 24 patients ,22 were African Americans (15 females). Mean GFR by serum creatinine was 143±30 ml/min/1.73m^2 and per cystatin C was 134.9±28.6 ml/min/1.73m^2,respectively. Most had vitamin D deficiency (15.6±6.1ng/ml), had normal serum calcium(9.4±0.5 mg/dl) and alkaline phosphatase(133±61.7 unit/L), but increased serum phosphorus for age (5.1±0.7mg/dl). TRP was elevated in most patients for serum phosphorus with average levels of 96.3±2.1% and TMP/GFR at 4.9±0.6mg/dl(normal 2.6-4.4). Intact FGF23 concentrations were elevated at 81.2±38.3pg/ml and C-terminal assays at 444.7±350.3RU/ml while the average PTH values were 50.4±26.7 pg/ml (Normal 15-65 pg/ml). Linear regression analysis showed significant correlations of serum phosphorus with age (r=-0.56,p=0.004),LDH (r=0.52,p=0.0108), TMP/GFR(r=0.98, p<0.0001),log Intact FGF23 (r=0.46,p=0.04), and alkaline phosphatase (r=0.66,p=0.0007).Significant correlation also existed between TMP/GFR and log intact FGF23 (r=0.5,p=0.01), but not with PTH or vitamin D level. Multiple regression analysis yielded significant effect of TMP/GFR on serum phosphorus (R2=97.3% and P =0.00), but not with other variables.

Conclusions: This cross sectional data done on children with SCD and normal kidney function shows that they have elevated serum phosphorus levels secondary to increased phosphate re-absorption at the proximal tubules. FGF23 levels were elevated in the presence of normal PTH values .Proximal tubular resistance to the action of FGF23 action is demonstrated with elevated serum phosphorus and concomitant high TMP/GFR. Further studies are needed to better understand the role of FGF23 and its cofactor Klotho in the physiology of proximal tubular function in sickle cell patients.

PREVALENCE OF CYP2D6, CYP2C9 AND CYP2C19 ALLELIC VARIANTS IN A PEDIATRIC SICKLE CELL DISEASE PATIENT COHORT

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Background: Allelic variability in the cytochrome CYP2D6, CYP2C9, and CYP2C19 enzymes are an important cause of interindividual variability in analgesic drugs prescribed for sickle cell disease (SCD) pain. The potential clinical consequences of these variants range from serious toxicity to ineffective drug therapy. Despite the functional significance of CYP2D6, CYP2C9 and CYP2C19 variants, relatively fewer studies have focused on their implications for SCD pharmacotherapy.

Objectives: The objective of our study was to determine the CYP2C9, CYP2C19 and CYP2D6 allelic and genotypic frequencies in a pediatric SCD patient cohort and highlight the benefits and challenges of pharmacogenetics testing for analgesic therapy.

Methods: Genomic DNA was isolated from blood samples of 30 patients, aged between 7 and 17 years. Eight variant CYP2C9 alleles (*2, *3, *4, *5, *6, *8, *11 and *13), eleven CYP2C19 alleles (*2, *3, *4, *5, *6, *7, *8,*9, *10, *11, and *17), and nineteen CYP2D6 alleles (*1xN, *2, *2A, *2AxN, *3, *4, *4xN, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, and *41) were genotyped across all patients. Genotyping of the CYP2D6 alleles and five CYP2C9 alleles was performed using the Tag-It™ Mutation Detection Kit (Tm Bioscience, Toronto, ON, Canada). The CYP2C9*8, *11 and *13 alleles were amplified by PCR and interrogated using RFLP assays. The CYP2C19 alleles were genotyped using the eSensor 2C19 Test (GenMark Diagnostics, Carlsbad, CA, USA).

Results: A total of 11 CYP2D6 alleles were detected in the cohort. The *3, *6, *7, *8, *9, *11, *12, *14, and *15 alleles were not detected. The most common alleles identified were *1, *2,*10, and *17 and their frequencies were 0.339, 0.210, 0.065 and 0.161 respectively. The CYP2C19*1 wild-type allele frequency was 0.533. Three different CYP2C19 alleles were identified with the *17 occurring in the highest frequency (0.300), followed by *2 (0.150) and *13 (0.017) respectively. The CYP2C19 *3,*4,*5, *5, *7, *8,*9, and *10 alleles were not detected. For the CYP2C9 enzyme, the wild type (*1) allele frequency was 0.823. No CYP2C9 *4 or *13 were identified in the cohort. CYP2C9*8 was the most frequent of the variant alleles (0.065). The combined frequency for all the variants, *2, *3, *5, *6, *8, and *11 was 0.177. Phenotypically, 67.7% of the cohort was extensive metabolizers; 29% and 3.2 % respectively were intermediate and poor metabolizers. For the CYP2D6, phenotypes were distributed into ultra-rapid – (6.5%), extensive - (77.4%), and intermediate- (12.9 %) metabolizers. No poor metabolizer was detected, and one patient (3.2%) had an unknown phenotype. The *17 allele was identified in all the intermediate metabolizers. For the CYP2C19, the predicted metabolic phenotypes were distributed as ultra-rapid (46.7%), extensive (20%) and intermediate (33.3%) metabolizers. The CYP2D6, CYP2C9, and CYP2C19 genotypes were in Hardy–Weinberg equilibrium.

Conclusions: Some of the CYP2C9, 2C19, and 2D6 variant alleles are being reported for the first time among SCD patients. The variant alleles are implicated in the analgesic effects and toxicity of the most opioids and NSAIDs analgesics. Future research should determining the CYP2C9, 2C19, and 2D6 metabolic profiles of pediatric SCD patients and perform appropriate pharmacokinetic studies that could potentially enable clinicians to identify patients with impaired drug metabolic capacity and tailor analgesic drug dosing accordingly to achieve optimal pharmacologic response.

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402

LONGITUDINAL NATURAL HISTORY STUDY OF TRICUSPID REGURGITANT JET VELOCITY IN UNTREATED CHILDREN WITH SICKLE CELL DISEASE

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Background: Elevated tricuspid regurgitant jet velocity (TRV) has emerged as an important biomarker in adults with sickle cell disease (SCD) and has been associated with clinical outcomes such as pulmonary hypertension, proteinuria, decreased exercise capacity and early death. TRV elevation has been reported in 16-30% of children, though data on its longitudinal progression is limited.

Objectives: To determine the natural history of TRV in untreated children with SCD.

Methods: Beginning in 2006, SCD patients (age >6) were enrolled in a prospective longitudinal study. Screening echocardiograms (ECHOs) were done during annual visits. TRV ≥2.5 m/sec was considered elevated. ECHOs were repeated yearly if TRV was elevated and every 2 years if TRV was normal. Clinical and laboratory data were collected at each visit. Patients on chronic transfusions or hydroxyurea prior to their first ECHO were included in the study. Follow up ECHO data was censored for patients who started hydroxyurea or chronic transfusions after their first screening ECHO.

Results: A total of 100 patients aged 6-21 years were included, 87 with HbSS and 13 with Sβ° thalassemia. At baseline screening, 67 patients had normal TRV <2.5 m/sec and 33 patients had elevated TRV ≥2.5 m/sec. Median follow up time was 3.59 years. Follow up ECHOs were available for 82% of patients (82 of 100). On follow up, 61.4% of patients with baseline normal TRV continued to have normal TRV on all subsequent ECHOs, whereas 38.6% of patients had at least 1 ECHO with an elevated TRV. Risk factors associated with TRV conversion were baseline low oxygen saturation, low hemoglobin and high reticulocyte count (all $p < 0.05$). On follow, 32% of patients with elevated TRV at baseline continued to have elevated TRV on all subsequent ECHOs, whereas 68% of patients had at least 1 ECHO with normal TRV without intervention. Risk factors associated with persistent TRV elevation were baseline elevated TRV, low hemoglobin, and high white blood count (all $p < 0.05$). Three of the 100 patients died during the follow up period, one with elevated TRV.

Conclusion: 32% of children with SCD and elevated TRV have persistent elevation on follow-up echocardiograms, whereas 61% of children with TRV <2.5 m/sec continue to have normal TRV on follow-up. Patients with high hemolytic rate as evidenced by low hemoglobin and high reticulocyte count are at high risk of TRV conversion and should be monitored closely.

358

A PHASE 1, FIRST-IN-MAN, DOSE-RESPONSE STUDY OF AES-103 (5-HMF), AN ANTI-SICKLING, ALLOSTERIC MODIFIER OF HEMOGLOBIN OXYGEN AFFINITY IN HEALTHY NORMAL VOLUNTEERS

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5-HMF (5-hydroxymethyl-2-furfural; Aes-103) is a breakdown product of glucose that has potent anti-sickling properties in vitro and in vivo (transgenic sickle cell mice) and produces concentration-dependent left shifts in p50 values of the oxygen equilibrium curve (OEC), indicating increased oxygen affinity. These pharmacological properties are likely based on the binding of 5-HMF to the valine residue of alpha globin chains of HbS and possibly to lysine. Increasing the oxygen affinity of HbS is known to reduce sickling. Aes-103 is being developed as a potential treatment for sickle cell disease (SCD).

The current first in man study was a double-blind, placebo-controlled, ascending single dose evaluation of the safety, pharmacokinetics and pharmacodynamics of 5-HMF given as an oral solution at 300 mg, 1000 mg, 2000 mg and 4000 mg to healthy normal subjects. In each dosing cohort, 6 subjects received 5-HMF and 2 received placebo. A total of 20 adult subjects of African descent with normal hemoglobin (Hb), received a single dose of study drug or placebo on up to 2 occasions separated by 2–4 weeks. The mean age of the subjects was 28 years, mean BMI was 25.8, and 13 were males, 7 were females. Written informed consent was obtained.

Safety measures consisted of adverse events (AEs), vital signs, ECG, clinical chemistry, hematology, urinalysis and physical exams. No subjects were discontinued from the study due to an AE. During the day of dosing a total of 14 AEs occurred. All were mild, with 3 occurring in the placebo arm (constipation, dry mouth, dizziness), none at 300 mg, 2 at 1000 mg (diarrhea, headache), 3 at 2000 mg (feeling hot, somnolence, dyspnea—during hypoxia testing) and 6 at 4000 mg (nausea (2), abdominal pain, dizziness, somnolence (2)). Following dosing, there were no clinically significant differences between drug and placebo treated subjects in respect to heart rate, blood pressure, ECG, physical exams, clinical chemistry, hematology and urinalysis results.

The pharmacokinetic profile of 5-HMF in plasma showed dose-proportional kinetics with an upward trend towards higher Cmax and AUC at higher doses. Mean plasma Cmax concentrations ranged from 34 to 699 ng/ml, Tmax ranged from 0.42 to 0.67 h, AUC ranged from 33 to 875 ng.ml/hr and t1/2 ranged from 0.38–0.76 h. 5-HMF levels in RBC hemolysate were typically 5–15 times that of corresponding plasma levels with Cmax ranging from 152–3640 ng/ml, Tmax ranging from 0.71–0.83 h, AUC ranging from 473–10103 ng/ml/h and half-life ranging from 1.61–2.13 h. Measurements of RBC hemolysate levels did not include the 5-HMF bound to hemoglobin. The elevated levels and longer half-life of 5-HMF in RBCs relative to plasma probably reflects the binding affinity of Hb for 5-HMF and the equilibrium between Hb bound 5-HMF, free 5-HMF in the RBC and in plasma.

The main pharmacodynamic endpoint was the change in blood oxygen level (SpO2) during a 5-minute hypoxia challenge test in which 12% O2 was inhaled. The hypoxia challenge was administered prior to dosing and then at 0.75, 2, 4 and 8 h post-dose. Results showed an appreciable attenuation of the drop in SpO2 values due to hypoxia. For example, at 2 hours post-dose for the placebo treated subjects the mean SpO2 values declined by an average of 12.3% after 5 minutes of hypoxia. In contrast, the 2000 mg 5-HMF treated subjects had a mean decline in SpO2 of 8.7%. The attenuation of hypoxia effects was dose-dependent (minimal effect at 300 mg of 5-HMF) and was time-dependent following 5-HMF dosing (largest protection seen at 2–4 h post-dose, no protection at 8 h post dose). At 2 hours after 5-HMF doses of 1000–4000 mg, the SpO2 values from 18 hypoxia test sessions showed significantly ($p<0.05$, t-test) smaller decrements than what occurred in the same time point in the pooled placebo treated subjects.

In summary, single oral doses of 300–4000 mg of 5-HMF given to healthy normal volunteers were well tolerated, rapidly absorbed and preferentially taken up into RBCs relative to plasma, had a dose-proportional pharmacokinetic profile and showed a pharmacodynamic change (protection against desaturation during hypoxia) consistent with the expected increase in oxygen affinity and with the compound's proposed mechanism of action in SCD patients. A similar ascending single dose, placebo controlled, double-blind study in patients with SCD at steady state is currently ongoing at the NIH (see www.clinicaltrials.gov).

246

RED BLOOD CELL ALLOIMMUNIZATION IS ASSOCIATED WITH TRANSFUSION FOR ACUTE SICKLE CELL DISEASE-RELATED COMPLICATIONS

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Introduction: Red blood cell (RBC) transfusion is an important therapy for complications due to sickle cell disease (SCD). However, RBC transfusion is associated with multiple complications, including alloimmunization, which can lead to acute as well as delayed hemolytic transfusion reactions. The rate of alloimmunization is known to be much higher in the SCD population compared to the general population. Studies in mouse models of inflammation suggest that the induction of inflammation can increase the rate of alloimmunization. As SCD is described as a chronic inflammatory state, we proposed that disease complications associated with increased inflammation are more likely to be associated with alloimmunization.

Methods: A retrospective chart review was conducted to explore the association of clinical complications of SCD with RBC alloimmunization. The records of patients with SCD followed at the University of North Carolina, Chapel Hill who were transfused from 2005 – 2012 were reviewed. The patients were identified using a combination of ICD-9 codes combined with billing codes for transfusion, and supplemented by a review of patient histories and blood bank records. Patients were included in the study if they had a confirmed diagnosis of SCD by hemoglobin electrophoresis and a follow up type and screen after RBC transfusion. The transfusions were categorized into 2 groups: transfusions for acute complications versus elective transfusions. Clinical complications (acute pain crises, active infection, acute chest syndrome, stroke, retinal artery occlusion, surgery, or leg ulcer) at the time of transfusion and laboratory variables pre- and post-transfusion (white blood cell count, platelet count, hemoglobin, absolute neutrophil count, absolute monocyte count, and lactate dehydrogenase) were recorded. Patients were excluded if they were on chronic RBC exchange transfusions, had a bone marrow transplant, or if they did not have a follow up type and screen.

Results: A total of 168 patients (SS = 123, Sβ0 = 6, SC = 25, Sβ+ = 9, Other = 4) with a total of 495 transfusion events and a total of 916 units of RBCs (median of 4.0 RBC units/patient [range: 1-65 units]) met inclusion criteria. One hundred sixty-three patients (97%) were African American, with a median age of 22.3 years (range: 3 days – 72.4 years). Twenty seven patients (16%) had a history of auto- or alloantibodies at the start of the review period. Twenty patients (12%) developed new antibodies following blood transfusions during the period of review. Three hundred and eighty one (77%) transfusion events occurred for an acute SCD-related complication. Two hundred and eighty nine (58%) RBC transfusions occurred during an acute painful crisis, 161 (32.5%) transfusions occurred during episodes of acute chest syndrome, 8 (1.6%) transfusions followed transient ischemic attacks/strokes, and 5 (1%) transfusions were for acute retinal artery occlusion. The median age of the transfused units was 22 days (range: 2-3640 days [some RBC units were frozen]). Although some patients (N = 47) transfused for acute complications were also transfused for elective indications, new antibody formation appeared to be higher in the group of patients who were transfused for acute complications compared to patients transfused only electively (14% v 3%, p=0.08). New antibody formation was associated with older age (p = 0.01) and appeared to be related to the number of RBC transfusions, although the difference did not reach statistical significance (4.75 events vs. 2.70 events, p = 0.06).

Conclusion: Our study suggests that RBC antibody formation in SCD is associated with older patient age at the time of transfusion and may be associated with transfusion during acute complications. The higher prevalence of antibody development in patients who were transfused for acute SCD-related complications suggests that host inflammation at the time of transfusion may contribute to the pathophysiology of alloimmunization. Further studies are required to better understand the contribution of inflammation to alloimmunization in SCD.

EVALUATION OF PURIFIED POLOXAMER 188 IN CHILDREN (EPIC) - KEY DESIGN CONSIDERATIONS

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Background: There is no currently approved disease modifying treatment for ongoing vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD). A prior phase 3 study investigating MST-188 (purified poloxamer 188) was suggestive of treatment effects; however, prospectively defined outcomes did not reach statistical significance, other than in subgroup analyses and post-hoc analyses1. Interpretation of that study was potentially confounded by a study population heterogeneous for age, genotype and variation in pain management practices, subjectivity of the primary endpoint, statistical imbalance in the numbers of patients in the placebo and treatment groups who did not achieve endpoints and missing or imputed data.

Objective: To achieve a phase 3 study design that could replicate the results of the subset analyses suggesting favorable responses in children and those receiving hydroxyurea, avoid the deficiencies of the previous trial, serve as the basis for registration with the US FDA and accomplish enrollment in a reasonable timeframe.

Methods: Discussion with medical experts in SCD, regulatory authorities, disease advocates and review of available studies of vaso-occlusive crisis.

Results:

1. The study should focus on children to achieve a more homogeneous population
2. The study should enroll only patients with the SS or S-Beta null genotype
3. The study should include guidelines for control of pain, minimizing variability in pain management practices among study centers.
4. Statistical assumptions (e.g., untreated duration of crisis) should reflect data from recent studies in SCD, including recently conducted NIH-funded studies.
5. The primary study endpoint should evaluate a clinically meaningful outcome that can be measured with as much objectivity as possible; for example, duration of crisis, as measured by the time from randomization to the last dose of parenteral opioid analgesia. An objective assessment of VOC resolution is preferable to complex, multi-part definitions and reliance on subjective pain scales.
6. The study should reduce "right censoring" and the potential for missing and imputed data by following subjects until discharge, rather than an artificial time-point (e.g., 168 hours after randomization, as in the previous study).

Conclusion: Incorporation of the above mentioned considerations should result in a study that overcomes the limitations of the prior study while maintaining rigor and feasibility of enrollment.

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328

UNHEALTHY ALCOHOL USE AMONG PERSONS WITH SICKLE CELL DISEASE: PREVALENCE AND ASSOCIATION WITH CLINICAL OUTCOMES

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Background: Little is known about the prevalence and impact of alcohol abuse among adults with sickle cell disease (SCD). The PiSCES Study, which is a large-scale epidemiologic cohort study of pain among adults with SCD, recently found that nearly a third of its cohort were categorized as alcohol abusers, but that alcohol abuse was not associated with pain or healthcare utilization (1). Continued study of alcohol abuse among adults with SCD is extremely important given the increasing numbers of persons with SCD living to adulthood, and the potential interaction between the known physiologic effects of alcohol on the body with complications of SCD.

Objectives: Our aim was to study the prevalence and impact of unhealthy alcohol use among a sample of adults with SCD.

Methods: We analyzed data on self-reported alcohol use among adults and adolescents participating in the Improving Patient Outcomes with Respect and Trust (IMPORT) Study, a federally funded cohort of SCD patients at two academic medical centers in the Baltimore/Washington Metro Area. Study participants provided data on demographic, psychosocial, and clinical measures. Self-reported alcohol use was measured using the Addiction Severity Index (ASI)-Lite. Participants were asked, "How many days in the past 30 days have you used alcohol to intoxication?" Participants were classified as current unhealthy alcohol users if they reported any drinking to intoxication in the past 30 days. For our analyses, we compared current unhealthy users to those with no unhealthy use on a number of demographic variables, and we adjusted for demographics while comparing these groups on healthcare utilization (number of ED and inpatient visits within the past year) and pain. Pain was measured using the summary severity and interference subscales on the Brief Pain Inventory, the number of self-reported days in a week that the participants say are "good days" in terms of pain, the level of their pain on their good days, and the presence of daily chronic pain.

Results: Out of 292 patients participating in our study, 284 provided information regarding their alcohol use history and are the subset used for this analysis. 17% of these patients were classified as current unhealthy alcohol users and 83% as having no unhealthy use. Current unhealthy users were younger (29.4 years vs. 35.6 years, $p = 0.0001$) and more likely to be male (22.7% vs. 12.5%, $p = 0.023$) than those without current unhealthy alcohol use. In multivariable models, we found no statistically significant relationships between alcohol use and utilization while adjusting for patient age, sex, education, and SCD genotype, though we observed trends suggesting lower levels of utilization among the current unhealthy users (ED use $\beta = -1.1$, $p = 0.075$; Inpatient use $\beta = -0.67$, $p = 0.09$). In multivariable models, we found no statistical relationship between alcohol use and levels of current pain interference and severity, but we did find that current unhealthy alcohol users reported having fewer "good days" in terms of their pain during the week ($\beta = -0.53$, $p = 0.048$), and they were more likely than those without unhealthy use to report having daily chronic pain (OR = 2.1, $p = 0.034$).

Conclusion: Our study suggests that current unhealthy alcohol users have a higher burden of pain on some measures than those without current unhealthy use. Similar to PiSCES, we also found trends suggesting that current unhealthy alcohol users had lower levels of healthcare utilization than those without current unhealthy use. Further work in this area is needed to determine the extent to which unhealthy alcohol use causes a higher burden of pain, or may in fact be a symptom of a higher pain burden, among patients with SCD.

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PERCEIVED STIGMA AND EMERGENCY DEPARTMENT VISITS FOR SICKLE CELL DISEASE PAIN

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Background: Pain is the hallmark characteristic of sickle cell disease (SCD) and its management is of significant import to health researchers. A well-established literature confirms that SCD pain has neurobiological, psychological, and social components. However, the psychosocial aspects of SCD pain – and the subsequent use of healthcare services – are rarely analyzed among adults, inhibiting what is known about specific causal mechanisms.

Objectives: Our goal was to describe the association between an important psychosocial construct – perceived stigma – and the use of emergency department services for SCD-related pain. Our recently developed tool, the Measure of Sickle Cell Stigma (MoSCS), has shown reliable psychometric properties and strong construct validity in large samples of adults. In this study, we evaluated its clinical usefulness with regard to emergency department utilization.

Methods: This study was a cross-sectional, within-group investigation. We recruited 71 adults who were seen at a Midwestern adult sickle cell clinic affiliated with a university teaching hospital. Participants completed a survey that assessed health care utilization, pain, stigma, and psychosocial functioning. All surveys were completed in the waiting area or in a private consultation room of the clinic and participants who completed the study received a $10 gift card to a local grocery.

Results: Overall, the entire sample reported an average of 1.28 emergency department admissions over the past three months. The average number of pain episodes over the same period was 4.94, while the average number of scheduled and unscheduled medical visits were 2.81 and 0.90, respectively. In terms of psychological status, participants reported a low level of depressive symptoms and anxiety, M = 1.07, SD = .79. In order to evaluate the unique contribution of perceived stigma to variance in emergency department visits, we conducted a hierarchical regression analysis in which we entered pain frequency, both types of health care utilization (i.e., scheduled and unscheduled visits), and psychological symptoms in the first step of the equation and each of the four stigma subscales in the second step. The variables entered in step 1 of the analysis accounted for 26.8% of the variance in emergency department visits. However, when the perceived stigma variables were entered in step 2 of the equation, the proportion of variance accounted for increased to 37.6%. The additional 10.8% of variance contributed by these variables was statistically significant, $\Delta F (8, 68) = 4.52$, $p < .05$, suggesting that perceived stigma accounts for a unique proportion of variance in emergency department visits. Inspection of the full regression model indicated that unscheduled health care visits ($\beta = .26$), social exclusion stigma ($\beta = .45$), and internalized stigma ($\beta = -.41$) were unique predictors of emergency department visits.

Conclusions: After adjusting for pain frequency, psychological symptoms, and scheduled medical appointments, participants who had more unscheduled health care visits for SCD and who reported greater levels of social exclusion stigma had significantly more emergency department visits in the past three months. Conversely, participants who reported greater levels of internalized stigma had significantly fewer emergency department visits. These findings provide further evidence of the multidimensional nature of SCD-related stigma and suggest that distinctive types of stigma may have unique effects on clinical outcomes. Further research should use prospective designs in order to elucidate causal mechanism of SCD stigma its long-term impact on health service utilization.

314

AN INNOVATIVE APPROACH TO ENHANCING THE TRANSITION TO ADULT CARE IN SICKLE CELL DISEASE

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Background: Research has found that there are several barriers to successful transition from pediatric to adult care for patients with sickle cell disease (SCD). Despite the identification of these barriers, the majority of proposed solutions have been developed by healthcare professionals with limited input from those most affected by transition, patients and caregivers. If we are to effectively improve the transition to adult care, it is essential that we utilize patient-focused research approaches that more clearly identify and address the barriers experienced by young adults with SCD. Design professionals have expertise in working with consumers to understand the context of a problem and then using creative strategies to generate insights and practical solutions. The current study describes how a healthcare team and a design team partnered to examine patient-focused barriers and strategies to the transition to adult care in SCD.

Objectives: The goals of this study were to: 1) examine patient and provider barriers to transition; and 2) develop tools that patients or providers could use to optimize the transition process.

Methods: A healthcare team at Cincinnati Children's Hospital Medical Center and the Live Well Collaborative, an academic-industry design center specializing in translating consumer research into products and services, conducted the study. A six-step qualitative research design process was utilized. First, the team conducted a comprehensive literature review to identify salient transition domains for this population. Second, in-depth interviews with patients and providers explored stakeholder perspectives relative to transitioning to adult care. Third, the team observed patient visits at both pediatric and adult hospitals. Fourth, interviews and observations were coded for themes and combined with data from the literature review to identify opportunity areas and insights across patients resulting in a comprehensive set of transition domains. Fifth, a concept ideation process was initiated and transition support tools were prototyped. Sixth, concepts and tools were refined and validated through co-creation sessions with patients and providers.

Results: Eight patients with SCD and six adult providers completed interviews. Patients had a mean age of 19 (SD = 2.04) and 60% were male. The providers had been caring for SCD patients for an average of 13.75 years (SD=16.3). Six overarching domains emerged: envisioning the future, social aspects of SCD, daily life, care provider interaction, self-management, and attitudes towards transitioning. Three patient-focused tools were developed and are currently being refined and tested. The interactive tools will be featured in the presentation and include: 1) individualized patient maps or visual representations of ideas corresponding to each domain, 2) patient profiles that rank each patient on each domain (e.g., positive, neutral or negative attitude towards transitioning), and 3) overall patient personas that reflect the most common patient reactions to the transition process and that will be used to inform the development of future interventions.

Conclusion: Through collaboration with design professionals, three innovative patient-focused tools to enhance the transition to adult care in SCD were developed. This patient-informed process was well-received by patients and providers. The inclusion of patient perspectives in this project allowed us to accurately capture salient barriers and then design tools to address those patient-reported difficulties. This study serves as a model for how designers and healthcare teams can work together to develop patient-oriented solutions for some of the major challenges in our healthcare system today.


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319 **AMONG EMERGENCY PHYSICIANS, USE OF THE TERM SICKLER IS ASSOCIATED WITH NEGATIVE ATTITUDES TOWARDS PEOPLE WITH SICKLE CELL DISEASE**

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Background: The word 'sickler' first appeared in the written English Lexicon in 1638 as an agricultural term to describe a laborer who used a sickle. The meaning of this term remained consistent for 300 years, until it was used in 1932 as a pathology term to describe an individual with sickled-shaped hemoglobin. Thus, the tern 'sickler' was used to refer to individuals with sickle cell disease and/or sickle cell trait. Many people with the disease find the term offensive and synonymous with negative qualities that are often ascribed to individuals with the disease. To explore the term 'sickler' and its association with attitudes of emergency physicians, we administered a validated survey at the 2011 meeting of the American College of Emergency Physicians. The hypothesis that we tested was physicians who use the term 'sickler' harbor more negative attitudes towards people with SCD than physicians who do not use the term.

Methods: At the conference, we approached attendees to participate in a written survey. The primary predictor variable for analyses was the following question: "How often do you refer to a patient with SCD as a 'sickler?'" Participants registered their answers on a 4-point likert scale (1=never, 2=rarely, 3=frequently, 4= always). Based on factor analyses, items from the attitudes portion of the survey were recoded into three attitude scales: the negative attitude scale (scored 0-100, mean 39.6, SD 21.9; higher scores indicate more negative views about people with SCD), the red flag behaviors scale (scored 0-100, mean 58.8, SD 22.4, higher scores indicate greater belief that certain SCD patient behaviors raise concern that the patient is inappropriately drug-seeking) and the positive attitude scale (scored 0-100, mean 37.2, SD 23.0; higher scores indicate an endorsement of more positive views about people with SCD). To explore associations between physician attitudes and use of the term 'sickler' with adjustment for race and gender, MANOVA was performed.

Results: Out of 795 participants, 655 were emergency physicians (99.22% of these participants completed the survey, or 650/655). The median age of the sample was 36 (IQR 32-45) with 67.5% males. Providers from academic or teaching hospitals were more heavily represented (67.9%). Provider demographics were similar to the overall population of emergency physicians in the United States.1-3 Use of the term 'sickler' was common with 13.1%, 34.7%, 43.3% and 8.7% indicating that they use the term 'never', 'rarely', 'frequently' or 'always' respectively. Multivariable analyses indicated a clear trend that, with increasing use of the term 'sickler,' providers harbored more negative and less positive attitudes (figure 1).

Conclusions: Our results demonstrate the use of the term 'sickler' by emergency physicians to refer to people with SCD is strongly associated with negative feelings towards people with the disease. This supports the widespread patient perspective that 'sickler' is a derogatory term often deployed by healthcare providers. The limitations of our study are: a) our sample (n=655) represents approximately 2% of all emergency physicians in the US and may not be representative of emergency physicians overall; b) there is potential sampling bias towards academic providers, and c) there is potential for reporting bias as all responses are self-reported and may or may not accurately represent actual practice.

In conclusion, this is the largest survey of emergency physicians on the topic of SCD. We demonstrated that use of the term 'sickler' is associated with negative feelings towards people with SCD. Providers should be discouraged from using the term, and interventions to improve cultural competency of emergency physicians may be of benefit, and may help repair the often tenuous patient-provider relationship in the emergency department.

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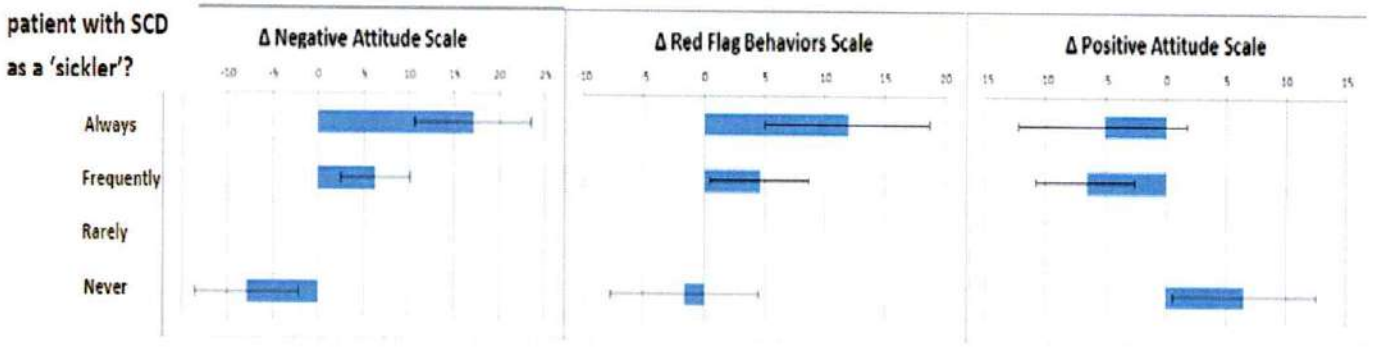
Figure 1: Association between use of the term 'sickler' and effect on attitudinal scales



Legend: Use of the term 'sickler' is associated with more negative and less positive attitudes towards people with SCD. The three attitude scales (negative attitudes, red flag behaviors and positive attitudes) are scored from 0–100. For each attitude scale, horizontal bars indicate the average change in attitudinal scale (error bars indicate 95% CI) associated with the frequency of use of the term 'sickler' (providers indicate never, rarely, frequently or always). Effects reported are adjusted for provider gender and race with those who 'rarely' use the term as the reference group. E.g. In response to the question "How often do you refer to a patient with SCD as a 'sickler'?", an answer of 'always' is associated with a 17.1 point increase (95% CI 10.7 – 23.6) in negative attitude scores in comparison to an answer of 'rarely'.

PATIENTS WITH SICKLE CELL DISEASE REPORT POORER COMMUNICATION THAN NATIONAL ESTIMATES OF AFRICAN-AMERICANS' EXPERIENCES

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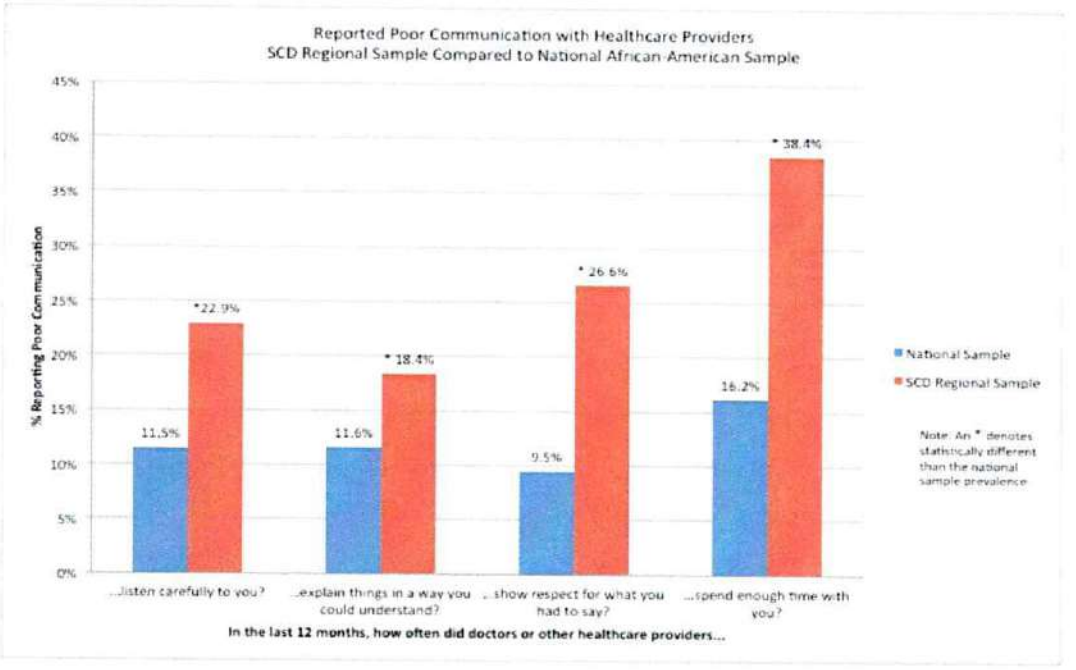
Background: Adults with sickle cell disease (SCD) report more problematic hospital experiences compared to adults generally, and it has been suggested that, because African-Americans report poorer communication with healthcare providers than white patients in the U.S., perhaps the predominantly African-American race of SCD patients explains the problematic interpersonal experiences with healthcare providers.

Objectives: Our aim was to compare reports of poor communication with healthcare providers between a sample of SCD patients and a national sample of African-American patients.

Methods: We collected data on patient ratings of communication quality among adults with SCD participating in the Improving Patient Outcomes with Respect and Trust (IMPORT) Study. The primary dependent variables used for this analysis were patient responses to the Provider Communication subscale of the Consumer Assessment of Healthcare Plans and Systems (CAHPS) survey, which assessed the extent to which patients believed that over the prior 12 months, their doctors or other healthcare providers listened carefully to them, explained things clearly to them, showed respect for what they had to say; and spent enough time with them. Response options were "never", "sometimes", "usually", and "always", with responses of "never" or "sometimes" being used to indicate "poor communication". We compared the SCD sample reports to national estimates of poor communication as reported by African Americans in the Agency for Healthcare Research and Quality's (AHRQ) 2011 National Healthcare Disparities Report, and made publically available through AHRQs' online query system. Binomial tests (2-sided) were used to compare each item. This comparison was conducted on the entire adult (age 18 years and older) SCD sample of our cohort.

Results: 271 SCD patients met our inclusion criteria. The SCD sample reported poor communication more frequently than the national African-American sample for all 4 of the items assessed. The specific levels of poor communication reported for each item are as follows: Listening (22.9% vs. 11.5%, $p < 0.0001$); Explaining (18.4% vs. 11.6%, $p = 0.0009$); Showing Respect (26.6% vs. 9.5%, $p < 0.0001$); and Spending Enough Time (38.4% vs. 16.2%, $p < 0.0001$).

Conclusion: A sample of adults with SCD reported worse communication with their healthcare providers when compared to a national sample of African-American patients. This suggests that the predominantly African-American race of SCD patients in the U.S. does not completely explain the higher rates of problematic interpersonal experiences frequently reported by African-American SCD patients. Other factors, possibly those that are specific to having SCD or the nature of the pain caused by SCD, must also contribute to these problems in healthcare quality, and should be targeted in efforts aimed at improving the quality of care for this population.


Reported Poor Communication with Healthcare Providers
SCD Regional Sample Compared to National African-American Sample
% Reporting Poor Communication
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
11.5%
*22.9%
11.6%
*18.4%
9.5%
*26.6%
16.2%
*38.4%
...listen carefully to you?
...explain things in a way you could understand?
... show respect for what you had to say?
...spend enough time with you?
In the last 12 months, how often did doctors or other healthcare providers...
National Sample
SCD Regional Sample
Note: An * denotes statistically different than the national sample prevalence

374

POPULATION-BASED SURVEILLANCE FOR SICKLE CELL DISEASE: PAST, PRESENT, FUTURE

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Background: In February 2010, the two-year Registry and Surveillance for Hemoglobinopathies (RuSH) pilot project began as a collaboration between seven State Health Departments, the National Heart, Lung, and Blood Institute/National Institutes of Health, and the Division of Blood Disorders/Centers for Disease Control and Prevention. A three-tiered case definition was developed to identify people with sickle cell disease (SCD) and data collection methods were established to obtain health status and services utilization of affected people, using multiple data sources including newborn screening, vital statistics, hospital discharge, Medicaid claims, and clinical records from hemoglobinopathy specialty care centers/clinics.

Objectives: The primary RuSH objectives were to determine the incidence and prevalence of sickle cell disease and to describe the demographic characteristics and geographic distribution of the affected population. The secondary objective was to describe pregnancy outcomes, health care utilization, mortality rates, and causes of mortality in populations with hemoglobinopathies.

Methods: The RuSH case definition employed both laboratory screening results and ICD codes to identify people with SCD in pre-existing data sources. After data were collected from each of the individual data sources, the information was linked and deduplicated to produce final, state-specific data sets. The information in the data sets was de-identified and sent to CDC for cleaning, storage, and analysis.

Results: The seven states were able to count and describe the residents in their state fitting the RuSH case definition. They will utilize this information to educate patients, families, health care providers, and policy makers about the population, which will bring about abetter understanding of the healthcare needs of people with SCD.

Conclusion: The novel methods that were developed for RuSH need to be evaluated and validated. The information gathered needs to be analyzed and shared with others. The knowledge gained needs to be used to make a positive impact in the field of SCD. CDC funded a new project in 2012, Public Health Research, Epidemiology, and Surveillance for Hemoglobinopathies (PHRESH), to address these issues.

PATIENTS WELCOME THE SICKLE CELL DISEASE MOBILE APPLICATION TO RECORD HEALTH CONTEXTS VIA TECHNOLOGY

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Background: Patients with sickle cell disease (SCD) characteristically have recurrent painful crises, in addition to chronic daily pain. The use of mobile technology has increased and provides a unique opportunity to provide an electronic method to record momentary health contexts for patients with SCD.

Objective: To determine the receptiveness of patients with SCD to technology and a mobile application designed specifically for SCD.

Research Design: Cross-sectional survey. Participants. A total of 115 patients followed at a Comprehensive Sickle Cell Center with diagnosis of a hemoglobinopathy.

Measurements: Phase I included 100 patients who completed a survey inquiring about receptiveness to technology and use of a mobile application to self-manage and communicate with providers. Phase II included 15 additional patients who tested a mobile application designed specifically for SCD and completed a questionnaire on its usability and utility.

Main Results:. Phase I: 84% of participants reported owning a computer device, i.e. desktops, laptops, tablets, or iPads, and 92% had a mobile phone. For all age and education groups, texting and emailing were preferred over social media ($p<0.0001$). There were no statistical differences in the comfort level in communicating with providers by education groups, except that, for communicating with providers by computers, those with higher academic education level showed higher comfort level ($p=0.01$). Utilizing a questionnaire, phase II found patients with SCD believed that the mobile app was easy to; useful to track pain; useful to help one communicate with his/her providers; and useful as a mobile app to help manage one's health.

Conclusion: We found mobile technology available to over 90% of patients with SCD. In addition, patients were highly comfortable and receptive using it for healthcare management. The patients viewed our SCD specific mobile app to be a very valuable tool for recording symptoms, for health management, and for communicating with providers.

NEURODEVELOPMENTAL OUTCOMES OF THE BABY HUG TRIAL: SAFETY AND BENEFITS OF HYDROXYUREA

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Background: Neurocognitive function may be compromised from infancy through adulthood in patients with sickle cell anemia (SCA).1 2 We recently reported that infants and toddlers with SCA between age 9 to 18 months have diminished behavioral regulation and adaptive function with older age, with trends toward inverse correlation with higher cerebral blood flow velocity and higher reticulocyte count.1 Hydroxyurea (HU) has been shown to be effective in reducing clinical events in infants and toddlers with SCA,3 but has not yet been shown to be effective at preventing neurodevelopmental dysfunction.

Objectives: As part of the BABY HUG Trial (Clinical Trials.gov #NCT00006400), we investigated whether hydroxyurea was safe in terms of neurodevelopmental outcomes, and whether it might provide protection against neurocognitive impairment in the early years of life.

Methods: 193 infants and toddlers with SCA, between ages 9 and 18 months at study entry, were enrolled in the BABY HUG Trial, a double-blind, placebo controlled, randomized clinical trial of hydroxyurea. Informed consent was obtained and participants were screened for study eligibility. Infants with a Mental Developmental Index (MDI) < 70 at study entry were excluded from participation. Participants were randomized to receive a fixed dose (20mg/kg/d) of liquid hydroxyurea (N=96) or placebo (N=97) over a 24-month period. There were no significant differences between the groups on any demographic or disease-related variables at study entry. Participants were administered the Bayley Scales of Infant Development, 2nd Edition (BSID-II) and the Vineland Adaptive Behavioral Scales (VABS) at study entry, 12 months, and 24 months. Transcranial Doppler ultrasonography (TCD) was used to measure cerebral blood flow velocities. Hematologic variables (hemoglobin, reticulocyte count) were also collected but not included in this analysis. 166 toddlers completed the study (HU N=85, Placebo N=81). Fisher's exact test or Chi square test was used as appropriate.

