TRANSFUSION PRACTICES IN THE MANAGEMENT OF SICKLE CELL DISEASE AMONG FLORIDA PHYSICIANS

By

LEVETTE NICOLE DUNBAR

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To those living with sickle cell disease everyday

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TABLE OF CONTENTS

page

ACKNOWLEDGMENTS 4

LIST OF TABLES 7

LIST OF FIGURES 8

ABSTRACT 9

CHAPTER

1 INTRODUCTION 11

Sickle Cell Disease 11
Epidemiology 12
Clinical Manifestations 14
Sickle Cell Crisis 15
Infection 16
Liver and Gall Bladder Disease 17
Skin Disease 18
Eye Disease 18
Renal Disease 18
Cardiovascular Disease 19
Pulmonary Disease 19
Stroke 21
Pregnancy 23
Treatments 23
Surgery 24
Hematopoietic Stem Cell Transplant 25
Hydroxyurea 25
Blood Transfusions 26

2 RESEARCH STUDY 29

Rationale 29
Methods and Materials 30
Study Design 31
Survey Analysis 31
Results 32
Use of Transfusion Guidelines 33
Administration Techniques, Selections and Modifications of RBCs 34
Acute and Chronic Transfusion Indications 34
Iron Overload and Iron Chelation therapy 37
Clinical Vignettes 38
Educational Resources 39

3 DISCUSSION 44

Limitations 46
Conclusion 47

REFERENCES 49

BIOGRAPHICAL SKETCH 53

LIST OF TABLES

Table page

2-1 SCD patients according to practice type 41

2-2 Clinical vignettes according to practice type 41

LIST OF FIGURES

Figure page

2-1 Use of practice specific guidelines and NIH monograph by respondents, p-values <0.0001 and <0.001 respectively. 42

2-2 Frequency of RBC modifications requested by respondents. LR, leukocyte reduced....42

2-3 Importance of reasons for not using deferoxamine....43

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By

Levette Nicole Dunbar

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Limited data exist on physician transfusion prescribing preferences in the management of sickle cell disease (SCD). To assess current practices, we conducted a survey of Florida hematologists/oncologists between fall 2005 and spring 2006. The 31-item survey addressed practice characteristics, SCD patient populations, practice guidelines, transfusion settings, indications and techniques, red blood cell (RBC) phenotype specifications/modifications, iron overload, and educational resource utilization. A total of 155 physicians (75% adult- oriented, 25% pediatric) completed the survey. The primary location was private practice (77%). Pediatric practices had more patients with SCD, overt strokes and receiving hydroxyurea than adult practices. The majority of pediatric practices (61%) had specific transfusion guidelines to follow in contrast to adult practices (8%). A minority of respondents requested limited (16%) or extended (23%) phenotypically matched RBCs on a routine basis when compared to not matching until antibodies were identified (61%). We queried several acute and chronic transfusion therapy indications with differences noted among pediatric and adult practices. Analysis of clinical vignette data revealed differences among physicians in the transfusion management of elective cholecystectomy, splenic sequestration, acute chest syndrome and secondary stroke prevention after prolonged chronic transfusion therapy. While most

respondents from pediatric practices used the NIH management of SCD monograph, only a small percentage of adult practice respondents used it. The data indicate variability in the incorporation of evidence-based approaches in transfusion management of SCD. These results provide insights into the need for the development of clinical tools and guidelines tailored to pediatric and adult practices.

CHAPTER 1
INTRODUCTION

Sickle Cell Disease

Sickle cell disease (SCD) is a blood disorder characterized by a genetic mutation of hemoglobin (Hb) causing polymerization of sickle hemoglobin (HbS) [1]. Hb is composed of two alpha (α) and two beta (β) globin chains. In SCD, α chains are normal and the β chains are abnormal. The HbS is due to a single point mutation resulting in a valine instead of a glutamic acid in position six of the β chain [2]. So, the abnormal β chains paired with two normal α chains form the abnormal HbS. These sickle hemoglobin polymers in sufficient concentrations form an insoluble gel with soluble normal hemoglobin molecules and cause red blood cell (RBC) membrane damage, decreased RBC deformability and the sickle-shaped morphology for which the disease is named [1]. The red cell abnormalities cause dehydration of the red cells, which leads to stiff, irreversibly sickled cells that result in sickle red cell adhesion to the vascular endothelium, hemolysis and ultimately blocks the normal blood flow through the microvasculature leading to anemia and vaso-occlusion [3].