Results: At study entry, 15 (15.6%) infants on the hydroxyurea arm had a Mental Developmental Index (MDI) score on the BSID-II in the below- average range (70-84), compared with 10 (10.3%) on the placebo arm. These were not significantly different (p=.272). At study exit (24 months), 14 (16.5%) on the hydroxyurea arm were in the below-average range (70-84), not significantly different from baseline. However, 18 (22.5%) on the placebo arm fell between 70-84 and 5 (6.3%) below 70. This represented a significant increase in the overall number with scores <85 (23 total), and most concerning, 5 dropped into the impaired range from entry to exit (Table 1). The difference in numbers of children with MDI<85 between the two study arms was statistically significant (p=0.029).

Conclusions: Hydroxyurea in infants and toddlers with SCA does not result in neurodevelopmental impairment over a 24-month treatment period. On the contrary, the significant difference in the number of children who had below average/impaired neurodevelopmental function on the placebo arm compared with those on the hydroxyurea

arm strongly suggests that the use of hydroxyurea in very young children may provide a significant level of protection from neurodevelopmental risk over the first three years of life. Thus, an additional benefit of hydroxyurea for infants and toddlers with SCA may be protection against neurocognitive impairment.

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Table 1. Number and percentage of patients on hydroxyurea (HU) and placebo arms in impaired, below average, or average or above categories on BSID-II MDI at study entry and study exit.

	Entry[a]		Exit[b]	
BSID-II MDI	HU	Placebo	HU	Placebo
<70 (Impaired)	0	0	0	5 (6%)
70-84 (Below Average)	15 (16%)	10 (10%)	14 (16%)	18 (22%)
>85 (Average or above)	81 (84%)	87 (90%)	71 (84%)	57 (71%)

[a]Chi-square test, p=0.272
[b]Fisher's exact test, p=.029 *(Combining <70 and 70-84 rows)*

428

IN VITRO HUMAN AND PRECLINICAL ANIMAL STUDIES OF ADENOSINE-BASED THERAPIES IN SICKLE CELL DISEASE

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Introduction: Sickle cell disease (SCD) is a debilitating hemolytic disorder with high morbidity and mortality affecting millions of individuals worldwide. Although SCD was first identified a century ago, we still lack effective mechanism-based safe therapies to treat this disease. Thus, identification of specific molecules triggering sickling, the central pathogenic process of the disease, is extremely important to advance our understanding of the molecular basis for the pathogenesis of SCD and to develop novel therapeutics. Using metabolomic profiling, we discovered that adenosine was highly elevated in the blood of SCD Berkeley transgenic mice and human1. Moreover, we demonstrated that elevated adenosine signaling via adenosine receptor A2B (ADORA2BR) contributes to sickling by induction of 2,3-bisphosphoglycerate (2,3-BPG), deoxygenation. Here we extend this finding to preclinical studies to assess adenosine-based therapy on morbidity and mortality in SCD.

Methods and Results: First, we assessed the efficacy of lowering adenosine concentrations by chronic treatment with polyethylene glycol-modified adenosine deaminase (PEG-ADA), a safe drug being used to treat ADA-deficient human for thirty years, in SCD Berkeley mice. After 8 week treatment, we found that sickling, hemolysis and multiple tissue damage were significantly reduced in the mice. Additionally, multiple organ dysfunctions including priapism, penile fibrosis and renal dysfunctions were significantly ameliorated. Subsequently, we found that PEG-ADA enzyme treatment significantly prevented hypoxia/reoxygenation enhanced further elevated adenosine levels compared to steady state in SCD mice and that PEG-ADA treatment successfully inhibited hypoxia/reoxygenation-induced acute sickle crisis, including remarkably increased sickling, hemolysis and pulmonary inflammation in these mice. Finally, we found that PEG-ADA treatment substantially prolonged life span of SCD mice and increased survival rate of SCD under hypoxia/reoxygenation-induced acute sickle crisis. Similarly, we further demonstrated that ADORA2B antagonists (PSB1115) successfully reduced sickling, hemolysis, tissue damage and dysfunction under steady state and prevented hypoxia/reoxygenation-induced acute sickle crisis and increased survival rate. More importantly, no obvious adverse effects of PEG-ADA enzyme therapy and ADORA2B antagonist treatment were observed in these mice under acute sickle crisis and chronic state.

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Conclusion and Significance: Overall, our findings reveal that lowering adenosine levels by PEG-ADA enzyme therapy and interfering ADORA2B signaling by specific ADORA2BR antagonists can treat and prevent sickling, progression to multiple life-threatening complications and prolong life span of SCD mice. Thus, our preclinical studies provide strong evidence that PEG-ADA and ADORA2B antagonist are likely novel and safe mechanism-based therapies for humans with SCD. We believe our animal studies are important and set up a strong foundation for future clinical studies in human suffering from SCD.

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382

Prasugrel in Children with Sickle Cell Disease: Pharmacokinetic and Pharmacodynamic Characteristics from an Open-Label, Adaptive-Design, Dose-Ranging Study

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Background: There are few approved treatments for children with sickle cell disease (SCD) who experience painful vaso-occlusive crises (VOC), and evidence suggests a pathophysiologic role for platelets. Thrombocytosis is common and markers of platelet activation are elevated in both children and adults with SCD. This activation may be mediated by adenosine diphosphate (ADP) released following hemolysis of sickled erythrocytes. Accordingly, platelets are a rational therapeutic target to explore with the aim to reduce the frequency and severity of VOC. Therefore, we studied prasugrel (pras), an irreversible P2Y12 platelet ADP-receptor antagonist that inhibits platelet activation and aggregation, in children with SCD.

Objectives: The primary objective was to identify doses of pras that produced a 30–50% inhibition of platelet reactivity for use in a pediatric phase 3 study of efficacy.

Methods: We conducted a phase 2, open-label, multi-center, adaptive-design, dose-ranging, pharmacokinetic (PK) and pharmacodynamic (PD) study of pras in children with SCD. Males and females 2–17 years of age (inclusive) with SCD (HbSS and HbSβ0-thalassemia genotypes) were eligible. To improve safety during dose identification, treatment was initiated with single pras doses expected to have no effect before dosage was increased. Patients (pts) were to receive up to 3 single doses of pras with the second and third doses being administered 14±4 days after the previous dose. Doses of pras were adjusted based on the PD response to previous doses among all pts. Age, body weight, and sex were considered during dose assignment to provide balance across the dose range.

Platelet inhibition was evaluated by the VerifyNow® P2Y12 (VN) and vasodilator-associated simulated phosphoprotein (VASP) assays at screening and 4 hours after each single pras dose. Venous blood samples were collected 0.5, 1, 1.5, 2, and 4 hr post-dose for PK analysis of pras's active metabolite allowing calculation of the area under the concentration-time curve (AUC). The PK/PD analyses were designed to assess the relationship between pras active metabolite AUC and platelet inhibition. Spearman correlation statistics were used to assess the relationship between dose and PD parameters.

Results: A total of 24 pts, ranging in age from 4–17 years of age, received at least one dose of pras. The mean age was 11.0 years; 58.3% were female; 87.5% had HbSS and 12.5% had HbSβ0-thalassemia. Body weight ranged from 14.4–80.1 kg. Pts received single doses of pras ranging from 0.03–0.60 mg/kg. Single-dose

range of 0.30–0.50 mg/kg and 0.40–0.50 mg/kg produced 30–50% mean inhibition of platelet reactivity as measured by the VN and VASP assays, respectively. Above 0.25 mg/kg, PD response increased with dose. A single 0.60 mg/kg dose produced >50% mean inhibition by both VN and VASP assays.

In general, higher doses resulted in increased exposure to pras active metabolite. Increased variability in exposure and in PD response was seen at higher doses. The PD results demonstrate significant correlations between dose and inhibition of platelet reactivity. Pras appeared to be safe and well tolerated in this small patient sample. Three serious adverse events occurred in 2 pts; none of which were considered possibly related to pras. No hemorrhagic events were observed, and no subjects discontinued participation due to an adverse event.

Conclusion: These data, in part, helped to determine the appropriate pras dosing for the second part of this study that is designed to target steady-state platelet inhibition of 30-50% during daily maintenance dosing. It is anticipated that the current findings will improve the design of a future efficacy studies investigating the reduction of VOC in children with SCD.

371

GENOMICS AND THE "INDIVIDUALIZED" APPROACH TO SICKLE CELL ANEMIA

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Paramount among our goals as caregivers is the ability to individualize treatment providing the most good with the least harm. Sickle cell anemia is associated with unusual clinical heterogeneity for a Mendelian disorder. Understanding the genetics underlying the heritable subphenotypes of sickle cell anemia would be prognostically useful, could inform personalized therapeutics, and might help the discovery of new "druggable" pathophysiologic targets. Advances in genomics, bioinformatics and cell biology are being applied to the study of sickle cell disease. Among the possible applications of these technologies is the use of pharmacogenomics to predict responses to different drugs, including fetal hemoglobin inducers, estimating drug response in vitro using patient-derived cells, and enhanced early diagnosis that predicts disease complications like stroke and vasculopathy.

POSTERS

265

DISEASE-SPECIFIC KNOWLEDGE VS. FUNCTIONAL HEALTH LITERACY AMONG CAREGIVERS OF CHILDREN WITH SICKLE CELL: IS THERE A DIFFERENCE?

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Background: Recent data suggests 20–30% of parents of young children in the United States have low health literacy. Caregiver health literacy has implications for recognizing illness and can affect child health outcome. Disease-specific knowledge (DSK) is an often overlooked, yet easily obtainable, measure of caregiver understanding of chronic childhood illness like sickle cell disease and may be as important as health literacy in predicting health outcome.

Objectives: We used the Short Test of Functional Health Literacy in Adults (S-TOFHLA), a 36-item validated measure of functional health literacy (FHL) that can be administered in a short period of time, to identify caregivers of children with sickle cell disease that had inadequate or marginal FHL. We further sought to identify caregivers' DSK deficits by administering our own unique questionnaire. We then determined if results from either affected emergency department visits and hospitalizations.

Methods: We conducted a cross-sectional study of caregiver-child dyads from a sample of children aged 12 months to 18 years that presented to routine visits in a comprehensive sickle cell clinic at an urban teaching hospital. Caregivers were administered the S-TOFHLA and also given a 22-item questionnaire assessing both demographic data and also qualitative and quantitative measures of DSK.

Results: A total of n=85 caregiver-child dyads were enrolled in the study during one year of recruitment. On the S-TOFHLA, only 3/85 caregivers (3.5%) had inadequate or marginal FHL. Of all 85 caregivers, 82% identified themselves as mothers to the patient, while 6% were fathers. Nearly 97% graduated from high school. We selected 12 unique items assessing DSK on our questionnaire and gave each item a value of 1 point. Questions tested caregiver knowledge of sickle cell genetics, clinical manifestations of the disease, sickle cell health numeracy, and their ability to appropriately respond to theoretical clinical scenarios involving their child. For example, 79% of caregivers knew sickle cell was associated with anemia and 74% did not think there was a cure for sickle cell disease. Caregivers were divided based on correct answers to a total of 12 items using a median split, with 49/85 caregivers (n1) scoring between 9–12 and 36/85 caregivers (n2) scoring 8 or less. Although there was no difference in FHL outcome between the two groups, those in n1 scored slightly higher on the 36-item S-TOFHLA than those in n2 (average 33/36 vs. 34/36, p=0.01). Group n1 was more likely to have attended college (p=0.03) and children of caregivers in this group were younger (average age 9 years vs. 12 years, p=0.008). Children of caregivers in n1 were nearly twice as likely to visit the ED than those in n2 (p<0.01). Rates of hospitalizations were similar between the two groups.

Conclusion: Only 3.5% of caregivers of children with sickle cell disease had inadequate or marginal FHL, while there was a significant difference of caregiver DSK. Our data suggests caregivers with more DSK were more educated and more likely to identify illness in their children. Knowledge-based questionnaires for chronic childhood illnesses such as sickle cell disease may be more useful than standard measurements of FHL to assess caregivers' ability to identify and react to illness.

EMERGENCY PROVIDER ATTITUDES TOWARDS SICKLE CELL PATIENTS

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Background: Patients with sickle cell disease (SCD) often present to the ED for treatment during a vaso-occlusive crisis and have reported experiencing negative attitudes from providers.

Objective: We sought to validate a survey that measures attitudes towards SCD patients in a sample of ED providers, and compare differences in attitude scores between provider types.

Methods: An attitudes survey, previously validated in a sample of medical providers, was administered to a convenience sample of ED providers at two North Carolina EDs in Nov and Dec 2011. The survey assessed provider perception of and satisfaction in caring for SCD patients and also gathered responses to the Medical Condition Regard Scale (MCRS). Principal factor analysis was performed to identify underlying subscales of the survey. Subscales, constructed by summing items with factor loadings of +0.40 or greater, were linear transformed onto a 0-100 scale. Provider types were compared using analysis of covariance, adjusting for years of practice. To assess construct validity of the subscales in the ED setting, Partial Spearman correlations were conducted to examine the relation between the subscales and MCRS total scores.

Results: The factor structure, based on 200 surveys, identified 3 subscales: Negative attitudes, Uneasiness with care, and Positive attitudes. Cronbach's alphas for the subscales and MCRS were 0.93, 0.83, 0.82, and 0.86, respectively. Means (SD) for the Negative, Uneasiness, and Positive subscales and MCRS were 61.5 (20.3), 66.1 (17.1), 41.2 (17.8), and 42.2 (SD=8.9). Compared to physicians (n=88), nurses (n=111) reported significantly higher Negative scores (nurses M=65.8, SD=22.4; physicians M=56.0, SD=15.8, p=.0003) and lower Uneasiness scores (nurses M=62.0, SD=17.0; physicians M=71.5, SD=15.9, p<.0001). Scores did not differ on the Positive scale. Nurses had significantly lower MCRS scores (M=41.2, SD=9.2) than physicians (M=43.6, SD=8.2, p=.0108). MCRS scores were significantly correlated with the subscale scores (Negative rs -0.64; Uneasiness rs 0.23; Positive rs .61, p <.002).

Conclusions: The attitudes survey tool provides a valid measure of ED provider attitudes towards SCD patients. Nurses have higher negative attitudes scores, lower uneasiness with care scores, and lower medical condition regard scores than physicians.

URINE SCREENING FOR BIOMARKERS OF ACUTE AND CHRONIC KIDNEY INJURY IN CHILDREN AND ADULTS WITH SICKLE CELL ANEMIA WITH AND WITHOUT ALBUMINURIA

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Background: Kidney injury is common among individuals with sickle cell anemia (SCA, HbSS). Screening for albuminuria is usually performed to detect patients with early kidney dysfunction. Urine biomarkers of kidney injury (KI) have been seldom studied in SCA. Objectives: To evaluate KI markers in individuals with SCA and to correlate those markers to the presence of albuminuria.

Methods: We measured KI biomarkers in random urine samples of 38 children and adults with SCA with or without albuminuria in a cross-sectional analysis. The presence of albuminuria was further confirmed with a second sample. Kidney injury molecule 1 (KIM-1), N-acetyl-ß-D-glucosaminidase (NAG), endothelin-1 (ET-1), and transforming growth factor-ß1 (TGF ß1) were measured by colorimetric assays. All results were normalized by urine creatinine. Prussian blue was used to identify intracellular hemosiderin (hemosiderin laden macrophages) in urine specimens. Kidney function was assessed by serum creatinine and serum cystatin C. Albuminuria was associated to the urine biomarkers by Pearson and Spearman correlation coefficients. Differences between the albuminuria (yes, no) groups were assessed by using t-test.

Results: Nineteen patients with albuminuria (mean urine albumin/creatinine 527.14±1070 mg/g, range 38.3-4190) and 19 patients without albuminuria (mean urine albumin/creatinine 15.93 ±5.17 mg/g, range 7.9-28.4) were studied; age range for the whole group 11-48 years of age; 47% males. Patients with albuminuria were older, had lower mean hematocrit, were more likely positive for urine hemosiderin, and had significantly higher KIM-1 and NAG to urine creatinine ratios. There was no statistical difference for hemoglobin, reticulocyte count or LDH. None of the patients had advanced kidney disease. Urine KIM-1 and NAG did not correlate to either serum creatinine or serum cystatin C. Urine hemosiderin strongly correlated to a higher LDH (P<0.001).

Conclusion: Despite all subjects having normal serum creatinine and serum cystatin C, individuals of SCA demonstrated the presence of KI biomarkers. NAG, a urine marker for proximal tubular injury, and KIM-1, an acute KI marker, correlated with the presence of albuminuria. The presence of urine hemosiderin, indicating hemolysis, also was associated with albuminuria. Further monitoring may help establish whether these biomarkers will be predictive of the onset of albuminuria in those patients who are negative now, or more importantly whether they will be predictive of future decline in kidney function

Parameter, units	Albuminuria (N=19) Mean±SD, range	No albuminuria (N=19) Mean±SD, range	*P* value
Age, years	23.3±10.2 (14-48)	16.2±3.8 (11-26)	**0.009**
Hct, %	24.0±3.1 (19.4-28.8)	26.2±3.3 (22.1-35.3)	**0.04**
Serum creatinine, mg dL	0.59±0.27 (0.3-1.5)	0.50±0.11 (0.4-0.7)	0.17
Serum cystatin C, mg L	0.69±0.19 (0.5-1.06)	0.68±0.14 (0.5-1.10)	0.88
KIM-1 urine creat, ng mg	0.93±0.73 (0.01-3.03)	0.35±0.31 (0-1.35)	**0.004**
NAG urine creat, unit g	10.33±8.25 (1.86-24.75)	4.26±2.97 (1.08-12.85)	**0.006**
ET-1 urine creat, pg mmol	3.32±2.96 (0.90-12.81)	2.76±1.94 (0.46-6.95)	0.49
TGF ß1 urine creat, ng g	0.22±0.87 (0-3.82)	0.01±0.02 (0-0.06)	0.32
Urine hemosiderin	12/19 (63%)	3/17 (18%)	**0.008**

HYDROXYUREA DECISION-MAKING DETERMINANTS IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE

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Background: Hydroxyurea (HU) treatment is associated with decreased pain crises and hospitalizations in children and adolescents with sickle cell disease (SCD).1 Results from a phase III study of HU in infants (BABY HUG) also indicate improvements in the number of pain, acute chest syndrome events, hospitalizations, and transfusions.2 Despite these benefits, HU is underutilized at many institutions. Potential barriers to medication use have included lack of knowledge about the medication and its effectiveness, poor compliance with required frequent clinic visits, and variability in prescribing patterns across institutions.1,3 However, little is known about whether sociodemographic and clinical factors are associated with a family's decision to initiate HU use.

Objective: Examine the associations between sociodemographic and clinical factors and HU acceptance or refusal among children and adolescents with SCD who were offered HU.

Methods: Participants included in the retrospective chart review met the following criteria: 1) HbSS or HbSB0-thalassemia genotype, 2) aged 2-18 years, and 3) been offered HU treatment. Participants were excluded if they were receiving chronic blood transfusion therapy or were never offered HU. The following socidemographic factors were examined: patient and caregiver age and gender, caregiver marital status, education, employment, insurance type, religion/spirituality, and number of patient's siblings with SCD. The following clinical factors were examined: genotype, hemoglobin concentration, reticulocyte percentage, and previous history of hospitalization, transfusion, pain, and acute chest syndrome episodes. We examined differences in sociodemographic and clinical factors between the two groups using chi-square tests and ANOVAs. The variables that yielded p-values < .10 significance were included in the multinomial logistic regression.

Results: Of 228 patients who were offered HU, 31 (14%) were not included because they did not have pre-HU medical information available or they had not initiated HU at the time of the medical record review. The total number of patients included in the analyses was 197 (85% HbSS; 50% female). Participants were classified into two groups: accepted HU (N=171; 87%) or refused HU (N=26; 13%). Univariate analyses yielded one sociodemographic variable (family with other children with SCD) and two medical variables (hospitalization history over the past two years and ACS event history over the past two years) that were significant. These three variables were entered into a multivariate model with the binary dependent variable accept HU or refuse HU. Of the three predictors, being in a family with other children with SCD was significant ($p < .05$). These families were 9.25 times more likely to accept HU compared to families without other children with SCD.

Conclusion: Our results show that families with more than one child with SCD are more likely to decide to initiate HU. At this institution, the large majority of patients (87%) offered HU accepted HU treatment. However, the relatively small number who declined HU limited the potential for finding significant differences between the two groups. A multi-site study potentially would yield more variance and significant findings. Future research should involve interviewing families about their specific reasons for accepting or declining HU and examining patient-provider communication when offering HU in order to provide tailored discussions about HU with families.

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DISTANCE LEARNING-TEACHING PROCESS AMONG PRIMARY HEALTH CARE PROFESSIONALS IN THE STATE OF MINAS GERAIS, BRAZIL

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Introduction: The incidence of Sickle Cell Disease (SCD) in the State of Minas Gerais, Brazil, is 1:1,400 newborns1. The status of SCD as a public health issue and the lack of trained health professionals to provide health care to people with SCD prompted CEHMOB-MG (Educational and Supportive Center for Hemoglobinopathies), supported by NUPAD (Center for Newborn Screening and Genetic Diagnosis), and the Hemominas Foundation to develop a Continuing Education Program in 2010. With the support of the Brazilian Ministry of Health, the Minas Gerais State Department of Health, and Municipal Departments of Health the program, entitled "Sickle Cell Disease: Care Guidance for Primary Health Assistance", aims at training health care professionals to provide sickle cell disease-specific assistance and thus better integrate it with the regular activities done at the primary care centers of the Brazilian Single Health System (SUS).

Objective: To describe the process of training primary health care professionals to follow up people with sickle cell diseases in compliance with SUS principles and focusing on holistic care and establishment of a network comprising professionals capable of replicating knowledge.

Method: The distance education course used the Moodle platform to train primary health care professionals building on a perspective of shared construction of knowledge. The classes focused on discussions of case studies in interactive forums with the participation of leading professionals and hematologists (monitors), as well as multidisciplinary teams of the health care centers. The course consisted of five modules distributed within 90 hours: 1) Health surveillance of children with SCD in the scope of the primary health center and family health strategy (PHC/FHS); 2) Health surveillance aimed at adolescents and adults with SCD in the scope of PCH/FHS; 3) approach to acute events in the scope of PCH/FHS; 4) the attitude of the PCH/FHS professionals towards the patients with sickle trait and other hemoglobinopathies; and 5) a final activity consisting of elaborating strategies to replicate knowledge on SCD in the outpatient units.

Results: The program trained 14 groups from 2010 through 2012, each group with 32 professionals in average. In total 456 professionals were trained as future facilitators of other professionals in 85 municipalities: 74 medical doctors, 319 nurses, 15 social workers, 7 dentists, 7 physiotherapists, 12 nutritionists, 8 psychologists, 7 pharmacists, 3 speech therapists, and others (4). These professionals are scattered over 85 municipalities. The replicating processes are in full operation in 6 municipalities and in high gear in 79 municipalities. Approximately 4,527 patients live in the municipalities with support from health professionals trained within the scope of the program herein described.

Conclusion: The distance learning-teaching process has contributed to awakening reflection, criticism and creativity in health professionals so they can support changes in the practices of promotion and education for SCD. The model adopted by the program has proved to be an effective tool to train professionals aiming at providing holistic care to people with sickle cell disease.

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PERCEPTIONS OF ADOLESCENTS AND YOUNG ADULTS REGARDING SCHOOL AND ENVIRONMENTAL ISSUES RELATED TO SICKLE CELL DISEASE

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Background: Pain is the hallmark of sickle cell disease. While research has focused on clinical events and health care utilization in relation to pain, little is known about the impact of pain on lives of adolescents and young adults. Further, research in order to be relevant to the patients must focus, not only on pain while in the hospital, but also during the course of their daily lives. Since patients in this age group spend much of their lives in school the study of patient reported concerns about the impact of pain in relation to school is crucial to the design of therapeutic interventions in adolescents and young adults with sickle cell disease.

Objectives: The purpose of this study was to explore the ways in which adolescents and young adults perceived pain and pain management in relation to functioning while at school.

Methods: We conducted a one year study of an electronic pain intensity dairy for adolescents and young adults with SCD. Participants then participated in an audio-tape recorded qualitative focus group interview. Data were analyzed for themes. Identified themes were validated with individual interviews of additional study participants.

Results: Twenty-two patients participated in this yearlong pain intensity diary study with 77% attending high school during a portion of this time. In the qualitative interviews two primary themes were identified in relation to SCD and pain in the school setting. The first theme indicated a lack of knowledge about sickle cell disease among nurses, teachers, and classmates. One participant cited an instance of being offered ice by nurses for a nose bleed. Students lacked accessibility to pain medications on days a nurse was not present in the building. Participants described how classmates were unaware of SCD, with this condition meriting only a single paragraph in their text book as compared to a 4 page discussion of diabetes. Participants were concerned about stigmatization by others asking if "we can catch it," or hearing statements such as "oh, that's what the guy from the Steelers team has." Questions asked of the research team included "why there aren't billboards and commercials to teach people about SCD" noting that everyone has at least heard the words cancer and diabetes. The second theme to be identified was the environmental impact of school on pain. Participants discussed their inability to bring opened containers of water into the school and the limited time between classes to access the water fountain or bathroom. The physical challenge and inflexibility of gym class was identified as problematic. Even with heated pools the room temperature was too cool causing instant chilling upon emergence from swimming. Students were not forewarned about going outside in 60° temperatures in gym shorts and a t-shirt, often being told that the temperature would not affect their disease. Some participants stated they were required to climb as many as 7 flights of stairs in less than 5 minutes between classes with one participant citing a resultant pain episode in which no one knew how to help her. Participants described having phones taken away or receiving reprimands secondary to contacting the sickle cell team when pain increased during school hours. The need to change position, including standing and stretching, during class was frowned upon and often forbidden by teachers. Students asked about the possibility of developing a program of education for school staff because school staff cannot "visibly see anything wrong" and questioned the motives of students who use the "excuse" of SCD when unable to participate in various activities.

Conclusions: Adolescent and young adults with sickle cell disease have significant concerns regarding the impact of pain on functioning in school. Further research is required to improve outcomes in school functioning of students with SCD. Additionally, research is needed to better understand the impact of the educational system and environmental issues on the students' abilities to manage SCD.

SCHOOL ETHOS: A PLAUSIBLE EXPLANATION OF REPORTED SCHOOL EXPERIENCES OF SICKLE CELL IN ENGLAND?

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Background: To understand the how the ethos of a school impacts on the school experience of young people with sickle cell disease (SCD).

Methods: A multi-method study using questionnaires (n=569) and taped qualitative interviews (n=40) with young people living with SCD in England. A questionnaire survey of schools (n=206) and case studies of young people with SCD (n=10).

Results: Reports of young people suggest the fact that either teachers or pupils know they have sickle cell makes no overall significant improvement to their treatment in terms of being supported, through preventive and precautionary measures, to ensure good health at school. Young people were divided as to whether it was better or not to disclose their illness to teachers or to their school peers. The results of the interviews suggest school ethos helps in three ways. First, school absences do not appear linked to factors such as number of painful crises or having had a stroke. School ethos may be judged from the institutional response to a young person with sickle cell missing lessons. These ranged from no action to arranging regular early evening catch-up sessions, with a teacher present to answer questions. Secondly, an institutional commitment to include young people in the full range of school activities appeared crucial to the experience of the young person at school. Thirdly, where reasonable adjustments were necessary to contribute to the well-being of the young person, these were much stronger where the school made the adjustment rather than drawing attention to the young person as different from their peers, something intensely disliked by the young people with sickle cell.

Conclusion: This study suggests that in order to understand what factors make for a good school experience, we need to look beyond simply "informing" teachers and look at t he overall school ethos.

Reference:

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352

Patient Perceptions of Treatment Options for Sickle Cell Disease: Transplant, Hydroxyurea & Gene Therapy

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Background: Currently, there only two treatment options for sickle cell disease (SCD), bone marrow transplant (BMT) from a matched sibling (which is curative) and hydroxyurea (HU). HU, if taken daily on a long term basis, increases fetal hemoglobin, which prevents sickling; however, these treatments are not being optimally utilized by patients. To date, there have been fewer than 350 bone marrow transplants performed for SCD patients worldwide due to the chemotherapy and immunological risks associated with the allogeneic (matched sibling) transplant procedure and the limitations of having a matched sibling donor (available to 10-15% of patients). In addition, daily adherence to HU remains a challenge. It is not well-tolerated by some patients, and may have unknown long-term oncogenic potential or increase the risk of infertility. Gene transfer of fetal hemoglobin into autologous bone marrow hematopoietic stem cells is currently being investigated as a treatment option for SCD. This would be a 'one-time' treatment and would not have the immunological toxicities associated with allotransplant. However, the knowledge, beliefs and acceptance of this potentially new therapeutic modality are unknown.

Objectives: The purpose of the study was to assess knowledge, cultural attitudes and beliefs about gene transfer therapy, HU and BMT in SCD, and gather information about educational needs regarding these treatments.

Methods: To more comprehensively explore patient perceptions of treatments, we utilized a multi-method approach including focus groups, surveys, and evaluation of educational materials. Of approximately 400 patients surveyed, 90% expressed in gene therapy and getting educational materials about it. Approximately, 50 patients with SCD who expressed interest in obtaining information and being contacted in the future on gene transfer therapy in the survey were contacted by letter and phone to participate in one of two focus groups. Patients between the ages of 18-30, the target population for early gene transfer therapy trials, were invited to the first focus group. For the second group, older patients (age 30-45) who have experienced more complications with SCD were invited to gain their perspective on these treatments. Participants completed quality of life and a medical decision-making survey during the two hour focus group, which was video- and audio-taped. Data from the first focus group was used to develop an educational brochure on gene transfer therapy. Patients attending a SCD adult consumer day event were invited to assess the brochure's usefulness, ease of understanding, and overall design.

Results: Thirty-two adults with Hb SS or Hb SβOThal participated in one of two focus groups: Group 1: N= 14; M age = 21.7 (SD=2.7); Group 2: N=12; M age = 42.8 (SD=12.2). Gender was approximately equal for both groups. Themes varied for each of the focus groups (by age), but the major themes across groups included: lack of understanding of current treatments; side-effects for all treatments are concerning; gene transfer therapy would be a viable treatment option; honest information about risks and benefits is important; explain basic laboratory therapy development. The presentation will include additional qualitative and contextual data including information on concerns about these treatments (see Table 1). The concerns and attitude towards gene therapy varied vastly between Group 1 versus Group 2. Eighteen participants evaluated the brochure (Mean age = 47.9; 72.2% Female). Overall, the brochurewas rated as well-liked: overall brochure (70.6%), layout (88.2%) and title (88.2%). Participants felt it was easy to understand (M= 8.83/10) and clearly explained the gene transfer therapy process (M=8.22/10).

Table 1. Ratings of Concerns About Gene Transfer Therapy

Ratings of Level of Concerns About the Risks of Gene Therapy Treatment (Scale of 0-10)[1]	Group 1 (N = 14) Mean Age = 21.7	Group 2 (N = 12) Mean Age = 42.8
Cancer later in Life	M = 6.43	M = 7.80
Leukemia	M = 6.36	M = 7.80
Problems with fertility	M = 6.36	M = 5.64

[1]Note: 0 = "Not at all" a concern - 10 = "Very Much" a concern

419

Pathological hemodynamic and inflammatory conditions in sickle cell disease regulate gelatinase and elastase mediated arterial remodeling: implications for co-morbid stroke development

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Background: Children suffering from sickle cell disease have an 11% chance of developing strokes, with the greatest risk as early as 3 to 5 years old. The elevated blood velocities that are highly correlative with stroke risk are thought to be a result of advanced remodeling of the arterial wall, similar to what is observed in other cardiovascular diseases, such as atherosclerosis; however, the underlying mechanisms that promote arterial remodeling in sickle cell disease have not been elucidated. One of the initiating factors of arterial remodeling in cardiovascular disease is exposure of the vascular endothelial cells to low wall shear stress and flow reversal, resulting in adhesion of peripheral blood mononuclear cells (PBMCs) and production of cysteine cathepsin proteases capable of degrading elastin and collagen within the arterial wall to promote atherosclerosis. Cathepsins K and V are two such proteases and are the most powerful mammalian collagenase and elastase, respectively. Previously, we have shown that under static conditions, cathepsin activity was increased in human aortic endothelial cells (ECs) in response to inflammatory conditions unique to sickle cell disease. Here, we expand this study utilize a cone-and-plate bioreactor capable of actuating either a unidirectional, high shear stress waveform, or a pro-remodeling waveform characterized by low wall shear stress and flow reversal. We will use this system to investigate the roles of shear stress on endothelial cell-PBMC co-cultures' expression and activation of cathepsin elastases and collagenases due to sickle cell disease inflammation.

Objective: The objective of this study is to test the hypothesis that pro-remodeling shear stress exacerbates cathepsin activity induced by TNFα and sickle PBMC-endothelial cell interactions.

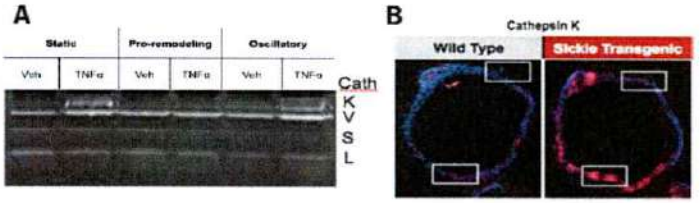

Figure 1: (A) Pro-remodeling shear stress induces cathepsin K activity independent of TNFα stimulation. (B) Mice with sickle cell disease have significantly higher expression of cathepsin K in regions of low wall shear stress compared to wild type animal.

Materials and Methods: Endothelial cells were stimulated with or without 10ng/mL TNFα, and co-cultured with PBMCs (500,000 cells/mL) isolated from people with (SS) or without (AA) or sickle cell disease. Co-cultures were maintained for 20 hours in static, unidirectional, or pro-remodeling shear stress conditions; cathepsin activities were quantified from cell lysates using multiplex cathepsin zymography technique developed by our lab. Additionally, aortas from sickle transgenic mice homozygous for the SS mutation or heterozygous (AS) littermate controls were isolated, and cathepsin activity was determined in tissue homogenates and by immunohistochemistry (IHC).

Results: Cathepsin zymography yields cleared bands of gelatinase activity on a dark Coomassie stained background, with increased intensity of the white bands corresponding to greater cathepsin activity present at that site of electrophoretic migration. It can be seen in Figure 1 that the pro-remodeling waveform is sufficient to induce cathepsin K activity, without exogenous TNFα stimulation; however, unidirectional shear stress inhibits TNFα induction of cathepsin activity. This finding was observed in vivo through IHC staining of cathepsin K in the lesser curvature of the aortic arch (low wall shear stress) compared to the greater curvature (high wall shear stress) of wild type and sickle transgenic mice. Additionally, sickle transgenic mice had overall increased expression of cathepsin K (Fig1B) and cathepsin V.

Conclusions: Together, these results suggest that the circulatory milieu of sickle cell disease, in conjunction with disturbed hemodynamics, uniquely stimulate cathepsin K and V proteolytic activity in endothelial cells both in vitro and in vivo. Elucidating the fundamental inflammatory and biomechanical mechanisms governing arterial remodeling in sickle cell disease will identify new therapeutic targets to treat children at risk for stroke.

426

UTILIZATION OF SOCIAL MEDIAS AND ITS IMPACT ON PATIENT AND PROVIDER SICKLE CELL EDUCATION

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Introduction: Social media has increased exponentially over the last decade with well over 500 million members on Facebook and 140 million on Twitter (Clemmitt, 2010). It was designed to promote and share a variety of information quickly including photos, health information, news reports and events. Social networking is widely used by teens and adults. Recent statistics show that half of Americans between 50-64 years of age and a quarter of them 65 and older now use social networking sites (Clemmitt, 2010). Social media sites are also used by many businesses and organizations. Since social media is proving to be an excellent approach to send information quickly to a large audience, we launched our health programs through this medium. Social media allows us to disperse health information from the Improving Health Outcome in Medical Education in Sickle cell Disease (iHOMES) network in a unique way to our patients, family and friends to improve sickle cell disease education in Maryland.

Objectives:

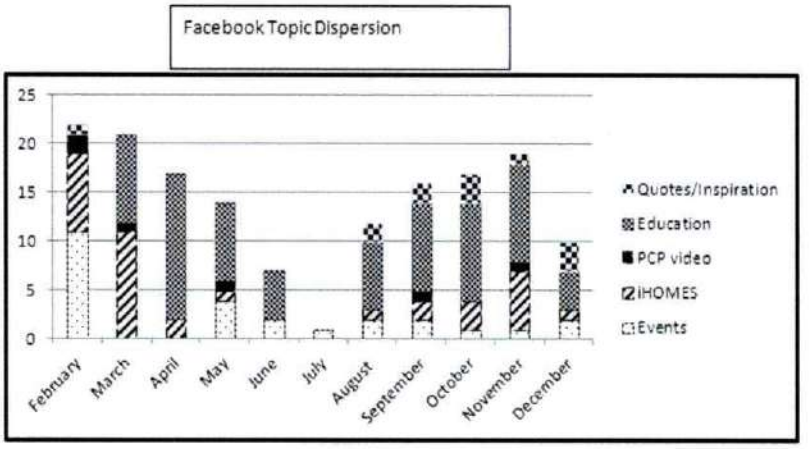
1) Promote our services by advertising our free dental and transportation services
2) Provide education on the management of sickle cell disease
3) To inspire sickle cell patients to live a healthy and fulfilling life
4) Educate patients on the importance of a primary care provider and to connect them with a provider that is knowledgeable about the disease
5) Promote upcoming sickle cell events to help increase awareness

Methods: Facebook, Twitter and YouTube accounts were created to educate subscribers about sickle cell disease and to promote services for people with sickle cell disease. On average a post a day was updated on our Facebook and Twitter page. Postings include sickle cell upcoming events, articles, facts, inspirational quotes, and services offered by iHOMES. Graph 1 breaks down our posts by the topic category. A video that explains the importance of medical care from both a primary care provider and a hematologist was also uploaded to our YouTube account and linked to our Facebook and Twitter page.

We plan to play the primary care video in the Johns Hopkins hematology clinic as sickle cell patients wait to be seen by their hematologists. Also, 200 flash drives containing content links to our webpage and social media sites promoting the iHOMES project were distributed to patients, friends, and families at all of our program events. As promotion continues our social media numbers are expected to increase.

Results: We have 68 "likes" on Facebook and 33 "followers" on Twitter. Nearly half of our post consists of educational material and a quarter consists of services offered by iHOMES. Our plan is to use social media to improve sickle cell education. Our short primary care video has 95 views while our long primary care video has 38. Through our social media we have received one self-referral for a primary care provider as well as several patients interested in upcoming sickle cell events.

Conclusion: Our patients and providers have continued to show interest in our educational and informative sickle cell articles by the increasing number of likes. Our future plan is to survey patients to see which social media sites they are most likely to use and which topics interest them. By creating a Facebook, Twitter and YouTube account it has allowed our patients, providers, friends and family a new way to learn about our program and improve their health.



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431

Primary Care Providers Comfort Levels in Caring for Patients with Sickle Cell Disease

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Introduction: Sickle cell disease (SCD) is an inherited red blood cell disorder affecting approximately 100,00 0 individuals in the United States, (Hassell, 2010). Studies have suggested primary care providers may not be comfortable treating individuals with SCD or have sufficient knowledge to do so (Okumura et al. 2008) (Gomes et al, 2011). Okumura et al conducted a survey of providers regarding comfort level (CL) treating chronic illnesses which originate in childhood such as SCD and Cystic Fibrosis. Approximately one-third of each group reported feeling comfortable being the primary care provider (PCP) for individuals with SCD (32% of internists and 35% of general pediatricians). Gomes et al conducted a survey of providers in Brazil regarding knowledge of SCD, which demonstrated a mean score of 66.9%, which the researchers felt was inadequate for caring individuals with SCD. Lack of comfort and knowledge among PCP can be especially problematic in a state such as Maryland where there is only one specialized SCD center which may not be accessible to all residents with SCD. The Improving Health Outcomes and Medical Education for Sickle Cell Disease (iHOMES) Network conducted a survey of PCPs to gain a better understanding of CLs and knowledge of providers in Maryland.

Methods: Surveys were administered during the annual Johns Hopkins Community Physicians Retreat. Providers rated CLs regarding: providing ambulatory care for individuals with SCD, managing SCD co-morbidities, managing SCD specific issues, and managing SCD chronic pain. Various factors were assessed as potential correlates of provider comfort for the aspects of SCD treatment listed above. Factors assessed included specialty, race, medical school graduation year (MSGR), currently treating patients with SCD (CP), having treated SCD patients in the past (PP), and resources utilized for patient management.

Results: Response rate was 69%. All provider attendees were invited to participate. Mean age of respondents was 44 years, and mean for MSGR was 1995. The majority of respondents were white (65%) and non-Hispanic (95%). Respondents' specialties were as follows: Internal Medicine 39%, Family Medicine 36%, Pediatrics 20%, Med-Peds 6%, OB 1%, and Other 6%. Sixty-one percent of respondents reported currently having at least one individual with SCD in their panel, and 81% reported having provided primary care for an individual with SCD in the past. Table 1 shows reported CLs and factors which increased CLs.

Conclusions: Our results concur with previous findings. The majority of PCPs do not feel comfortable managing individuals with SCD. However, CLs increase with experience. There is a relationship between all 4 of our comfort factors and having PP. Our data also suggest a relationship between having CP and comfort providing ambulatory care and managing SCD specific issues. The majority of our respondents (80%) listed what they learned in residency as a resource utilized to manage patients with SCD. The relationship remained statistically significant, even when controlling for MSGR. Our data may suggest a need for increased training on SCD during residency, and making continuing medical education readily available so PCPs have the most up to date knowledge regarding treatment and care for individuals with SCD. There appears to be a relationship between volume of sickle cell patients treated and quality of care received during hospitalization (McCavit et al 2011). Because of the significant association of comfort with number of patients, and relative infrequency of SCD among primary care populations, best options for providing primary care to SCD patients may be to identify a subset of PCPs willing to work with SCD while promoting education and referrals to that group.

Table 1 Reported Comfort Levels and Factors Increasing Comfort levels.
*Only statistically significant p values were reported below. *

	Comfort Providing Ambulatory Care	Comfort Managing SCD Co-Morbidities	Comfort Managing SCD Issues	Comfort Managing Chronic Pain
Reported Comfort Levels				
Very Uncomfortable	9.45%	7.09%	25.00%	14.73%
Somewhat Uncomfortable	29.92%	34.65%	36.72%	40.31%
Neither Uncomfortable nor Comfortable	15.75%	16.54%	17.97%	17.05%
Somewhat Comfortable	33.07%	28.35%	17.19%	24.03%
Comfortable	11.81%	13.39%	3.13%	3.88%
Factors Increasing Comfort Levels				
Current SCD Patients	p=.04		p=.01	
Past SCD Patients	p=.0001	p=.0001	p=.001	p=.0000
Using Knowledge from Residency as Resource	p=.04			
Using Colleagues as a Resource				p=.03
Med School Graduation Year	p=.03			
Number of SCD Patients	p=.03		p=.002	
Specialization in Internal Medicine		p=.02		
Specialization in Pediatrics	p=.04			

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297

INCIDENCE OF SERIOUS BACTERIAL INFECTIONS IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) affects nearly 100,000 people nationally, mainly African Americans. Inherited in an autosomal recessive fashion, individuals with SCD can exhibit significant morbidity and mortality related to chronic hemolysis in addition to direct vascular occlusion by red cell sickling. It is well known that patients with SCD are at increased risk for developing serious bacterial infections (SBI) given inadequate splenic function, particularly in the first 5 years of life. Initiation of penicillin prophylaxis in early childhood has significantly decreased SBI incidence, specifically invasive pneumococcal infections. The development of improved vaccinations has also played a role in decreased SBI in this patient population. Recommended vaccines for patients with SCD include (but are not limited to): Pneumovax 23 vaccine, the Prevnar vaccine, and the Meningococcal vaccine. In February 2010, the Food and Drug Administration (FDA) approved the Prevnar 13 vaccine. Prior to that, patients received Prevnar 7. Despite continued vaccination efforts in combination with antibiotic prophylaxis, however, we continue to treat SBI in this patient population.

Objective: The primary objective was to review the incidence of SBI in pediatric patients followed at a large, comprehensive Sickle Cell Anemia Center.

Methods: Inpatient records from January 2007 through December 2012 for patients age 0-18 years were assessed for a discharge diagnosis code of SCD (any type) and sepsis/bacteremia/positive blood culture. Our Sickle Cell Anemia Center follows approximately 250 children with SCD.

Results: 23 patients met the search criteria, representing approximately 10% of our patient population. Of those, the majority of positive blood cultures reported (n=11) were ultimately considered to be contaminants and not true SBI. 5 out of the remaining 12 (42%) had pneumococcal bacteremia/sepsis. One patient had 2 episodes of pneumococcal bacteremia (serotype 23A). Additional serotypes identified included 15A, 15B, and 35B. Serotype 15B is the only isolate found in the pneumococcal vaccines (Pneumovax) which represents 25% of the serotypes identified. Two patients had serotype 15B – one was 18 months old at the time of his bacteremia, so had not yet received the Pneumovax vaccine but was on amoxicillin prophylaxis. The other patient was 8 years old; he had stopped amoxicillin prophylaxis but had received both Pneumovax vaccines, at ages 2 and 5 years. For the non-vaccine serotypes, 2/3 were penicillin sensitive. Of the non-pneumococcal SBI, one patient had E coli urosepsis, one had Salmonella bacteremia with osteomyelitis, and one had Enterobacter cloacae line infection in the setting of a prior diagnosis of osteomyelitis and PICC line placement for extended intravenous antibiotics.

Conclusions: With our current comprehensive clinical care, including antibiotic prophylaxis and immunizations, patients with SCD are at significantly decreased risk of developing SBI, particularly pneumococcal bacteremia/sepsis. In patients found to have a positive blood culture, the majority were considered to be contaminants and not a true infection. For those patients who had pneumococcal bacteremia/sepsis, the majority of serotypes identified were, interestingly, not in our current vaccines but most were penicillin sensitive."

323

TRAINING PATIENT NAVIGATORS FOR RECRUITING PATIENTS TO SICKLE CELL DISEASE SPECIALTY CARE: THE SHIP HU STUDY

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Background: Patient navigator (PN) programs have enhanced access to care for patients, over the last 40 years. More recently, PN programs have been shown to improve outcomes in health behaviors such as smoking cessation, weight loss, and addressing barriers to health care. Experts estimate that over 100,000 Americans have Sickle Cell Disease (SCD) yet few, if any, federally funded studies targeting SCD have included PNs in their research. The SHIP HU (Start Healing in Patients with Hydroxyurea) study, funded by NHLBI, includes training PNs to build relationships in communities towards recruiting patients into specialty care. To prepare PNs, we have developed and tested a comprehensive training curriculum.

Objective: Plan, develop, and deliver a comprehensive 4-day training program to fully prepare patient navigators to successfully fulfill their roles and assignments including recruiting patients to a clinical trial for individuals with SCD.

Methods: Towards reaching our study goals, we identified curriculum objectives, major skills and resources needed for PNs, approaches used to deliver the curriculum, and speakers for presenting specialized clinical topics. In weekly conference calls linking our team with our collaborators, we sifted through materials and developed a grid to identify topics, teaching methodologies, educational materials and resources, time frame and the person(s) responsible. In tandem, the training manual leaders were working to reflect the content and resources needed for the manuals. The full curriculum training was presented successfully to eight newly hired patient navigators. Pre/post surveys were administered to assess any changes in content knowledge.

Results: Several key features of the training program were noteworthy including the multidisciplinary skills represented in our study team, a commitment to acknowledge literacy levels by previewing presenter's slides, the diversity of methods used including didactic lectures, case studies, role play, videos, and discussions, strong speaking skills, and quality companion training manuals. We also scheduled two practice sessions in order to get credible feedback and to fine-tune the content. Lessons learned included the need for more focus on recruitment skills, for more time allotted for Q & A with clinicians and for more real life role/play scenarios for patient navigators.

Conclusions: We learned through the planning and development phases of our comprehensive training curriculum for patient navigators that it takes much more time and almost a full "village", to complete such a large training project. Our study staff, including clinicians and researchers from both study sites, was tremendously helpful in providing significant amounts of feedback throughout the entire process. As we move through the first year of the study and evaluate the training, we are eager to see how the PNs utilize the curriculum and how well they are able to apply their learning to recruit study patients.

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HEMOGLOBIN IN SICKLE CELL ANEMIA IS POSITIVELY CORRELATED WITH 25-HYDROXYVITAMIN D, THE CLINICAL INDICATOR OF VITAMIN D STATUS

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Background: Anemia is associated with vitamin D deficiency in the general population and vitamin D analogs improve anemia in patients with end stage kidney disease. Patients with sickle cell anemia often have profound vitamin D deficiency; however, the relationship between hemoglobin and 25-hydroxyvitamin D [25(OH)D], the clinical indicator of vitamin D status, has not been investigated.

Objectives: To define the relationship between 25(OH)D and markers of sickle cell disease activity in adult patients.

Methods: Medicals records of 50 adult sickle cell patients receiving care at the Mount Sinai Medical Center were reviewed with IRB approval (GCO 10-0032). Pearson correlation coefficients were calculated for pairwise comparisons of 25-hydroxyvitamin D, hemoglobin, and other markers of disease activity, using a p-value below 0.05 as the cutoff for significance.

Results: The median age of the 50 patients was 27 years [interquartile range (IQR): 23-36]; 46% were female; 70% were homozygous HbSS and 30% were heterozygous HbS/β0 thalassemia. Twenty percent had proteinuria, 16% had avascular necrosis, 70% were on hydroxyurea, and 24% were on long-acting opioids. Fifty-four percent used vitamin D supplements. The median 25(OH)D level was 19.6 ng/mL (IQR: 11.7–29.2) for supplement users and 13.0 ng/mL (IQR: 10.6–19.6) for non-users. Pearson correlation coefficients for pairwise comparisons between vitamin D, hemoglobin, and markers of disease activity are shown in Table 1. There was a significant POSITIVE correlation between 25(OH)D and hemoglobin levels ($r = 0.30$, $p = 0.03$, moderate strength) and a significant NEGATIVE correlation between 25(OH)D and total bilirubin ($r = -0.31$, $p=0.03$) and platelets ($r = -0.35$, $p=0.01$, moderate strength). Hemoglobin levels were negatively correlated with LDH, reticulocyte percentages and platelets. Bilirubin, reticulocyte percentages, white blood cell counts, and LDH were positively correlated with each other, in keeping with published data.

Conclusions: 25-hydroxyvitamin D levels were higher in vitamin D supplement users and were positively correlated with hemoglobin levels in adults with sickle cell disease. Raising 25-hydroxyvitamin D levels with vitamin D supplements might reduce disease severity in patients with sickle cell disease. Clinical trials of vitamin D supplements are warranted (NIH DA031095).

Table 1. Relationship between 25(OH)D, hemoglobin, and markers of hemolysis						
	LDH	White Cells	Retic %	Platelets	Total Bilirubin	25(OH)D
Hemoglobin	- 0.53 p<0.01 - - -	- 0.21 p=0.15 .	- 0.41 p<0.01 - -	- 0.34 p=0.02 - -	- 0.27 p=0.06 .	0.30 p=0.03 + +
25(OH)D	- 0.14 p=0.34 .	- 0.22 p=0.12 .	- 0.08 p=0.60 .	- 0.35 p=0.01 - -	- 0.31 p=0.03 - -	
Total Bilirubin	0.47 p<0.01 + +	0.43 p<0.01 + +	0.41 p<0.01 + +	0.21 p=0.12 .		
Platelets	0.22 p=0.13 .	0.32 p=0.03 + +	0.35 p=0.02 + +			
Retic %	0.35 p=0.01 + +	0.39 p< 0.01 + +				
White Cells	0.12 p=0.40 .					

Yellow ++ (moderate positive correlation), white . (no significant correlation), pale blue - - (moderate negative correlation) , darker blue - - - (strong negative correlation).

ALPHA THALASSEMIA AND TNF-A G308A POLYMORPHISM INFLUENCES THE RISK OF STROKE IN CHILDREN WITH SICKLE CELL ANEMIA

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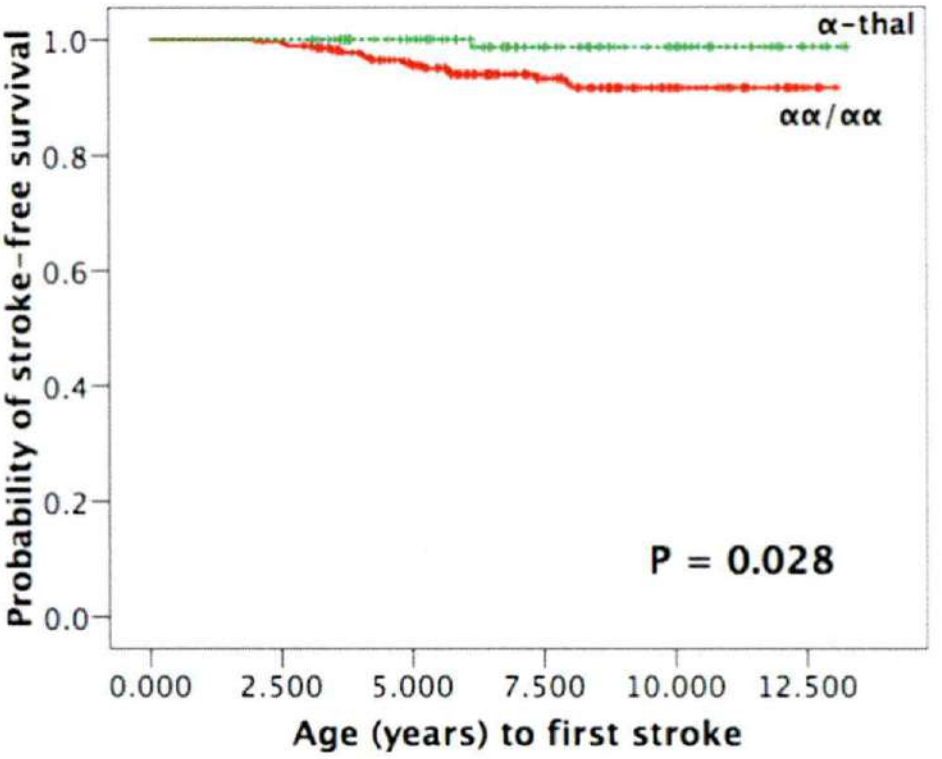
Background: Historically, 11% of individuals with sickle cell anemia (SCA) had an ischemic stroke (IS) before age 20 (1). Currently, transcranial Doppler (TCD) ultrasonography is the only clinical tool available to detect increased risk of IS. TCD is a very sensitive but only moderately specific test: 60% of untreated children with high risk will not develop a IS and would be unnecessarily subjected to prophylactic blood transfusions. The identification of additional more specific biomarkers is clearly needed.

Objectives: To analyze association of TNF-α G308A and VCAM1 G1238C polymorphisms, alpha-thalassemia (α-Thal) and sickle cell genotype with IS in children with SCA. METHODS: 369 children with SCA (345 SS and 24 Sβ0-thalassemia; mean age 9.0±2.9 y) from the Minas Gerais Newborn Screening Program cohort, born between 1999 and 2008, and followed-up at the Blood Center in Belo Horizonte until 07/2012. α-Thal genotyping was carried out by multiplex PCR for -α3.7; -α4.2; --SEA; --FIL; --MED; -(α)20.5 e --THAI alleles. TNF-α G308A and VCAM1 G1238C polymorphisms were determined by PCR-RFLP. IS-free survival curves were estimated using the Kaplan-Meier method and were compared with the log rank test. Beginning of chronic transfusion program or hydroxyurea treatment, bone marrow transplantation, death by causes unrelated to IS, and the last clinical visit without IS were reasons for censored observations. Cox's regression was used to determine the independent effect of each genetic risk factor.

Results: The point prevalence of IS was 4.9% and the estimated cumulative probability up to age 8y was 6.4±1.5%. 265 subjects (71.8%) were αα/αα, 97 (26.3%) –α3.7/αα and 1.9% –α3.7/–α3.7. In relation to TNF-α G-308A polymorphism, 270 (73.2%) had GG genotype, 92 (24.9%) GA, and 7 (1.9%) AA. About VCAM1 G1238C, 320 (86.7%) had GG genotype and 49 (13.3%) GC. No child with Sβ0-thal had IS but statistically significant difference between IS-free survival for SS and Sβ0-thal groups has not been detected yet (p=0.26). IS-free survival was significantly higher for children with co-inherited α-Thal (1/104 vs 17/265; p=0.028; Figure). IS-free survival was lower in children with GA+AA TNF-α genotypes when compared with those with GG genotype (p=0.016). IS-free survival curves for VCAM1 GG and GC genotype groups were not different (p=0.75). Multivariate Cox model indicated that both α-Thal (OR=6.54, 95%CI, 0.87-49.18; p=0.068) and TNF-α G308A (OR=2.77, 95%CI, 1.1-6.98; p=0.031) were independently associated with IS.

Conclusion: The point prevalence and the cumulative probability of IS were high in the studied population, demonstrating the importance of early identification of children at high risk of developing IS. Our findings contradict results from others, in which the GG genotype (TNF-α G308A) and GC genotype (VCAM1 G1238C) were associated with higher and lower risk of IS, respectively (2, 3). The minor allele A has been associated with higher TNF-α levels, and pathophysiologic consequences secondary to high production of this proinflammatory cytokine would be consistent with increased risk of IS. VCAM1 G1238C mutation leads to a conservative amino acid change (Gly>Ala) at the 413th position of the immunoglobulin domain 5 of VCAM1 molecule. The similar chemical properties of these amino acids suggest that the protein may remain fully functional; this may explain the similar risk found in both groups. As previously described, co-inheritance of α-Thal was associated with a decreased risk of IS (1). Children with Sβ0-thal did not have IS, but the difference to SS children was not statistically significant probably because the number of Sβ0-thal cases was small.



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7TESIA BRAIN MRI PILOT/FEASIBILITY STUDY OF COGNITIVE IMPAIRMENT IN ADULT PATIENTS WITH HBSS DISEASE

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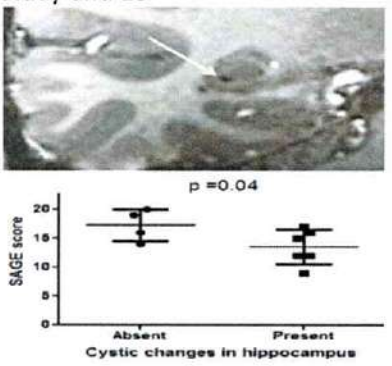
Background: Sickle cell disease (SCD) is characterized by cerebral small and large vessel vasculopathy and infarction. Cognitive impairment (CI) is an emerging neurovascular complication of SCD responsible for functional limitations in schooling, occupation and compliance with SCD therapy. It is unknown how SCD vascular risk factors lead to CI as the main published neuroimaging study showed that the majority of patients with CI had no lesions detectable by routine 1.5Tesla MRI testing. A major barrier of current 1.5Tesla methodologies is that they miss subtle small vessel disease in areas important for cognitive function, such as the hippocampus. To address these barriers, we applied novel 7Tesla MRI technology and imaging protocols developed at the University of Pittsburgh in adult SCD patients to explore how neuroimaging findings are associated with CI.

Objectives: We performed a cross-sectional pilot/feasibility study to study the association between 7Tesla brain MRI findings and cognitive performance as assessed by the Self-Administered Gerocognitive Examination (SAGE) test in adult patients with HbSS from the UPMC Adult Sickle Cell Program outpatient clinic in Pittsburgh, PA. Methods. 95 SCD patients were screened in clinic within a 5 months period (August-December 2012). The main exclusion criterion was having received a blood transfusion within the prior 2 months. 33 patients met entry criteria, 32 agreed to participate in the study and 15 were found to be MRI ineligible (8 had implanted infusion ports and 7 had tattoos).

Results: 10 SCD patients with a median age of 27 (IQ range: 22-35) underwent MRI examination to date, including Tra and Cor SWI-2D, 0.6 mm and/or 0.7mm MPRAGE- 3D- T1WI, GRE-T2*WI. All patients showed various degrees of iron deposition in the basal ganglia. Hypointense signal in the hippocampus on T1 indicating dilated perivascular spaces with a cyst-like appearance was found in 6 cases on MPRAGE-T1WI and was associated with lower SAGE scores (Figure). Encephalomalacia was visible in 2 cases. A vascular malformation was suspected in 1 case.

Conclusion: Approximately half of the patients were ineligible for MRI testing, either because of tattoos or having implanted infusion ports, a finding that will need to be considered when planning future MRI studies. We found that, as reported in elderly populations without SCD, hypointense cystic changes in the hippocampus detected by 7Tesla MRI were associated with worse cognitive function as measured by the SAGE test in a small sample of patients with HbSS disease. A larger longitudinal study is underway to ascertain whether this novel finding may translate into an imaging biomarker to identify SCD patients at risk of developing CI.



399

NOVEL APPROACH TO DESCRIBING PAIN IMPACT ON FUNCTION OF SICKLE CELL YOUTH HOSPITALIZED FOR VASOOCCLUSIVE PAIN

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Background: Youth with sickle cell disease (SCD) are frequently hospitalized for painful vasoocclusive episodes (VOE). Understanding of the acute pain experience requires not only measurement of pain intensity but also pain's impact on mood, quality of life, and physical function.

Objectives: To describe the pain experience of youth with SCD hospitalized for a VOE using the Children's Acute Pain-Functional Ability Questionnaire (CAP-FAQ), a recently validated measure of physical function in acute pain as well as other measures of pain, function, mood, and quality of life.

Methods: 159 children and adolescents with SCD, ages 7-21, hospitalized for VOE were enrolled at four urban children's hospitals. The study was approved by the Institutional Review Boards at all institutions. Written informed consent was obtained from all parents or subjects and written assent was obtained from those under age 18 years. Subjects were excluded if they had a primary diagnosis other than VOE, had concurrent Acute Chest Syndrome, or were unable to speak or understand English. Subjects completed 3 measures assessing their pre-hospital experience in the domains of function (Child's Activity Limitations Interview (CALI-21)), pain burden (Sickle Cell Pain Burden Interview-Youth (SCPBI-Y)), and quality of life (Pediatric Quality of Life Inventory (PedsQL)). Subjects also completed 6 measures reflecting their acute experience: 2 measures of pain (pain location (Adolescent Pediatric Pain Tool (APPT)) and average pain over the previous 24 hours (11-point [0-10] Numeric Rating Scale (NRS)), 2 measures of function (Children's Acute Pain-Functional Ability Questionnaire (CAP-FAQ)) and (the FIM™), and 1 measure of mood (Positive Affect Negative Affect Scale (PANAS)). All measures were collected once on a single day of hospitalization. Data analysis was conducted using SPSS 16.0.

Results: Mean age was 15.7 years (IQR 12.9 – 18.7 years of age); 55% were females; 85% of the sample reported their race as Black American; 67.3% of the population's sickle cell genotype was HgB SS; 14% received chronic blood transfusions; 43% were taking Hydroxyurea; mean length of stay was 4.5 days (IQR 2.5 – 5.1 days); 69% (109 patients) were enrolled within the first 2 days of admission for VOE. See Table 1 for detailed descriptive results of study measures.
There was a significant but weak correlation between pain intensity and CAP-FAQ scores ($R = 0.18$, $p = 0.03$).

Conclusions: Youth with SCD hospitalized for VOE endorse moderate to severe pain, decreased physical function and altered mood. In the weeks leading up to hospitalization evidence of decreased function, increased pain burden and decreased quality of life is reported in this patient group. There is a wide variability in functional ability for these hospitalized individuals. Further study will focus on the use of physical function as an outcome measure for youth hospitalized with VOE.

Table 1: Study Measures

Measure	Mean (Std. Dev.)	Range
APPT	6.4 (7.2)	0.0 – 39.0
CALI	24.0 (17.6)	0.0 – 70.4
CAP-FAQ	17.6 (12.0)	0.0 – 46.2
FIM	56.6 (15.2)	21.0 – 91.0
NRS-Pain Score	5.9 (2.1)	0.0 – 9.8
PANAS	26.5 (11.0)	12.0 – 56.0
SCPBI-Y	10.5 (5.5)	0.0 – 23.0
PEDSQL	61.7 (17.1)	14.1 – 100.0

POPULATION-BASED ANALYSIS OF HIGH HOSPITAL UTILIZATION (HHU) AMONG CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE (SCD)

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Background: Sickle cell disease (SCD) is characterized by marked heterogeneity in clinical manifestations, severity and utilization of health care services. This heterogeneity is particularly evident with regards to utilization of inpatient services, which account for a large percentage of total health care costs and significant absence from school and work. Previous studies of utilization, based on analysis of administrative datasets, have been limited by inaccuracies in ICD-coding, inability to differentiate among SCD genotypes, and/or inability to capture individuals never hospitalized. Single center studies have been limited by potential disease severity referral bias, inability to capture service utilization at outside facilities, and relatively small numbers.

Objectives: We sought to identify children and adolescents with SCD with high hospital utilization (HHU) and to determine the relationship of HHU with age, SCD genotype, insurance coverage, and use of hydroxyurea (HU).

Methods: The clinical database of the SCD Program at Children's Healthcare of Atlanta (CHOA) was used to identify all patients with SCD, ages > 5 years, who received comprehensive outpatient, acute care, and inpatient services at three CHOA facilities in metro Atlanta during 2010. SCD genotype was confirmed for each patient by review of hematologic and clinic data, including results of diagnostic hemoglobin electrophoresis. Treatment with HU and chronic transfusions (CT) was determined by review of medical records. All outpatient clinic, emergency department, and inpatient utilization was captured as well as insurance (payer) status at each encounter. HHU was defined as >3 admissions or >8 inpatient days during the year. Data were analyzed by SCD genotype, age, and payer using Chi-square. Relationship of HHU with HU was determined by subset analysis of individuals with SS/S β°thal, exclusive of those on CT. The extent to which the data were population-based was determined from the Georgia Hospital Association database with includes DRG-level data for all inpatient hospitalizations.

Results: During 2010, 1083 children and adolescents > 5yr of age with SCD received comprehensive care at CHOA: 760 (70.2%) had SS/S β°thal , 257 (23.7%) SC, 66 (6.1%) S β+thal; 410 (37.9%) were 5-9 yr of age, 376 (34.7%) 10-14 yr, 297 (27.4%) > 15 yr; 438 (40.4%) had traditional medicaid (MC), 191 (17.6%) managed-care medicaid (MMC), 358 (33.1%) private payer (PP), and 96 (8.9%) multiple payers (MP). Use of HU was 36.5% of patients 5-9 yr, 42.7% 10-14 yr, and 34.0% >15 yr. Hospitalizations at CHOA accounted for 96.1% of all SCD admissions for children within the 28-county greater metro Atlanta area. HHU (> 3 admissions) was identified in 120 of 1083 patients (10.5%); HHU (> 8 inpatient days) in 112 (10.3%). Analysis using both HHU criteria yielded similar results. The Table shows HHU (> 3 admissions), n (%), by age, genotype, and payer. HU was not associated with HHU (ages 5-9 yr and 10-14 yrs), but was associated with HHU in >15 yr (p <.01).

Conclusions: HHU was significantly associated with the SS/S β°thal, age > 15 yr, MC and MP insurance coverage. HU use among SS/S β°thal patients >15 yr on HU was associated with HHU.

	5-9	10-14	≥15	P	SS/S β°	SC	S β+	P	MC	MMC	PP	MP	P	Total
HHU	34 (8.2)	36 (9.6)	50 (16.9)	< .01	102 (13.4)	15 (5.8)	3 (4.5)	< .01	66 (15.1)	8 (4.1)	27 (7.5)	19 (19.8)	< .01	120 (10.5)
non-HHU	376 (91.8)	340 (90.4)	247 (83.1)		658 (86.6)	242 (94.2)	63 (95.5)		372 (84.9)	183 (95.9)	331 (82.5)	77 (88.2)		963 (89.5)
Total	410	376	297		760	257	66		438	191	358	96		1083

418

HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR SICKLE CELL DISEASE IN AN EIGHT-YEAR-OLD GIRL WITH SIGNIFICANT PSYCHOSOCIAL RISK FACTORS: AN ETHICAL CASE STUDY

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Background: LT is an 8-year-old African American girl with sickle cell disease (SCD) resulting in frequent pain crises, removal of the gall bladder and spleen, and risk for stroke revealed by abnormal transcranial Doppler. LT receives preventative chronic blood transfusions without complication. She lives with a single mother who is actively involved in her medical care. The family faces multiple psychosocial stressors, including poverty, limited social support, and mother's mental health issues. LT has demonstrated significant treatment-related anxiety as well as defiant and aggressive behavior during medical procedures and clinic visits. Hoping to cure LT's SCD, her mother sought enrollment in a Phase 1 clinical trial of hematopoietic stem cell transplantation (HSCT) for SCD patients with umbilical cord blood donors. Given patient's history of noncompliance and the family's unstable social situation, concerns were raised about the safety of proceeding with HSCT.

Objective: To explore ethical, medical, and psychosocial issues related to whether or not to proceed with HSCT as treatment for LT's SCD.

Methods:Determining whether or not to proceed with HSCT involved a series of family and team meetings and an ethics consultation with the hospital's Pediatric Ethics Program. Additionally, LT and her mother received psychotherapy (30 sessions) with an advanced psychology graduate student under supervision of a licensed clinical psychologist. Treatment was conducted in partnership with a multidisciplinary team of physicians, nurses, social workers, art therapists, and child life specialists, and LT made significant gains in regulating her anxiety during medical procedures. Gains were threatened, however, by increased psychosocial stressors, which included unemployment, mother's continued mental health issues, lack of social support, and ultimately, the family's relocation into a homeless shelter. As a result, the team questioned whether the risks of HSCT for this child may outweigh the potential benefits. First, noncompliance with the treatment protocol would put LT at risk for complications that could result in death. The family's lack of stable housing posed an additional medical risk, as it was unclear whether LT would have a safe recovery environment after HSCT. The team also considered the potential psychological consequences of denying the family the option for cure they had planned for, including anger, disappointment, and guilt on the part of LT's mother and the possibility of losing the family to continued mental health treatment.

Results: With input from the Director of the Pediatric Ethics Program, the treatment team ultimately concluded that proceeding with HSCT was not in LT's best interest at this time. Given multiple behavioral and environmental concerns, the risks of HSCT outweighed its potential benefits. The team's decision was also influenced by the fact that HSCT with a partially-matched cord as a treatment for SCD is an experimental procedure rather than standard of care. This decision was guided by the ethical principle of non-maleficence (i.e., "first do no harm").

Conclusion: LT's case provides an opportunity to consider the ethics related to risky, elective, experimental procedures, particularly in situations where psychosocial factors may impact the balance of risks versus benefits. Researchers are encouraged to consider psychosocial factors and basic safety (e.g., housing) when writing exclusionary criteria for research protocols. Importantly, providers are challenged to consider what can be done to ensure that equitable medical care is provided to high-risk children such as LT, who may be denied procedures due to factors (e.g., parental mental health, poverty) that are outside of their control.

294

AN ASSESSMENT OF NATIONAL VARIATIONS IN CLINICAL PRACTICE OF TREATMENT OF AN ACUTE VASO-OCCLUSIVE CRISIS IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) affects approximately 1 per 375 to 500 US live births. The Centers for Disease Control and Prevention (CDC) has declared SCD a major public health concern. Despite SCD's prevalence, patients continue to have less access to comprehensive team management than other genetic disorders. Patients with SCD are frequently seen in the emergency department (ED) during acute painful vaso-occlusive crisis (APVOC), the most common cause of morbidity. Currently available guidelines for treatment of APVOC have not been sufficiently evidence-based, specific, or current. The research on optimal management of pediatric APVOC is deficient and conflicting. We felt it was important to assess and compare practice variation amongst healthcare providers in the ED who treat pediatric patients presenting with an APVOC.

Objectives: This survey aids in providing baseline data regarding practice variation in the management of an APVOC occurring in the pediatric population presenting to the emergency department (ED). It serves to describe clinical variation in fluid management, analgesic administration, and physician attitudes when managing the pediatric patient with an APVOC. We also attempted to determine if there is correlation between specific healthcare worker characteristics as it relates to management decisions.

Methods: This study was a exempt study determined by the institutional review board of University of Missouri Kansas City. Healthcare providers who participated in the listserv of the American Academy of Pediatrics Section of Emergency Medicine (AAP-SOEM) were asked to complete an electronic survey. Participants were emailed a unique survey web link and a request for participation from the AAP Section on Emergency Medicine. Communication with individuals to solicit their participation was via a standardized email and there was no personal solicitation for participation directly from the investigators. Inclusion criterion was that the respondent be a physician who clinically evaluated and managed at least 1 patient, ages 0-21 years of age, with an APVOC in the past 12 months. Survey recipients who did not meet the inclusion criterion were asked to indicate this and complete the demographic information. Completion of survey implied consent. Survey items were generated through a literature review and discussion by a multidisciplinary team. The items were revised iteratively by the authors. Resulting iterations were pilot tested with a total of 9 individual of local PEM faculty and local PEM fellows. The final tool had 30 questions, and in pilot testing took a mean of approximately 9 minutes to complete. The questions focused on physician management of fluids, analgesia, and test ordering, as well as attitudes and characteristics of interest.

Results: A total of 334 physicians completed the survey out of a reported total of 1088. The overall response rate was 30.5%. While we found significant variation among practices of physicians, there was no one set of physician characteristics that correlated with certain treatment decisions made by the providers. We also found variations in management, basis of management, and exposure to APVOC based on demographics.

Conclusion: Practice variation is significant amount healthcare providers and not based on one sole evidence based guideline. Multiple contributing factors play a role in how healthcare providers decide to treat APVOC, however there has not been a true standard of care established and/or practiced. Providing this foundational research, can serve as platform for future research regarding management of an APVOC in acute care setting and help provide a starting point for future clinical trials and establishment of practice guidelines for acute care.

233

PREVALENCE OF THE BETA-S GENE AMONG SCHEDULED CASTES, SCHEDULED TRIBES AND OTHER BACKWARD CLASSES IN CENTRAL INDIA

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Background: Sickle Cell Disease, (SCD) an inherited disorder of the red blood characterized by vaso-occlusive pain crises, risk for pneumococcal infections, acute chest syndrome, stroke and organ failure and is associated with substantial morbidity and premature mortality. [1] It is a major public health problem. India, with a population of 1.2 billion individuals, is estimated to be home to over 50% of the world's patients with sickle cell disease. bs gene has the highest prevalence in ethnic groups that reside in central, eastern , western and pockets of southern India. While sickle cell disease is common among all ethnic groups, high prevalence has been reported in three socio-economically disadvantaged ethnic categories: the Scheduled Castes (SC), the Scheduled Tribes (ST), and Other Backward Community (OBC) groups in India. [2,3] Each of these categories consists of several distinct large ethnic groups who have practiced endogamy for millennia and thus represent genetic isolates. Prevalence of the bs gene has been well described in the scheduled Tribe population, but precise estimates are not available for the scheduled caste or other backward cast communities. The scheduled caste population consists of over 1900 groups constitute 15% and other backward casts represent approximately 50% of the Indian population. The tradition of endogamy practiced by the numerous ethnic groups in India provides the rationale for the screening of individual populations to better understand the distribution of the bs gene and guide counseling and awareness programs and aid development of public policy. Further, published studies to date have not distinguished between community based screening of the general population and secondary screening of family members as a result of detection of a sickle cell mutation in an index case. This limits the utility of these studies in describing reliable estimates of population prevalence of bs gene

Objectives: We undertook a study to describe the prevalence of the bs gene in the scheduled caste population and other backward casts in the district of Nagpur, Maharashtra in Central India.

Methods: The study was performed over a span of eight years (2003-2012) and included the screening of target populations in all age groups (newborns, school age children, young adults, and pregnant mothers) as well as screening in hospital for individuals considered to be at high risk of carrying the bs gene. Informed consent was obtained from all adults and parents of children once the individuals were educated on the reasoning behind screening. We defined ethnic groups by using standardized terminology used in the Census of India and in government regulations as well as by grouping ethnic groups that are closely related, have social interactions, and practice inter-marriage to determine the prevalence rates of the bs gene

Results: Through community screening and subsequent target screening of high risk individuals, 35,636 individuals were screened of whom 5,437 were found to have sickle cell trait (SCT) and 1,010 were identified with sickle cell disease (SCD). Community wide screening revealed a sickle cell trait prevalence of 13% among the scheduled caste who belonged primarily to the Mahar ethnic group. Prevalence of the bs gene was 12% among the scheduled tribe population. bs gene prevalence was 3.4% among the other backward caste population mainly in the Kunbi and Teli ethnic groups.

Conclusion: This paper for the first time describes the prevalence of the bs gene in scheduled caste and groups within Central India determined by community based screening. This population screening program has also uncovered previously undiagnosed cases, provided detailed information for population based disease counseling, prevention programs and comprehensive care programs.

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TRAINING PROVIDERS ON ISSUES OF RACE AND RACISM TO IMPROVE HEALTH CARE EQUITY

Stephen Craig Nelson, MD, Heather W. Hackman, EdD

Background: Disparities based on race that target communities of color are consistently reported in the management of many diseases. This topic is of particular importance in the sickle cell disease (SCD) community of North America where the vast majority of health care providers are white and the vast majority of people with SCD are black. Barriers to health care equity include the health care system (insurance, funding, white-domination in provision of care), the patient (poor health literacy, fear, mistrust), the community (awareness, advocacy), and health care providers (unconscious bias, attitudes, racism). Patients and providers perceive race to be a factor in the delivery of quality health care. Health care providers receive little to no training on issues of race and racism.

Objectives: The goal of this pilot study was to assess the effectiveness of training in improving providers' awareness of race and racism and in affecting providers' comfort in caring for people of color.

Methods: We developed a training module for health care providers to address issues of race, racism, and whiteness. A group of residents participated in three 2-hour sessions over a 3-month period. Participants completed a 5-point Lickert scale survey before and after the training. Results were compared using a two-sample t-test. Details about the training and the survey will be presented.

Results: Nineteen residents completed the training course (5 males, 14 females). Ten identified as white, 7 Asian, and 2 black. The mean age was 31.9 years. The awareness level of issues of racism in the U.S increased significantly in all participants (3.40 to 3.89, p=0.036), but was most striking in participants of color (3.40 to 4.50, p=0.009). The impact of racism on health care in general as well as individuals' ability to deliver care was felt to have increased in all (3.89 to 4.52, p=0.0004 and 2.58 to 3.58, p=0.004 respectively). White participants showed a significant decrease in feeling as effective in caring for patients of color when compared to white patients and they felt less equipped to care for patients of color following the training (4.00 to 2.55, p=0.0016 and 3.70 to 3.00, p=0.039 respectively). See Table I.

Conclusion: Health care providers receive little training around issues of race and racism. As a result, awareness of racism and its impact on health care delivery is low. Following training, awareness increased significantly in all participants. However, feelings of effectiveness in delivering equitable care went down significantly in the white provider group. This may seem like a failure of the training. But, this training was successful in undoing white providers' previously held beliefs about race and racism. This is the first step in working on our own racism and unconscious biases to improve the quality of health care for all of our patients. Until racial issues are honestly addressed by members the health care team, it is unlikely that we will see significant improvements in racial health care disparities for Americans.

Table I. Survey results

Statement		Pre	Post	*P*
Awareness of racism	ALL	3.40	3.89	0.036
	WHITE	3.40	3.45	0.422
	POC	3.40	4.50	0.009
Impact of racism on health care	ALL	3.89	4.52	0.0004
	WHITE	4.00	4.54	0.0108
	POC	3.78	4.50	0.013
Effective caring for white patients as POC	ALL	4.10	3.10	0.0018
	WHITE	4.00	2.55	0.0016
	POC	4.22	3.87	0.1785
Well-equipped to care for POC	ALL	3.84	3.36	0.037
	WHITE	3.70	3.00	0.039
	POC	4.00	3.87	0.329
Impact of racism on delivering quality care	ALL	2.58	3.58	0.0046
	WHITE	2.70	3.82	0.0055
	POC	2.44	3.25	0.1206

VIRTUAL MENTOR PROGRAM FOR YOUNG ADULTS WITH SICKLE CELL DISEASE TRANSITIONING FROM PEDIATRIC TO ADULT CARE

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Introduction: Transition from Pediatric to adult care can be particularly critical for teenagers with chronic health issues like sickle cell disease (SCD). Receiving support or mentorship by an older peer also with SCD can be very beneficial in ensuring a smooth transition, i.e. complying with medication regimen, fulfilling first and subsequent appointments with the adult provider and being available to answer any questions related to the transition process. Since January 2012, St. Jude Children's Research Hospital in partnership with Sickle Cell Foundation of Tennessee (SCFT) has facilitated a Virtual Mentor Program (VMP) for young adults living with SCD. All young adults (ages 18 to 25) with SCD followed by our program are eligible to participate in the VMP. Eligible recruits are invited by the transition nurse case manager to participate. Upon verbally agreeing to participate, the young adult signs a consent form allowing the release of demographic information to the SCFT. The name, email address, and contact number of the participant is forwarded to The SCFT, which contacts the mentees and pairs them with a young adult of the same gender, who also has SCD. The mentor contacts the mentee to provide support and give their perceptions of living with SCD as an adult. The mentor contacts the mentee at least once every 3 months by email, text message, or FaceBook. The mentor cannot offer medical advice to the mentee, but encourages the mentee to seek care if needed.

Methods: In order to evaluate the success of the program, Mentors and Mentees complete a survey in Survey Monkey that provides information on their satisfaction with the program and the frequency of communication between mentors and mentees. SCFT monitors survey results and communication between mentors and mentees on a regular basis. In addition, clinical out comes, such as compliance with SCD treatment and medical visits are tracked.

Results: Numerous mentors were trained for the program and mentees agreed to participate; however, mentors had a difficult time establishing consistent contact with mentees. There were several barriers including difficulty reaching the mentees due to incorrect emails and cell numbers, and mentees not fully participating in the program. The SCFT held a brainstorming session to determine ways to overcome the barriers and it was agreed a face to face social meeting between mentors and mentees would help make electronic communications more natural and meaningful. The face to face was held with good turnout and program results will be examined pre/post event to determine whether the event made a difference in erasing contact barriers.

Conclusion: A virtual mentor program may help ease transition for young adults with SCD. The program will be monitored for mentor/mentee participation and program satisfaction. Also, to effectively evaluate the success and progress of the program, mentee participation will be evaluated to determine if participation increases medical compliance.

A CHANGING PATTERN OF CEREBRAL VASCULAR DISTRIBUTION OF STROKE IN SCA: A SINGLE CENTRE EXPERIENCE FOLLOWING THE IMPLEMENTATION OF STOP

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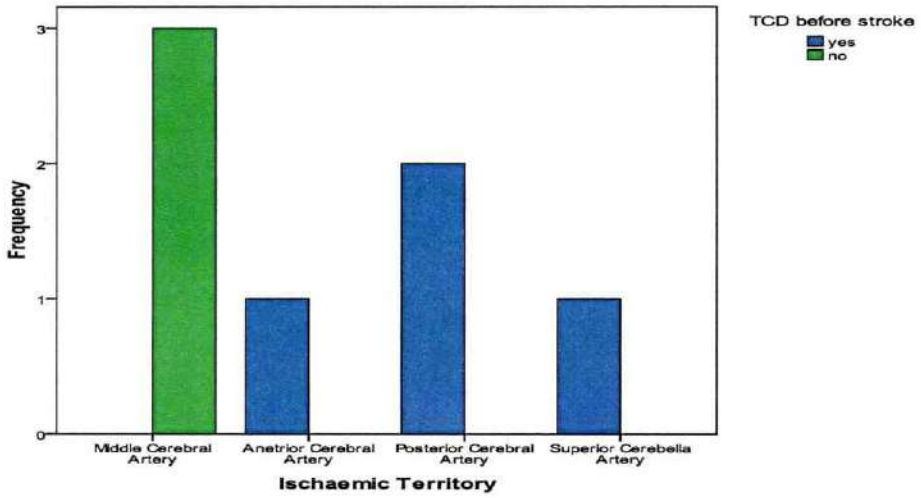
Background: One of the most severe complications of sickle cell disease in childhood is stroke (Strouse et al., 2006). The Stroke Prevention Trial in Sickle Cell Anemia (STOP; Adams et al., 1998) demonstrated that the risk of stroke can be identified and thus prevented with the use of Transcranial Doppler (TCD) ultrasound screening. The current guidelines based on this trial suggest chronic blood transfusion therapy for patients with increased time-averaged maximum mean velocities (TAMMV) of the middle cerebral arteries (MCA) and the internal carotid arteries (ICA) (NHS Guidelines, 2009). Currently, the provision of transfusion therapy is not recommended for patients with increased TAMMVs in the posterior cerebral arteries (PCA) or anterior cerebral arteries (ACA). In light of this we suggest that the rigid implementation of the STOP trial findings accounts for an increased proportion of strokes in the PCA and ACA territories.

Objectives: To compare the frequency and distribution of strokes in paediatric sickle cell patients before and after the implementation of TCD screening.

Methods: This was a retrospective study analyzing clinical & laboratory data from the health records of paediatric patients with HbSS phenotype with a diagnosis of stroke during the period 1988 to 2011. Patients were divided into two groups: those who had a stroke before the full implementation of TCD screening (pre-implementation) and those who had a stroke following full implementation of TCD screening (post-implementation). Of the post-implementation group, a proportion did not receive a TCD scan (unscreened), either because they were < 2 years old or did not have access, being referred from other geographic areas where screening was not yet available.