Although the polymerization of HbS is the central event in the pathophysiology of the disease, nitric oxide depletion (NO) is also a key contributor as well [1, 3, 4]. NO depletion results from the release of large quantities of hemoglobin and red cell arginase from the chronic breakdown of red cells that occurs in SCD plasma [3]. The hemolysis and red cell adhesion leads to a pro-inflammatory state with white cell adhesion and platelet aggregation [4]. Also as a result of the NO depletion, the down-regulating effects of NO on both inflammation and activation of coagulation are lost [3]. NO normally causes vasodilation in smooth muscle. So, unregulated vasoconstriction promotes vaso-occlusion and contributes to tissue hypoxia.

Elevated concentrations of fetal hemoglobin (HbF), which is observed in some patients with SCD, inhibit HbS polymerization and correlate with less severe manifestations of sickle cell disease [1]. The inhibition of HbS polymerization occurs by two distinct mechanisms [1]. First, as HbF increases, HbS must decrease to have a total RBC hemoglobin concentration that is constant and second, HbF dimers mix with HbS dimers and form hybrids that are not capable of polymerization (note that normal hemoglobin/HbS hybrids are capable of HbS polymerization).

Epidemiology

SCD affects one in every 350 African American newborns in the United States every year and more than 72,000 Americans live with SCD currently [5]. Individuals with HbSS disease (the homozygous condition) have sickle cell anemia. Those with one gene encoding HbS and the other encoding normal hemoglobin (HbA) have sickle cell trait (the heterozygous condition or HbAS). Others have one sickle hemoglobin gene and a gene encoding a different hemoglobin mutation, such as hemoglobin C or hemoglobin thalassemia (resulting in HbSC disease or HbSβ-Thal^{+} or HbSβ-Thal^{0}) [2]. Individuals with HbSC or HbSβ-Thal^{+} have the disease but often have less severe manifestations whereas HbSS and HbSβ-Thal^{0} are considered more severe forms of the disease. Chronic hemolytic anemia is observed in all patients with SCD. People with sickle cell trait do not have the disease but are at risk of passing the disease to their offspring if they mate with someone who also has the trait or the disease. Rare problems associated with sickle cell trait include persistent hematuria, inability to concentrate the urine and sickling associated with severe infection, flying in unpressurized aircrafts and more rarely, exercise-induced dehydration and hyperthermia [2].

Brambilla et al. reported that Sir John Dacie described SCD as a disease of childhood in 1960 with relatively few patients surviving to adulthood [6]. In 1972, the National Sickle Cell Disease Control Act was passed by Congress. As a result, the National Sickle Cell Disease

Program mandated that scientific research programs should be funded to improve care and quality of life of patients with SCD [5]. Health related quality of life (HRQOL) is one of the most important health outcome measures in any disease. This need to address SCD-HRQOL measures has basically evolved because SCD is no longer a disease of childhood since more patients survive into adulthood. The Cooperative Study of Sickle Cell Disease (CSSCD) started in 1979 as a large, multi-institutional study because very little information had been collected prospectively on the clinical course of SCD [7]. The CSSCD is the main source of the medical advances for SCD, especially with respect to transfusions in SCD.

Major medical advancements in SCD have occurred over the past 30 years to improve survival. These include the development of conjugate vaccines and prophylactic penicillin in infants and children with SCD to prevent overwhelming pneumococcal sepsis, chronic blood transfusions to prevent first and recurrent strokes, and HU to reduce the number of painful episodes [8]. As a result, SCD life span has increased and resulted in a new and growing population of adult SCD patients with a need for coordinated care beyond the pediatric arena.