Results: 16 patients were included in this study, mean age 7.7 years (range 9 months to 15 years and 5 months). 7 were in the pre-implementation group and 9 in the post-implementation group. Stroke occurrence was in older children in the post-implementation group (mean 8.9 ± 6.0) compared to the pre-implementation group (mean, 6.0 ± 3.0) p=0.339. Mean systolic BP was 115 (±14.9) in the post-implementation group, and 112 (±7.5) in the pre-implementation group. Ischaemic territory was similar in both groups. Infarct distribution in the pre-implementation group consisted of 4 (57%) MCA/ICA territory infarcts and 3 (43%) PCA/ACA territory infarcts. In the post-implementation group there were no MCA/ICA territory infarcts in patients who had had a TCD scan, but there were 3 (60%) ACA/PCA infarcts, 1 (20%) superior cerebellar artery infarct and 1 (20%) subarachnoid hemorrhage. For those in the post-implementation group who remained unscreened there were 3 (75%) MCA infarcts and 1 subarachnoid hemorrhage. Occurrence of strokes in the MCA/ACA territory in the post-implementation group who were screened to prior to the stroke event was significantly reduced compared to those who remained unscreened (p =0.008).

Conclusions: These results suggest that MCA/ICA infarcts were prevented in patients who received TCD screening, but still occurred in patients who did not take up TCD screening for logistical reasons. However, the presence of stroke in territories other than MCA/ICA suggests that these are not prevented by the current TCD screening protocol. Future TCD screening protocols require revision to reduce stroke, particularly in patients



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401

FURTHER EVIDENCE FOR VALIDATION OF THE ADOLESCENT PEDIATRIC PAIN TOOL IN YOUTH WITH SICKLE CELL HOSPITALIZED FOR VASOOCCLUSIVE PAIN

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Background: Youth with sickle cell disease (SCD) are frequently hospitalized for painful vasoocclusive episodes (VOE). Age specific pain assessment tools can be helpful in providing meaningful information for pain management. The Adolescent Pediatric Pain Tool (APPT) has been utilized in pain populations to assess body surface area impacted by pain. In a previous study of 27 pediatric SCD patients hospitalized for VOE, the APPT more accurately reflected recovery than pain intensity scores.

Objectives: To demonstrate the validity of the Adolescent Pediatric Pain Tool (APPT) in a population of SCD youth hospitalized for VOE.

Methods: 157 children and adolescents with SCD, ages 7-21, hospitalized for VOE were enrolled at four urban children's hospitals. The study was approved by the Institutional Review Boards at all institutions. Written informed consent was obtained from all parents or subjects and written assent was obtained from those under age 18 years. Subjects were excluded if they had a primary diagnosis other than VOE, had concurrent Acute Chest Syndrome, or were unable to speak or understand English. The APPT is a multidimensional pain instrument for children and adolescents composed of a body outline with an analog scale that a participant colors and shades to describe their current pain, as well as a pain quality word descriptor list. In this study the APPT body outline was utilized for illustrating pain location in SCD youth hospitalized for a VOE. In addition to the APPT subjects completed 3 measures assessing their pre-hospital experience in the domains of function (Child's Activity Limitations Interview (CALI-21)), pain burden (Sickle Cell Pain Burden Interview-Youth (SCPBI-Y)), and quality of life (Pediatric Quality of Life Inventory (PedsQL)). Subjects also completed 5 measures reflecting their acute experience: average pain over the previous 24 hours (11-point [0-10] Numeric Rating Scale (NRS)), 2 measures of function (Children's Acute Pain-Functional Ability Questionnaire (CAP-FAQ)) and (the FIM™), mood (Positive Affect Negative Affect Scale (PANAS)). All measures were collected once on a single day of hospitalization. Data analysis was conducted using SPSS 16.0.

Results: Mean age was 15.7 years (IQR 12.9 – 18.7 years of age); 55% were females; 85% of the sample reported their race as Black American; 67.3% of the population's sickle cell genotype was HgB SS; 14% received chronic blood transfusions; 43% were taking Hydroxyurea; mean length of stay was 4.5 days (IQR 2.5 – 5.1 days); 69% (109 patients) were enrolled within the first 2 days of admission for VOE. The frequency of body location for pain reported within this population was as follows: legs (67%), back (53%), arms (43%), chest (39%), abdomen (25%), head (24%), and face (5%). The APPT demonstrated significant weak correlations with other study measures as shown in Table 1.

Conclusion: This study provides further evidence that the APPT body outline may be an appropriate tool for assessing pain in SCD youth hospitalized for VOE. The APPT body outline correlated weakly with validated study measures of function, pain, pain burden, mood, quality of life, as well as length of stay. The APPT should be considered as a standard measure to be utilized in the assessment of pain in hospitalized youth with VOE.

Table 1: APPT Correlations with Study Measures	
Measure	**Pearson Correlation (p-value)**
CALI	0.17 (0.04)*
CAP-FAQ	0.27 (0.001)***
FIM	-0.09 (0.31)
Length of Stay	0.18 (0.03)*
NRS-Pain Score	0.21 (0.01)**
PANAS	-0.21 (0.01)**
PEDSQL	-0.17 (0.04)*
SCPBI-Y	0.27 (0.001)***
*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001	

THE PSYCHOSOCIAL FUNCTIONING AND ACADEMIC ACHIEVEMENT IN SIBLINGS WITH AND WITHOUT SICKLE CELL DISEASE

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Background: Sickle cell disease can have a profound affect on adolescents' psychosocial development. Self-esteem issues and poor body image due to delayed growth and sexual maturation may cause significant psychological distress. Frequent pain crises, leg ulcers, and avascular necrosis of the hip and shoulder are significant threats to adolescents' self-esteem. Problems with parental and peer relationships are also sources of distress. In addition, frequent hospitalizations and clinic appointments may affect an adolescent's ability to become independent of their parents. As a result, poor psychosocial adjustment in adolescents with SCD may lead to low self-esteem, social isolation and poor academic achievement.

Objective: The aim of this study was to compare the psychosocial functioning and academic achievement in siblings with and without SCD.

Methods: Using convenience sampling, we recruited (N=133) 45 siblings with SCD, 43 siblings without SCD, and 45 primary caregivers from the Children's National Medical Center Sickle Cell Program in Washington, DC. We controlled for age, family environment, socioeconomic status, and parent education in the dyad. Siblings with and without SCD, ages 12-18, completed the Youth Self Report. Their primary caregivers completed the Child Behavior Checklist for each sibling.

Results: Siblings with SCD (M=53.70, SD=9.01) reported more internalizing behaviors than their healthy siblings (M=46.51, SD=7.73); t=4.52, p=0.00. They also reported less social competence (M=43.52, SD=9.55) than their healthy siblings (M=50.38, SD=7.23); t=-3.78, p=0.00. Primary caregivers reported similar results. They reported more internalizing behaviors in children with SCD (M=54.96, SD=8.45) than in children without SCD (M=47.31, SD=8.16); t=4.83, p=0.00. They also reported more problems with social competence in children with SCD (M= 42.20, SD=13.75) than in children without SCD (M=52.11, SD=3.96); t=-4.71, p=0.00. And lastly, primary caregivers reported more academic problems in children with SCD (M=42.16, SD=11.20) than in children without SCD (M=50.82, SD=7.39); t=-4.55, p=0.00.

Conclusion: This study provides strong evidence that adolescents with SCD are at risk for psychosocial adjustment problems and poor academic achievement. More longitudinal studies are needed to understand the impact of SCD from adolescence to adulthood. This study highlights the need for additional resources and interventions to address the needs of this particular patient population.

412

DEVELOPMENT AND PRELIMINARY EVALUATION OF THE ASSESSMENT OF OPIOID TAKING BEHAVIORS AND ADHERENCE SCALE (AOTBA) IN PATIENTS WITH SICKLE CELL DISEASE

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Introduction: Various disease-specific and general (Morisky, etc.) scales have been developed to assess medication adherence. However, we found no sickle cell disease (SCD)-specific measures of opioid taking behavior and adherence, especially for as-needed medication. The objective of our study therefore was to develop a disease-specific research instrument describing prescribed opioid adherence and opioid taking behavior in patients with SCD.

Method: As part of a multiphase, mixed-method study, we used an adaptation of several published methods to construct 20 sequential, chronological steps for developing a new scale. We then customized these steps for relevant sickle cell disease SCD opioid-taking domains. We report here on steps 1-6, which included wide-ranging quantitative and semi-structured, qualitative interviews of 11 male and 10 female African-American adults with SCD (average age 36 years). We used a grounded theory approach to analyze the qualitative data.

Following this, we used priori procedures for domain specification and survey item delineation, specifically a linguistic-transformation approach. We are currently using posteriori procedures to conduct a preliminary appraisal of translational (content and face) validity.

Result: Scale development results have led to inclusion in the draft scale of a new concept—momentary medication taking behavior—not previously described in the literature. The scale also captures concrete patterns of adherence for as-needed medication as well as for scheduled medication. Lastly, it allows for several discovered conceptual domains that explain observed opioid taking behavior. These domains can be categorized under a biopsychosocial- spiritual schema. Domains include but are not limited to: forgetfulness, carelessness, social stigma, fear of addiction,, side effects, cost of medication, excruciating pain, maintaining functionality at work/ school, meeting life obligations.

Conclusion: The emerging draft scale reflects that, rather than chaos in adherence and opioid taking behavior in SCD, there appear to be underlying discernable behavior patterns. Second, the scale reflects new concepts of medication adherence in general. These concepts challenge the current theories and models of medication-taking behavior and adherence.

CLINICAL PRESENTATION OF SICKLE CELL DISEASE FROM A SINGLE CENTER IN CENTRAL INDIA: A PROSPECTIVE ANALYSIS

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Background: Sickle Cell Disease (SCD), is a major public health problem in India which is home to approximately half of all SCD patients in the world. [Kate et al. 2003] The highest prevalence of the βs gene in India is in three historically disadvantaged ethnic groups identified as the: Scheduled Castes, aboriginal ethnic groups (Scheduled Tribes) and Other Backward Classes, together representing 24% of India's population of over a billion individuals. [Patra et al. 2011] It has been suggested that the phenotype of SCD is milder in India; however, there is a lack of detailed phenotypic studies of SCD in India. [Mohanty et al. 2002]

Objectives: To determine the clinical phenotype associated with SCD in Central India.

Methods: A prospective study of the clinical events in a large cohort of patients with SCD, followed in a single center in Nagpur, Maharashtra, in central India, was performed between 2008 and 2012 to determine the clinical phenotype of SCD. Data were collected during hospital and clinic visits. Deaths outside the hospital were ascertained by verbal autopsy. Descriptive statistical analysis was carried out using SAS software (Cary, NC, USA). The rates of clinical events were compared to rates reported in the Cooperative Study of Sickle Cell Disease (CSSCD). Patients on Hydroxyurea were excluded from the study and came off the study if they started the drug during the period of the study. Demographics and clinical events were also compared between the Scheduled Castes, Scheduled Tribes and Other Backward Classes.

Results: A cohort of 732 patients (303 females, 424 males; age range 3 months – 43 years) was followed for 1768.1 patient years. The rates of painful crisis (66.63 vs. 32.4 cases per 100 person-years), fever (58.43 vs. 39.3 cases per 100 person years) severe anemia (7.13 vs. 4.3 cases per 100 person-years (PY)) and mortality (1.70 vs. 1.1 cases per 100 PY) were all higher for the Nagpur cohort than the CSSCD cohort. Causes of death include infection, splenic sequestration, severe anemia and stroke. Intriguingly, the rates of sequestration crisis (1.64 vs. 3.63 cases per 100 PY), acute chest syndrome (1.13 vs. 24.5 cases per 100 PY) stroke (0.4 vs. 1.15 cases per 100 PY) and meningitis (0.11 vs. 0.81 cases per 100 PY) were lower in the Nagpur cohort compared to the CSSCD cohort. Malaria, not reported in the CSSCD, was observed in 0.90 cases per 100 PY. Demographic characteristics and the incidence of these clinical events observed were similar between the three ethnic groups.

Conclusion: This is the first report of a large prospectively phenotyped cohort of patients with SCD in India. These data suggest that the clinical phenotype of SCD is at least as severe in Nagpur, India as described in the CSSCD. The experience of this cohort should reflect the true clinical course of those individuals with homozygous SS and Sβ+/Sβ0 disease. Since the clinical presentation of disease was similar in all ethnic groups studied, severity may not be related to ethnic background. The observation of a severe of phenotype of SCD in India makes the case for public health interventions such as newborn screening, comprehensive care and disease modifying therapy such as Hydroxyurea. Further studies of populations with SCD in different regions of India are required to further delineate phenotype of SCD in India.

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296

DEPRESSIVE SYMPTOMS AND DISEASE MANAGEMENT SELF EFFICACY, NOT CATASTROPHIZING, PREDICT PAIN INTERFERENCE INDEPENDENT OF PAIN SEVERITY IN SICKLE CELL DISEASE: RESULTS FROM THE BASELINE IMPORT STUDY.

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Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy that causes both acute and chronic pain. Adults with SCD also carry a high burden of medical complications which impair function and quality of life. This study aimed to determine psychosocial variables that predict pain interference beyond that predicted by pain severity, disease complications, and basic demographics (age and sex). Participants were enrollees in the Improving Patient Outcomes with Respect and Trust (IMPORT) SCD cohort study who had complete data for all predictors (n=235, mean age 35.6 yr., 55.3% female). A "best subset" model selection procedure was used to find the best model predicting pain interference measured by the Brief Pain Inventory (BPI). Predictors included a comprehensive group of psychosocial measures: disease management self-efficacy, BPI pain severity, pain-related catastrophizing (Pain Catastrophizing Scale, PCS), stress (Urban Life Stress Scale), and depressive symptoms (10-item Center for Epidemiologic Studies Depression Scale, CES-D). Chart abstracted comorbidities that might indicate more severe disease or greater impairment were entered as well, including depressive disorder, avascular necrosis of bone, a history of cerebrovascular accidents, prior acute chest syndrome, and pulmonary hypertension. We used an automated algorithm in the R statistical computing environment to produce the best models of each possible length according to Bayesian Information Criterion (BIC). Thereafter, these models were compared on BIC. The best model contained three predictors: pain severity, depressive symptoms, and disease management self-efficacy. A two-predictor model lacking self-efficacy was only marginally inferior. These findings suggest that psychosocial interventions for pain-related function in SCD should target depressive symptoms, and possibly disease management self-efficacy.

IMPROVING EMERGENCY DEPARTMENT CARE FOR CHILDREN WITH SICKLE CELL DISEASE

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Background: Children with sickle cell disease present to the emergency department with complex medical and psychosocial needs. Little research has been conducted to understand elements necessary to provide a comprehensive management approach. The Emergency Department Sickle Cell Assessment of Needs and Strengths (ED-SCANS)© is a decision support tool and set of seven algorithms that can be used as a quality improvement framework to guide management of the adult with SCD in the ED. We aimed to inform modifications of the adult version of the ED-SCANS for use with children.

Objectives: The aim of the study was to identify themes to (1) improve comprehensive, family centered, quality care, and (2) identify health service referral needs, for children with sickle cell disease (SCD) in an emergency department (ED).

Methods: A series of focus groups and individual interviews were conducted with emergency physicians, nurses and parents of children with sickle cell disease. ED physicians and nurses were recruited from within the Region 4 Health Resources and Services Administration HRSA funded Pediatric Genetic Collaborative (Kentucky, Ohio, Minnesota, and Wisconsin). Parents were recruited for focus group participation who attended either a state (Illinois) or national meetings (Tennessee). A total of nine clinician focus groups (two parent, three EM physician, four EM nurse), and two individual interviews (SCD NP and pediatric hematologist with SCD focus) were conducted. Focus groups were conducted until saturation of themes was noted and no new themes emerged. All participants provided verbal consent prior to participation. Participants reviewed the adult ED-SCANS and made discussed key differences between adults and children in each algorithm. Transcripts were analyzed and key themes identified.

Results: The following main themes were identified: Role of the Parent, Triage, Analgesic Management, Diagnostic Evaluation, Disposition, and High risk evaluation and referrals needed at discharge. Participants identified critical areas that can be used to organize and improve the assessment, management, and disposition/referral decisions to improve the quality of care provided to children with Sickle cell disease in the Emergency department.

Conclusions: Management of children with SCD in the ED may benefit from a strong multi-disciplinary approach and model of care, including nurses, physicians, social workers, child life specialists. At the center of optimal care is the important role of the child, parent and family. Patient and family centered care can guide important aspects of the management of children with SCD in the ED including elements of triage, analgesic management, diagnostic evaluation, decisions regarding disposition, and the need for referrals for unmet medical and psychosocial needs.

SOCIAL BEHAVIORAL NEEDS OF PATIENTS WITH SICKLE CELL DISEASE

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Background: Patients with sickle cell disease (SCD) frequently experience either complex social situations or behavioral health co-morbidities such as anxiety and depression.

Objective: The objective of this study is to report the number of patients who expressed a desire to have a social or behavioral health referral made during an Emergency Department (ED) visit and the response to these requests, including the number of referrals actually made, and number of patients who self-reported anxiety or depression during the same visit.

Methods: An observational, multi-site study was conducted in two teaching EDs in North Carolina. Adult SCD patients with an ED visit for an acute vaso-occlusive crisis were eligible for inclusion. Thirty five adults (mean age 32, 51% male) completed a total of 40 different interviews; five patients completed more than one interview. Informed consent was obtained prior to conducting patient interviews or medical record reviews. Forty interviews were conducted within two weeks of an ED visit, over a period of six months. All attempts were made to select patients for interview using stratification based on admission or discharge ED status (50% each), and the number of ED visits (5) in the three months prior to the ED visits. Patients were asked "Do you feel it would have been helpful to receive a social work referral at your last ED visit?", and "Do you feel it would have been helpful to receive a psychiatrist or behavioral health specialist referral at your last ED visit?" Patients were also asked if they generally felt depressed or anxious. The medical record was reviewed for evidence of a referral made during that visit. Descriptive statistics were used to analyze the self-reported desire for a referral and evidence of a referral made.

Results: Patients reported the need for a social service referral during 15 visits (37%, 3 additional patients reported already receiving services and 2 were unsure), and behavioral health referral during 9 visits (23%, 3 additional patients were already receiving services and 3 were unsure). No social service referrals were made, and one psych-behavioral health referral was made. During 30% of the visits patients reported feeling depressed and 25% reported feeling anxious.

Conclusion: The perceived need for either a social or behavioral health referral was common among adults with SCD, yet referrals were rarely made. Interventions to address social and behavioral health needs are an important component of the comprehensive care of chronically ill patients. The SCD research and quality improvement teams are currently developing a strategy to partner with ED social workers to perform a basic social-behavioral health screen for all SCD patients seen in the ED. Any patient who screens positive will be referred to the out-patient or in-patient social worker for further interventions focused on the patients' social behavioral health needs.

A REVIEW OF VITAMIN D DEFICIENCY, TREATMENT AND PATIENT KNOWLEDGE AMONG SICKLE DISEASE PATIENTS AND PARENTS

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Background: Vitamin D deficiency (VDD) is known to be common in patients with sickle cell disease (SCD). Despite the high prevalence of VDD in the SCD population, routine screening and treatment of VDD is not yet the standard of care. Research thus far has been almost exclusively cross-sectional and focused on VDD and bone metabolism in SCD. A number of small studies have investigated the relationship between VDD and SCD. One study has shown a relationship between VDD and chronic pain in SCD. We have previously looked at a variety of genes related to the vitamin D receptor (VDR) in association with SCD severity and have found no major association.

Methods: This study was designed as a retrospective chart review on the diagnosis and treatment of vitamin D deficiency in the University of North Carolina pediatric and adult sickle cell clinics. In addition, there was a telephone survey of patients or their parents about their recollection of their diagnosis and treatment for vitamin D (VD) deficiency. Charts were reviewed for those who had a 25 hydroxy vitamin D level (D3) done within the last 5 years. We recorded the first D3 level and the most recent D3 level within the 5 year period. Those with a D3 level in this time frame were contacted by phone and after giving permission, underwent a brief telephone survey about their VDD diagnosis and treatment.

We reviewed the charts of 200 patients who have been tested in this time frame. Descriptive statistics were preformed on the vitamin D levels, prescriptions provided and patients' recall of treatment. Analytic statistics examine relationships between patients' recall of diagnosis / treatment, and the effectiveness of treatment as determined by vitamin D levels.

Results: A total of 207 subjects were surveyed. 141 of the subjects had D3 levels within the 5 year time period. Of the 115 subjects who had D3levels prior to the survey, 63% were male and 37% female. The majority of the patients were SS, accounting for 66% of the population. About half of the patients remembered being tested for VDD and 40% remembered being informed of their deficiency though only 30% recalled filling a prescription for vitamin D. The mean of the first recorded D3 level for all subjects was 15.9; 79% were deficient at the time of the first level. The mean of the most recent D3 level was 22.8; 65% were deficient at the most recent time. The mean time between the two D3 levels was 4.9 years. In general, women had higher initial VD levels than men and there was a trend towards the more severe genotypes having lower levels than the milder genotypes. Those subjects who remembered being tested for VD deficiency had mean initial VD level of 16.1 vs 19.7 for those who did not remember being tested; this difference was not significant. However, those who remembered being tested had significantly higher subsequent VD levels (25.4 vs 14.7, p=0.0034). Those patients who reported receiving a prescription for VD had significantly lower initial VD levels than those who reported not receiving a prescription (14.8 vs 19.9, p= .013). The most recent VD level for these two group was not different however (23.3 vs 21.7, p=0.67).

Conclusion: As previously described by others, we observed that the majority of patients with SCD have moderate to severe vitamin D deficiency, even after at least one attempt at treatment. Despite a uniform protocol for testing and treating VDD in the clinic, we are generally unsuccessful in achieving adequate levels in most of our patients. Our data show that those patients who remembered being told about their vitamin D deficiency had much better subsequent vitamin D levels than those who did not remember. This may be a clue to an approach to patient education and treatment.

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239

SICKLE CELL CONNECTS WITH THE CHRONIC PAIN SERVICE: A COLLABORATIVE CLINIC A QUALITY IMPROVEMENT PROJECT

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Background: Acute vasocclusive pain is the hallmark of sickle cell disease (SCD) and may transition to chronic debilitating pain(SCD). Patients who have chronic pain and high healthcare utilization are at risk for opioid toxicities, increased psychiatric morbidities and impaired quality of life. These patients pose a significant therapeutic challenge and require the novel multi-disciplinary approaches to management.

Objectives: To develop a multidisciplinary chronic pain team with a focus on patients with sickle cell disease

Methods: A sickle cell chronic pain team team consists of an anesthesiologist, two nurse practitioners specializing in pain, a pain psychologist, a physical therapist and sickle cell nurse practitioners. The team saw patietns when they were admitted to hospital as well as on a regular basis in a dedicated outpatient chronic sickle cell pain clinic. During hospitalizations for pain exacerbation, the pain service rounded with the hematology team and provided assistance with dosing and titration of opioids medications, low dose ketamine, nerve blocks, neuropathic pain modalities, topical analgesics and acupuncture. The sickle cell NP, who knows the patients' medical and psych-social history, presents new patients to the team prior to the clinic visit and remains an important resource for determining primary medical needs. The pain physician with a background in anesthesia, adult and pediatric chronic pain treatment, leads the team and helps design customized pain plans. The goals are that this complex group of patients becomes more compliant with and less reliant on opioid analgesia while continuing to have adequate pain control when it is needed. The individualized pain plans are tailored to target the patient and her functionality as a whole, not merely sickle cell disease. Because of the high rate of co morbid psychiatric issues surrounding chronic pain syndromes, we provide thorough psychiatric evaluations and treatments. Physical reconditioning and rehabilitation issues through physical therapy and treatments are an integral part of the management. The team also educates individuals and their families about tolerance of opioids, signs of hyperalgesia and how this can affect efficacy of treatment in the future. By encouraging patients to take charge of their lives and their pain management, this clinic plays a vital role in preparation for transition to adult care. Pain plan contracts have been established and patients are held to clear guidelines and compliance. Patients are required to provide urine drug screens. Patients are required to visit the pain clinic every month and all opioid prescriptions are only given by the pain physician.

Results: Children's hospital of Pittsburgh follows 255 patients of whom 9 patients (3.6%) were identified with chronic pain. All 9 patients have been referred to chronic pain clinic. Two patients were scheduled several times have not participated due to in-patient on scheduled clinic day. One was followed by adult chronic pain provider transferred care. One had no hospital admissions, and decreased prescriptions for Oxycodone but added fentanyl patch. One had increase in-patient days, medication switched from Nuycnta plus fentanyl patch to Oxycodone, topical Lidocaine, TENS unit acupuncture and Neurontin.

One patient had increased admission days but decreased Oxycodone usage. Two patients had decreased in-patient days and decrease oxycodone usage one with no change in in-patient days and increase in Oxycodone however sustained acute lumbar sacral injury. Interestingly, all seven patients followed in clinic have 1oo% compliance for out-patient follow up; there have been no questions of drug diversion. Several patients were diagnosed fibromyalgia as a co-morbidity. We are helping the patient to distinguish between fibromyalgia pain and sickle cell pain

Conclusion: Chronic debilitating pain is a serious often recalcitrant problem in sickle cell disease. A multi-disicplinary team approach offering ongoing multi-modality care is described. Prevention, early identification and intensive multi-modality approaches are key to optimal management of chronic pain.

IMPLEMENTATION OF AN INCENTIVE PROGRAM TO INCREASE MEDICATION ADHERENCE IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: The clinical benefits of hydroxyurea (HU) are well established for patients with sickle cell disease (SCD). While there are currently no evidence-based guidelines outlining the use of hydroxyurea, its use as a preventative therapy is becoming more common in patients with SCD as providers aim to decrease painful events, acute chest syndrome, transfusions and mortality. Assessing HU adherence can often be challenging and make dosing adjustments and treatment decisions difficult. Lack of response to hydroxyurea is often thought to be due to non-adherence instead of lack of efficacy of HU.

Objectives: The primary objective was to establish a program in our outpatient clinic setting to increase medication adherence by providing incentives.

Methods: At our center, approximately 30% of the sickle cell patient population are currently prescribed hydroxyurea. A twelve month hydroxyurea log was created identifying date lab drawn, hemoglobin, MCV, ANC, percent fetal hemoglobin, dose of hydroxyurea and stated compliance. On initiation of the program, a goal MCV for each patient was created based on current laboratory values and what was deemed to be an achievable goal with hydroxyurea compliance. Each month, patients earned points based on current lab values, with the main focus being an increase in MCV or attainment of goal MCV. Patients could also earn points by telling the provider the reason for hydroxyurea treatment and mechanism of action of the medication. Patients earned additional points for coming to lab visits on time, another mechanis m of assessing adherence to treatment. During provider visits education was done including mechanism of action of hydroxurea, need for compliance and ways to increase medication adherence. Educational pamphlets were created, distributed and reviewed during visits. Patients earned points each month and could redeem them for a prize, or allow points to accumulate and redeem at a later time for a prize with greater value.

Results: Our goal of implementation was to encourage medication adherence and active participation in the treatment process. A great number of our patients showed increase in interest in their hydroxyurea therapy, coming for monthly lab and provider visits, inquiring as to their lab values and points earned. Graphs were often provided and reviewed showing overall trends in MCV, ANC and fetal hemoglobin levels. Several patients showed an increase in hydroxyurea compliance including marked increase in fetal hemoglobin, increase in MCV and/or decrease in ANC.

Conclusions: During the implementation of this project, anecdotally we did see an increase in medication compliance for those patients who were actively involved in the sickle cell rewards program. Of note, a similar rewards program was created simultaneously for deferasirox adherence in chronic transfusion patients. Similar interest and increase in adherence was seen in those who actively participated in the rewards program. As the project continues, compliance pre and post-implementation of the project will be analyzed for effectiveness. Further assessment of treatment adherence is needed including statistical analysis of data comparing adherence of those who do and do not actively participate in the sickle cell rewards program. The earning of points for hydroxyurea compliance may more accurately reflect compliance by combining a variety of adherence monitoring techniques including additional lab values such as ANC and fetal hemoglobin in addition to MCV, as well as patient medication logs and monthly pill counts.

313

NUTRITIONAL IMPACT OF SICKLE CELL ANEMIA: OBESITY CAN ALSO BE A PROBLEM IN SICKLE CELL ANEMIA

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Introduction: The nutritional impact of SCA has been evaluated in several reports, most of them demonstrating an increased risk for denutrition occurring particularly during late childhood and adolescence. Few studies evaluated the risk for obesity and possible influence on therapy such ashydroxyurea (HU).

Objectives: Evaluate morphometric parameters, phenotype and severity of sickle cell anemia (SCA) in a cohort of patients (pts) followed at CHU Ste-Justine, Montreal Canada.

Methods: Pts aged 5 to 20yrs old, using retrospective chart review were evaluated. Using WHO growth charts, patients were divided into 4 categories: underweight, normal, overweight and obese based on BMI percentile <5, 5-85, 85-95 and >95 respectively. Hematological and clinical parameters included SCA phenotype (HbSS, SC, SBThal0, SBThal+), hemoglobin (Hb), white blood cell and platelet count, number of hospitalization and length of stay (LOS) per year. Incidence of SCA complications included retinopathy, osteonecrosis, stroke and microalbuminuria. Chi-square, t-test and Fisher exact tests were used for statistical analysis, with p value of <0.05 defined as significant.

Results: 171 pts were evaluated (84 SS, 72 SC, 7 SBthal+, 8 SBTHal0). All BMI groups were similar for age. While a majority had BMI within normal limits, 14 (8%) were underweight, 21 (12%) overweight, and 16 (9%) obese. In contrast to most studies, we found no differences in denutrition between sex, though males tended to be more overweight and obese but the difference was statistically not significant (p=0.2). While SS/SBThal0 tended to be underweight (OR 2.3, p=0.1), SC/SBThal+ were more frequently overweight or obese (OR 7.2, p<0.0001). Among various parameters, severity of anemia correlated mostly with BMI (see fig). Among HbSS, the proportion of HU treated pts was higher in the overweight and obese groups compared to those with low or normal BMI (3/3 obese and 2/4 overweight, vs 0/8 underweight and 23/70 with normal BMI HbSS pts were on HU– p=0.006). There were no correlation with hospitalization rate and LOS. Except for higher systolic blood pressure in overweight and obese pts, there was no increase in the rate of retinopathy, osteonecrosis, microalbuminuria, and stroke.

Conclusion: Healthcare professionals taking care of SCA patients should be aware of the nutritional impact of SCA. Our study suggest that severity of chronic anemia and hemolysis is the main factor influencing BMI, as SS or SBThal0 phenotype and those with more severe anemia are at increased risk for being underweight, while those with SC or SBThal+ with near normal Hb are at increased risk for obesity. The increased proportion of overweight and obsese among SS pts treated with HU is also consistent with such observation. Further studies should define long-term consequences of nutritional variations in adulthood, particularly in those with obesity and hypertension, as well as the impact of early nutritional interventions.

SICKLE CELL AND SCHOOL POLICY: EVIDENCE FROM A STUDY OF SICKLE CELL IN SCHOOLS IN ENGLAND.

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Background: As new-born screening and improved pediatric care enhance the life chances of young people with SCD, attention turns to how well or poorly young people with SCD are cared for in schools. This paper suggests that simply raising teacher and peer awareness is insufficient and that the strong enabling framework of a school policy guide is required.

Methods: The research aimed to describe experiences of young people with SCD at school, and consisted of a survey (n=569) and qualitative interviews (n=40) with young people with SCD.

Results: Pupils with SCD miss 16.2 days of schooling a year, typically in short periods of two or three days. Only 6% report that they are helped to fully catch up these school absences. 57% of children reported not being allowed to use the toilet when needed and 46% not being allowed water in class. 36% reported being made to take unsuitable exercise and 34% being called lazy when tired. Children perceived both physical environment (temperature, school furniture) and social environment (being upset by teachers or by school peers) as triggers to episodes of their illness. Whether or not teachers or pupils knew that they have sickle cell made no significant improvement to the treatment of young people with SCD in terms of being supported, through preventive measures, to ensure good health at school. The apparently "obvious" idea that teacher or peer awareness would be sufficient to improve school experience for young people with SCD is not borne out by this study.

Conclusions: A change in wider school environments is required such that young people with SCD are supported irrespective of whether they disclose or hide their SCD. Advancement for people with SCD thus depends on changing institutional arrangements, inorder to complement medical advances. A Guide to School Policy has therefore been devised.

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APPLICATION OF CLINICAL MICROSYSTEMS TO IMPROVE THE OUTPATIENT CARE OF PATIENTS WITH SICKLE CELL DISEASE (SCD)

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Background: Patients with sickle cell disease (SCD) face many challenges from their chronic disease, including inpatient admission for vaso-occlusive crises. Long Island Jewish (LIJ) Medical Center, a part of the North Shore-LIJ Health System is a 500 adult bed, tertiary care facility with more than 500 yearly admissions for acute vaso-occlusive crisis. Although great strides have been made to improve care of the sickle cell patient population, there is an unfortunate gap in outpatient care that often develops in the transition from pediatric to adult care. This gap leads to unnecessary hospital admissions and poor perception of the medical establishment. The National Institutes of Health has stressed that care for these individuals should be done at specialized clinics. Studies have shown that timely follow-up can help prevent hospitalization and improve quality of life (Leschke, 2012.) The aim of our microsystem initiative was to improve the outpatient management of our sickle cell population at LIJ Medical Center.

Objectives: To create a comprehensive sickle cell program at LIJ Medical Center that meets the varied needs of our sickle cell patients. To establish an outpatient clinic dedicated to the care of our patients with sickle cell disease. To deliver high value care across the continuum and increase the number of outpatient sickle cell visits.

Methods: An interdisciplinary team which included an adult hematologist, a pediatric hematologist, a general internist, a nurse educator, a social worker, medical residents, community leaders, and a patient with SCD was assembled to study the sickle cell micro system. The team was educated in Clinical Microsystems methods (Nelson, 2007), implementing process mapping and fishbone analysis to help understand the barriers to effective care. Outpatient follow up was identified as a major impediment to quality of care, and this data led to the development of a dedicated outpatient sickle cell clinic. The inpatient discharge process was intervened upon to include consultation with the sickle cell clinic attending. We used a PDSA cycle method to implement and test our intervention. The specific aim was to achieve a doubling of sickle cell referrals, and interventions were put into place to increase visit adherence. The interventions included a visit with a social worker during the inpatient admission and a phone call 24 hours prior to the scheduled outpatient visit.

Results: The SCD outpatient clinic had 21 patient encounters from 9/1/2012-11/25/2012 with a no-show rate of 52%. After the adherence and referral interventions, from 11/26/2012-2/12/2013 the clinic has had 59 patient encounters with a no-show rate of 20%. 64% of referrals came from inpatient admissions and the pediatric hematology clinic.

Conclusion: The Clinical Microsystems Methodology is an effective means of engaging an interdisciplinary team in improving the care of sickle cell population. Future aims of the team will be to assess the rate of hospital readmission and patient satisfaction.

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393

SICKLED RELATIONSHIPS: THE DILEMMA OF BEING A MODEL GENETIC CITIZEN IN THE PREVENTION OF SICKLE CELL ANEMIA IN NIGERIA

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Background: Sickle cell anaemia (SCA) is an under-reported public health issue in the West African country Nigeria, yet an alarming 25% of her 140 million population are estimated to be carriers while 150,000 children are estimated born with sickle cell anaemia annually. Currently, there is no formal recommendation for sickle cell screening rather premarital screening is enforced by individual churches and couples actively encouraged to not marry if carriers.

Objectives: Using anthropological theories and ethnographic methods, this paper explores perceptions and attitudes towards sickle cell disease and premarital screening and the acceptability of prenatal and neonatal screening among an online population of Nigerians.

Methods: A total of 143 participants were recruited from online social media platforms through snowball sampling with a link to a self-administered questionnaire included in mails. The questionnaire which supported both quantitative and qualitative data gathering probed their knowledge of sickle cell disease, their experiences of premarital genetic screening and their views of prenatal and neonatal screening. The choice of open ended questions was to make the responses as natural, self-representing and descriptive as possible. Data analysis followed accepted conventions for qualitative studies and grounded theory development process.

Results: Awareness of sickle cell disease was high in this sample and participants largely associated the disease with poor physical appearance, pain, constant hospitalizations and early death, comparable to AIDS and Cancer. Their perception about the value and quality of life of affected individuals differed significantly from the positive disposition of respondents who are living with Sickle cell anemia.

The majority of respondents understood the implications of their genotype status and the reproductive risks pertinent to it and embodied this genetic responsibility leading to stigmatizing attitudes towards marriage to individuals with AS/SS genotype and even towards AS/AS intermarriage. This attitude was significantly high among participants who self-reported their genotype as AA.

Participants who had SCA or SCT are found to experience 'tentative relationships' and struggle with disclosure in their bid to be responsible genetic citizens.

Prenatal diagnosis was accepted by most as a means to ascertain the genotype of the fetus but rejected as a signpost for termination. Neonatal screening had a high acceptability.

Conclusion: The Nigerian population in this sample privileged prevention by conception/marriage over prevention by selective birth leading to stigma of individuals with SCT/SCA for their marital and reproductive choices. This attitude may potentially affect uptake and acceptability of government-subsidized prenatal screening and termination services in the future. The paper also highlights the importance of public health educational programs that will address the deficit in knowledge about informed choices, other types of screening, and the ability to manage sickle cell anemia.

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PERCEIVED RACISM AND STIGMA AMONG ADOLESCENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a genetic disorder that prominently affects Black Americans. Little information is known about the role of race among patients with SCD and stress that may stem from perceived racism, both in the community and medical settings. Research on perceived racism and health disparities have been conducted in adult SCD populations. To our knowledge, no study has been conducted to assess the experience of adolescents with SCD regarding perceived racism. The majority of the research has focused on the psychological impact of medical symptoms, such as pain, fatigue, and functional ability.

Objective: The purpose of this study is to explore the prevalence of perceived racism among adolescents with SCD and the relationship between perceived racism and perceived stigma as well as negative health outcomes, such as disease severity, psychological distress and quality of life.

Methods: To date, 12 patients with SCD (75% female), ages 13-21 (M=18.36, SD=2.13), were recruited from outpatient (N=9) and inpatient settings (N=3). Participant completed measures of perceived racism (Perception of Racism in Children and Youth), perceived stigma (Child Stigma Scale), depression (Center for Epidemiology Studies Depression Scale), pain burden (Sickle Cell Pain Burden Interview), and quality of life (Pediatric Quality of Life Inventory).

Results: While recruitment is ongoing, preliminary results demonstrate a significantly strong relationship between perceived racism and perceived stigma ($r=0.64$, $p<0.05$). There are also moderate correlations trending towards significance between perceived racism and quality of life ($r=-.53$, $p=.14$), pain burden ($r=.50$, $p=.17$), and psychological distress ($r=.40$, $p=.28$).

Conclusion: While preliminary, these results support the relationship between perceived racism and psychosocial and physiological features of SCD. Specifically, greater perceived racism was strongly associated greater perceived stigma. While trending towards significance, our results also supported that greater perceived racism was moderately related to greater pain burden and depression symptoms as well as lower quality of life. These findings can inform interventions and disease management within community and medical settings. As recruitment continues, it is anticipated that the relationships trending towards significance will become significant as our sample size increases.

403

VITAMIN D DEFICIENCY IN AN ADULT POPULATION WITH SICKLE CELL DISEASE

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Objectives: to examine the prevalence of Vitamin D deficiency in adults with sickle cell disease, response to treatment of deficiency, relative risk determination of vitamin D deficiency for variations in hepatic and renal function, implications for avascular necrosis, and fractionation of exogenous vs endogenous vitamin D levels before and after treatment.

Background: Vitamin D deficiency has been well documented in large portions of the North American population. Children with sickle cell disease are known to have a prominent incidence of low Vitamin D that appears to persist into adulthood. The measurement of serum Vitamin D25(OH)D level is generally recognized as the clinical standard for evaluation Vitamin D status in both children and adults with normal with normal liver and kidney function, and represents the primary circulating form of Vitamin D. Vitamin D is obtained endogenously by conversion of 7-dehydrocholesterol to its D3 form (cholecalciferol) via ultraviolet irradiation in the skin, or by ingestion of exogenous D2 (ergocalciferol) in the diet. Both forms are bound in the blood stream by Vitamin D binding protein (DBP) and albumin, and transported to the liver for conversion to VitaminD 25 (OH)D. Principally in the kidney, Vitamin D25(OH)D is further metabolized to Vitamin D1,25(OH)2D, which is the principal bioactive form of vitamin D. The purpose of this study was to analyze the incidence of vitamin D deficiency and response to treatment in a population of patients with various forms of sickle cell disease.

Methods: In a retrospective study, we reviewed serum Vitamin D25(OH)D and/or VitaminD1,25(OH)2D levels obtained in 116 patients with Hgb SS(n = 73), Hgb SC(n = 30), HgbS/thalassemia(n = 11), and Hgb S/lepore(n = 2) over a period of 21 months beginning in February 2010, ending in November 2011. Along with Vitamin D levels, LFTs, total protein, albumin, and creatnine levels were reviewed that coincided with vitamin D levels or were obtained within 3 months. Vitamin D levels were measured utilizing liquid chromatography–mass spectrometry (LC-MS). Normal ranges were 30-100 ng/ml for Vitamin D25(OH)D and 18-72 pg/ml for VitaminD1,25(OH)2D. Data included post treatment vitamin d levels and chemistries, within 6 months, in the portion of patients that were treated with oral ergocalciferol 50,000 units twice per week for 15 weeks. Presence or absence of avascular necrosis (AVN) prior to treatment in each patient was also noted.

Results: Results were divided into HgbSS and HgbS/other (SC, S/thalassemia, S/lepore). The mean baseline Vitamin D25(OH)D level in Hgb SS patients (n = 57) was 11.1, and in HgbSother patients was 15.79 (n = 39), A Welch Two sample t-test yielded p-value = 0.03401. Following treatment the mean level in Hgb SS patients (n = 21) was 22.74, and in HgbS/other patients was 17.00 (n = 9), A Welch Two sample t-test yielded p-value = 0.4627.

The mean baseline Vitamin D1,25(OH)2D level in HgbSS patients (n = 13) was 45.55, and in HgbS/other patients was 25.55 (n = 15), A Welch Two sample t-test yielded p-value = 0.8635. There was insufficient data for analysis of post treatment Vitamin D1,25(OH)2D levels.

Conclusion: Initial results in our sample of adults with sickle cell disease, reveal those with HgbSS disease had significantly lower baseline Vitamin D25(OH)D levels compared to those with other subtypes. Furthermore there was no significant difference in levels following treatment between the two groups, while the mean for both groups remained below normal after treatment. Baseline Vitamin D1,25(OH)2D levels were not significantly different between adults with HgbSS disease and those with other subtypes. Further analysis will include relative risk determination of vitamin D deficiency for variations hepatic and renal function, implications for avascular necrosis, and fractionation of exogenous vs endogenous vitamin d levels before and after treatment.

410

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Background: Sickle Cell Disease (SCD) is the most common inherited blood disorder with a documented history of increased risk for invasive pneumococcal disease (IPD). The 23-valent pneumococcal polysaccharide vaccine (PS-23) and the 7-valent protein polysaccharide conjugate vaccine (PCV-7) have been used to minimize the risk of developing IPD with great success1. As a result of both the anti-pneumococcal vaccines and newborn screening/penicillin prophylaxis, there has been a significant improvement in childhood mortality in SCD in the United States. Yet a large percentage of patients with SCD are noted to be non-responders who fail to mount a proper immune response to vaccination2. Early re-vaccination has been successful but routine analysis of immune response and clear guidelines for non-responding patients with SCD are needed3.

This study was performed to assess the percentage of patients with SCD who fail to respond to more than 50% of the serotypes covered by the PS-23. Demographics were collected to evaluate the risk factors for non-responders including age, SCD genotype, duration of time since last PS-23, and number of total PS-23 received per patient. Patients included in the study had received at least one PS-23 vaccine and were greater than 2 years of age.

Methods: Data was collected retrospectively from a cohort of patients treated for SCD at the Sickle Cell Center of Southern Louisiana (New Orleans, LA). Anti-pneumococcal titers were measured clinically to assess vaccine response and booster vaccination was given in patients who demonstrated response to less than 50% of serotypes measured. When patients required re-vaccination, antibody titer response was assessed between 4-6 weeks after re-vaccination. Immunoglobulin titers were measured by ARUP laboratories by quantitative multiplex bead assay. Demographic information was collected regarding patient's age, SCD genotype, and vaccination history. All patient data was de-identified at the time of collection.

Results: We collected antibody titer data on 53 patients with SCD. The cohort included 31 males and 22 females with an average age of 12.8 years (range 4-22 years). Thirty-seven patients had HbSS disease, 12 patients had HbSC disease, 3 patients had HbSB+ disease, and 1 patient had SB0 disease. Of the 53 patient records reviewed, only 38% of patients had responded to more than 50% of the 23 serotypes assessed. In addition, 25% of patients had responded to less than 25% of serotypes tested. Patients with a positive response to more than 50% of the serotypes assessed, were slightly older (average age of 13.75 years versus 12.12 years) and had received the PS-23 more recently (26.61 months versus 49.41 months).

Conclusion: An alarmingly high proportion of patients with SCD in our cohort demonstrated sub-optimal antibody titer responses to routine pneumococcal vaccination. In addition, 25% of patients exhibited a response to less than 25% of the serotypes covered by the PS-23 despite having received the appropriate vaccinations. Seven of the thirteen patients with markedly poor titer response have been re-vaccinate. Obviously larger studies of patients with SCD are needed for better evaluation. Studies are continuing to better analyze predictors for poor antibody titer response, assessment of serotype-specific response, response to re-vaccination, and immune-mediated pathophysiology of poor vaccine response. From this initial retrospective study, it appears that all patients with SCD should undergo S. pneumoniae antibody titer evaluate if greater than 2 years has elapsed since their last PS-23. In addition, it is highly recommended that all patients with less than optimal anti-pneumococcal vaccine response continue to receive penicillin prophylaxis.

Table 1:

% titer response	Total patients (n=53)	Age (years)	HbSS (n=37)	Hb SC (n=)	HbSB+ (n=3)	SB0 (n=1)	Duration since PS23 (months)
76-100%	0.226415	13.75	65%	15%	15%	5%	26.61
50-25	0.377358	11.85	81%	19%	0	0	50.3
<25%	0.245283	12.8	62%	38%	0	0	46.31

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FACTORS ASSOCIATED WITH EARLY MORTALITY IN ADULT PATIENTS WITH SICKLE CELL DISEASE

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Background: Advances in the care of patients with sickle cell disease (SCD), such as neonatal screening, parental and patient education, advances in red blood cell transfusion medicine, iron chelation therapy, penicillin prophylaxis, pneumococcal immunization, and hydroxyurea therapy, have led to significant increases in life expectancy. However, while it is no longer considered a disease of childhood, SCD continues to be associated with early mortality. As patients age, they manifest evidence of end-organ damage, including pulmonary hypertension (PHT) and chronic renal failure, that are known to be associated with an increased risk of death.

Objective: We evaluated the frequency of death as well as clinical and laboratory variables associated with mortality in a cohort of adult patients with SCD at an academic medical center.

Methods: Patients in the cohort were enrolled from August 2000 through May 2012 in a study to determine the pathophysiology and natural history of echocardiography-defined PHT in SCD. The patients were evaluated while in the non-crisis, "steady state"; had not experienced an episode of acute chest syndrome in the 4 weeks preceding enrollment; and had no clinical evidence of congestive heart failure. Doppler echocardiography was used to determine the tricuspid regurgitant jet velocity (TRV) and the pulmonary artery systolic pressure (PASP) was calculated using the modified Bernoulli equation (PASP = 4V2 + estimated right atrial pressure). A suspected diagnosis of PHT was based on estimated PASP values adjusted for age, sex, and body mass index. Univariable and multivariable logistic regression were used to evaluate the association of clinical (age, gender, SCD genotype, number of pain crises in the past year, history of acute chest syndrome, use of hydroxyurea, TRV, and suspected PHT) and laboratory (white blood cell count, hemoglobin, fetal hemoglobin, reticulocyte count, creatinine, lactate dehydrogenase, and d-dimer) variables with mortality.

Results: One hundred and seventy seven patients (female = 105, male = 72; SS = 133, Sb0 = 12, Sb+ = 10, SC = 21, SD = 1), with a median age of 34 years (range: 18 – 71 years) were evaluated. There were 30 deaths during the follow up period (17%). The risk of death was significantly decreased with the use of hydroxyurea, but increased with age, TRV, and suspected PHT (Table 1). When TRV was dichotomized (TRV < 2.5 m/s vs. ≥ 2.5 m/s), high TRV was associated with an increased risk of death. Every one tenth unit increase in TRV was associated with an 18% increase in the risk of death. In addition, the risk of death was significantly associated with hemoglobin and d-dimer levels. In a multivariable analysis with age, suspected PHT and hemoglobin in the model, age (odds ratio [OR]: 1.07, 95% confidence interval [CI]: 1.031 – 1.11, p = 0.0003) and suspected PHT (OR: 2.99, 95% CI: 1.83 – 7.55, p = 0.021) remained associated with an increased risk of death.

Conclusion: Although right heart catheterization was not obtained to confirm the diagnosis, suspected PHT (based on echocardiography) was an independent risk factor for death in this patient cohort, confirming and extending the findings of other studies. Furthermore, increased TRV, d-dimer, as well as low hemoglobin were associated with increased mortality, while the use of hydroxyurea was associated with decreased mortality. In addition to encouraging hydroxyurea use, new therapies to modify disease risk are required to further improve patient survival in SCD.

Table 1:

Covariate	Number of deceased patients	Number of living patients	Odds Ratio	95% Confidence Interval	p-value
Age (years)	30	147	1.08	1.04 – 1.12	<0.0001
TRV* (m/s)	22	105	5.35	1.94 – 14.70	0.001
TRV* (>2.5 m/s vs. ≥2.5 m/s)	22	105	2.73	1.05 – 7.09	0.04
Suspected pulmonary hypertension (Yes/No)	29	139	3.87	1.67 – 8.98	0.002
Hemoglobin (g/dL)	30	147	0.73	0.57 – 0.94	0.01
Use of Hydroxyurea (Yes/No)	30	147	0.41	0.18 – 0.94	0.03
D-dimer (ng/mL)	11	70	1.00	1.00 – 1.00	0.04
Creatinine (mg/dL)	13	104	1.99	0.94 – 4.23	0.07
Reticulocyte count (%)	29	143	0.93	0.84 – 1.04	0.21
Hemoglobin F (%)	28	144	0.97	0.92 – 1.03	0.32
SCD genotype	30	147	1.17	0.84 – 1.63	0.36
Lactate dehydrogenase (U/L)	13	102	1.00	0.99 – 1.00	0.36
Number of pain episodes in past year	13	104	0.95	0.81 – 1.12	0.55
History of acute chest syndrome (Yes/No)	30	147	1.23	0.43 – 2.15	0.70
Gender (M/F)	30	147	0.97	0.43 – 2.15	0.93
White blood cell count (x 10^9/L)	30	147	1.00	0.87 – 1.14	0.96

*TRV - Tricuspid regurgitant jet velocity

298

SPINAL INFARCTION IN SICKLE CELL DISEASE, A RARE AND UNEXPLAINED COMPLICATION

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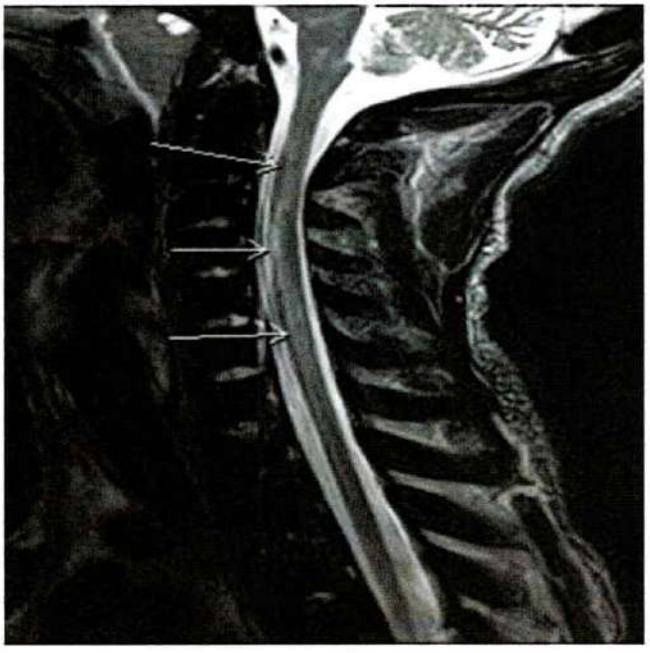
Vasculopathy of large vessels occurs commonly in sickle cell disease (SCD) and as a result cerebral infarction is a well characterized complication of SCD. However spinal infarction appears to be rare. Spinal infarct is infrequent in the non-sickle cell population as well, accounting for only about 1% of all CNS infarcts. Here the authors present the case of a 19yo male with SCD who experienced an anterior spinal infarct and subsequent quadriplegia. He was incidentally noted to be a heterozygote for Factor V Leiden. We review the literature and found 2 previous cases of spinal cord infarction and sickle hemoglobin. The literature search did not demonstrate that heterozygocity for Factor V Leiden plays an important role in spinal cord infarction. The paucity of cases associated with sickle hemoglobin does not allow us to postulate any particular risk factors within sickle cell disease that might predispose to spinal cord infarction.



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READINESS CHECKLIST: PREPARING FOR TRANSFER OF MEDICAL CARE

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Background: Adolescence is a period of growth and challenges for all young people. It is a time of contradictions: wanting independence but still dependent, desire to be an adult while still being a minor. In the midst of these contradicting desires young people will experience many challenges. Many young people living with sickle cell disease (SCD) experience additional hurdles related to their chronic condition and risk a lack of preparedness when they transfer their care to an adult health care setting. In developing a program that begins at birth and helps families and patients identify changes to grow on, this abstract describes a quality improvement project with the goal of piloting a tool to assess young people's readiness to become active participants in their care.

Objectives: 1) To assess medical knowledge and health systems navigation skills in pre-transfer adolescents and post-transfer adults with SCD. 2) To compare parent perception of adolescents' knowledge with adolescents' self-reported knowledge. 3) To compare parents' perception and adolescents' self-reported knowledge with assessment of adolescents' knowledge through provider interview.

Methods: A specific checklist was developed for individuals with SCD by adapting the "Got Transition?" Transition Readiness Changing Roles tool available from the National Health Care Transition Center (NHCTC). Permission for adaptation was obtained from the NHCTC. This modified checklist was completed independently by six adolescents 12 years of age and older and by their parent/guardian when they checked in for a routine visit to the pediatric hematology clinic. Subsequently, during the clinic visit, the adolescent and parent were interviewed using the same checklist to guide discussion about medical transfer skills. The same checklist was used to interview adults with SCD followed by the adult sickle cell provider, during an elective visit for routine exchange transfusion.

Results: In very preliminary work, 6 adolescents and their parents independently completed the checklist and were interviewed. In addition, 6 adults who established care with an adult sickle cell provider, 3 within the last year, were interviewed using the checklist. When completing the checklist, significant variability in the number and type of transfer skills and knowledge reported by adolescents was observed, independent of age. The responses were often discordant with the parent's assessment. Adolescent interviews compared with completed checklists showed both over- and under- estimation of the adolescents' knowledge and skills. Adult interviews, guided by the checklist, demonstrated more skills in the navigation and self-care domains than in the medical knowledge domain, and overall more skills than those of the adolescents.

Conclusion: Based on initial results of this quality improvement project, valuable information may be obtained using a skills and knowledge checklist, followed by an interview of both adolescents and their parents when preparing for transfer of care. Ongoing work will include ongoing modification of the checklist in response to findings from adolescents and parents. Annual use of a checklist and review by a provider offers the opportunity for common focus within families and with providers on medical knowledge and development of navigation skills. Interviews with adults and adult providers may provide additional insight into the skills and knowledge necessary for a successful transfer of care.

PROGRAM FOR CONTINUING LEARNING ON SICKLE CELL DISEASE FOR PRIMARY HEALTH CARE PROFESSIONALS IN THE STATE OF MINAS GERAIS, BRAZIL

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Introduction: The incidence of sickle cell disease (SCD) in the State of Minas Gerais, Brazil, is 1 in 1,400 newborns, according to the State Program for Newborn Screening (PTN-MG)1. Minas Gerais is a state in Southeastern Brazil holding an area of 585,528 km2 and a population of 19.9 million inhabitants. Nowadays 6,200 patients with SCD are under follow-up at Hemominas, an institution aimed at blood care funded by the State of Minas Gerais. Most of them are insured by the Brazilian Single Health System, a national public system for health insurance. Primary health care consists of actions aimed at health assistance, surveillance, prevention, and promotion. About 4,500 family health care teams provide primary health care in every 853 municipalities in the state of Minas Gerais. The program for continuing learning on SCD has been proposed to face obstacles such as impossibility of health care professionals leaving their centers to attend training courses, the large number of target professionals from different areas, and the need for support of each municipal administration to the educational initiative. OBJECTIVE: To describe the Program for Continuing Learning on SCD aimed at primary health care (PHC) professionals in the State of Minas Gerais.

Method: In 2010, CEHMOB (Educational and Supportive Center for Hemoglobinopathies), supported by NUPAD (Center for Newborn Screening and Genetic Diagnosis), and the Hemominas Foundation started developing an educational program aimed at multidisciplinary PHC teams. The project, entitled "Sickle Cell Disease: Care Guidance for Primary Health Care", was based on the Logical Model2, a resource used for planning, monitoring and assessing intervention programs in diversified social contexts. This model supports the identification of multiple causal and functional interdependence relations across its constituting elements, as well as the engagement of all social actors.

Results: The program for continuing education was developed in three stages (Figure), namely: 1) mobilization of public managers to join the proposal; 2) training of facilitators (professionals holding a bachelor's degree) to disseminate knowledge among the other professionals of the health care teams (training courses were provided as 90-hour distance education courses focused on discussing clinical cases); and 3) dissemination based on educational practices developed by the own facilitators in their municipalities and aimed at spreading knowledge on SCD among the other primary health care professionals. From 2010 to 2012, a total of 333 public health managers (both at the state and the municipal levels) were sensitized to join the training proposal. In sum, 456 health professionals were trained as facilitators: 74 medical doctors, 319 nurses, 15 social workers, 7 dentists, 7 physiotherapists, 12 nutritionists, 8 psychologists, 7 pharmacists, 3 speech therapists, and others (4). These professionals are scattered over 85 municipalities. The facilitation process is in full operation in 6 municipalities and in high gear in 79 others. Approximately 4,527 patients presently live in the municipalities with support from health professionals trained within the scope of the program herein described.

Conclusion: The use of the Logical Model to support the Program Architecture proved to be valid for planning, monitoring, and assessing the aforementioned stages. This has resulted in effective implantation of the program, which has the potential to be replicated in other states in Brazil and other countries with similar health structure.

Architecture Project
"Sickle Cell Disease: care line in Primary Health Care".

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415

PATIENT CENTERED APPROACH TO DESIGNING SICKLE CELL TRANSITION EDUCATION

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Background: Transition from pediatric to adult care can be a high risk time for patients with sickle cell anemia. Increased morbidity and mortality from disease complications can occur from the unique barriers that are presented during the time of transition. This process could be helped by a sickle cell transition education program that addresses the educational and sociocultural issues that impact transition to adult care.

Objective: To develop a patient-centered approach to designing sickle cell transition education. We identified patient characteristics associated with understanding transition education, topics for additional patient education, and solicited ideas for user-centered, technological education platform desired by adolescents.

Methods: Interviews were conducted with 37 patients between the ages of 12 and 20 years (mean:15yrs), living in urban (n=25) and rural (n=11) settings as defined by Alabama Rural Health Association. Likert scales identified preferred educational platform and understanding of educational topics. Dichotomous variables were developed for age (older: >15 years; younger: ≤15 years), therapy (on therapy: hydroxyurea or chronic transfusion, vs. no therapy), grades (A or A and B, vs. B average or lower). Statistical analysis was performed using JMP 10 software. Descriptive statistics were generated to identify mean, standard deviation, and interquartile range. Dichotomous variables were analyzed by Pearson's chi-squared test or Fisher's exact test.

Results: Twenty-three adolescent patients (62%) knew their sickle cell genotype. Patients who knew their diagnosis were more likely to have better grades in school (p=0.01), but did not differ based on age, therapy, gender, or location (rural vs. urban). Forty-three percent of patients had been told they were transitioning to an adult doctor; however, only 21% received transition education. Patients that had been informed about transition were older (p=0.002), and receiving sickle cell therapy (p=0.04); results did not differ by location. Adolescent patients believed that transition education should begin at 16.1 years (IQR: 15.0 - 17.5 years). The majority of patients (54%) believed that transition education should occur at both the doctor's office and at home, with 27% of patients believing education should occur only at the doctor's office, and 19% only at home. Adolescents preferred YouTube as the platform for interactive transition education. The second preference was a dedicated transition website. Twitter and books were least often chosen media. The majority of patients preferred transition education lasting one hour. Adolescents reported least knowledge about several topics, i.e. obtaining health insurance, effects of sickle cell on organ functions, differences between pediatric and adult doctors, and physician specialty areas. Patients believed they already were well informed about sickle cell genetics and how to treat pain events. A notable finding was the preference to meet their adult doctor before transitioning expressed by 92% of those surveyed. Regarding medical history documentation, 46% of patients wanted a medical history card for their wallet, 38% wanted a Smartphone application, and 32% wanted an usb memory card.

Conclusion: Despite institutional efforts to increase transition education, some patients may not understand their diagnosis and need effective transition education. This sample of clinic patients preferred YouTube videos or a dedicated website to receive transition education. Patients identified four topics for additional education about sickle cell disease and its management. Patient-centered research can identify strategies to improve sickle cell transition education.

AT THE CROSSROADS OF INFLAMMATION AND COAGULATION: HSP90 INHIBITION IN SICKLE CELL DISEASE

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Background: It is well established that sickle cell disease (SCD) manifests global perturbations of homeostasis. Vaso-occlusion, inflammation, and coagulopathy all likely contribute to the protean complications of SCD. Central to both inflammation and coagulation is the monocyte. These cells can be profoundly pro-inflammatory and can express tissue factor on their surface and thus influence both inflammation and coagulation. Monocytosis is common in SCD as is steady state monocyte activation. Exaggerated monocytic response to stimulus may also contribute to the severity of acute events. Thus, agents that regulate monocyte function are potentially of significant relevance in SCD.

To this end, we have discovered that the heat shock proteins (Hsp) are potential master regulators of these cells. We previously demonstrated that inhibition of one such HSP, Hsp90, could completely ablate the profound and hyper-responsive monocytic inflammatory release upon lipopolysaccharide (LPS) challenge. Inhibition of Hsp90 also blocked LPS-induced NF-kB translocation to the nucleus. Thus, these results suggested a potent role for Hsp90 in bacterially-induced monocyte based inflammation. However, the role of Hsp90 in cytokine-induced monocyte activation was speculative. The role of Hsp90 in monocyte tissue factor expression, or reactive oxygen species generation remained unknown.

Objectives: We sought to determine the role of Hsp90 in regulating the pro-inflammatory, pro-coagulant, and ROS generating potential in monocytes.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from whole blood using Ficoll density separation. Cytokine release from PBMCs or the THP-1 monocytic cell line was evaluated with cytometric bead array in conditioned media. Cytokine induction of ROS generation and tissue factor expression was implemented via stimulation with an endothelin-1, IL-β, TNF-α combination. Monocyte tissue factor expression was detected via flow cytometry. ROS generation was detected in aggregate using L012 based chemiluminescence or visualized in individual cells using flow cytometry with CELLROX. NF-kB translocation to the nucleus was detected via cell fractionation followed by western blotting or indirect immunofluorescence. PBMCs or THP-1 cells were pre-treated with 17-DMAG, an Hsp90 inhibitor, overnight for ROS and cytokine assays, or for 2 hours prior to tissue factor detection. Similar results were obtained with 17-AAG, an Hsp90 inhibitor in the same chemical class. Differences between groups were evaluated using Mann-Whitney tests. Unless otherwise stated $p<0.05$.

Results: At baseline, PMNCs from SCD patients consistently demonstrated higher levels of pro-inflammatory cytokine release, ROS generation, and monocyte tissue factor expression than those from healthy controls. Inhibition of Hsp90 with either inhibitor significantly reduced these measures of steady state monocyte activation. Hsp90 inhibition also inhibited both LPS and cytokine induced tissue factor expression in PBMCs and THP-1 cells ($p<0.001$). Cytokine induced ROS generation was significantly interrupted in monocytes upon inhibition of Hsp90. We also noted a profound translocation of NF-kB to the monocyte nucleus upon cytokine stimulation. Consistent with the effects on tissue factor expression, pro-inflammatory potential, and ROS generation, this translocation could be completely ablated with Hsp90 inhibition.

Conclusions: Our data suggest that Hsp90 inhibition significantly reduced the both pro-inflammatory and pro-coagulatory potential of PMNCs from patients with SCD. These results thus position Hsp90 as a potential master regulator of homeostasis and an attractive therapeutic target in patients with SCD.

385

NATIONAL ESTIMATES OF SICKLE CELL DISEASE WITH PEDIATRIC STROKE AMONG AFRICAN-AMERICANS—UNITED STATES, 1997-2009

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Background: Sickle cell disease (SCD) is a known risk factor for stroke and stroke is a major complication of SCD. Stroke is a leading cause of death among children. Approximately 10-20% of children with SCD develop strokes, but no consistent national estimates exist.

Objectives: The purpose of this study is to determine the rate of stroke among the African-American pediatric population with SCD.

Methods: We used the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID) 1997-2009. African-American patients aged 6 months to 18 years with ≥1 ICD-9-CM diagnosis code for ischemic or hemorrhagic stroke were included. Stroke cases were stratified by the presence or absence of SCD. Age (in years) at time of stroke was divided into four groups: 0.5-4, 5-9, 10-14, and 15-18. Data were weighted to provide national estimates and analyzed using SAS survey procedures. Pediatric stroke risk factor diagnoses co-existing with ischemic and hemorrhagic stroke were frequency ranked.

Results: During the 12 year period, there were 2809 stroke cases among African-American children. SCD was present in 599 (21%) of stroke cases and 523 (87%) of the stroke and SCD cases were ischemic stroke. There were more stroke cases among children aged 0.5-4 years without SCD (815 (37% and in children aged 5-9 years with SCD (224 (37%)) than in other age groups. For African-American children, SCD is the highest risk factor for ischemic stroke (29%) and the 7th most common risk factor for hemorrhagic stroke (8%)

Conclusions: SCD is a leading risk factor to pediatric stroke in African-American children. Reducing the number of strokes among children with SCD would have a significant impact on the rate of strokes among African-American children.

AN ASSESSMENT OF DISEASE KNOWLEDGE DIFFERENCES BETWEEN ADOLESCENTS WITH SICKLE CELL DISEASE AND THEIR CAREGIVERS AND ITS CORRELATION TO QUALITY OF LIFE

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Background: As per the Health Belief model, health behaviour is determined by personal beliefs or perceptions about a disease. This is more so in a chronic illness like Sickle Cell Disease {SCD}. In pediatrics, health education is mostly parent centered. Disease knowledge of caregivers affecting outcomes is well studied, but disease knowledge amongst pediatric patients of SCD themselves has been less explored. We believe this is important, especially in the age group of 12-21 yrs., as disease knowledge would be a fundamental skill for transition readiness.

Objective: We wish to assess disease knowledge amongst our adolescents with SCD and their caregivers and compare the two. We would like to assess patients' reported impact of disease on quality of life (QoL) and evaluate their caregivers' perception of the same. We would also assess whether disease knowledge has a correlation to quality of life.

Design/Methods: We enrolled 40 patients with SCD, between 12-21 yrs of age and at least one caregiver of each patient. Patients and caregivers were administered two questionnaires each. The first pertained to disease knowledge and the second, was a standardised QoL questionnaire, PedsQLTM.

Results: Of 40 patients, 75% had Hb-SS, while almost 7% had Hb-SC disease. We observed caregiver knowledge scores to be significantly ($p=0.016$) higher than patient's scores.

With regards to the QoL scores, we observed a significant difference ($p=0.04$) between caregiver perceived social QoL and patient's reported social QoL, while there was no significant difference between physical, psychosocial, emotional QoL scores. But there was a significant difference ($p<0.05$) in total QoL reported by patients with HbSS and their caregivers, which was not seen in other disease subtypes.

Disease knowledge and QoL appeared to be correlated with a positive correlation coefficient of 0.36.

Conclusions: Our study demonstrates a marked disparity in disease knowledge and perceptions of QoL between adolescents with SCD and their caregivers. There also appears to be a link between disease knowledge and QoL. These findings underline the importance of patient focused health education in adolescent pre-transition age group. It seems that enhancing their knowledge would not only add to transition readiness, but ultimately help them cope better with a life of chronic illness. Our study also reflects the need to encourage health communication within families of children with SCD. This would contribute to dissemination of knowledge and also to an improved caregiver perspective of how the disease affects their child.

DEVELOPMENT AND PRELIMINARY VALIDATION OF A MULTI-DIMENSIONAL ELECTRONIC PAIN DIARY FOR CHILDREN WITH SICKLE CELL DISEASE

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Background: Vaso-occlusive crisis (VOC) is the hallmark of sickle cell disease (SCD). Health care utilization for VOC however, underestimates the burden of pain in SCD. In the PiSCES study adult patients reported pain on > 50% of the diary days; however, unplanned health-care utilization occurred on only 3.5 percent of diary days. The burden of daily pain in pediatric SCD is unclear. Paper based pain diaries studies are limited by recall bias, errors and falsely high compliance due to backfilling of entries. Electronic pain diaries overcome these limitations by facilitating real-time data capture. These have been used in children with arthritis, cancer, abdominal and musculoskeletal pain. They are also more acceptable to children and teens when compared to paper pain diaries. We have previously created a web-based electronic pain intensity diary for children with SCD that recorded pain intensity scores 3 times a day and demonstrated feasibility by collecting 4,931 responses representing a 71 percent compliance rate. Qualitative interviews of participants suggested a need for a more comprehensive assessment of pain. Participants also expressed a preference for documentation of daily pain trends to facilitate better management of pain. Patients also appreciated the monitoring of their pain and timely intervention by a staff member through the pain intensity diary and felt that it was an important benefit of the diary.

Objective: To develop and determine the face and content validity of a web-based multi-dimensional electronic pain diary for older school-age children and adolescents with SCD.

Methods: A web-based diary that can be accessed via a secure website using a smartphone or computer was created. The 18 items in the pain diary were adapted for SCD from "e-Ouch ", an electronic pain diary validated for use in children with cancer and arthritis. Twice daily, the items assess pain intensity, duration, interference with daily tasks, sleep, fatigue, precipitating factors, pain relieving treatments and response to treatments using the Numerical rating Scale (0-10). Experts in SCD pain and psychometrics were asked to review and rate the items on a 5 point Likert scale for content, language, clinical relevance, comprehensiveness of the answer choices and likely feasibility and acceptability in children with SCD. Expert responses were tabulated using Survey Monkey and free text responses for each question were analyzed. These were used as a guide for modification, addition or removal of items. Cognitive interviews and usability studies with patients with the finalized pain diary are planned.

Results: The pain diary items were reviewed by 15 experts in sickle cell pain and psychometrics. The number of items was reduced to 16 and the questions modified for content, language and clinical relevance. These items are now undergoing re-review for expert feedback and consensus prior to testing in children with SCD. Children have indicated their willingness to participate in a study using the multidimensional pain diary.

Conclusions: A web based multi-dimensional electronic pain diary has been developed for use in children with SCD. This instrument can be easily accessed using a smartphone or a computer. Face and content validity will now be determined using semi-structured cognitive interviewing methods.

295

CREATION OF A PATIENT DATA REGISTRY COULD IMPROVE CARE FOR SICKLE CELL DISEASE PATIENTS

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Background: Sickle Cell Disease is a group of disorders characterized by sickling of erythrocytes when they are deoxygenated due to a mutation in the B globin gene of hemoglobin. The sickled erythrocytes obstruct blood vessels and disrupt endothelial cell function, leading to tissue hypoxia and clinical complications. Sickle cell disease used to be a pediatric disease and patients did not survive into adulthood. With advancements in sickle cell disease care, many of these patients are making it into adulthood and knowledge of disease complications and management is still evolving. One of the limitations is complete and accurate collection of patient information.

Objectives: The purpose of this research project was to establish a database of the necessary and appropriate information in adult sickle cell patients to be utilized for their clinical care and to identify important research questions for future study. This registry for sickle cell disease patients will make it easier to retrieve accurate and complete data on patients which could lead to better patient management and care for patients.

Methods: We reviewed the literature including clinical reviews and research studies to create a data form that highlighted information necessary for physicians to treat sickle cell disease patients. This included basic information such as patient's sickle cell genotype, current medications and complications from their sickle cell disease. Information was gathered from the current electronic medical record (EMR) and patient interviews during sickle cell clinic.

Results: Our sample registry consisted of 10 patients who all identified as Black or African American. There were 3 males and 7 females within an age range of 27 to 43 years. We found that information on patient's sickle cell genotype and complications from their sickle cell disease was missing, incomplete or difficult to retrieve. The EMR noted patients with sickle cell disease but the specific genotype was missing. Several medication inconsistencies were also found for example, one patient was taking three times more of a medication prescribed for chelating of iron. In addition, four out of the ten patients interviewed reported taking less medication than what was listed in the EMR. Patients reported reasons for the discrepancy included financial limitations, medication reconciliation errors after hospitalization and fear of side effects of medications. These inconsistencies can severely compromise patient care.

Conclusion: The purpose of this research project was to establish a data base of the necessary and appropriate information in adult sickle cell patients to be utilized for their clinical care and to identify important research questions for future study. This registry for sickle cell disease patients will make it easier to retrieve accurate and complete data on patients which could lead to better patient management and care for patients. The problems encountered such as inconsistencies between the medical record and patient answers show that care for the adult sickle cell patient may be compromised. The creation of a database linked to the current medical record with relevant medical information on patients will lead to a complete and accurate medical record. This ensures that physicians have the pertinent information needed to make decisions that could lead to better treatments and outcomes for sickle cell disease patients.

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405

ASPEN SYNDROME REVISITED (ASSOCIATION OF SICKLE CELL DISEASE, PRIAPISM, EXCHANGE TRANSFUSION AND NEUROLOGICAL EVENTS)

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Background: Priapism is a known complication of sickle cell disease (SCD) with a reported prevalence of 3.6% (Furtado et al. Int J Hematol 2012). Exchange transfusion to treat priapism in SCD patients has been associated with neurological events such as severe headache, seizures, focal neurological deficits and obtundation and has been termed as ASPEN syndrome (Siegel et al. J Urol 1993). Case reports of ASPEN are infrequent and reported 15 years ago, giving rise to debate and a lack of consensus regarding its existence and cause.

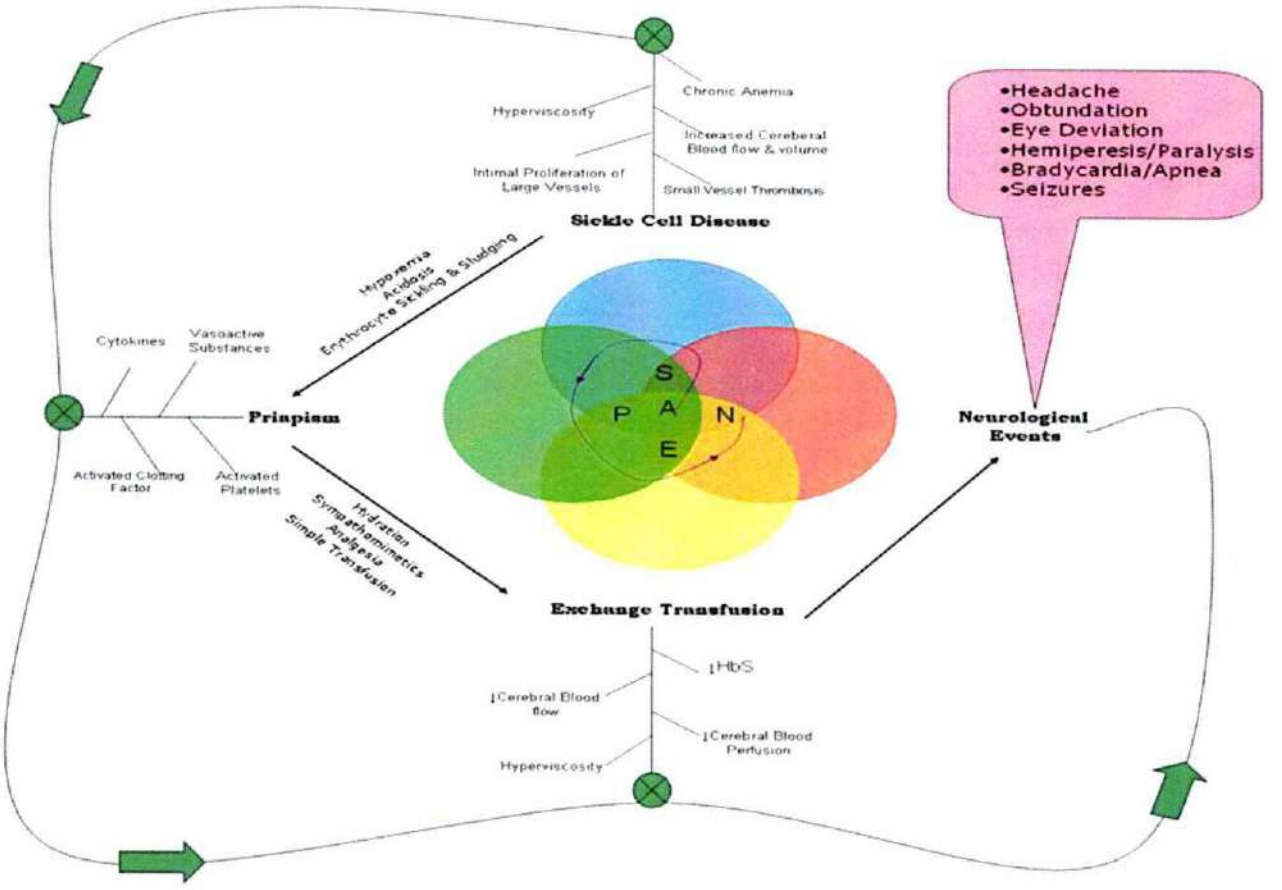
Case Report: A 16 year old African American male with HbSS disease presented with recurrent episodes of priapism. He has history of silent cerebral infarct and was on SITT trial in the past. During the first 4 episodes of Priapism, conservative management involving intravenous hydration, analgesics, Sudafed and simple blood transfusion had been sufficient to relieve priapism. During this reportable episode the patient presented to the clinic more than 6 hours after the onset of Priapism. His blood pressure was 160/100 with a heart rate of 140/minute at presentation. He was given a fluid bolus, Sudafed,(Intravenous) and IV Fentanyl . Due to the persistence of priapism he was hospitalized and was started on IV hydration, Fentanyl Panda Sudafed. He received 2 units of PRBC transfusion on Day 2. These measures failed to relieve priapism. Subsequently an exchange transfusion was performed but failed to improve the symptoms. Due to persistence of symptoms the patient underwent penile aspiration and irrigation with epinephrine on Day 2. The patient continued to have priapism and underwent a 2nd aspiration and irrigation with epinephrine and another exchange transfusion. He complained of severe headache, abdominal pain and developed altered mental status immediately following the exchange transfusion pending transfer to surgery for corporavenous shunt. On examination he was non-responsive, had absent pulses, pinpoint pupils, clenched jaw, lateralizing gaze and inadequate respiratory effort. Cardio respiratory monitoring did not show waveforms. Chest compression and bag mask ventilation was initiated and the patient received epinephrine. Central pulse was eventually palpable. The patient also received a dose of lorazepam for possible seizure. The episode lasted for less than 5 minutes. He was then transferred to the PICU and was intubated. CT of the brain was negative for intracranial hemorrhage. MRI and MRV were negative for acute stroke but did show old unchanged infarcts. Sepsis work up was negative. The hemoglobin (Hb) levels of the patient started at 8.3 with a hemoglobin S (HbS) level of 86%. After the 1st simple transfusions the Hb had increased to 9.1 with a steep decrease in HbS to 60%. After the 2nd simple transfusions the Hb rose to 11 with a fall in HbS to 50%. The 1st exchange transfusion resulted in an Hb of 11 with a decline of HbS to 38%. He subsequently had complete neurological recovery.

Discussion: Exchange transfusion to treat priapism in SCD can be associated with neurological events. The optimal timing and rate of exchange transfusion and the maintenance of resultant HbS level to prevent ASPEN syndrome needs to be investigated. A possible pathophysiology of ASPEN is shown in Figure 1.

Questions:

1. Is ASPEN syndrome an entity? What is the pathophysiology of this entity?
2. What is the role of exchange transfusion in the management of SCD associated priapism? Is there a target HbS level desired?
3. What are the benefits and risks of exchange transfusion in priapism management?

Figure 1. Pathophysiology of ASPEN Syndrome



240

SPONTANEOUS EPIDURAL HEMATOMA COMPLICATING SICKLE CELL ANEMIA

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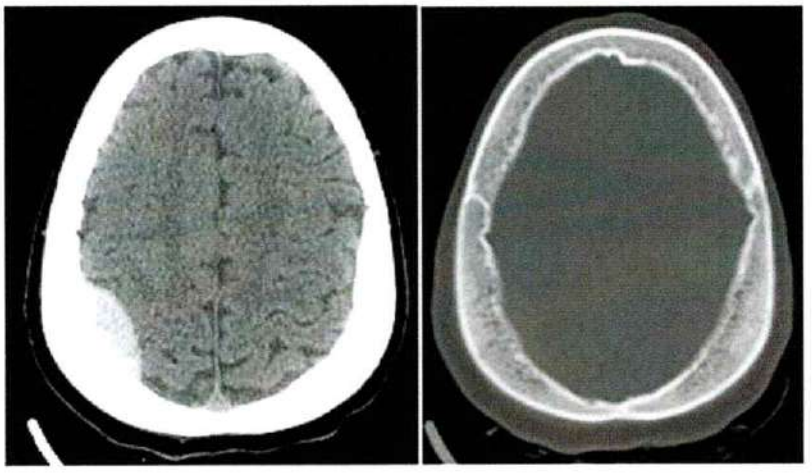
Affiliation: University of Miami

Introduction: Epidural hematomas are unusual manifestations of sickle cell anemia (SCA). We report the case of a child with SCA who presented with a sickle cell crisis that was complicated by the development of acute epidural hematoma.

Case report: A 14-year-old female, known case of SCA, was admitted with a 1 day history of pain in back, arm and extremities. There was no history of trauma, headaches, seizures, or other neurological symptoms. On admission, the patient was alert and could obey vocal commands and had no focal neurological deficit. She was managed with intravenous morphine and ketorolac. On day 2 of hospitalization she was transferred to the Intensive Care because of hypoxemia secondary to acute chest syndrome. She also had decreased in mental status. An exchange transfusion was performed. Post exchange patient developed thrombocytopenia; nucleated red blood cells were increased. Due to the persistence of decreased mental status and considering the possibility of stroke, a head computed tomography (CT) [Figure 1] was obtained, followed by a magnetic resonance imaging (MRI) which revealed right parietal epidural hematoma (1.5 cm x 4 cm) with no mass effect and no other signs of impending herniation or compression. Our patient was successfully managed with no surgical intervention with full recovery.

Discussion: Acute neurological complications in patients of SCA can be ischemic or hemorrhagic. Although rare, clinicians should be aware of the possibility of an epidural bleeding as part of the spectrum of neurological complications in patients with sickle cell disease. Our patient did not have headache and did not have any focal neurological sign, except for decreased sensorium. Hypoxemia and the sedative effect of morphine contributed to a delay in 2 days in obtaining any brain imaging. The precise cause of epidural hematoma is not well known, but it is probably related to the vaso-occlusive episode and the tearing of small vessels. Other contributing factors could have been platelet dysfunction due to medications, low platelet count, and hypoxemia.

Figure 1. Non contrast brain CT



349

Beta-S gene prevalence among socio-economically disadvantaged ethnic groups in Central India

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Background: Sickle Cell Disease,(SCD) an inherited disorder of the red blood characterized by vasoocclusive pain crises, pneumococcal infections, acute chest syndrome, stroke and organ failure is associated with substantial morbidity and premature mortality.[1] It is a major public health problem. India, with a population of 1.2 billion individuals, is estimated to be home to over 50% of the world's patients with SCD. Bs gene has the highest prevalence in ethnic groups that reside in central, eastern , western and pockets of southern India. While SCD is common among all ethnic groups, high prevalence has been report ed in three socioeconomically disadvantaged ethnic categories: the Scheduled Castes (SC), the Scheduled Tribes (ST), and Other Backward Community (OBC) groups in India. [2,3] Each of these categories consists of several distinct large ethnic groups who have practiced endogamy for millennia and thus represent genetic isolates. Prevalence of the Bs gene has been well described in the scheduled Tribe population, but precise estimates are not available for the scheduled caste or other backward cast communities. The scheduled caste population consists of over 1900 groups constitute 15% and other backward casts represent approximately 50% of the Indian population. The tradition of endogamy practiced by the numerous ethnic groups in India provides the rationale for the screening of individual populations to better understand the distribution of the Bs gene and guide counseling and awareness programs and aid development of public policy. Further, published studies to date have not distinguished between community based screening of the general population and secondary screening of family members as a result of detection of a sickle cell mutation in an index case. This limits the utility of these studies in describing reliable estimates of population prevalence of Bs gene.

Objectives: We undertook a study to describe the prevalence of the Bs gene in the scheduled caste population and other backward casts in the district of Nagpur, Maharashtra in Central India.