In 1994, the CSSCD estimated median survival for individuals with HbSS was 42 years for males and 48 years for females [6]. The median survival age for HbSC was 60 years for males and 68 years for females. Accordingly, the pediatric hematologist's responsibility must now include collaboration with adult health care professionals to achieve successful continuity of care for their pediatric sickle cell patients to achieve a better quality of life as adults living longer with the significant impact of SCD complications. An important component of achieving improved quality of care for SCD patients which warrants further investigation is the treatment management practices of SCD among physicians caring for this population of patients. A tremendous amount of variation in the treatment of SCD complications exist among healthcare

providers. One major reason for the variation in the treatment management of SCD patients may be that individuals with SCD are now living longer and therefore requiring care from adult providers who may not be as familiar with the disease once considered a childhood disease. Also, some controversies exist for accepted SCD therapy. In some cases, there are different ways of approaching a single problem with no supported standard of care. So, many areas of debate exist in the management of SCD. The best supported practice guidelines for the management of SCD are represented by a few randomized controlled trials (RCTs) [9]. To truly understand proper management of SCD, one must understand the pathogenesis of the clinical manifestations of the disease in order to address how to treat them properly.

Clinical Manifestations

Clinical manifestations of SCD are variable. Some individuals are completely without symptoms while others experience varying degrees of anemia, sickle cell crisis, damage to organs (including but not limited to eyes, skin, spleen, liver, lungs, heart and kidneys), increased infection and strokes. The anemia (as a result of a lower than normal number of RBCs or hemoglobin, or both) results in symptoms such as a tachycardia, fatigue, generalized weakness, headache or dizziness. The anemia is generally well tolerated secondary to cardiovascular compensation, but there are conditions in which the anemia is symptomatic and requires intervention in the form of RBC transfusions. The normal RBC has a life span of approximately 120 days. However, the deformed sickle RBC life span is shortened to roughly 15-25 days resulting in the moderate to severe hemolytic (the abnormal breakdown of blood cells) anemia, with a usual steady state hematocrit of 24% (range 18-32%) in HbSS disease [10]. The hematocrit is a blood test that gives the percentage of RBCs in whole blood and normally ranges from 36-40%. The range varies based on age and gender. Laboratory abnormalities for

individuals with SCD include low hemoglobin and hematocrit, elevated bilirubin levels, increased numbers of circulating reticulocytes, and elevated leukocyte levels.

Sickle Cell Crisis

Vaso-occlusive crises are acute, often painful events that are one of the hallmarks of SCD. Any tissue that does not have blood flow constantly (and therefore is ischemic) is severely damaged and leads to problems. Vaso-occlusion leads to tissue ischemia, infarction and inflammation. Acute pain is one of the major symptoms of vaso-occlusion that can strike at anytime without warning and is generally sharp and/or throbbing [3]. The pain can occur anywhere in the body, and be localized to one area or generalized. The pain can also be neuropathic in nature and feel like burning or tingling. When chronic vaso-occlusive events occur in the bones, it is called avascular necrosis or osteonecrosis (literally bone death) and often leads to a need for replacement, for example of knees or hips. When vaso-occlusion occurs in the penis, the result is a painful, prolonged erection or priapism. When standard therapies are unsuccessful for acute priapism, some physicians try transfusions acutely. However, close attention must be given to avoiding hyperviscosity and therefore automated exchange transfusion is recommended [9, 11]. Some physicians advocate chronic transfusions or HU for recurrent priapism since the risk of impotence is high [9]. When vaso-occlusion occurs in the lungs, it results in serious lung injury and hypoxia and is known as acute chest syndrome and is considered a medical emergency (see the acute chest syndrome section). Vaso-occlusion in the brain can result in a stroke. This can lead to devastating complications and limitations of cognition, speech and/or movement (see the stroke section).

Acute splenic sequestration crisis is a significant cause of death in children with SCD [9]. It is a rapid crisis that results in massive enlargement of the spleen secondary to trapping of red blood cells. Splenic sequestration can result in hypotensive shock with cardiac compromise

because of severe anemia, and requires emergent red blood cell transfusions. If splenic sequestration recurs, splenectomy is sometimes considered.

Transient aplastic crisis is the result of a viral infection known as parvovirus B19 causing suppression of the bone marrow activity (i.e., production of new RBCs) leading to severe anemia in SCD [12]. Other viral and bacterial infections in SCD may also induce an aplastic crisis resulting in bone marrow suppression. Infections causing aplastic crises are usually self-limiting and resolve spontaneously without the need for therapy. However, there are aplastic episodes that require multiple red blood cell transfusions to avoid cardiac compromise in SCD patients.

Infection

Bacterial infections contribute to a higher proportion of deaths in children with SCD than any other single cause. The increased risk of infection is the result of splenic dysfunction [2]. The spleen normally provides protection from infection because of antibody production and phagocytosis [2]. As a result of functional asplenia/splenic dysfunction, individuals with SCD, especially children, are more susceptible to severe bacterial infections especially from organisms such as Streptococcus pneumoniae [13].