Methods: The study was performed over a span of eight years (2003-2012) and included the screening of target populations in all age groups (newborns, school age children, young adults, and pregnant mothers) as well as screening in hospital for individuals considered to be at high risk of carrying the Bs gene. Informed consent was obtained from all
adults and parents of children once the individuals were educated on the reasoning behind screening.
We defined ethnic groups by using standardized terminology used in the Census of India and in government regulations as well as by grouping ethnic groups that are closely related, have social interactions, and practice inter-marriage to determine the prevalence rates of the Bs gene.

Results: Through community screening and subsequent target screening of high risk individuals, 35,636 individuals were screened of whom 5,437 were found to have sickle cell trait (SCT) and 1,010 were identified with sickle cell disease (SCD). Community wide screening revealed a sickle cell trait prevalence of 13% among the scheduled caste who belonged primarily to the Mahar ethnic group. Prevalence of the Bs gene was 12% among the scheduled tribe population. Bs gene prevalence was 3.4% among the other backward caste population mainly in the Kunbi and Teli ethnic groups.

Conclusion: This paper for the first time describes the prevalence of the Bs gene in scheduled caste and groups within Central India determined by community based screening. This population screening program has also uncovered previously undiagnosed cases, provided detailed information for population based disease counseling, prevention programs and comprehensive care programs.

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396

A NOVEL IMAGING MODALITY FOR MANAGEMENT OF SICKLE CELL DISEASE PATIENTS WITH MOYAMOYA SYNDROME Arun Panigrahi, Leila Khorasani, Radhika Peddinti, John M. Cunningham

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Background: Cerebrovascular accidents (CVA) are a well known and severe manifestation of sickle cell disease (SCD) which affect 5-10% of patients. A portion of SCD patients with CVA also develop Moyamoya disease, a pattern of large vessel occlusion with a telangiectatic network of collateral vessels. The etiology of this phenomenon may be idiopathic, or secondary to systemic diseases such as SCD. Recent studies have revealed that SCD patients with Moyamoya vasculature have markedly worse neuropsychological evaluations compared to the overall SCD population. Moyamoya vasculature is also one of the strongest predictors of stroke recurrence in children with SCD(1).

Despite these factors, uniform guidelines for management of Moyamoya syndrome in SCD have not been established. Furthermore, in cases where surgical intervention was chosen for select patients, a variety of surgical approaches have been utilized. Finally, although digital subtraction angiography has been diagnostic of Moyamoya vasculature, angiography has been avoided in the SCD population due to the risk of precipitating a cerebrovascular accident or other complications of SCD. Due to this difficulty, diagnosis, management, and long term follow-up of Moyamoya syndrome in SCD has been less than ideal. MR perfusion has been shown to correlate with conventional angiography findings for idiopathic Moyamoya syndrome in both adult and pediatric patients(2).

MR perfusion analysis often relies on manual selection of the arterial input using the anterior circulation to determine arterial input function (AIF). SCD patients often have involvement of bilateral internal carotid arteries and potentially posterior cerebral arteries. We hypothesize that in patients with SCD the basilar artery, which is typically not involved in the disease process, may provide a more accurate analysis of perfusion defect.

Objectives: Our primary aim is to evaluate the pediatric SCD population with secondary Moyamoya Syndrome and characterize the functional status of Moyamoya vasculature using MR hemodynamic parameters via MR perfusion scan. Specifically, we will evaluate whether the selection of a vertebro-basilar arterial input is more appropriate than a internal carotid arterial input for determination of cerebral hypoperfusion. This is done with the intent to optimize surgical patient selection based on cerebral oxygen demand. Our secondary aim, is to use MR perfusion to follow our moyamoya syndrome patient population post-operatively to establish long term outcomes.

Methods: All pediatric patients with SCD as part of their comprehensive care receive transcranial doppler(TCD) ultrasound examinations on a yearly basis. Patients with abnormal TCD results or concern for acute CVA subsequently undergo MRI and MRA examinations. Those with evidence of Moyamoya syndrome are referred to neurosurgery, where MR perfusion exams will be employed to delineate appropriate surgical candidates. Subsequently MR perfusion scans will be obtained on a regular basis to monitor cerebral reperfusion.

Results: Preliminarily three SCD patients with Moyamoya syndrome have been evaluated via MR perfusion scans. Two out of three patients have had abnormal scans warranting surgical intervention. Additionally, one SCD patients with Moyamoya vasculature did not have a perfusion defect warranting surgical intervention and has been followed conservatively without a CVA.

Conclusion: MR perfusion is a non invasive modality that identifies abnormal tissue perfusion in patients with Moyamoya syndrome and hence can be used to accurately identify surgical candidates. Greater patient accrual and follow-up are required to determine the prognostic value of MR perfusion as well as long-term outcomes. This pilot study though, has laid the foundation for further investigation and standardized care for SCD patients with Moyamoya syndrome at our institution.

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MANAGEMENT AND MEASUREMENT OF PRURITUS IN SICKLE CELL DISEASE PATIENTS (SCD)

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Background: Sickle Cell Disease (SCD) affects 70,000 – 100,000 people in the United States. Many patients report pruritus, yet the prevalence is unknown and no instruments for measurement have been recommended for clinical use.

Objectives: The objective of this study was to provide an understanding of the prevalence, severity and assessment of pruritus in patients with SCD using the Visual Analog Scale (VAS) and the National Cancer Institute Common Toxicity Criteria (CTC) Scale. The aims of this study are to describe the incidence and severity of pruritus in a sample of SCD patients, compare the sensitivity and specificity between the VAS and the CTC scales to measure pruritus, and identify which complications of SCD predict pruritus.

Methods: This prospective, cross sectional study sampled patients diagnosed with SCD who presented for care at a Midwestern comprehensive cancer center. Patient characteristics such as age, gender and clinical complications were recorded. The CTC and VAS instruments were used to assess pruritus. The CTC is a 3 point scale with 3 being "intense or widespread" and the VAS is a 10 point scale with 10 being "worst."
Analysis consisted of descriptive statistics, correlation, ROC curves and logistic regression models.

Results: Total number of subjects was 78; 77 had complete data. The number of inpatients was 33 and ambulatory was 44. Eighty seven percent (87%) of inpatients and 38.6% of outpatients reported pruritus. For the total sample, 57.7% reported itching. The mean VAS score for the total population was 3.3 and the mean CTC score was 1.4. For inpatients (N=33), the mean VAS was 4.6 and the mean CTC was 1.5. Seventy three percent (73%) of subjects reported requiring chronic pain medications. The use of chronic pain medications was predictive of pruritus (p=.01). Common complications of SCD, i.e., pulmonary hypertension, liver insufficiency, acute chest syndrome, renal insufficiency and iron overload were not predictive of pruritus. Areas under the curve for the VAS and CTC were .81 and .57 respectively.

Conclusion: These findings suggest that pruritus is common in hospitalized patients with SCD. Further, the VAS is a more sensitive and specific instrument for measuring pruritus compared to the CTC scale.

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430

UTILIZING REFLECTIVE WRITING TO IMPROVE MEDICAL EDUCATION AND CULTURAL COMPETENCE REGARDING THE CARE OF SICKLE CELL DISEASE

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Background: Increased training in reflection, and an educational focus on a more humanistic approach to care, holds great promise for care experiences for patients with sickle cell disease (SCD). Teaching reflection through reflective writing assignments is common in medical school curricula (Branch et al, 2009) and helps students progress from superficial observations to critical reflection and personal growth (Tobias et al, 2011) (Nishigori & Sriruksa, 2011). Reflection is a skill that can be improved upon and applied throughout one's career (Kind et al, 2009). But is a skill requiring practice and directed education (Gans, 2009). Reflective thinking directed towards cultural competency helps medical students empathize with patients and develop a shared understanding of individual struggles.

Methods: Johns Hopkins University School of Medicine implemented its 'Genes to Society', curriculum (GTS) in 2009 (Wiener et al, 2010). GTS includes a Longitudinal Ambulatory Clerkship (LAC). LAC engages first-year medical students in clinical medicine, and exposes them to social and behavioral aspects of health care (Stewart et al, 2011). All students are asked to reflect on 10 discrete experiences based on their clinic time. Some students completed activities in a sickle-cell infusion center (SCIC), and several reflected on these experiences.

Results: Our SCIC is a specialized clinic providing comprehensive care to adults with SCD. One student's reflection is provided as a sample of student experiences with sickle cell treatment (Figure 1). It recounts a SCD patient's categorization of healthcare providers based on the patient's lifetime of experiences in receiving care for his SCD. This patient categorized healthcare providers into 3 categories. The first is the physician who saw nothing but the genetics of SCD and had little to no interest in the patient as a person. While this may sound troubling, the patient believed that this type of physician would at least prescribe enough medication to relieve the patient's symptoms. The second type of physician is one that views all patients with SCD as drug-seeking. This provider will prescribe very small amounts of medication and does not work to ensure a patient's pain is relieved. The final category of physicians is what the patient referred to as soft-touch. The patient used this term to describe providers that could not stand to see anyone in pain, and due to that perspective, may over-prescribe opioids. These "soft-touch" providers are the ones that this patient most feared, because their compassion was seen as potentially life-threatening.

Conclusion: As a result of this experience the student was able to begin to develop a philosophy towards an approach to SCD patients that is more humanistic than described by many SCD patients. Developing healthcare providers that understand pathophysiology of the disease, have compassion for their patient's pain and as well as an understanding of individual patient's experiences, yet knows how to temper that compassion with sound medical practice, is the holy-grail of medical education and in particular SCD stakeholders. Teaching culturally competent medical care is essential to professional development of providers (Irby 2009). LAC's reflective writing requirement is not especially popular among students - only 35% of students in the first 3 years of LAC felt these exercises helped learning. However, examples like the one attached reveal insights incurred when new providers are trained to listen carefully to their patients. In illnesses like SCD, where culturally competent care is arguably especially important, reflection, ideally with discussion with experienced practitioners, may ultimately improve the patient's experience and safety.

Sample 1: He (the patient) described how his interactions had been with health care providers. He had the dubious pleasure of having been able to get to know many different physicians over the course of his 40-year fight with sickle cell. He described that all the "memorable" (in this case, memorable for being inadequate in some way) health care providers that he knew could be broken down into 3 categories. One of these categories was a physician who looked a sickle cell as purely genetics, looked at a patient as nothing more than having a vaso-occlusive disorder. This type of physician would take no steps to understand how the disease affected the patient, how the patient hoped to improve his life, what the patient's goals and dreams were. Rather, this type of provider would just treat the symptoms, would prescribe the medications, and would leave it at that. He/she would be detached, but a least would do enough to alleviate the patient's symptoms.

The second type of provider was the kind who looked at all young, black people as drug seekers. He/she would be the most difficult to plead with, the most reluctant to prescribe even short acting medications to help alleviate the patient's pain. Theses physicians, as the patient describes, were the most jaded, the most difficult to get through to. They didn't find any pleasure from their job and worse, probably, were constantly facing an antagonistic battle with the patients.

Finally, the patient described that another class of providers were called the "soft touch" and that these physician/nurses were by far the most dangerous. The patient described that "soft touch" providers were the ones who couldn't bear to see a patient in severe pain, who would overreact to the situation, and would compromise their medical derision making in order to "help: the patient as quickly as possible. When I questioned him as to how this was possible, the patient went on to tell me about his near death experience. He once has a sickle crisis, when to an ER, and a "soft touch" pushed the narcotics so quickly that his heart stopped and he had to have a crash team revive him. So, these "soft touch" providers would act in the patient's best interest to such a degree that they would ultimately jeopardize the patient's life. When I asked him about which type of physician he would most hope to see, he said that the "soft touch" is the most dangerous type of provider. He claimed that he would much rather think that a physician thought he was drug seeking than encounter a "soft touch."

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PROCESS OF DISSEMINATING KNOWLEDGE ON SICKLE CELL DISEASE TO PRIMARY HEALTH CARE PROFESSIONALS IN THE STATE OF MINAS GERAIS, BRAZIL

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Affiliation: *NUPAD/FM/UFMG, Fundação Hemominas*

Introduction: Sickle Cell Disease (SCD) has a high incidence in the state of Minas Gerais, Brazil (1:1,400 live births), but it usually remains poorly known in primary health centers. The Brazilian Single Health System (SUS) considers Primary Health Care as the main type of access to the national health assistance network. National policies for primary health care include the family health model. In Minas Gerais, approximately 4,500 family health teams (FHT) join health professionals from different domains.1 CEHMOB-MG (Educational and Supportive Center for Hemoglobinopathies), supported by NUPAD (Center for Newborn Screening and Genetic Diagnostics) and the Hemominas Foundation have elaborated a distance learning course proposal aimed at training all the categories of primary health care professionals focusing on SCD-oriented interdisciplinary holistic care and assistance organization. Course takers are expected to disseminate knowledge in their respective primary care centers in the municipalities in the State of Minas Gerais.

Objective: To describe the development of the process of disseminating knowledge on sickle cell disease in the municipalities of Minas Gerais.

Methods: The process of knowledge dissemination consisted of workshops building on a participative methodology and resorting to educational resources such as image flip charts, group dynamics, and case studies involving professionals in the primary health care centers. The workshops comprised the following topics: physiopathology; clinical manifestations and care of children; clinical manifestation and care in adolescence and childhood; dental health and care guidance; and rights of the citizens. The assessment of the dissemination process was built on semi-structured questionnaires filled out at the end of each workshop.

Results: The replication process is fully operational in six municipalities and under implementation in other 79. The use of workshops contributed to enlarge participants' knowledge of the physiopathology and clinical handling of the disease at the primary health care centers, as well as to promote learning building on their professional practice and drawing on each facilitator's strategies. The workshops were considered a pedagogic strategy that enables easy understanding, interaction, and ludic activities.

Conclusion: The workshops represented an important tool for improved technical qualification and, hopefully, for improved quality in providing care to people with SCD. Direct measurement of better clinical care is under way.

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PILOT PROGRAM FOR ESCAPE: ELECTRONIC SICKLE CELL APPLICATION FOR PAIN EVALUATION FOR PATIENTS ENROLLED IN NKT 120-SCD1

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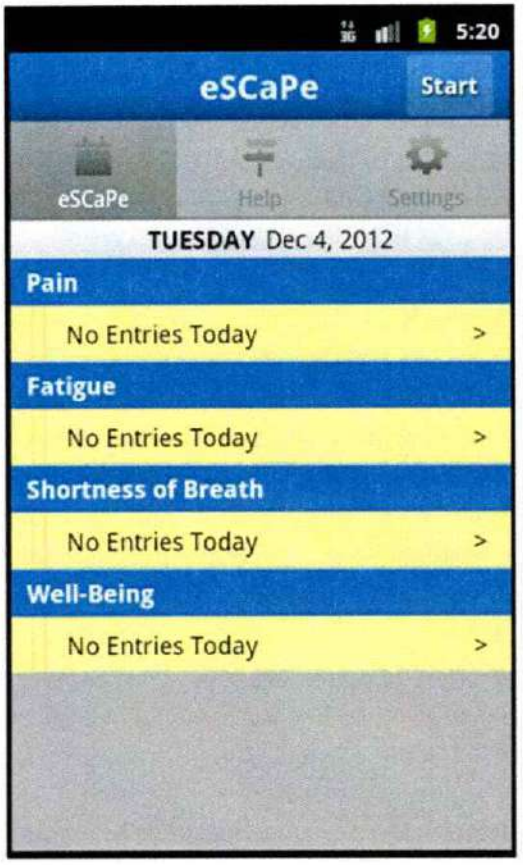
Background: The determination of true symptomatic endpoints and safety signals (e.g. pain) in the development of new therapeutics depends on timely and accurate communication between patients and clinicians. Historically, documentation of patients' symptoms relied on memory that has been found to be problematic. We describe an electronic diary (eDiary) for adults with non-acute sickle cell disease (SCD) to use before, during, and after the depletion of their iNKT cells (a white cell implicated in SCD crises) by the investigational monoclonal antibody, NKTT120. Our hypothesis is that the eDiary data, collected on mobile smartphones, may have high adherence rates and provide useful symptom data collection relative to the infrequently administered standard tools.

Objective: In designing Quality of Life (QoL) and pain assessment endpoints in therapeutic trials for SCD, the ASCQ-Me and PROMIS tools are essential components; however they have at least a 7 day look-back. To get real-time daily assessments of pain, fatigue, shortness of breath, and overall well-being, an eDiary was designed to accompany the ASCQ-Me and PROMIS tools for non-acute SCD adults. This tool, eSCaPe, will be used by patients enrolled on a phase I trial of treatment with an iNKT cell-depleting monoclonal antibody, NKTT120 as part of the assessment for NKTT120 mediated reduction of inflammation associated with the sequelae of SCD.

Methods: An electronic symptom diary was assembled, based on features of other tools used to collect pain and QoL assessments. This eDiary included daily severity ratings of pain, fatigue, shortness of breath and general well being. This diary was delivered to the patients, and their data was entered and uploaded daily by a smartphone app. Patients enrolled on the trial will have a 2-week run-in period to assess their baseline prior to administration of study drug. Patients enrolled in the trial of NKTT120 will continue their eDiary reporting until completion of the study endpoint (the recovery of their iNKT cells).

Results: Overall adherence of daily e-reporting for patients enrolled to date on the NKTT120-SCD1 trial will be reported. Any differences between their baseline 2 week run in period and their post treatment symptoms will be described. Technical difficulties encountered in the administration of a mobile phone eDiary will be reported.

Conclusions: An eDiary tool for adult SCD patients undergoing investigational treatments is in development. The data may provide improved reporting of symptom characteristics, which may reflect either beneficial effects, or adverse effects of the treatment.


5:20
eSCaPe
Start
eSCaPe
Help
Settings
TUESDAY Dec 4, 2012
Pain
No Entries Today
Fatigue
No Entries Today
Shortness of Breath
No Entries Today
Well-Being
No Entries Today


5:20
eSCaPe
Pain
Save
Please use the slider to show your Pain Level today.
More Pain
Less Pain

255

PEER MENTORING FOR ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Background: Nationwide Children's Hospital Comprehensive Sickle Cell Disease Program participated in a Children's Hospital Corporation of America discharge collaborative with a goal of reducing 30 day readmissions for patients with sickle cell disease (SCD) and pain. Early in the initiative we learned that 5 of 370 total SCD patients were responsible for > 50% readmissions. Previous studies on readmissions for SCD and pain have excluded these highest utilizers. We felt that addressing this group is essential and would lead to the greatest reduction in readmission.

Objectives: Our initial goal was to decrease unplanned admissions within 30 days by 20%.We planned to accomplish this by providing programming and psychosocial support for this group outside of the inpatient setting. Second, we wanted to meet this goal by equipping and empowering this group to become self-advocates through the provision of education and coping strategies for successful disease management.

Methods: Patients with the highest number of hospitalizations for SCD and pain over the previous 12 months were identified by admission codes. These patients were invited to participate in a new Peer Mentoring Program for Adolescents and Young Adults with SCD. The sickle cell team also invited 7 young adults with SCD who had previously been high utilizers but are currently admitted fewer than 3 times per year for pain. An initial overnight retreat was held to kick off the group, followed by monthly events facilitated by the team program manager, social worker, psychologist, and therapeutic recreation specialist. Mentors and mentees were paired and participated in several educational and skill(s) building activities, then, instructed to communicate by phone or text at least one time per week. Mentors were trained in a one day workshop and had ongoing support from the sickle cell psychosocial staff.

Results: Seven out of 9 mentees and 7 out of 7 mentors invited chose to attend the first Peer Mentoring overnight retreat. The mentees ranged in age from 15 to 20 with a mean of 18.3, and mentors ranged in age from 18 to 23 with a mean of 20.4. One mentee left the retreat the first night due to pain and was unable to come to other events due to recurrent hospitalizations. Over 6 months, monthly events were held, with a mean attendance of 3 mentees and 5 mentors at each event. Mentors and mentees report that only 1 out of 7 total pairings have made weekly phone calls. Six months into the project, 30 day readmissions among mentees has not decreased. However, no mentor has left the group and only 1 mentee has left due to extenuating circumstances. The group subjectively reports a positive experience and the desire to continue with the project.

Conclusion: The majority of adolescents and young adults with SCD have fewer than 3 hospitalizations per year for pain, but a small group is responsible for recurrent readmissions. Maximizing medical care with hydroxyurea, transfusion therapy, physical therapy, pain medication, and nursing follow-up phone calls has not decreased readmissions among this group. We started a Peer Mentoring Program that meets monthly as a group and pairs successful young adults with struggling adolescents in hopes that this psychosocial network would help promote staying healthy outside the hospital. While readmissions have not decreased 6 months into the project, the subjective feedback from the group is positive. Mentors and mentees have not been in weekly contact as we had hoped. Mentors need more training and ongoing coaching by professionals to help their mentees on a weekly basis. We plan to continue the group and expand membership, with the eventual goal of mentees graduating to become mentors.

301

ERYTHROPOIETIN LEVEL IN SICKLE CELL DISEASE PATIENTS NOT IN CRISIS

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Background: Patients with sickle cell disease (SCD) have lower than expected values of erythropoietin for the extent of their anemia. SCD may be complicated by hypoxia, renal insufficiency, and inflammation, all of which may change erythropoietin levels. We previously examined the relationship between erythropoietin level and hemoglobin and renal function as measured by glomerular filtration rate (GFR) in patients with SCD not in crisis and found that the expected correlation between erythropoietin level versus hemoglobin and renal function was not clearly maintained in SCD.

Objectives: Here, we examine the relationship between erythropoietin and inflammation and hypoxia.

Methods: Charts of patients treated in the outpatient hematology clinic were reviewed. Patients who had sickle cell anemia (SCA), SC disease, or sickle-thalassemia and in whom erythropoietin had been measured on an outpatient basis while they were not in crisis and who did not receive exogenous erythropoietin were eligible for inclusion. Erythropoietin level, hemoglobin (hgb), platelet count, white blood count (WBC), mean corpuscular volume (MCV), oxygen saturation, reticulocyte count, serum creatinine, and patient characteristics including age, gender, and disease type were recorded. GFR was calculated using the CDK-EPI equation. Because direct measurements of inflammation such as erythrocyte sedimentation rate and c-reactive protein are not measured as part of standard of care, WBC and platelet count were used as proxy markers for this preliminary study.

Results: Data from a total of 54 patients was obtained, including 39 with SCA, 9 with SC disease, 5 with sickle-thalassemia, and one with S-O(Arab). Median hemoglobin was 8.3 and median erythropoietin level was 62 for all patients. Oxygen saturation ranged from 90% to 100% on room air. All patients had at least adequate iron stores. Because hemoglobin levels were higher and therefore corresponding erythropoietin levels lower in patients with SC disease, patients with SCA and sickle-thalassemia null were examined separately.

Among patients with SCA and sickle-thal0, lower hemoglobin levels (<7 versus 7+) were only marginally associated with higher erythropoietin levels (96 versus 64, p=0.07). When patients with oxygen saturation of less than 96% were compared to patients with an oxygen saturation of greater than 96%, no statistically significant difference in erythropoietin level was observed. However, patients with higher oxygen saturation had slightly higher hemoglobin levels (8.7 gm/dl versus 6.9 gm/dl, p=0.02). Similarly, no difference in erythropoietin level was observed for patients with normal versus elevated WBC and platelet count. However, in contrast to hypoxia, high WBC was not associated with differences in hemoglobin. Interestingly, patients receiving hydroxyurea had a higher erythropoietin level, despite showing no difference in GFR, oxygen saturation, or WBC. However, median MCV was higher in patients taking hydroxyurea, suggesting that compliance was acceptable.

Conclusions: Patients with sickle cell disease have low levels of erythropoietin, even when no kidney disease is evident. Hypoxia did not correlate well with erythropoietin levels. This may reflect the worsening clinical state of patients with hypoxia and sickle cell disease, but hypoxic patients did not show lower GFR than patients without hypoxia. Inflammation, as measured by the proxy measures of WBC and platelet counts, did not appear to affect erythropoietin levels. Hydroxyurea appears to preserve erythropoietin levels in patients with SCA and sickle-thal0, but the mechanism by which it is protective is unclear.

342

EFFECTS OF DENTAL CARE ON ACUTE CARE UTILIZATION FOR INDIVIDUALS WITH SICKLE CELL DISEASE

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Introduction: Oral health has been shown t o have a variety of health effects, including an association bet ween poor oral health and an increased risk of mortality from cardiovascular disease (Jansson et al, 2001) and a negative correlation between rheumatoid arthritis and periodontal disease (Marshall et al, 2000). Sickle cell disease is an inherited red blood cell disorder which affects hemoglobin. In the United States, it primarily affect s African Americans and has an estimated prevalence of 100,000 individuals. Studies havedemonstrated relationship between SCD and poor oral health including an increased risk in self-reported oral pain, significant changes in the structure of SCD patients' teeth, and a higher risk for dental carries (Laurence et al, 2002) (Laurence et al, 2006). We hypothesized that better access to dent al care would improve health outcomes in adults with SCD.

Methods: In January of 2012, the Health Resources and Services Administration funded Improving Health Outcomes and Medical Education for Sickle Cell Disease(iHOMES) Network began to provide dental care through a contract with the Johns Hopkins Dental Clinic to help provide a much needed medical home benefit . The iHOMES Network purchased two dental visit s a week for patient s who were referred to us by the Johns Hopkins Adult Sickle Cell Program's social worker. The Dental Clinic services included basic preventive dentistry (cleanings, fillings, x-rays, single extractions). We examined each patients' medical records for 6 months pre and post the initial dental appointmentfs. We determined the number of acute visit s, which was defined as a visit t o t he Sickle Cell Infusion Center (SCIC) and/or the Emergency Department (ED), number of admissions, and number of days admit t ed. If a patient was seen in bot h the ED and the SCIC on the same day, it was only counted as one A Wilcoxon rank sum test was performed to determine if there were
any statistically significant differences following the initial dental visit.

Results: Eleven patients completed initial appointment s between January and March of 2012. The mean age of the patient s was 40.2 years, and 55.5% were female. Eighty-two percent of patient s had Hemoglobin SS disease, 9% had hemoglobin SC disease, and 9% had Sβ+ Thalassemia. Examining the 6 months pre and post the patients' initial dental visit, there were trends towards improvement for all of the assessed variables (Table 1). Improvement s in the acute visit and length of stay variables were statistically significant.

Conclusion: Dental treatment may be an effective tool for lowering acute healthcare utilization and for improving health for people with sickle cell disease. The small sample size, the short duration of the study, and the high likelihood of confounding variables, such as seasonal variations in SCD acute healthcare utilization, limits the validity and generalizability of the study. The impressive result s, however, should prompt further study. Our next steps include studying a full year of pre and post initial visit and expanding the sample size. Understanding the mechanisms by which dental services affect acute care utilization and examining barriers to receipt of dental services are essential next steps to improving the care for people with SCD.

373

LONGITUDINAL ANALYSIS OF EMOTIONAL AND BEHAVIORAL PROBLEMS IN YOUTH WITH SICKLE CELL DISEASE USING THE PROBLEM SYMPTOM CHECKLIST-17

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Background: Sickle cell disease (SCD) is a chronic, autosomal recessive, hematologic disorder with physical, psychological, and social complications. The clinical manifestations include, for example, acute and/or chronic pain, renal dysfunction, and pulmonary disease. These physical complications may result in a loss of social and academic opportunities. As such, SCD affects youth's medical, social, personal, and educational functioning. Research indicates that youth with SCD are at risk for developing psychosocial problems, primarily internalizing symptoms. However, the stability of either internalizing or externalizing behavioral problems is unclear. Global cognitive deficits and specific deficits in attention have also been found in youth with SCD. Periodic screening of functioning has been recommended to identify those patients for whom early intervention services would be beneficial.

Objectives: The objectives of this study were to: 1) assess the presence of psychosocial problems in youth with SCD in comparison to normative values, 2) examine the relationship among psychosocial problems, demographic variables, mental health, and medical factors, and 3) explore how demographic variables, medical factors and mental health may impact psychosocial problems over time.

Methods: Participants were the parents of 80 children between the ages of 4 and 12 years old, who were attending a regularly scheduled appointment in a Comprehensive SCD Clinic at a mid-western pediatric hospital. Parents completed the Problem Symptom Checklist – 17, with over ½ filling out the forms on at least two occasions. The PSC-17 provides three subscale scores (i.e., Internalizing, Externalizing, Attention) and a Total Score. Electronic chart reviews will be completed to obtain documented disease genotype, insurance coverage, co-morbid medical conditions, healthcare utilization variables, and mental health diagnoses.

Results: Descriptive statistics will be conducted on the PSC-17 for all participants and then according to sex and age. Independent sample t-tests will be run to compare sample scores to PSC– 17 norms. Independent sample t-tests will be performed to determine presence of differences among genotype, sex, insurance coverage, and mental health on PSC-17 subscales, and continuous medical factors. To examine how medical factors and mental health may impact psychosocial problems over time, generalized linear mixed models will be performed.

Conclusion: Screening for psychosocial problems would allow for early detection of such problems and referral for intervention. Such screening measures are easy to administer and score within a Comprehensive Clinic. Identifying factors that predict poor adjustment may also lead to development of interventions that reduce the risk of future psychosocial problems by maximizing adaptive functioning.

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DEVELOPMENT OF A MULTI-DISCIPLINARY INPATIENT PROGRAM FOR CHILDREN WITH SICKLE CELL DISEASE ADMITTED FOR VASO-OCCULUSIVE CRISIS

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Background: Pain is the most common reason for hospitalization among pediatric patients with sickle cell disease (SCD). Chronic pain results in reduced quality of life, school absenteeism, diminished academic performance, and missed caregiver work days1. Current guidelines recommend a multidisciplinary approach to pain management, which has been shown to improve patients' pain, decrease health care utilization, and reduce hospital cost among adults with SCD2.

Objectives: To develop a comprehensive program for hospitalized pediatric patients with SCD which will reduce length of stay, decrease use of Patient Controlled Analgesia (PCA), reduce 30-day readmission rates, and increase patients' use of positive coping skills.

Methods: A multidisciplinary work group met monthly over a period of 6 months. The group was composed of representatives from social work, psychiatry, psychology, and nursing. Nurse practitioners specialized in SCD, pain management and palliative care, as well as a physician with prior experience in inpatient program development for the eating disordered child, joined the hematologist to identify goals and to devise a program.

Results: A three-pronged approach was developed: 1) Changes to the milieu emphasizing routine and structure (e.g., wake up and bed times) and goals for self-care (e.g., eating, bathing, walking), implemented by the nursing staff; 2) Execution of twice weekly groups to provide psychoeducation (e.g., what is pain, how to prevent a crisis) and to teach cognitive-behavioral pain management strategies (e.g., relaxation, distraction, cognitive restructuring), led by 2 mental health professionals; and 3) Creation of an individualized Pain Action Plan, modeled after the Asthma Action Plan, with medications, dosages, and instructions for increasing levels of pain, provided at discharge by the attending physician. This plan was implemented on September 22, 2012.

Conclusion: After 3 months of implementation, participation in group cognitive-behavioral sessions is 75 percent. Thirty-one patients, over 46 admissions, have received an Individualized Pain Action Plan. Nursing satisfaction is high. After 6- and 12- months of program implementation, pre- and post-data will be compared on the objectives stated above.

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258

RAPIDLY FATAL PNEUMOCOCCAL SEPSIS IN A YOUNG ADULT WITH SICKLE CELL DISEASE

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Background: Streptococcus pneumoniae bacteremia was the leading cause of death in infants and children with sickle cell disease (SCD) until the institution of penicillin prophylaxis following early diagnosis through newborn screening as a result of the landmark PROPS1 study. Further reduction in S. pneumoniae bacteremia resulted from the use of the polysaccharide pneumococcal vaccine introduced in 1986 and especially after the utilization of the 7-valent pneumococcal conjugate vaccine, which could be administered at an early age. In addition, infants and children who present to the ED with fever or with symptoms suggestive of bacteremia are treated with a long acting cephalosporin (ceftriaxone) empirically without awaiting the blood culture results. These measures have resulted in a sharp decline in mortality from S. pneumoniae bacteremia in infants and children with SCD. In adults, the spectrum of bacteremia is shifted more toward gram negative agents, the presentation is usually less dramatic, and therefore well-developed protocols or algorithms for ED treatment do not exist.

Objectives: We present a 19-year-old African-American female with SCD (SS) with SCD who had a fatal outcome within several hours of presenting to the ED with findings highly suggestive of sepsis. The patient was recently transitioned from pediatric to adult care. At the time of her transition visit, she was doing well. Her history was significant for frequent ED visits and hospitalizations with pain episodes. She was hospitalized twice during the previous 12 months. She had one episode of acute chest syndrome in 2003 and AVN of the right shoulder and right hip. Her past surgical history was significant for cholecystectomy and appendectomy. She had been on hydroxyurea for several years.

Methods: Three weeks after her visit to the GRU Adult Sickle Cell Clinic, she presented to her local ED with a several hour history of abdominal pain, nausea, and bilateral knee pain. At presentation, she was afebrile with a heart rate of 119. Her admission labs showed hemoglobin of 7.8, HCT 23, WBC 7.7 with 12% bands in differential. Her potassium was low at 2.8. She was treated with antiemetics (ondansetron), ketorolac, and meperidine for pain and was given IV fluids and potassium. Six hours after arrival to the ED, while she was about to be discharged, she developed altered mental status and fever up to 103°F. A femoral line was placed and blood cultures were drawn; she was given acetaminophen and haloperidol.

Results: Eight hours after presentation, she developed respiratory arrest, was coded for 50 minutes, did not respond, and was pronounced dead. A lumbar puncture was performed and IV ceftriaxone was administered during CPR. Two days after the patient's demise, blood cultures grew S. pneumoniae sensitive to every antibiotic tested.

Conclusion: This unfortunate case illustrates the gravity of the prognosis in patients with SCD who present to the ED and who are not evaluated and treated with the vigilance required by their underlying disease and presentation. The presence of 12% bands in WBC differential on arrival should have served as a warning sign for an evolving infectious process and prompted a more thorough workup including blood cultures. The administration of IV antibiotics was delayed for three hours after the patient developed fever and was done during CPR. Despite the lack of a definitive diagnosis leading to the patients demise, an autopsy was not performed. Adult patients with SCD presenting to the ED with findings suggestive of an evolving sepsis/bacteremia should be treated with the same degree of vigilance as infants and children with prompt administration of broad spectrum antibiotics.

EFFECT OF VITAMIN D AND CALCIUM SUPPLEMENTATION ON BONE MINERAL DENSITY IT PEDIATRIC SICKLE CELL DISEASE PATIENTS

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Background: The prevalence of osteopenia and osteoporosis in patients with sickle cell disease is high. Patients are likely to face long-term sequelae of osteoporosis, including vertebral fractures and osteonecrosis

There is limited data on bone mineral density (BMD) in patients with sickle cell disease in > 5 years of age. Even less data exists on treatment of low Vitamin (vit) D levels and its effect on BMD.

In a study by Chapelon et al, 53 patients with sickle cell disease age 9-19 years had BMD evaluation by DXA scan showing a significantly lower Z-score in girls than in boys in the pre-pubertal age group.

Adewoye et al, 2007, studied 14 adult patients followed over 12 months receiving treatment with Vit D and calcium and showed a small, but statistical, improvement in BMD.

Objectives: To describe correlations between Vit D and calcium supplementation on BMD (g/cm2) in a pediatric population with SCD.

Methodology: This is a cross-sectional, retrospective analysis of children with SCD. Selection criteria included patients aged 5-21 years with a diagnosis of HbSS, a vit D level 80% is very compliant. Treatment groups were divided into intervals of 6 months of replacement therapy.

Exclusion:

1. Factors affecting bone mineral density, such as high dose steroids for > 2 weeks and other co-morbid conditions
2. Age

Age(years)	S/N	Gender	Vitamin D	Treatment interval (months)	% Vitamin D compliant	% BMD change
6	1	F	7	5	0	3
10	2	M	16	5.5	100	0
19	3	F	4	5.5	0	9.2
17	4	F	10	6	71	-1.5
18	5	M	6	6	100	4.3
11	6	F	8	8	100	8.8
9	7	F	9	9	60	4.1
15	8	M	15	10	100	3.2
8	9	M	20	11	100	-4.6
9	10	M	23	12	51	8.4
10	11	F	16	12	83.3	21.6

Effect of Vit D/Calcium on BMD between the 1st and 2nd DXA Scans

424

MOBILE DIRECTLY OBSERVED THERAPY: MONITORING AND IMPROVING HYDROXYUREA ADHERENCE IN PEDIATRIC SICKLE CELL PATIENTS

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Introduction: Hydroxyurea (HU) is an efficacious medicine that reduces complications in pediatric patients with sickle cell disease (SCD).1 Poor medication adherence, however, is common and limits effective HU utilization.2

Directly observing therapy (DOT) involves healthcare workers traveling to observe patients ingest medication. DOT is a successful strategy to improve medication adherence in tuberculosis,3 but high cost, inconvenience, and intrusiveness limit this strategy in chronic medications such as HU. We hypothesize that a modified version of DOT that uses mobile phones and computers (Mobile DOT) will be a feasible strategy, can achieve high HU adherence rates, and will be acceptable to patients.

Methods: Patients with SCD were eligible for this 6-month pilot study if they were 1-22 years old, prescribed HU for ≥6 months, and had daily access to a mobile phone or computer capable of recording and submitting videos.

Mobile DOT participants record a daily video of their HU administrations with their phone or computer and submit these videos to a secure website for review. Participants receive daily reminder electronic messages to take their hydroxyurea, and they are called to encourage adherence if needed. Participants receive token monetary compensation if they meet adherence goals and complete surveys.

This study uses the Morisky Medication Adherence Scale (MMAS-4), the medication possession ratio (MPR), hemoglobin F percentage (HgbF), mean corpuscular volume (MCV), and direct observation to measure adherence. Participants complete a Mobile DOT satisfaction survey intermittently.

Results: Investigators discussed this study with 19 prospective participants and 15 enrolled. One participant withdrew immediately because of lost computer access. Videos were approximately 15 seconds long and an investigator performed the observations, tracking, and phone calls in <1 hour each day. Mean participant age was 13.7 years (SD ± 6.3 years, range 4-21 years), and most participants had Hemoglobin SS disease (n=11) and took HU for frequent pain crises (n=7) or acute chest syndrome (n=6).

At enrollment, mean MMAS-4 score was 2.0 (SD ± 0.4) indicating moderate self- reported adherence, and MPR was 67% (SD ± 26%). Three participants had labs indicating good adherence (MCV>100fL and HgbF>15%), 4 had moderate adherence labs (MCV≥90fL and HgbF>12%), and 7 had labs suggesting poor adherence (MCV<90fL or HgbF<12%).

To date, all participants have completed ≥120 days of the study. Direct observation shows mean adherence to be 90.1% (SD ± 14.2%) and median adherence to be 93.3% after 120 days. After 2 months, MMAS-4 scores decreased 1.1 (SD ± 0.9), mean MCV increased from 99.5fL (SD ± 11.8fL) to 106.3fL (SD ± 11.4fL) and mean HgbF increased from 12.9% (SD ± 7.9%) to 14% (SD ± 6.9%), which all suggest improved HU adherence. Satisfaction surveys suggest that participants agree that Mobile DOT helps them remember to take HU, it is easy to use, it takes <5 minutes each day, and does not invade their privacy.

Conclusion: These results suggest that Mobile DOT is a feasible way to monitor and improve HU adherence in patients with pediatric SCD. Patients were willing to enroll and surveys suggest that participants find Mobile DOT convenient, non-intrusive, and acceptable. A larger clinical trial is needed to determine if long-term Mobile DOT can impact clinical outcomes in pediatric SCD.

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IMPROVING HEALTH LITERACY AMONG THE SOCIO-ECONOMICALLY DISADVANTAGED SCHEDULED TRIBES FOR SICKLE CELL AND OTHER DISEASES IN SOUTHERN INDIA

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Background: Culture is known to influence all aspects of human behavior including its role in defining illness, health, and wellness and in help-seeking and health maintenance behaviors. Healthy People 2010 has defined health literacy as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." Persons with low literacy skills are less likely to: seek and receive health care, understand and make decisions based on their diagnosis, understand and respond to informed consent forms, understand medication instructions and be knowledgeable about the health effects of risks, behaviors, and diseases.
In India one of the socio-economically disadvantaged groups predominantly affected with sickle cell disease (SCD) are the scheduled tribes. These groups are historically known as the Adivasis or the "depressed classes". The scheduled tribes are extremely socially, educationally and economically backward arising out of age-old practice of untouchability, lack of proper infrastructure facilities and geographical isolation. Developing culturally competent literature to increase the health literacy among the scheduled tribes is essential for overall health promotion and health education in the community.

Objectives: Develop health education materials for sickle cell disease, diabetes, hypertension and other common health conditions in the tribal community of Gudalur, Tamil Nadu.

Methods and Results: Members of the Gudalur Adivasi Hospital and tribal community were actively involved in developing the health promotion materials. Educational booklets titled, "Living well with Sickle Cell Anemia" and "Living well with Diabetes" were developed in the local language of Tamil to be distributed to patients and families affected by either condition. Information included a basic explanation of the condition, signs and symptoms, inheritance, management, medication and how to properly care for someone with the condition. The information was explained at a fifth grade reading level so that both children and adults alike would be able to understand the material. In addition, these booklets were made into educational videos for patients and families to view during their wait at the hospital.

Conclusion: The future of the tribal health depends on understanding, addressing, reducing and eliminating disparities. Utilizing community members and learning their concerns and barriers was an essential component in the process of creating and developing print material and media to effectively communicate and tailor the information their needs. Ultimately, these materials will help empower individuals and allow them to make proper medical management decisions.

425

ETHICAL AND CLINICAL CONSIDERATIONS IN AN ADOLESCENT JEHOVAH'S WITNESS WITH SICKLE CELL ANEMIA

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Background: Sickle Cell Anemia is a hematologic disorder resulting in chronic hemolytic anemia. Therapeutic and prophylactic transfusion therapy in children with this illness has been shown to decrease severity of symptoms and minimize complications. Jehovah's Witnesses are known for their non-acceptance of transfusion. Children are transfused only for lifesaving reasons with administrative approval, often without parental consent.

Objective: Present the ethical and clinical dilemmas faced in the treatment of a sickle cell Jehovah's Witness patient.

Methods and Results: VL, an eighteen year old girl with sickle cell anemia (SS type) born to a family of Jehovah's Witnesses was admitted in crisis with profound anemia of 3.8g/dl and impending cardiac failure. The risks and benefits of transfusion were explained and she expressly refused. Multiple meetings were held with VL, parents, social worker, child psychologist, risk management and the ethics committee to determine the validity of her refusal of life-saving therapy. The committee concluded that she had the right to make her own decisions as an adult. She received early aggressive therapy with Darbepoetin, hydroxyurea, folate and continuous opioid pain control, and was monitored closely. Within a week her anemia improved and she was discharged with hemoglobin of 7.1g/dl.