With the advent of prophylactic penicillin and appropriate conjugate vaccines against Streptococcus pneumoniae and Haemophilus influenza type b, there has been a tremendous decrease in the number of infections and deaths of children with SCD and infections [8]. An important randomized clinical trial published in 1986 demonstrated that prophylactic penicillin reduced the risk of Streptococcus pneumoniae infections by 84% when compared to placebo [13]. This study concluded that all neonates should be screened for sickle hemoglobinopathies, and those with SCD should be placed on prophylactic penicillin. In a published report on a large Dallas newborn cohort, the widespread use of the conjugated pneumococcal vaccine (PCV-7) reduces the risk of invasive pneumococcal infections as well [8].

Ideally, all children with SCD should be treated with daily oral penicillin from birth until age five (the age at which the risk of infection is deemed no different from the general population) [14]. Also, all children with SCD should receive immunizations per the recommended schedule for healthy children (which include the PCV-7 and the Haemophilus influenza type b vaccine) and additionally receive the pneumococcal polysaccharide vaccine PPV23 at two years and five years and then every ten years [3]. The lower mortality rate from infections can be attributed to improved care with universal newborn screens, vaccines and penicillin prophylaxis, but also with coordinated SCD care including continuous parental education about information relevant to SCD.

Liver and Gall Bladder Disease

Liver and gall bladder complications are common in SCD. Chronic hemolysis leads to a constant turnover of red blood cells leading to accumulation of bilirubin. The accumulation of bilirubin leads to pigmented gallstones (cholelithiasis) which in turns leads to acute and chronic cholecystitis and choledocholithiasis [9]. Fever, nausea, vomiting abdominal pain and increased jaundice may occur acutely. Laparoscopic cholecystectomy on an elective basis is the standard approach to symptomatic patients [9].

Vaso-occlusive crisis may occur in the liver and consists of right upper quadrant pain, liver enlargement, fever, jaundice, and elevated liver transaminases. It is treated like a vaso-occlusive pain crisis. Sequestration also occurs in the liver with similar consequences to splenic sequestration. In liver sequestration, the liver enlarges rapidly with a sudden drop in the hemoglobin/hematocrit and a significant rise in the number of reticulocytes. The preferred treatment is exchange transfusion since simple transfusions may be accompanied by the return of sequestered RBCs in to the circulation leading to a hyperviscosity syndrome [9]. The return of sequestered RBCs may also be seen in transfused splenic sequestration patients and thus carries

the same caution. Iron overload results from frequent blood transfusions and the excess iron may deposit in the liver and lead to a high liver iron load and liver dysfunction [15].

Skin Disease

Leg ulcers occur in 10-20% of SCD patients [9]. The etiology of the leg ulcers likely relates to the hypoxia and infarction of the distal ankle skin. Some resolve quickly while others can take years and they do recur. Most importantly, the ulcers can be extremely painful and become infected. Treatments generally involve pain management, antibiotics for infections, bed rest and leg elevation as well as local topical care and dressings such as those used for burn victims. Ulcers may correlate with the degree of anemia and therefore transfusion may be helpful but there is no evidence to support the use of transfusion for leg ulcers [9].

Eye Disease

Sickle cell vaso-occlusive events can also affect the vascular beds in the eyes. Often the disease has progressed significantly before visual problems are observed by the individual. Therefore, comprehensive eye exams are recommended regularly, regardless of signs or symptoms. Ocular manifestations of SCD are classified by the presence or absence of neovascularization in the eye [16]. Progression to neovascular changes can result in vitreous hemorrhages and retinal detachment, retinal artery occlusion and ischemia and risk for visual loss. Surgical intervention may be necessary but also comes with great risk of ocular ischemia, recurrent hemorrhage and elevated eye pressure [9].

Renal Disease

The kidney is often a site of injury and abnormalities in SCD because the kidney is very susceptible to dysfunction because it promotes HbS polymerization and red cell sickling [17]. One of the most frequent renal abnormalities is an inability to concentrate the urine which can lead to dehydration, which in turns leads to a vaso-occlusive crisis [9]. This may be avoided by

encouraging individuals to drink liberal amounts of fluids in order to compensate for the fluid losses. Hematuria, proteinuria and renal failure may occur in SCD patients as well. Chronic renal insufficiency occurs in up to 30% of adults [11]. Erythropoietin levels may fall with worsening renal function in individuals with SCD requiring erythropoietin therapy or frequent blood transfusions [17]. Some individuals with SCD progress to end stage renal disease requiring dialysis and/or renal transplantation.

Cardiovascular Disease

Cardiomegaly is usually observed in most individuals with SCD secondary to a cardiovascular compensatory mechanism for the anemia [18]. Myocardial infarctions are not common but do occur [9]. Congestive heart failure may also occur and may be associated with fluid overload. Patients with falling hemoglobin and congestive heart failure may benefit from slowly correcting their severe anemia with transfusions [9]. In the CSSCD study of heart disease, the two factors most important to cardiac disease were increasing age and decreasing hemoglobin and no specific cardiomyopathy was observed [18]. Also, significant cardiac dysfunction does occur in the setting of iron overload in the heart.

Pulmonary Disease

Acute chest syndrome (ACS) is a type of vaso-occlusive crisis observed in SCD that involves lung injury leading to the onset of chest pain. ACS is defined as new lung infiltrates on chest X-ray with the presence of fever and chest pain and respiratory symptoms such as cough, wheezing and tachypnea [19]. ACS results in acute decompensation of the patient respiratory status and sometimes requires oxygen supplementation and/or ventilation assistance. ACS is a leading cause of hospitalizations and death in the SCD population [6, 20]. High morbidity and mortality in ACS is also linked to repeated episodes of ACS and may result in chronic lung disease [19].

Predisposing factors for ACS included asthma, pain crisis of the chest or any area of severe pain crisis resulting in narcotic use and hypoventilation, pulmonary fat embolism (a piece of fat that usually travels from an area of bone marrow injury to the lungs through blood vessels), underlying infection (typical and atypical bacteria, viruses, mixed infections), and/or recent surgery (postoperative status) [19]. Management of ACS includes oxygen, pain management, aggressive incentive spirometry (a small bedside device to encourage ventilation by blowing into plastic tubing to take deep breaths) to counteract hypoventilation from the effects of the narcotics and/or pain itself leading to splinting (restriction of the breathing pattern), antibiotics, IV hydration, bronchodilators such as albuterol to open up the airways, simple blood transfusions, and exchange transfusions if simple transfusion is ineffective [19]. Exchange transfusions involve the incremental removal of the patient's blood with HbS and replacement with fresh blood free of HbS [9]. Exchange transfusion is considered a more aggressive treatment since it involves more units of blood than a simple transfusion and therefore is associated with more transfusion-related reactions and complications. Exchange transfusions are often preferred in certain situations such as ACS for an individual with HbSC to avoid hyperviscosity.

Pulmonary hypertension (PH) is also a common manifestation of SCD and it is also associated with high mortality [21]. PH increases the risk for right sided heart failure, syncope, and sudden death [21]. Thirty percent of adults with SCD have PH and PH is associated with a mortality rate up to 50% at 24 months after diagnosis and around 40% at 40 months [21-22]. PH is defined as an elevation of the pressure in the pulmonary vasculature (either pulmonary arterial or venous system) [22]. Pulmonary arterial pressure above 25 mmHg is considered to represent PH. PH is thought to be directly related to NO depletion as a result of chronic hemolysis in SCD [21-22]. Some of the other causes of PH postulated include systolic hypertension, chronic

oxygen desaturation or sleep hypoventilation, chronic pulmonary damage from recurrent ACS, repeated episodes of thromboembolism, and high pulmonary blood flow from chronic anemia [21]. PH is also associated with iron overload and, therefore may be caused by iron overload [21-22].

There are no controlled trials of treatments for PH associated with SCD. Therefore, most therapies are based on what is known about primary pulmonary hypertension treatments. Hydroxyurea and chronic transfusions are being explored as possible therapies to improve outcomes for patients with SCD to prevent the underlying complications of SCD that increase the risk of PH.