Conclusion: This case raised many ethical and clinical issues. Pediatric nursing and house-staff were unaccustomed to dealing with a critically ill young adult who had the right to refuse lifesaving treatment. The social worker, psychologist, and members of the ethics committee and legal affairs worked with the patient and clinical staff. Valuable lessons were learned in patient-provider communication and provider preparedness in dealing with difficult patient decisions.

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PERCEPTIONS OF HOSPITAL READMISSION IN PATIENTS DIAGNOSED WITH SICKLE CELL DISEASE

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Background: Sickle Cell Disease (SCD) affects 70,000-100,000 people in the United States. This research study is important in that it seeks to understand psychosocial components of hospital readmission.
Objective: Hospital readmission is a common occurrence for many SCD patients. In addition to pain crises, it is important to understand other dynamics associated with hospital readmissions. The objective of this study is to illustrate factors that influence readmission and wellness.

Methods: This prospective, cross-sectional, open-ended interview study included patients diagnosed with SCD who were either inpatient or outpatient at a Midwestern cancer hospital. A seven item questionnaire addressed the subjects' perceptions of hospital admission, responsibilities and stressors at home, support persons, and coping strategies. Participants could relate multiple responses for each item. Responses were grouped according to like themes and were analyzed with frequencies.

Results: Patients (N=77) consisted of 45 women and 32 men, with a mean age of 30 years. Perceptions of reasons for hospital readmissions or clinic visits were pain (n=21), weakness (n=3), check-ups (n=37), anemia (n=3), and dehydration (n=1). Most suggested they were able to perform chores or daily activities (N=57) although some (N=18) specified assistance was needed. Causes of stress were family (n=33), finances (n=17), pain (n=4), hospital visits (n=3), job or school (n=12), chores (n=4) and other (n=20). Support person consisted of family (n=69), friends (n=28), and church (n=7). Coping strategies included relaxation (n=16), medications (n=2), TV (n=7), exercise (n=6), keeping active (n=5), faith (n=3), and hydration (n=2).

Conclusions: Subjects perceived that hospital readmissions are associated with pain. Many SCD patients are very independent at home. While family are most often reported as support persons, they are also reported as a cause of stress. Most patients use relaxation as a coping mechanism.

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EFFECT OF WEATHER ON FREQUENCY OF VASO-OCCLUSIVE CRISIS IN CHILDREN WITH SICKLE-CELL DISEASE IN OUR POPULATION

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Background: SCD is an inherited disorder, characterized by hemolytic anemia, increased susceptibility of infection and vaso-occlusion that can occur in vascular beds leading to intermittent episodes of acute severe pain, known as vasocclusive crisis. Environmental factors are known to play a role in frequency and severity of VOC in SCD patients. Several studies have been done to clarify the possible effect of weather changes and occurrence of VOC in SCD patients.

Objective: To analyze the relationship between weather changes (temperature and humidity) and rate of sickle cell crisis in our local sickle cell disease population in Brooklyn, NY.

Methods: Daily census of children < 20 years old presenting with sickle cell VOC from July 26, 2011-July 25, 2012 were retrieved from our Health Information Systems database. The study was conducted at an inner city NY community teaching hospital. Data on average daily temperature and humidity for New York City was collected from the websites of the National Oceanic and Atmospheric Administration (NOAA). Data was analyzed to determine correlations of daily temperature and humidity with sickle VOC using Pearson Correlation Co-efficient and Time series statistics.

Results: The study included patients from ages 2-20 yrs, with 52 % males (n=133) and 48 % females (n=125). The total number of sickle cell visits for VOC during the study period was 344, with 218 outpatient and 126 inpatient visits. Total visits for VOC peaked during the month of January (n=44), almost 75% contributed by outpatient visits, while they were lowest in July (n=16). For total sickle cell VOCs, weak correlation detected with lower temperature levels ($r = -0.05$, $p=0.04$) and almost no correlation with high humidity ($r=-0.01$, $p=0.85$). When sickle cell VOC visits were moved to one day from the data, weak but highly significant correlation was observed with lower temperature ($r = 0.3$; $p < 0.001$) but continued to be weak with high humidity ($p=0.25$). No significant correlation was observed between change in temperature and humidity and number of VOC.

Conclusion: Our study shows weak correlation between change in temperature and number of crisis while no significant correlation was observed with change in humidity and number of VOC.

EFFECTIVENESS OF EDUCATIONAL INTERVENTION IN IMPROVING KNOWLEDGE AND PERCEPTION AMONG HEALTHCARE PROVIDERS AT A COMMUNITY-BASED HOSPITAL

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Background: Sickle cell disease (SCD) patients often face barriers to optimal medical care due to inadequate knowledge and misperceptions among healthcare providers. Furthermore, mistrust of patient's subjective reporting of pain as well as stigmatization and bias leads to inadequate pain management.

Objective: To evaluate knowledge and perceptions about SCD among healthcare providers at The Brooklyn Hospital Center (TBHC) and to assess the effectiveness of an interactive educational session in improving knowledge and eliminating misperceptions.

Methods: Multiple interactive educational seminars were conducted by one of the two Pediatric hematology/oncology attending. A paired pre and post seminar 26-point anonymous questionnaire was distributed at the beginning and end of these sessions. Participation was voluntary and included physicians, medical students, nurses, physician assistants and other support staff including pharmacists and patient care associates. Eighteen questions addressed knowledge (sub-grouped into pathophysiology (8), clinical presentation (6) and management (4)) while 8 focused on perceptions (sub-grouped into addiction (4) and impact on quality of life (4)) of the health care staff. The primary outcome was measured by the change in individual scores between the pre and post-intervention responses. Paired t-test was utilized to analyze the change in score of the participants (alpha=0.05).

Results: Of the 540 participants (representing 25% of TBHC employees), 339 (63%) were physicians and nurses, 62% (n=331) being female. Asians (37%) and African-Americans (30%) constituted majority of participants. Educational intervention resulted in significant improvement in the cumulative score for knowledge and perception (71% vs. 83%; $p<0.001$), as well as in respective subgroups (except impact on quality of life). Misperception about addiction in SCD patients decreased significantly post-intervention ($p<0.001$). Most noticeable difference was observed in questions related to knowledge about disease management (mean score 3.5 vs. 5.2; $p<0.001$), pathophysiology (5.1 vs. 6.3; $p<0.001$) and perception about addiction (2.1 vs. 2.7; $p<0.001$). Significant improvement in knowledge and perception was also noticed in these sub-groups when stratified based on gender, race and profession.

Conclusion: Low-cost, effective educational interventions can help reduce the barriers to knowledge and misperceptions among healthcare providers about SCD patients. Improvement in knowledge and perception translates into better practice and hence enhanced quality of care.

362

IS THERE A ROLE FOR A RHEOLOGIC AGENT IN TRANSFUSION?

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Background: Decreased microvascular blood flow and hemodynamic changes potentially compromising tissue oxygen delivery have recently been reported in some sickle cell anemia patients following transfusion1, 2. While transfusion increases blood oxygen carrying capacity, it also increases blood viscosity. The anticipated benefits of transfusion could be diminished or lost if the net effect of decreased blood flow more than offsets increased O2 carrying capacity. Red blood cell (RBC) aggregates impair blood flow in the microcirculation where the majority of oxygen and nutrient exchange occur. Since older RBC aggregate more than younger RBC, we hypothesized that increased RBC aggregation following transfusion of older or "storage lesioned" RBC may contribute to decreased blood flow. MST-188 (purified poloxamer 188) is a rheologic agent currently under investigation in a phase 3 trial in pediatric sickle patients hospitalized with acute vaso-occlusive crisis. We hypothesize that this poloxamer may inhibit aggregation of older or storage-injured RBC and potentially have utility in transfusion.

Objective: To determine the relative effect of poloxamer 188 on the aggregation of "older" versus "younger" RBC

Methods: RBC obtained from 4 healthy donors were age-separated via centrifugation into younger (least-dense 10%) and older (most-dense 10%) cells, then re-suspended in 3% dextran 70 containing poloxamer 188 at 1 or 5 mg/ml. The extent of RBC aggregation (Aggregation Index) was measured using a Myrenne aggregometer system.

Results: Older RBC exhibited a mean aggregation index (AI) approximately 140% greater than younger RBC. Addition of poloxamer 188 resulted in a concentration dependent reduction in AI for both older and younger RBC, with the effect more pronounced for older RBC. At 5 mg/ml there was a greater than a 2- fold reduction in mean AI compared to control for older RBC.

Conclusion: Poloxamer 188 inhibits aggregation of older and younger RBC and may have utility for treating and/or preventing transfusion-induced decreases in microvascular blood flow. Studies of MST-188 using storage lesioned RBC are planned.

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THE IMPORTANCE OF PARENTAL SUPPORT IN BUILDING A STRONG PEDIATRIC SUPPORT GROUP: THE HAVE A HEART FOR SICKLE CELL ANEMIA FOUNDATION

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Too often, even if it is not necessarily voiced, siblings and other family members are often isolated and have some feelings of abandonment during the time spent by the primary caregiver caring for the individual/child with sickle cell disease. The Have A Heart organization recognizes that the individual with the disease is a part of a unit - the family, and takes pride in offering a unique program that not only focuses on the individual with sickle cell disease, but also the entire family.

The Have A Heart for Sickle Cell Anemia Foundation is a Chicago based non-profit 501(c)(3) organization established in 1990 by Linda Collins – a former patient at the University of Illinois Hospital and Health Sciences System. Having the disease herself, Linda saw a lack in community based sickle cell programs that included the individual and family in year-round structured activities. Ms. Collins succumbed to Leukemia in 2002, but her vision to fill the void of the lack of a family centered comprehensive support group program in Chicago was brought to life with the creation of her Youth Development Program. The Youth Development Program was launched in 2003 to focus on enriching the lives of youth living with sick cell disease and their families and instill in them her motto "sickle cell disease is what you have not who you are."

The Youth Development Program offers a variety of activities to suit the participants and their family's academic, recreational, and self improvement needs, and is highlighted by our homework assistance program. Because of the unpredictability of pain crisis associated with the disease, many pediatric patients with the disease miss a lot of days from school due to pain thus affecting their education, social development, and quality of life. The Have A Heart Foundation tries to fill these voids by offering tutoring, arts, and enrichment activities for the individual with the disease and their siblings. Field trips are scheduled throughout the yearto give the participants unique cultural experiences that will expand their minds and help them grow both physically and intellectually. Along with the Youth Development Program, the Have A Heart for Sickle Cell Anemia Foundation has a Parent Support Group that meets simultaneously with the youth group to provide a forum for parents to support each other and express their joys, frustrations, and limitations of caring for a child with sickle cell disease.

The Youth Development Program will be celebrating its 10 year anniversary in February 2013. Since the start of the Have A Heart program 10 years ago, over 60 children have participated in the Youth Program, many during this time having also transitioned from pediatric centered sickle cell care to adult centered care at the University of Illinois Hospital. Currently, with the support of the parents, the Youth Development Program is a thriving group that includes 9 families, 22 youth participants, 13 active parents, and growing.

The purpose of this presentation is to describe the process of building a strong youth and parent support group, the stages of group development and its effects on group stability and growth, and community/enrichment activities that the group has been actively involved in within the past year.

SAFETY AND LONG-TERM EFFECTS OF SPLENECTOMY AT THE AGE OF TWO FOR ACUTE SPLENIC SEQUESTRATION IN SICKLE CELL DISEASE: A RETROSPECTIVE REVIEW

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Objective: Despite improved awareness and education about acute splenic sequestration (ASS) in sickle cell disease (SCD), such episodes remain potentially fatal and treatment options are limited. We report our local experience in children splenectomized at the age of two by evaluating long term complications related to sepsis, thrombosis and iron overload.

Methods: Retrospective charts review of children with SCD and a history of ASS who underwent total splenectomy between 1996 and 2012 at Ste-Justine Hospital in Montreal, Canada. T-test and Fisher's exact test were used for statistical analysis.

Results: 20 patients were included in the study. Median age at splenectomy was 2 years old (range: 2-9 y.o). Median post-splenectomy follow-up was 4 years (range: 1month-16 years). 7 patients (35%) had limited fever in the postoperative setting, including one requiring antibiotics for pneumonia. Median length of stay was 4 days (range: 2-8 days). Three patients were hospitalised for documented sepsis at extended follow-up: two for salmonella at 1 and 12 years post splenectomy, while the third had hemophilus influenzae sepsis five months post-op but also within two months of a sibling cord blood transplantation. Platelet count increased within one month of surgery, and remained elevated at 6 and 12 months post splenectomy ($p<0.001$ at 1, 6 and 12 months compared to pre-surgery). Deep venous thrombosis was documented in one patient 4 years post splenectomy during hospitalisation for pain crisis. The thrombosis resolved with a three months treatment with enoxaparin. Thrombophilia work-up was negative. 75% of patients were on a transfusion program prior to splenectomy for a median duration of 13 months (11-20 months). Preliminary evaluation of iron overload in seven patients revealed a decrease in ferritinemia in all but two. One patient remained with severe iron overload and still requires oral chelation therapy. HbSS and HbS-Bthal splenectomized patients were more likely to be placed on hydroxyurea (HU) therapy than non-splenectomized patients with an odds ratio of 3 (11/20 vs 39/136 of our local population, $p=0.023$; 95% CI 1.17-7.9). 2 patients are on a regular transfusion program for elevated transcranial Doppler velocities. One patient underwent match sibling allogeneic transplantation.

Conclusion: Our data suggest that performing total splenectomy at a very young age is a welltolerated and efficacious treatment modality for children with severe and/or recurrent ASS. Performing splenectomy at a younger age may avoid unnecessarily extended transfusion programs and contribute to lessen the degree of iron overload. We consider ASS as a marker of SCA severity, as illustrated by the high rate of HU use in splenectomized patients. Whether splenectomy leads to biological modification contributing to increased SCD severity should be further studied. Concerns over possible increased thrombotic risk should also be further evaluated.

422

HYDROXYUREA THERAPY IN SICKLE CELL DISEASE: AN ALTERNATIVE APPROACH TO PREOPERATIVE RED CELL TRANSFUSION?

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Background: Patients with sickle cell disease (SCD) are at high risk for peri-operative complications. Preoperative red cell transfusions are recommended to decrease the risks of these complications. Red cell transfusions can be associated with transfusion reactions, alloimmunization, transmission of infections and iron overload. Additionally some families and patients may be resistant to transfusions due to cultural or religious beliefs. Hydroxyurea (HU) is the only FDA-approved treatment for SCD. HU has been shown to reduce vaso-occlusive complications for both adults and children with SCD resulting in a decreased incidence of acute chest syndrome, pain and fewer hospitalizations along with increased levels of hemoglobin, fetal hemoglobin and decreases in the reticulocyte, platelet and white blood cell counts.

Objectives: To describe 2 SCD patients treated with hydroxyurea who did not require red cell transfusion prior to their elective surgeries.

Methods: To determine the perioperative course, we reviewed the medical records of children with SCD who underwent elective surgeries without requiring red cell transfusion.

Results: One patient with sickle beta zero thalassemia underwent laproscopic splenectomy while the other with homozygous sickle cell disease had laproscopic cholecystectomy. Both patients were on stable dose of hydroxyurea with good hematologic response preoperatively. The range of the hydroxyurea dose was 24.7-28.7 mg/kg/day. Mean hemoglobin concentration was 9.9 ± 0.9 g/dL and mean fetal hemoglobin was 28.8± 7 %. Both patients tolerated the surgical procedure well and had no complications in the immediate post- operative period or at follow-up.

Conclusion: Hydroxyurea therapy should be explored as an alternative to blood transfusion in select group of SCD patients undergoing elective surgeries.

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THE USE OF SUPPLEMENTAL OXYGEN IN PRIAPISM ASSOCIATED WITH SICKLE CELL DISEASE

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Background: Priaprism is a complication of sickle cell disease (SCD) that receives very little attention. Lack of effective prevention and definitive treatment options for this condition may result in serious and even permanent consequences such as irreversible penile fibrosis and impotency.

Case Report: A 15 year old male with HgSS presented with sustained, painful episode of priapism at 9 years of age. These episodes typically occur in the early morning hours or upon awakening at school and last for up to 4 hours. He has had multiple painful erections that responded to administration of oral opioids, hydration and Sudafed. The frequency and severity of these episodes has escalated as he was undergoing puberty and resulted in an increased rate of hospitalization for more aggressive medical and surgical interventions. He underwent corporal body irrigation with instillation of phenylepinephrine in 2008 following a markedly sustained erection that lasted for more than 9 hours despite hydration, use of blood transfusions and a variety of analgesics. In addition to these sustained priapism episodes, he has had episodic pain crises involving his legs and knees that have affected his ability to perform more intense aerobic exercise.

He was seen in the multi-disciplinary Pulmonary-Sickle Cell clinic because of complaint of chest tightness with activity. He occasionally snores at night but no report of witnessed apnea, or gasping. He feels sleepy in the morning and does fall asleep in school. He takes a nap at the end of the day. His daytime Spo2 varies from 92 to 95%. Spirometry showed very mild small airway obstruction with significant response to bronchodilator. He was started on Singulair and Albuterol for symptoms of exercise induced bronchospasm which has resulted to improvement in his pulmonary symptoms.

Since his pattern of priapism typically occurred in early morning sleep or upon awakening, an overnight polysomnography was performed to investigate the relationship between sleep related events and his recurrent episodes of priaprism. This study (Fig 1) showed mild obstructive sleep apnea with a total apnea-hypopnea index (AHI) of 5.3 respiratory events per hour. These events were associated with mild oxygen desaturations of >3% from the baseline. Interestingly, it was noted that his average, baseline oxygen saturation during sleep was in the mid 80%. His oxygen saturation during sleep increased to 95-97% after initiation of 1LPM of oxygen. In a case control study performed by Roizenblatt and colleagues, they demonstrated a non physiological distribution of penile rigidity events throughout sleep and the influence of oxyhemoglobin desaturation rather that rapid eye movement (REM) sleep, lung involvement, hyperhemolysis or AHI on priapism. They stipulated that an increased relative duration of oxyhemoglobin desaturation during sleep in the priapism group may explain the higher penile rigidity in percent total sleep time (TST). Based on these findings, we have recommended to the patient the use of 1 LPM of humidified supplemental oxygen at night. Six months later, he reported a decrease in frequency, severity and duration of priapism events. Priapsim now occurs once a month; the pain intensity has decreased significantly and now lasts for 10 minutes or less. He likewise has not had any pain crisis and has not used any pain medications. He feels more energetic nowadays and has not fallen asleep in school.

QUESTIONS:

1.Should all patients with SCD be screened for sleep related breathing disorders?

2.Should all patients with recurrent episodes of priapism undergo an overnight polysomnogram?

3.What is the role of supplemental oxygen in preventing recurrent pain crisis and priapism episodes in sickle cell population?

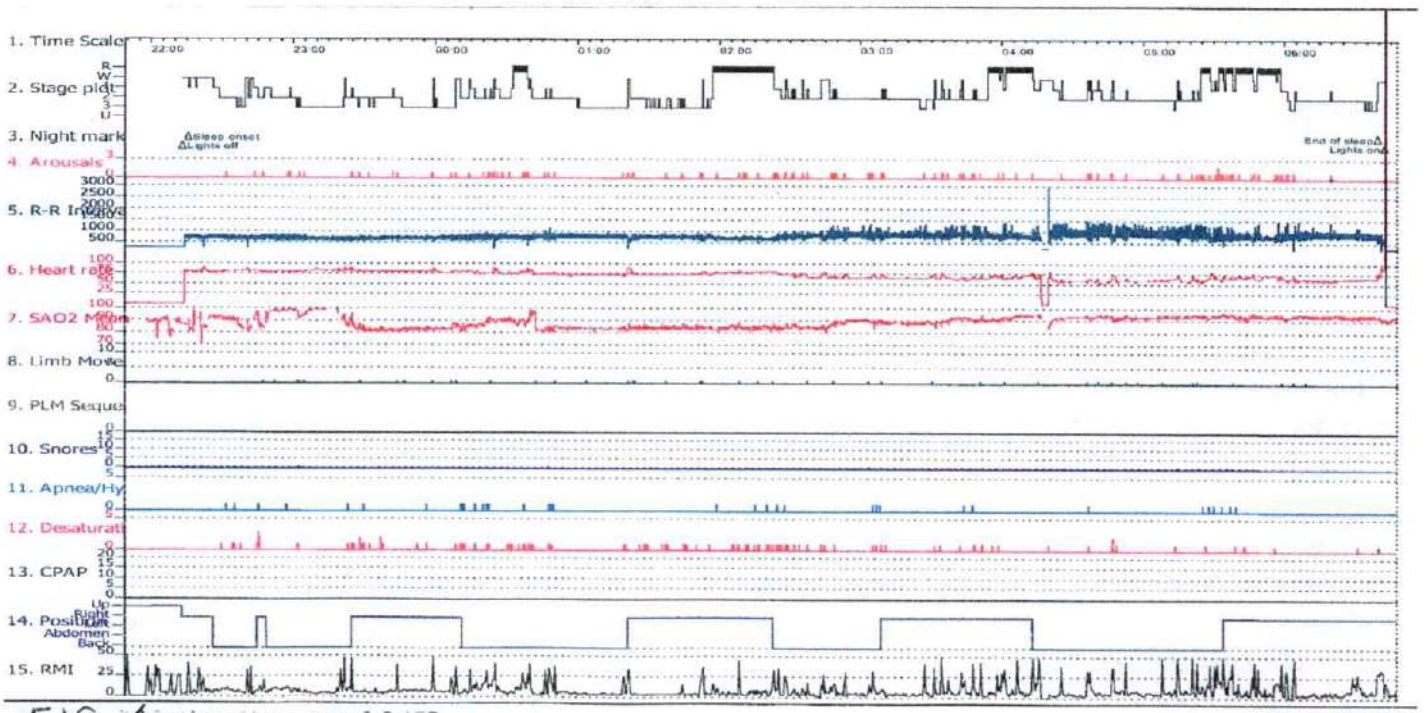

FIG. 1

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253

EPIDEMIOLOGY AND VARIABLES DEFINING SEVERITY OF SICKLE CELL DISEASE: A SINGLE INSTITUTION EXPERIENCE

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Background: Sickle cell disease is an autosomal recessive genetic blood disorder characterized by abnormal and rigid sickle shaped blood cells. While per WHO (World Health Organization), there are estimated to be around 275,000 births globally with sickle cell disease per year, the prevalence in United States is about 90,000, affecting every 1 in 5000 births. Several complications and stigmata emanate from this unfortunate diagnosis and a lot of efforts are directed towards either eliminating the disease itself at a genetic level, or at the very least alleviating some of the disabling complications.

Objectives: To find correlation between severity of disease and other variables, which may be altered to reduce the long and short term sequelae.

Methods: We collected data, retrospectively obtained at our institution, on adult sickle cell patients within the hospital registry, spanning over 5 years from 01/01/2008 to 01/01/2013. Total number of patients studied was 65, with a slight female predominance with a female to male ratio of about 6:4 (40 females and 25 males). These were further subdivided into 3 different age groups: <25; 25-30 and >30 years. We attempted to look for variables defining severity of disease such as number of hospitalizations per year, average length of stay, average degree of reticulocytosis, average degree of hemolysis as defined by LDH (Lactate Dehydrogenase) and average number of blood transfusions. We also tried to look for beneficial effects of elevated Hb F (Fetal Hemoglobin) if any and possible differences in disease severity conferred by age or gender.

Arbitrary cut off values were deployed for the biochemical markers, felt to be most suitable for our population mix. Hb F was divided into greater than or less than 10%; reticulocytosis was also defined as greater than or less than 10%; LDH was divided into greater than or less than 500 units/L and ferritin was divided into greater than or less than 1000 ng/ml. Lower values of reticulocyte count, LDH and ferritin were felt to denote a better disease process as compared to higher values.

Results: Our data reflected the following findings: (See Table)

Hb F >10% in 60.6% females and 21.7% males with a total of 44.6% patients. This is clearly representing a female majority. All cases were on hydroxyurea with the exception of one case with hereditary persistence of Hb F.

With higher Hb F values; reticulocyte count, LDH and ferritin were all more desirable by being lower in a significant percentage of patients, representing 44%, 60% and 52% respectively of the total group. All of these beneficial effects were quite similar in both the genders with the exception of ferritin which tended to be higher in the female group.

Looking for gender differences, independent of Hb F values, there were no significant differences between female and male patients with respect to average number of hospital admissions. Number of sickle cell related hospitalizations, though overall equal in both genders, was highest for males in the age group 25-30 years. There was a slight trend towards female patients staying an average of 1.46 days longer when admitted and requiring about 1.64 more transfusions per year, compared to their male counterparts. The overall rate of severe disease related complications was very similar in both genders, defined as acute chest syndrome, sepsis, pneumonia, stroke, loss of pregnancy and exchange transfusion for any reason. Interestingly, males had more episodes of acute chest syndrome and females had more of the other complications.

Conclusions: Sickle cell disease is a devastating illness fraught with multiple complications and shortened life

span in both genders across all age groups. In our single institution experience based upon a total of 65 patients studied over a course of 5 years, higher levels of Hb F correlated with better measurable disease parameters. The female patients represented the majority within that group, thus doing better than male patients overall. One important distinguishing characteristic is the higher rate of compliance in females with the use of hydroxyurea, thus significantly raising the levels of Hb F. No other significant gender differences were discovered. Dedicated research for similar agents and intensive education of patients about its utility may help improve the overall outcome of sickle cell disease in the community.

Table

* 3 patients in this age group were over 50 years of age, all females

** Only 33 females and 23 males had Hb F results available

	FEMALES	MALES	TOTAL
Total Number	40 (61.6%)	25 (38.4%)	65
Age < 25	14	12	26
Age 25-30	16	6	22
Age > 30	*10	7	17
Hb F > 10%	**20/33 (60.6%)	**5/23 (21.7%)	25/56 (44.6%)
Hb F > 10% and Reticulocyte count < 10%	9/20 (45%)	2/5 (40%)	11/25 (44%)
Hb F > 10% and LDH < 500 units/L	12/20 (60%)	3/5 (60%)	15/25 (60%)
Hb F > 10% and Ferritin < 1000 ng/ml	9/20 (45%)	4/5 (80%)	13/25 (52%)
Average hospital admissions/ year	12.79	13.17	
Average length of stay (days)/ admission	6.52	5.06	
Average number of Transfusions/ year	8.26	6.62	
Severe complications/ year	4.01	4.04	

ASYMMETRICAL IMPACT OF SICKLE CELL ANEMIA ON CARDIAC CAVITIES

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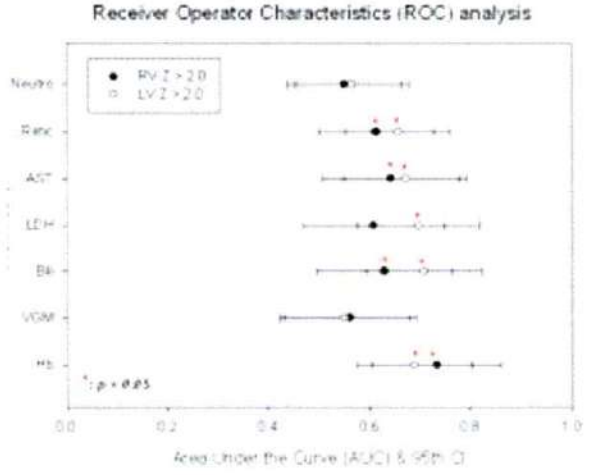
INTRODUCTION: Sickle Cell Anemia (SCA) is known to cause various degree ofvasculopathy, including impact on heart function, as a result of vaso-occlusion and chronic anemia.

OBJECTIVE: In this study we assessed the impact on cardiac compliance and function beyond the cardiovascular damage.

METHODS: Single center retrospective study based on recorded echocardiograms in a cohort of SCA patients followed at CHU-Ste Justine, Montreal (Canada). Echocardiogarphy is rountinely performed in our SCA patients^{3}10 yr, or for clinical reasons in younger patients. Right ventricle (RV) and left ventricle(LV) diastolic diameters, LV mass estimate, myocardial performance index (MPI) and an index of myocardial relaxation (E/E') were calculated for all eligible patients. Cardiac parameters were correlated with various hematological values evaluating severity of hemolysis defined as Hb< 5th percentile per gender and age group, LDH >400 AST>30UI/L, total bilirubin>18mM/L, Reticulocytes>120x109/L, microcytosis defined as MCV<80fL and relative neutrophilia defined as Neutrophils>5x109/L

RESULTS: 110 patients (61% HbSS, 34% HbSC and 5% HbS-Beta-thal) had echocardiography performed at 12.14±5.2 yo(25%<10yo). RV and LV dilatation was present in 65%, and 43.4% respectively. 20.6% had abnormal LV mass, 28% had low MPI and 32% had abnormal E/E'. An ROC/AUC analysis(figure) determined that cardiac dilation was best correlated with Hb, AST, reticulocytosis and bilirubine. Cumulative hematological abnormalities significantly increased the risk for dilated ventricles in 70-100% for RV, and 50-60% for LV. Best subset regression analysis yielded significant additional prediction for RV or LV dilatation with Hgb, Bilirubin, and LDH. Low MPI was best predicted with Hgb, LDH, AST and reticulocytosis. Abnormal E/E' was solely predictable with Hgb.

CONCLUSION: In our patients, SCA is more likely to cause RV dilatation than LV dilatation. This suggests that the increased cardiac output is not the main culprit in SCA-related dilated hearts. The long term consequences of right ventricular dilation, clinical consequences and association with pulmonary vasculopathy needs to be further determined.



SICKLE CELL DISEASE AND WEATHER

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Background: Sickle Cell Disease (SCD) is a well known yet debilitating disease process that affects children around the world by plaguing their everyday lives with the potential of spiraling into a sickle cell painful episode for reasons that are fairly unknown. Vasoocclusive painful episodes are one of the key features of sickle cell disease that brings children to the emergency department routinely.

Objective: To complete a retrospective chart review on children 0-21 with sickle cell disease who present to the emergency department with vasoocclusive painful episodes and if the painful episode correlates with the weather. Hypothesis #1: Weather plays a role in vaso-occlusive pain crisis in children with Sickle Cell Disease. Hypothesis #2: Identification of weather triggers may elucidate prevention measures specific to each child.

Methods: This is a retrospective chart review on children 0-21 with sickle cell disease who present to the emergency department with vasoocclusive painful episodes and how the painful episode correlates with the weather. The day of year will be referenced with the weather (i.e temperature, humidity, barometric pressure) at that time and the patients corresponding zip code.

Results: Study is ongoing currently

Conclusions: If this research study concluded that weather plays a statistically significant role in triggering acute painful episodes, education of preventative measures could be put in place to help reduce the number of painful episodes and hospital admissions, and ultimately cost to the families. If the study shows no relationship to vasoocclusive pain crisis, other variables may need to be further explored to help predict what triggers a pain crisis.

366 A

THE LUNGS AND BRAIN IN SICKLE CELL DISEASE: ORGANS AT RISK OF INJURY DUE TO PERTURBATIONS IN THE HEME DEGRADATION PATHWAY

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Background: Sickle cell disease is an inherited hemoglobinopathy which is characterized by hemolytic anemia, increased oxidant stress, diminished availability of intravascular nitric oxide, vasculopathy, acute clinical events and chronic organ damage. There is considerable variability in morbidity even among patients who share the same sickle cell genotype. Other mutations which affect related proteins, such as a globin impact on disease severity. There are data suggesting that in SAD mice whose endothelium is exposed to heme, unlike the kidneys and liver, there is no increase in heme oxygenase (HO)-1 in the lungs and brains.(1) Furthermore intravenous administration of lysed red blood cells (free heme) into the circulation of sickle mice increased vascular permeability significantly in the lung while not increasing permeability in other organs. (2) We have recent data that suggest that adults with haptoglobn 2 alleles are more likely to have restrictive lung disease than those with Hp 1 alleles. (3) We hypothesize that factors affecting the efficiency of protective molecules in the heme degradation pathway to degrade free heme released into the bloodstream by hemolysis, in particular haptoglobin polymorphisms and heme oxygenase-1 expression, may explain some of the variability seen in the neurological and lung complications of patients with SCD.

Objectives:

1. To determine whether premedication with increasing doses of haptoglobin attenuates the adverse impacts seen in mouse models of free hemoglobin, including differences in HO-1 expression and vascular permeability;

2. To determine whether haptoglobin allele frequencies and levels differ in age matched SCD controls, children with SCD who have suffered strokes or frequent vaso-occlusive crises.

Methods: Murine experiments would be conducted with collaborators at Emory University. Clinical experiments would be conducted at the SCU, UWI, Jamaica. Once ethical approval is obtained, samples could be taken during routine blood draws or using buccal swabs.

Importance: Haptoglobin allele status may be a useful marker of risk of particular complications in SCD. If data suggest its possible usefulness, therapeutic trials with haptolobin could be undertaken.

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372 A

NEWBORN SCREENING FOR SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES IN IBADAN, NIGERIA

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Phase 1

Methodology: This is a pilot study to commence newborn screening for sickle cell disease in Nigeria by first establishing a data and sample management center in the University College Hospital, Ibadan Nigeria. In the first 3 months, samples and demographic information will be collected from all newborn babies born in Ibadan, Oyo State. In the subsequent 9 months, more peripherally located hospitals will be recruited with the target of covering the entire state by the end of the first year of this project. The samples will be collected in duplicate on the second day of life and will be sent every day to the data and sample management center at Ibadan. These samples will be stored in a desiccant and shipped by courier to the Newborn Screening laboratory in Minnesota for processing. Results of the tests will be transmitted electronically by the second week of life back to Nigeria and through the same channels the information will be communicated to the families of these babies.

Any infants identified to have a hemoglobinopathy will be added to a web-based secure database and their care will be established. Their providers will have access to these databases as well as paper guidelines that will be forwarded to these providers at the time of receiving the positive results. Recommended comprehensive care will be outlined and these children will be seen within a month of the diagnosis by a counselor, geneticist or hematologist and then subsequently once a year for an annual check either in their home clinic by a traveling Pediatric Hematology team, or at the Teaching Hospital depending on where the family lives.

Discussions will be started in the first year at a National level on developing a protocol to expand the newborn screening to a national level. These discussions will include soliciting government commitment, procurement of equipment and training of personnel. During the second year, a newborn screening laboratory will be equipped in Ibadan. The laboratory will have all necessary equipment including High Performance Liquid Chromatography, Iso-electric focusing and Citrate Agar Electrophoresis systems. By the 19th month of the program, 50-75% of the samples will be screened locally while the remainder will be sent to the United States for testing. Also some quality control samples will be sent to the US for testing.

By the 22nd month, all screening will take place in Ibadan while samples will be sent to the University of Minnesota Division of Hematology, Oncology and Transplant for quality control as well as identification of rare variants.

From years 3 to year 5 it will involve the establishment and implementation of a National newborn Screening program for the country and evaluation of the program on an annual basis for 3 consecutive years.

Study Duration

This study will last five years

Study Center(s)

The study will be multi-centered. The main sites will be

(1) Minnesota Department of Health Newborn Screening Laboratory

(2) Division of Hematology, Oncology and Transplant, University of Minnesota

(3) University College Hospital, Ibadan, Nigeria

Objectives:

(1) Commence newborn screening for Sickle Cell Disease in Oyo State, Nigeria;

(2) Establishment of a statewide sickle cell disease comprehensive care and follow-up program;

(3) Implement a centralized, web-based information system for follow-up and management of infants identified with sickle cell disease, sickle cell trait and other hemoglobinopathies

(4) Develop a multi-stage inter-professional protocol to expand newborn screening for sickle cell disease and other non-communicable diseases in Nigeria country-wide over the following 5 years

Number of Subjects:

The projected number of subjects for this study is 10,000 live born babies

Diagnosis and Main Inclusion Criteria

To be included in this pilot project, the baby would have been born in a center that is recruiting at the time of birth. Also parents would have been interviewed with a study questionnaire and they would have given written informed consent.

Study Product, Dose, Route, Regimen

This study is a pilot for the establishment of newborn screening for sickle cell disease in Nigeria with subsequent discussions about expanding to involve all other parts of the country.

Duration of administration

Not applicable

Reference therapy

Not applicable

Statistical Methodology

Data generated will be analyzed with with the help of a statistician using standard statistical package

ASSOCIATION BETWEEN RESTRICTIVE LUNG DISEASE AND HAPTOGLOBIN POLYMORPHISMS IN ADULTS WITH SICKLE CELL ANEMIA

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Background: The protein product of the haptoglobin (Hp) 2 allele is less efficient at clearing free hemoglobin. The 2-2 haptoglobulin polymorphism is therefore associated with decreased heme scavenging and raised intravascular free heme. (1) An increase in the bioavailability of intravascular free heme may be associated with chronic organ injury in some patients with sickle cell disease (SCD). Chronic lung disease is patients with SCD is characterized by restrictive lung disease (RLD). (2)

Objectives: We tested the hypotheses that the Hp "2" allele would be associated with RLD and furthermore that there would be a graded effect of the number of Hp "2" alleles (0,1,2) as has been previously seen in diabetes. (3)

Methods: Haptoglobin genotype was ascertained and lung function and pulmonary history were also assessed in 63 adults from the Jamaica Sickle Cell Cohort who were participating in a study of lung function.

Results: The haptoglobin genotype frequencies among the controls were not significantly differentfrom Hardy-Weinberg expectations (c2 = 1.9, P = 0.2, 1 df). Total lung capacity (r2 = -0.29, p=0.02) and forced vital capacity (r2 = -0.31, p=0.02) were negatively correlated with the number of previous episodes of Acute Chest Syndrome (ACS). Female sex (OR=6.8, 95% CI: 2.2-21.6, p =0.001), a history of at least one episode of ACS (OR=3.7, 95% CI: 1.3-10.7, p =0.02) and haptoglobin genotype (trend analysis c2 = 7.4, p =0.006) were significantly associated with RLD. In multivariable analyses, logistic regression demonstrated that RLD was independently related to female sex (b=3.2, P=0.004) and ACS (b=3.2, p=0.004). Patients with the 2-2 haptoglobin genotype were 10 times more likely to have RLD than those with Hp 1-1 phenotype (p=0.03).

Conclusions: RLD, a characteristic finding in chronic sickle cell lung disease, is more common in patients with the 2-2 haptoglobin genotype and there may be a 'dose response' effect of Hp 2 on lung function.

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Florida Journal of Sickle Cell Disease and Hemoglobinopathy
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ABSTRACTS

IN VITRO HUMAN AND PRECLINICAL ANIMAL STUDIES OF ADENOSINE-BASED THERAPIES IN SICKLE CELL DISEASE

(Presented April 15, 2013 during Plenary Session)

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Introduction: Sickle cell disease (SCD) is a debilitating hemolytic disorder with high morbidity and mortality affecting millions of individuals worldwide. Although SCD was first identified a century ago, we still lack effective mechanism-based safe therapies to treat this disease. Thus, identification of specific molecules triggering sickling, the central pathogenic process of the disease, is extremely important to advance our understanding of the molecular basis for the pathogenesis of SCD and to develop novel therapeutics. Using metabolomic profiling, we discovered that adenosine was highly elevated in the blood of SCD Berkeley transgenic mice and human1. Moreover, we demonstrated that elevated adenosine signaling via adenosine receptor A2B (ADORA2BR) contributes to sickling by induction of 2,3-bisphosphoglycerate (2,3-BPG), deoxygenation. Here we extend this finding to preclinical studies to assess adenosine-based therapy on morbidity and mortality in SCD.

Methods and Results: First, we assessed the efficacy of lowering adenosine concentrations by chronic treatment with polyethylene glycol-modified adenosine deaminase (PEG-ADA), a safe drug being used to treat ADA-deficient human for thirty years, in SCD Berkeley mice. After 8 week treatment, we found that sickling, hemolysis and multiple tissue damage were significantly reduced in the mice. Additionally, multiple organ dysfunctions including priapism, penile fibrosis and renal dysfunctions were significantly ameliorated. Subsequently, we found that PEG-ADA enzyme treatment significantly prevented hypoxia/reoxygenation enhanced further elevated adenosine levels compared to steady state in SCD mice and that PEG-ADA treatment successfully inhibited hypoxia/reoxygenation-induced acute sickle crisis, including remarkably increased sickling, hemolysis and pulmonary inflammation in these mice. Finally, we found that PEG-ADA treatment substantially prolonged life span of SCD mice and increased survival rate of SCD under hypoxia/reoxygenation-induced acute sickle crisis. Similarly, we further demonstrated that ADORA2B antagonists (PSB1115) successfully reduced sickling, hemolysis, tissue damage and dysfunction under steady state and prevented hypoxia/reoxygenation-induced acute sickle crisis and increased survival rate. More importantly, no obvious adverse effects of PEG-ADA enzyme therapy and ADORA2B antagonist treatment were observed in these mice under acute sickle crisis and chronic state.

Conclusion and Significance: Overall, our findings reveal that lowering adenosine levels by PEG-ADA enzyme therapy and interfering ADORA2B signaling by specific ADORA2BR antagonists can treat and prevent sickling, progression to multiple life-threatening complications and prolong life span of SCD mice. Thus, our preclinical studies provide strong evidence that PEG-ADA and ADORA2B antagonist are likely novel and safe mechanism-based therapies for humans with SCD. We believe our animal studies are important and set up a strong foundation for future clinical studies in human suffering from SCD.

EFFECT OF AES-103 ANTI-SICKLING AGENT ON OXYGEN AFFINITY AND STABILITY OF RED BLOOD CELLS FROM PATIENTS WITH SICKLE CELL ANEMIA

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Background: Aes-103 (5-hydroxymethylfurfural, 5-HMF) is a putative anti-sickling agent that has undergone pre-clinical testing for potential treatment for sickle cell anemia (SCA). It is an organic compound derived from dehydration of certain sugars, found commonly in small amounts in foods such as coffee and prunes. It binds to alpha subunits of hemoglobin and increases its oxygen affinity. At millimolar levels, it inhibits hypoxia-induced sickling in vitro and when dosed orally it protects sickle cell mice against hypoxia-induced death. We investigate the in vitro effects of a range of concentrations of Aes-103 on oxygen affinity and red cell stability in blood from healthy volunteers, and from patients with SCA with or without hydroxyurea treatment.

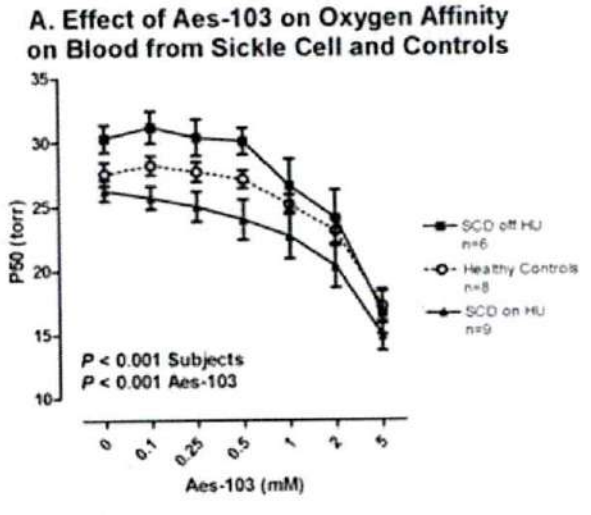
Methods: Blood specimens from healthy control adults and adults with SCA were incubated in vitro with a range of concentrations of Aes-103 between 0.1 and 5 mM for one hour at 37 degrees C. Oxygen equilibrium curves were determined for each sample using the HemOx Analyzer. Samples were diluted in HemOx buffer and then loaded into the Analyzer, which exposed the samples to increasing partial pressure and then deoxygenated with nitrogen gas to produce the oxygen equilibrium curve. The P50 value for each curve was determined at the oxygen tension that produced 50% oxygen saturation. In additional experiments, samples of human control blood and SCA blood were treated with Aes-103 and incubated at 37ºC for 1 hr, and then the samples in tubes were subjected to shear stress by rotation on a vertical rotator at 21 revolutions per minute for 3 hrs. The samples were centrifuged for 2 minutes and plasma was collected and free hemoglobin levels as an indicator of red cell membrane disruption were measured by ELISA.

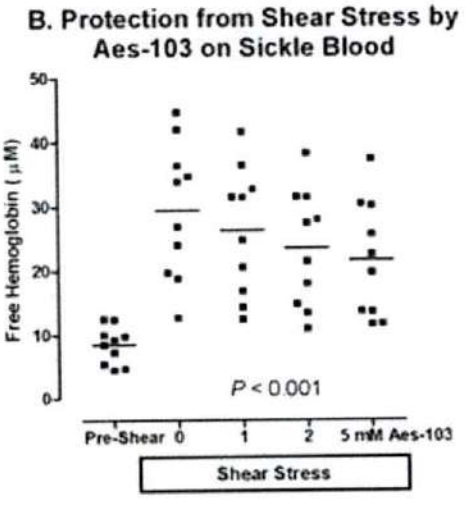
Results: Blood samples from SCA patients off hydroxyurea (n=6) without Aes-103 tended to have higher baseline p50 values than healthy controls (n=6)(30.3 ± 1.1 vs. 28.3 ± 0.8 torr, p=0.15), consistent with previous reports of high intracellular 2,3-DPG, known to increase P50. The P50 remained right shifted in SCA compared to controls at Aes-103 concentration below 1mM, converging with controls at higher concentrations (p=0.035). At baseline, P50 of SCA patients on chronic hydroxyurea (n=9) was significantly lower than SCA patients not on hydroxyurea (26.3 ± 0.8 vs. 30.3 ± 1.1 torr, p=0.008), compatible with the lower P50 contributed by fetal hemoglobin induced by hydroxyurea. At every concentration of Aes-

103, P50 was lower for specimens SCA on hydroxyurea compared to those off hydroxyurea ($p<0.001$)(Figure 1A). Overall, the delta decrease in P50 from baseline in all subjects at all concentrations of Aes-103 was comparable, on regression analysis showing -2.16 torr for each mM increase in Aes-103 ($r2=0.64$, $p<0.001$).

In vitro shear stress under normoxia promoted hemolysis in blood samples from patients with SCA compared to baseline (n=10, free hemoglobin 29.4 ± 3.4 vs. 8.4 ± 0.9 uM, $p<0.001$). Addition of Aes-103 at increasing concentrations reduced the extent of shear-stress induced hemolysis, by 15% at 1mM Aes-103; by 28% at 2mM Aes-103; and by 37% at 5mM Aes-103 ($p<0.001$, Figure 1B). Interestingly, although shear stress promoted less hemolysis in blood samples from healthy controls, Aes-103 at these concentrations also reduced this hemolysis to a comparable extent, suggesting a red cell stabilizing mechanism distinct from anti-sickling effect. Shear stress experiments under hypoxic conditions are underway. In pilot experiments using an imaging flow cytometry assay described in detail in a separate abstract, Aes-103 showed preliminary ability to repress sickling induced by hypoxia in vitro.

Conclusions: Red cells from SCA adults treated with hydroxyurea have significantly higher affinity for oxygen than those from patients not treated with hydroxyurea, presumably related in part to the high affinity of fetal hemoglobin induced by the drug. Aes-103 increases oxygen affinity in sickle erythrocytes in a concentration-dependent fashion, and this effect is even more prominent when combined with that of hydroxyurea. Aes-103 at high concentrations stabilizes red cells against shear stress in vitro. With our collaborators at AesRx, LLC, a phase 1 safety and pharmacokinetics study of Aes-103 in healthy volunteers has been completed and we now are conducting a similar study at the NIH Clinical Center in adults with sickle cell anemia.





299

FINAL RESULTS OF A RANDOMIZED, OPEN-LABEL, MULTICENTER, 26-WEEK DOSE ESCALATION STUDY OF HQK-1001 (2,2-DIMETHYLBUTYRATE, SODIUM SALT) IN SICKLE CELL DISEASE (SCD)

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Background: Fetal hemoglobin (Hb F) induction is an effective therapeutic strategy in SCD. HQK-1001, an orally bioavailable short-chain fatty acid, promotes Hb F synthesis and prolongs erythroid survival and proliferation in pre-clinical models. This study evaluated the safety, pharmacodynamics (PD) and pharmacokinetics (PK) of HQK-1001 given at higher doses and for longer duration than previously studied.

Primary objective: Safety and tolerability of HQK-1001 administered at 3 dose levels. Secondary objectives: Effect on Hb F, PK, and pain crises.

Methods: Subjects with SCD at least 12 years old were randomized to receive HQK-1001 at 30, 40, or 50 mg/kg/day for 26 weeks. Subjects were stratified by HU at enrollment, and those on HU had to be on a stable dose for at least 6 months. HQK-1001 was discontinued after a transfusion. Oral iron was given daily if plasma ferritin was < 700 ng/mL. Week 4 PK was evaluated in 4 subjects at each dose. Pre-dose plasma concentrations were measured at each 4-weekly visits to assess compliance.

Results: 52 subjects were randomized to HQK-1001 at 30 mg/kg (n = 15), 40 mg/kg (n = 18), and 50 mg/kg (n = 19). There were 28 males and 24 females with a median age of 21 years (range, 12-46). The phenotype was Hb S-S in 45 subjects and Hb S-β thal0 in 7, and 31 subjects (60%) were on HU. Subjects were enrolled in the US (n = 21), Canada (n = 1), Jamaica (n = 8), Lebanon (n = 18) and Egypt (n = 6). Baseline characteristics were comparable across regions.

The median duration on study was 114 days (range, 8-192), with 27 subjects (52%) having discontinued HQK-1001 early, 12 due to a transfusion and 15 for other reasons including withdrawal of consent and adverse events (AEs). The most common drug-related AEs, nausea (44%), vomiting (29%), somnolence (25%), headache (17%) and upper abdominal pain (17%), were usually mild or moderate. Grade 3 gastritis was reported in 3 subjects at 40 mg/kg/day, and was deemed the dose-limiting toxicity. HQK-1001 was subsequently dosed at 30 mg/kg/day and oral iron supplementation was discontinued. No new drug-related Grade 3 AEs were reported after administering HQK-1001 at 30 mg/kg/day and stopping iron. To further improve tolerability,

HQK-1001 was switched to 15 mg/kg twice a day (BID). Average plasma concentration half-lives ranged from 9.8 to 11.7 hours, were dose independent, and supported BID dosing.

In 21 subjects receiving HQK-1001 alone, Hb F increased in 18 (86%), with a mean increase of 2% (range, -2% to +10%), total Hb increased by a mean of 0.5 g/dL (range, -1.2 to +1.8 g/dL), and reticulocytes increased by a mean of 4.1% (range, -4% to +15%) [$p < 0.005$ for all 3 parameters]. In 31 subjects receiving HQK-1001 + HU, Hb F increased in 25 (80%), with a mean increase of 2.7% (range, -3% to + 10%) [$p < 0.0001$], total Hb increased by a mean of 0.75 g/dL (range, -0.7 to + 2.4 g/dL) [$p < 0.0001$], and reticulocytes increased by a mean of 1.4% (range, -6% to +15%). For 6 of 8 subjects with Hb F increases > 6%, the peak occurred after 3 months of dosing. There was a significant positive correlation between change in Hb F at peak value and baseline ferritin ($p = 0.008$) and negative correlation with TIBC (, $p < 0.0001$).

Conclusions: HQK-1001 at 30 mg/kg/day is usually well tolerated. Gastritis was the dose limiting toxicity. Plasma concentrations at 30 mg/kg/day were in the range shown to induce Hb F and erythropoiesis in pre-clinical models. Hb F increased in most subjects, both in HU and non-HU groups. A placebo-controlled Phase 2 study in subjects with SCD not currently on HU evaluating the effect on Hb F, safety, and clinical benefit of HQK-1001 at 15 mg/kg BID for 48 weeks is expected to complete enrollment in Q2-2013."

STUDIES OF CLINICAL STAGE HBF INDUCERS IN SUB-GENOTYPED SICKLE ERYTHROID PROGENITORS AND PRIMATES

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High-level expression of fetal gamma-globin ameliorates clinical complications in sickle cell disease and is achieved with hydroxyurea (HU) in young children. However, non-cytotoxic high-potency therapeutics, particularly which can be utilized with HU, are needed for many adolescent and adult patients who have continued and serious clinical events. To identify additional compounds which induce gamma-globin gene expression without cytotoxicity, we adapted a gamma-globin promoter construct linked to GFP for robotic high-throughput screening, and screened five diverse chemical libraries, including a library of drugs which are approved for treatment of other medical conditions. A small panel of the approved therapeutics have benign safety profiles and are suitable for long-term use. The most promising three candidates were evaluated in anemic baboons, and these induced gamma-globin mRNA by 15-33-fold over baseline. In erythroid progenitors cultured from sub-genotyped sickle cell patients, 3 novel inducers (BENZ, DLT, RSV) and two clinical stage HDAC inhibitors, MS-275 and SB939, induced 4 to 40-fold higher gamma-globin mRNA above untreated control levels in different subjects' progenitors. The new agents demonstrate activity at nanomolar concentrations. One candidate, BENZ, has been used for decades as an excipient solely to prolong the half-life of an active ingredient, and offers a potentially rapid registration route. In sickle erythroid progenitors sub-genotyped for SNPs in 3 major QTL loci (Bcl-11A, HMIP, Xmn-I), each therapeutic is active in 60-75% of progenitors studied, with differential gamma-globin mRNA responses observed. Progenitors with Xmn-1 SNPs appear associated with higher induction to most agents, eg, BENZ and HDAC inhibitors. Some HDAC inhibitors suppress Bcl-11A expression, and these demonstrate activity in higher proportions of progenitors from subjects who do not have any underlying polymorphism in Bcl-11A. These in vitro and in vivo studies identify a growing pipeline of HbF-inducing therapeutics, both epigenetic and targeted, which are suitable for clinical trials in sickle cell patients, but also suggest that personalized therapeutic combinations may be required to guide and achieve high-level efficacy.

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340

DEVELOPMENT OF THE ANTI-P-SELECTIN ANTIBODY, SELG1, FOR THE PREVENTION AND TREATMENT OF SICKLE CELL-RELATED PAIN CRISES

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Extensive data published over the last decade establish P-selectin as a key mediator of critical cell-cell interactions in the vasoocclusive process in sickle cell disease (SCD). Blockade or genetic absence of P-selectin decreases or eliminates vasoocclusion in murine models of SCD. In addition, blockade of P-selectin significantly reduces the interactions of human sickle red blood cells with platelets and endothelial cells in ex vivo models. We have developed a humanized antibody directed against human P-selectin, SelG1, as a potential therapeutic modality to reduce vasoocclusion and associated pain crises in patients with SCD.

We recently conducted a Phase I placebo-controlled, double-blind, first-in-human, single ascending dose (0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg and 5.0 mg/kg) and multiple dose (2 x 8.0 mg/kg, 2 weeks apart) study of intravenously administered SelG1 in healthy adult male and female subjects for the evaluation of safety, tolerability, PK, PD and immunogenicity. Based on AEs, clinical laboratory evaluations, vital signs measurements, physical examinations, and ECG evaluations, administration of SelG1 in single or multiple doses was well-tolerated in this group of healthy male and female subjects (27 subjects total; 20 SelG1 and 7 placebo). There were no infection-related AEs and no demonstrable changes in coagulation parameters or increased bleeding tendencies. Mean t1/2 values of SelG1 increased in a dose-dependent manner and concentrations slowly declined. The increases in mean Cmax were greater than dose proportional. The SelG1 t1/2 was approximately 15 days. Pharmacodynamic analysis showed that a single 5.0 mg/kg dose of SelG1 was sufficient to completely block P-selectin activity for a minimum of 28 days. Immunogenicity data generated during the Phase I clinical trial indicated that no specific antibody response to SelG1 occurred in any subjects. Finally, SelG1 administration did not produce any notable treatment related changes in peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, CD4/CD8 double positive T cells, B cells, natural killer cells, total CD45+ cells, or CD4/CD8 ratio).

In summary, preclinical studies have established P-selectin as a key mediator of vasoocclusion in models of SCD. An initial Phase I clinical study suggests that SelG1 is safe and well tolerated in healthy subjects and has highly favorable pharmacokinetic/pharmacodynamic profiles allowing for once-a-month chronic administration. Further, preclinical studies suggest that treatment with SelG1 could prevent or reduce vasoocclusion and affect the associated morbidities of vasoocclusive pain crisis. Based on these data, Selexys proposes to conduct a large Phase II, multicenter, randomized, placebo-controlled, double-blind, 12-month study to assess safety and clinical efficacy of SelG1 in SCD patients with sickle cell-related pain crises (SUSTAIN study). A synopsis of the Phase II study will be presented.

370

DRUG DISCOVERY AND HIGH-THROUGHPUT SCREENING AT THE UNIVERSITY OF KANSAS

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The Drug Discovery and Development at the University of Kansas at Lawrence and the Kansas University Medical Center (KUMC) is a cross-campus, multi-institutional program. The integrated drug discovery and development organization is designed to bring pharmaceutical best practices to academic setting. The program efficiency is maintained via high performance and highly collaborative project teams through effective planning and management. The program also seeks to leverage relationships with other institutions and industry partners to advance projects and strengthen the program. One of the starting points in drug discovery is high-throughput screening, which allows researchers to conduct tens of thousands of chemical, genetic or pharmacological tests in a very short period of time. The automation and miniaturization technologies of a high-throughput screening lab allow thousands of chemical compounds to be rapidly tested against diverse biochemical and cell-based assays. The state-of-the-art screening technology in the lab at Lawrence makes KU a major player in drug discovery.

POSTERS

A PHASE 1, FIRST-IN-MAN, DOSE-RESPONSE STUDY OF AES-103 (5-HMF), AN ANTI-SICKLING, ALLOSTERIC MODIFIER OF HEMOGLOBIN OXYGEN AFFINITY IN HEALTHY NORMAL VOLUNTEERS

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5-HMF (5-hydroxymethyl-2-furfural; Aes-103) is a breakdown product of glucose that has potent anti-sickling properties in vitro and in vivo (transgenic sickle cell mice) and produces concentration-dependent left shifts in p50 values of the oxygen equilibrium curve (OEC), indicating increased oxygen affinity. These pharmacological properties are likely based on the binding of 5-HMF to the valine residue of alpha globin chains of HbS and possibly to lysine. Increasing the oxygen affinity of HbS is known to reduce sickling. Aes-103 is being developed as a potential treatment for sickle cell disease (SCD).

The current first in man study was a double-blind, placebo-controlled, ascending single dose evaluation of the safety, pharmacokinetics and pharmacodynamics of 5-HMF given as an oral solution at 300 mg, 1000 mg, 2000 mg and 4000 mg to healthy normal subjects. In each dosing cohort, 6 subjects received 5-HMF and 2 received placebo. A total of 20 adult subjects of African descent with normal hemoglobin (Hb), received a single dose of study drug or placebo on up to 2 occasions separated by 2–4 weeks. The mean age of the subjects was 28 years, mean BMI was 25.8, and 13 were males, 7 were females. Written informed consent was obtained.

Safety measures consisted of adverse events (AEs), vital signs, ECG, clinical chemistry, hematology, urinalysis and physical exams. No subjects were discontinued from the study due to an AE. During the day of dosing a total of 14 AEs occurred. All were mild, with 3 occurring in the placebo arm (constipation, dry mouth, dizziness), none at 300 mg, 2 at 1000 mg (diarrhea, headache), 3 at 2000 mg (feeling hot, somnolence, dyspnea—during hypoxia testing) and 6 at 4000 mg (nausea (2), abdominal pain, dizziness, somnolence (2)). Following dosing, there were no clinically significant differences between drug and placebo treated subjects in respect to heart rate, blood pressure, ECG, physical exams, clinical chemistry, hematology and urinalysis results.

The pharmacokinetic profile of 5-HMF in plasma showed dose-proportional kinetics with an upward trend towards higher Cmax and AUC at higher doses. Mean plasma Cmax concentrations ranged from 34 to 699 ng/ml, Tmax ranged from 0.42 to 0.67 h, AUC ranged from 33 to 875 ng.ml/hr and t1/2 ranged from 0.38–0.76 h. 5-HMF levels in RBC hemolysate were typically 5–15 times that of corresponding plasma levels with Cmax ranging from 152–3640 ng/ml, Tmax ranging from 0.71–0.83 h, AUC ranging from 473–10103 ng/ml/h and half-life ranging from 1.61–2.13 h. Measurements of RBC hemolysate levels did not include the 5-HMF bound to hemoglobin. The elevated levels and longer half-life of 5-HMF in RBCs relative to plasma probably reflects the binding affinity of Hb for 5-HMF and the equilibrium between Hb bound 5-HMF, free 5-HMF in the RBC and in plasma.

The main pharmacodynamic endpoint was the change in blood oxygen level (SpO2) during a 5-minute hypoxia challenge test in which 12% O2 was inhaled. The hypoxia challenge was administered prior to dosing and then at 0.75, 2, 4 and 8 h post-dose. Results showed an appreciable attenuation of the drop in SpO2 values due to hypoxia. For example, at 2 hours post-dose for the placebo treated subjects the mean SpO2 values declined by an average of 12.3% after 5 minutes of hypoxia. In contrast, the 2000 mg 5-HMF treated subjects had a mean decline in SpO2 of 8.7%. The attenuation of hypoxia effects was dose-dependent (minimal effect at 300 mg of 5-HMF) and was time-dependent following 5-HMF dosing (largest protection seen at 2–4 h post-dose, no protection at 8 h post dose). At 2 hours after 5-HMF doses of 1000–4000 mg, the SpO2 values from 18 hypoxia test sessions showed significantly ($p<0.05$, t-test) smaller decrements than what occurred in the same time point in the pooled placebo treated subjects.

In summary, single oral doses of 300–4000 mg of 5-HMF given to healthy normal volunteers were well tolerated, rapidly absorbed and preferentially taken up into RBCs relative to plasma, had a dose-proportional pharmacokinetic profile and showed a pharmacodynamic change (protection against desaturation during hypoxia) consistent with the expected increase in oxygen affinity and with the compound's proposed mechanism of action in SCD patients. A similar ascending single dose, placebo controlled, double-blind study in patients with SCD at steady state is currently ongoing at the NIH (see www.clinicaltrials.gov).

A Pilot Study of Eptifibatide for Treatment of Acute Pain Episodes in Sickle Cell Disease

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BACKGROUND: Despite the abundant laboratory evidence of platelet activation and inflammation in sickle cell disease (SCD), the contribution of these changes to the pathogenesis of SCD remains uncertain. Patients with SCD exhibit increased platelet activation in the non-crisis, "steady state," and further increases with acute pain episodes. In addition, levels of the inflammatory mediator, CD40 ligand (CD40L) are increased in the plasma and significantly reduced in the platelets of SCD patients compared to healthy individuals. CD40L may contribute to the pathogenesis of acute pain episodes. Despite an improved understanding of the pathophysiology of SCD, the treatment of acute pain episodes is supportive. We performed a randomized, placebo-controlled study to evaluate the safety and efficacy of eptifibatide, a synthetic peptide inhibitor of the glycoprotein (GP) IIb/IIIa receptor, in patients with SCD during acute painful episodes.

METHODS: In this single site placebo-controlled trial, eligible patients admitted for acute painful episodes received eptifibatide (two 180 ug/kg boluses 10 minutes apart, followed by a continuous infusion at 2 ug/kg/min for 6 hours) or placebo at a ratio of 2:1. The Post-Treatment Phase lasted for up to 7 days or until resolution of the crisis, whichever was shorter, but no less than 24 hours after discontinuation of infusion. The Follow-up Phase included safety evaluations obtained 14 to 17 days and 28 to 35 days after discontinuation of infusion. The primary outcomes were major bleeding episodes and the largest observed decrease in platelet count during the study. We also evaluated the effect of eptifibatide on the duration of acute pain episodes, pain intensity, duration of hospitalization, total opioid use and acute chest syndrome.

RESULTS: Thirteen patients (SS - 10, Sb0 - 2, SC - 1) were randomized to receive either eptifibatide (N=9; 6 females; median age - 25 years) or placebo (N=4; 3 females; median age - 31 years). One patient in the eptifibatide arm withdrew consent following completion of study drug infusion and 1 patient in the placebo arm was withdrawn early because she did not meet eligibility criteria. In the intent-to-treat analysis, there were no major bleeding episodes in either group (point estimate of difference in eptifibatide vs. placebo proportion: 0.0, 95% CI; -0.60, 0.37).There was one minor bleeding episode in a patient on the eptifibatide arm (point estimate of difference in eptifibatide vs. placebo proportion: 0.11, 95% CI: -0.502, 0.494). There was a trend for the largest decrease in platelet count to be greater in the eptifibatide arm compared to the placebo arm, although the difference was not statistically significant (Hodges-Lehman estimate of location shift for eptifibatide vs. placebo: -82, 95% CI; -281, 54). There was no significant difference in the proportion of patients with thrombocytopenia between the treatment groups (point estimate of difference in eptifibatide vs. placebo proportion: 0.11, 95% CI: -0.587, 0.495). The median time to discharge and the median time to crisis resolution were 3.0 days for both treatment arms. The median total opioid use was 400.2 morphine equivalents (ME) for the eptifibatide group and 1471 ME for the placebo

group (Hodges-Lehman estimate of location shift for eptifibatide vs. placebo: -65.8, 95% CI: -2519, 1700). There was one episode of acute chest syndrome in each treatment arm.

CONCLUSIONS: In this small study of SCD patients hospitalized with acute painful episodes, eptifibatide appeared to be safe, but did not improve the times to crisis resolution or hospital discharge. Eptifibatide appeared to be associated with a reduced requirement for opioid analgesics, although the difference was not statistically significant. Clinicaltrials.gov Identifier: NCT00834899.

411

LOST IN TRANSLATION: COMPLEX INTERACTIONS IN SICKLE CELL DISEASE MAY INTERFERE WITH TARGETED THERAPEUTICS

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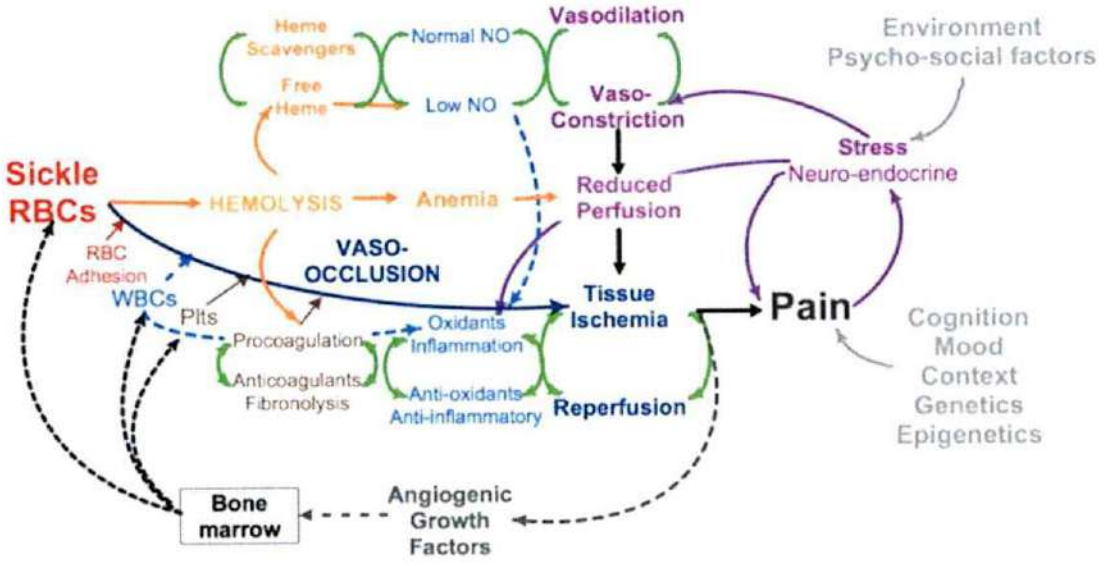
BACKGROUND: Sickle cell disease (SCD) is caused by a single mutation in beta-globin, but triggers several pathophysiologic pathways and results in a highly complex disease. Several processes in SCD, such as hemolysis, ischemia and reperfusion injury, inflammation, oxidative stress, or activated coagulation, are likely to interact simultaneously to contribute to SCD complications. The role of each pathway is likely to be dynamic and situation-dependent, e.g. during acute infection, hypoxia, hyper-hemolysis, cold exposure, or stress. This complexity is likely to be one of the major barriers to the development of successful new treatments which, to date, has largely concentrated on individual mechanistic pathways. The unexpected outcomes of promising clinical trials may be the result of a reductionist approach, correcting a single mechanistic pathway without having first evaluated its relative contribution to SCD complications.

OBJECTIVES: A visual model was developed to help better understand complex interactions of pathophysiologic mechanisms in SCD, and was then applied to the analysis of select clinical trials.

METHODS: Applying concepts of systems theory and network biology, a model was developed showing relationships between the primary defect of sickle hemoglobin (Hb S) polymerization and the clinical outcome of acute pain (Figure 1). Using this framework, the primary process of Hb S polymerization is followed by secondary pathways of hemolysis and vaso-occlusion. Pathophysiologic processes such as inflammation and oxidative stress are downstream by-products of hemolysis and/or vaso-occlusion. Pain is itself a complex process and may be influenced by additional circumstances, such as the nervous system, environment and psycho-social factors.

RESULTS: When viewed from this perspective, it becomes apparent that treatments targeting a single pathway, e.g. erythrocyte adhesion to endothelium or nitric oxide deficiency, may not be effective in halting acute vaso-occlusive pain if other processes continue to actively contribute. Red cell replacement with either transfusions or stem cell transplantation is currently one of the most effective therapies because it corrects the underlying defect of Hb S polymerization and consequently the downstream effectors.

CONCLUSIONS: Research approaches that better address biologic complexity are needed to advance the field of SCD science and help identify new therapeutic targets. When testing targeted therapies, it would be helpful to demonstrate the relevance of individual pathways on important sickle cell outcomes in vivo prior to investing in expensive and labor-intensive clinical trials. There is also opportunity for applying state-of-the-art systems biology or "omics" methods (proteomics, genomics, and/or epigeonomics) and bioinformatics analysis to understanding the cumulative effects of the sickle cell internal milieu on the body and to help identify "master regulators" that may be involved in multiple mediator pathways.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RBC Adhesion
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Tissue Ischemia
Pain
Oxidants Inflammation
Procoagulation
Cognition
Mood
Context
Genetics
Epigenetics
Anticoagulants Fibronolysis
Anti-oxidants Anti-inflammatory
Reperfusion
Bone marrow
Angiogenic Growth Factors

IMAGING FLOW CYTOMETRY FOR FULLY AUTOMATED QUANTIFICATION OF PERCENTAGE OF SICKLED CELLS IN SICKLE CELL ANEMIA

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Introduction: In preclinical and early phase pharmacologic trials in sickle cell anemia (SCA) the percentage of sickled cells after deoxygenation, in a so called sickling assay, has been used as an outcome variable. Although this sickling assay is a highly useful test, this method has the disadvantage of being subjective, operator-dependent and with low sensitivity and high variability due to the lack of automated method to quantitate the percentage of sickled cells from a large sample. Imaging flow cytometry is an emerging technology with potential to improve this assay. Therefore, we have explored the capability of this new technique to discriminate sickled cells from unsickledcells in this assay.

Methods: This study had regional ethics committee approval, and all patients gave written informed consent. To perform the sickling assay peripheral blood was drawn, diluted 1:100 with HemOx buffer (TCS Scientific Corp., Southampton, PA, USA) and aliquoted onto a 96 well plate and placed in a glovebox in hypoxic conditions (2% oxygen) for 2 hours (or as otherwise specified). After incubation, samples were fixed with glutaraldehyde, washed and placed on ice before analyzing the samples with imaging flow cytometry. Cells were analyzed on the ImageStreamx imaging flow cytometer (Amnis Corporation, Seattle, Washington, USA). Data were acquired using the INSPIRE acquisition software and using the 60X objective. Data from a minimum of 5000 cells were collected for each sample and analyzed using IDEAS 5.0 software. Single in-focus cells were identified using data from the brightfield images using various masks. As a learning population for the IDEAS software we hand tagged populations of sickled and unsickledcells.

Results: Using various combinations of pre-defined and self-defined masks we found that shape-ratio (the ratio between the shortest width of the mask divided by the longest part of the mask) identified our hand-tagged populations the best. We customized the algorithm with tight masks and a spot count feature to eliminate doublets and other artifacts. We were able to identify sickled or unsickled cells and a continuum between the two morphological extremes (figure 1a,1b). We selected three different shape ratio cut-off values for further analysis (table 1). To test the classifying algorithm, we spiked normal control blood with different amounts of SCA blood before incubation under variable hypoxia. At 3% oxygen the relation between percentage of sickled cells and percentage of SCA blood in the sample was strong (a Spearman rho for all cut-off values higher than 0.925) and significant ($P \leq 0.001$). At 4% oxygen the relation was less strong (Spearman rho higher than 0.725 for all cut-off values) but still significant ($P \leq 0.05$). As an additional validation, we found (as expected) lower percentages of hypoxia-induced sickling in blood from patients with SCA according to the level of fetal hemoglobin (HbF) expression (figure 1c). At

all shape ratio cut-off values HbF percentage seems to suppress the amount of cells identified as sickled. While additional experiments are underway in an attempt to validate this finding, we preliminarily observe that fetal hemoglobin has a large effect on this flow cytometry sickling assay. Furthermore, ex vivo treatment of erythrocytes with the anti-sickling agent 5-hydroxymethyl-2-furfural (Aes-103) has a profound effect on the number of sickling cells as well.

Conclusion: This study shows that imaging flow cytometry has potential as a fully automated, operator independent method to quantify sickled cells in a sickling assay. While additional experiments are ongoing, our early data suggest that the presented technique seems discriminative enough to identify patient dependent and independent differences in sickling capacity of SCA red cells.

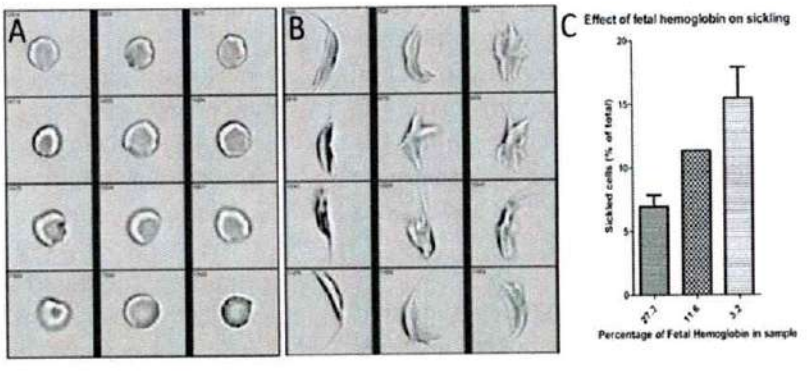

Figure 1.
A,B: Random brightfield images of cells with shape ratios higher than 0.9 (A) and smaller than 0.2 (B)
C:Effect of fetal hemoglobin percentage in sample on percentage of sickled cells. Results shown for shape ratio cut-off value of 0.5.

Table 1. Statistical parameters of different shape ratio cut-offs

Shape ratio cut-off	Sensitivity	Specificity	CV
0.3	60.7	100	11.6
0.4	82.0	100	8.2
0.5	100	99.1	6.4

364

EVALUATION OF PURIFIED POLOXAMER 188 IN CHILDREN (EPIC) - KEY DESIGN CONSIDERATIONS

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Background: There is no currently approved disease modifying treatment for ongoing vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD). A prior phase 3 study investigating MST-188 (purified poloxamer 188) was suggestive of treatment effects; however, prospectively defined outcomes did not reach statistical significance, other than in subgroup analyses and post-hoc analyses1. Interpretation of that study was potentially confounded by a study population heterogeneous for age, genotype and variation in pain management practices, subjectivity of the primary endpoint, statistical imbalance in the numbers of patients in the placebo and treatment groups who did not achieve endpoints and missing or imputed data.

Objective: To achieve a phase 3 study design that could replicate the results of the subset analyses suggesting favorable responses in children and those receiving hydroxyurea, avoid the deficiencies of the previous trial, serve as the basis for registration with the US FDA and accomplish enrollment in a reasonable timeframe.

Methods: Discussion with medical experts in SCD, regulatory authorities, disease advocates and review of available studies of vaso-occlusive crisis.

Results:

1. The study should focus on children to achieve a more homogeneous population
2. The study should enroll only patients with the SS or S-Beta null genotype
3. The study should include guidelines for control of pain, minimizing variability in pain management practices among study centers.
4. Statistical assumptions (e.g., untreated duration of crisis) should reflect data from recent studies in SCD, including recently conducted NIH-funded studies.
5. The primary study endpoint should evaluate a clinically meaningful outcome that can be measured with as much objectivity as possible; for example, duration of crisis, as measured by the time from randomization to the last dose of parenteral opioid analgesia. An objective assessment of VOC resolution is preferable to complex, multi-part definitions and reliance on subjective pain scales.
6. The study should reduce "right censoring" and the potential for missing and imputed data by following subjects until discharge, rather than an artificial time-point (e.g., 168 hours after randomization, as in the previous study).

Conclusion: Incorporation of the above mentioned considerations should result in a study that overcomes the limitations of the prior study while maintaining rigor and feasibility of enrollment.

Reference:

1. Orringer et al., JAMA. 2001;286 (17):2099-2106

351

A PHASE I SINGLE ASCENDING DOSE STUDY OF NKTT120 IN STABLE ADULT SCD PATIENTS

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Affiliations: *1.Blood Center of Wisconsin, and 2.Medical College of Wisconsin, Milwaukee WI; 3.NKT Therapeutics, Waltham, MA, 4.Dana-Farber Cancer Institute, 5.Boston Children's Hospital and 6.Harvard Medical School, Boston, MA*

Background: Multiple lines of evidence point to iNKT cells as critical mediators of the chronic inflammatory cascade in sickle cell disease (SCD). Increased numbers of act ivated iNKT cells are seen in both preclinical models of SCD, and in adult patients with the disease. In preclinical models, inhibition of iNKT cell function leads to improvement in organ function. NKTT120 is a humanized monoclonal antibody that specifically depletes iNKT cells. Preclinical studies show that NKTT120 has high affinity and specificity for iNKT, is very potent, depletes iNKT cells in vivo in a dose-dependent manner, and that once depleted, iNKT cells return to the peripheral circulation in a dose- and time-dependent manner.

Objective: This ascending single dose Phase 1 study will evaluate the safety, maximum tolerated dose(MTD) pharmacokinetics, and pharmacodynamics of NKTT120 in adult patients with non-acute SCD. Clinical and laboratory markers of inflammation and disease activity will also be measured. The primary endpoint (MTD) will determine the dose that allows periodic dosing in phase 2 studies in the same patient population.

Methods: This phase 1 study will evaluate single doses that are escalated in a 3+3 design over a range from 0.001 mg/kg t o 0.1 mg/kg (0.001, 0.003, 0.01, 0.03, and 0.10 mg/kg). For the purpose of this protocol, stable SCD is defined as not having experienced acute pVOC or ACS or other SCD associated event requiring hospitalization or out patient care within one month prior to dosing. In addition to determining the primary objectives, this study will also examine pain, analgesic use, Quality of Life (QoL), and pulmonary function. During the two week screening run-in period and throughout the follow-up, subjects will keep a daily smart phone eDiary (eSCaPe) for pain, fatigue and analgesic and inhaled SABA use. The ASCQ-Me and PROMIS QoL questionnaires will be administered at clinic visits. The screening run-in outcomes will be used as baseline comparison for values obtained post-dosing.

Results: The most current results from the early cohorts of patients enrolled will be presented.

Conclusions: NKTT120 is being developed as a first in class agent for the treatment of chronic inflammation associated with SCD. The expected in vivo mechanism of action of NKTT120 is the dose dependent depletion of the pro-inflammatory iNKT cells in blood and tissues of SCD patients, and this reduction should result in a suppression of the inflammatory stimuli that promote many of the pathophysiologic sequelae seen in SCD.

362

IS THERE A ROLE FOR A RHEOLOGIC AGENT IN TRANSFUSION?

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Background: Decreased microvascular blood flow and hemodynamic changes potentially compromising tissue oxygen delivery have recently been reported in some sickle cell anemia patients following transfusion1, 2. While transfusion increases blood oxygen carrying capacity, it also increases blood viscosity. The anticipated benefits of transfusion could be diminished or lost if the net effect of decreased blood flow more than offsets increased O2 carrying capacity. Red blood cell (RBC) aggregates impair blood flow in the microcirculation where the majority of oxygen and nutrient exchange occur. Since older RBC aggregate more than younger RBC, we hypothesized that increased RBC aggregation following transfusion of older or "storage lesioned" RBC may contribute to decreased blood flow. MST-188 (purified poloxamer 188) is a rheologic agent currently under investigation in a phase 3 trial in pediatric sickle patients hospitalized with acute vaso-occlusive crisis. We hypothesize that this poloxamer may inhibit aggregation of older or storage-injured RBC and potentially have utility in transfusion.

Objective To determine the relative effect of poloxamer 188 on the aggregation of "older" versus "younger" RBC

Methods: RBC obtained from 4 healthy donors were age-separated via centrifugation into younger (least-dense 10%) and older (most-dense 10%) cells, then re-suspended in 3% dextran 70 containing poloxamer 188 at 1 or 5 mg/ml. The extent of RBC aggregation (Aggregation Index) was measured using a Myrenne aggregometer system.

Results: Older RBC exhibited a mean aggregation index (AI) approximately 140% greater than younger RBC. Addition of poloxamer 188 resulted in a concentration dependent reduction in AI for both older and younger RBC, with the effect more pronounced for older RBC. At 5 mg/ml there was a greater than a 2- fold reduction in mean AI compared to control for older RBC.

Conclusion: Poloxamer 188 inhibits aggregation of older and younger RBC and may have utility for treating and/or preventing transfusion-induced decreases in microvascular blood flow. Studies of MST-188 using storage lesioned RBC are planned.

Reference:

1. Detterich et. al. (2012) Transfusion. doi:10.111/j.1537-2995.2012.
2. Cheung et at., (2012) Pediatr. Hematol. Oncol. 2012; 00: 000-000.

433

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, EFFICACY AND SAFETY COMPARISON OF PRASUGREL AND PLACEBO IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is a genetic blood disorder that results in a hypercoagulable state. Intermittent microvascular occlusion and repeated ischemia-reperfusion injury progressively damage tissues and organs. As a result, SCD is debilitating and typically results in recurrent hospitalization, organ damage, disabilities, and even death. Vaso-occlusive crisis (VOC) is a hallmark of SCD and typically is first observed after 6 months of life, sometimes increasing in frequency and severity into adulthood. VOCs are caused by hemoglobin polymerization causing red cell rigidity, and activated platelets contribute to the adhesion of sickled red blood cells to the endothelium, thereby reducing blood flow to organs and tissues. Hemolysis of sickled erythrocytes releases ADP, which induces platelet activation and further contributes to VOC. There is some evidence that suggests antiplatelet therapy in patients with SCD may reduce biomarkers of platelet activation and the frequency and severity of painful crisis; however, there have been no large, controlled studies of efficacy. Currently there are limited treatment options for patients with SCD, particularly in children.

Objectives: The primary objective of this study is to assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD as measured by reduction in the rate of VOC, which is a composite endpoint of painful crisis or acute chest syndrome.

Methods: Study H7T-MC-TADO (TADO) is a Phase 3, double-blind, randomized, parallel group, multinational study. TADO will investigate the efficacy and safety of prasugrel for the reduction of VOC in pediatric patients with SCD who are ≥2 to <18 years of age. During the double-blind treatment period, patients will be titrated to once-daily doses of either placebo or prasugrel for a minimum of 9 months to a maximum of 24 months. Dosing is weight based (mg/kg) and patients will be titrated to a dose that produces a VerifyNow® P2Y12 reaction units (PRU) within the target range of 231–136, corresponding to approximately 30–60% platelet inhibition. Platelet function and pharmacokinetics will be assessed during the study. There will be an optional open-label extension with a minimum duration of 12 months in which patients will be titrated to an appropriate prasugrel dose.

Results: The study is planned to start in early 2013 (NCT01794000). There are no available data to report.

Conclusion: Study TADO will test the hypothesis that prasugrel, an inhibitor of platelet activation and aggregation , will reduce the rate of VOC and improve the quality of life in pediatric patients with SCD.

SANGUINATE – A NOVEL OXYGEN TRANSFER AGENT TO TREAT SICKLE CELL CRISIS

Dr. Abraham Abuchowski

Affiliation: *Prolong Pharmaceuticals*

Hypoxia is the pathological condition in which the body as a whole or a region of the body (tissue or localized hypoxia) is deprived of an adequate supply of oxygen. Tissue hypoxia can lead to anaerobic metabolism and metabolic acidosis, induction of an inflammatory response, tissue damage, organ dysfunction, and ultimately to organ failure due to cell death.

Hypoxia is implicated in a number of ischemic conditions – chronic wounds, retinopathy, neuropathy, neurologic deficits, ischemic rest pain, nephropathy and Sickle Cell crisis. The solution to hypoxia is simply to provide the tissues with an adequate supply of oxygen, however the mechanism to supply that oxygen has been difficult to achieve. Hence, there is considerable interest in the development of an Oxygen Transfer Agent (OTA) – capable of delivering oxygen to those tissues not readily accessible to red blood cells.

Prolong Pharmaceuticals has developed and is testing a novel OTA called Sanguinate. This molecule is a long acting form of bovine hemoglobin in the carbon monoxide (CO) form. Small molecules that release CO have been shown to exert vasodilatory, anti-inflammatory, and antiapoptotic properties in a variety of models in the peripheral circulation. The release of CO from Sanguinate takes advantage of these pharmacologic effects prior to acting as an OTA, thereby providing the maximum effect to overcome hypoxia.

Sanguinate has been tested in animal models of cerebrovascular ischemia, peripheral ischemia in diabetes, traumatic brain injury and cardiovascular ischemia. An IND to treat Sickle Cell crisis has been filed with the US FDA and Phase 1 trials have commenced ex-US. Results of these animal studies will be presented.

INDEX