Stroke

Stroke is one of the most debilitating and devastating aspects of SCD. Stroke occurs in approximately 11% of individuals with HbSS under the age of 20 and 24% by the age of 45 [23]. Cerebral infarction occurs mainly in children whereas hemorrhage occurs mainly in adults [23]. The signs and symptoms associated with ischemic strokes include speech disturbances, gait disturbances secondary to hemiparesis and altered sensation, seizures, headaches, abnormal behavior and confusion. Hemorrhagic strokes may present with headaches, vomiting, stupor or coma [9]. Silent infarcts present with deficits in cognitive areas such as deficits in mathematics, reading, and/or memory. Silent infarcts may predispose individuals for ischemic strokes [24]. The silent infarct transfusion (SIT) trial is a prospective multi-center study currently underway to determine the effectiveness of blood transfusions for the prevention of recurrent silent infarcts [24].

As a result of acute and chronic SCD problems such as anemia, ACS, vaso-occlusive crisis, aplastic crisis, and nocturnal hypoxemia leading to decreased oxygenation, ischemic injury occurs in the brain. Treatments for acute strokes involve the acute management of the signs and

symptoms such as seizures, cerebral bleeding or clotting with anticonvulsants, hematoma evacuation and anticoagulation but, most importantly, involve blood transfusions (specifically exchange transfusion) to reduce the amount of HbS immediately. The prevention of morbidity in SCD (POMS) study has been designed to evaluate the effectiveness of overnight continuous positive airway pressure in patients with low nocturnal oxygen saturations to see if it has an effect on future central nervous system events such as strokes or vaso-occlusive events [24].

Recurrence of stroke occurs in two-thirds of the SCD patients after an initial stroke, usually within two to three years [25]. Several studies have demonstrated the effectiveness of chronic transfusions for the reduction of recurrent stroke rate [25, 26]. Currently, transfusions are recommended indefinitely for the prevention of a second stroke [25, 27]. Limited data demonstrated the use of HU and phlebotomy may be an effective alternative treatment to blood transfusion for the prevention of secondary strokes in a single institution prospective study of 35 patients, and a national multi-center trial is currently underway [24, 28]. Several reports have also documented the effectiveness of stem cell transplants in the prevention of stroke recurrence by eliminating the sickle β globin gene and replacing sickle cells with healthy donor cells [29].

The most common cause of cerebral infarction is an occlusion of the intracranial internal carotid and middle cerebral arteries [30]. These abnormal occlusions can be detected by transcranial Doppler (TCD) ultrasonography measuring blood flow velocity. An abnormal TCD velocity of greater than 200 cm/sec was associated with a 40% risk of stroke in HbSS [31]. In the stroke prevention in sickle cell anemia (STOP) trial, 130 children who were at risk for a stroke based on abnormal TCD velocities were randomized to either chronic transfusion or standard care/observation [30]. A 92% reduction in stroke risk was observed in the group that received transfusion. In the STOP II trial, the length of transfusion therapy for first stroke

prevention was explored [32]. Discontinuation of transfusion in this group resulted in a high rate of stroke and reversion to abnormal blood flow velocities. The study concluded a high risk associated with stopping regular transfusion and stressed the importance of continuing chronic transfusion until an effective alternative is available.

Pregnancy

A healthy pregnancy and delivery in women with SCD is very possible. However, special multi-disciplinary care must be given before, during and after to reduce mortality and morbidity of the fetus and mother. Increased pre-eclampsia, preterm labor and low birth weight newborns have been observed in women with SCD [33]. However, prophylactic transfusion from the onset of pregnancy did not change the outcomes for the fetus and mother in a RCT of 72 pregnant patients with SCD [34]. In a retrospective study, data supported the use of prophylactic transfusions for uncomplicated pregnancies beginning at 20 weeks [33]. The study revealed a reduction in pain crises, ACS, low birth weight and perinatal deaths. Prophylactic transfusions are generally not used in uncomplicated pregnancy and are reserved for those women with complications such as pre-eclampsia, ACS, severe anemia, increasing episodes of pain crises [34].

Treatments

The major therapies for the management of SCD include blood transfusions, hydroxyurea (HU), and hematopoietic stem cell transplants. SCD pain leads to frequent hospitalization for painful episodes necessitating intravenous opioid medications and aggressive hydration as therapy. Many of the complications of SCD can be life-threatening and/or life-limiting, such as acute chest syndrome, strokes, infections, transfusion-related reactions and iron overload, acute/chronic vaso-occlusive pain crisis and depression. The only cure for SCD is a bone marrow transplant, which is not available to most people, and is also associated with an

increased risk of death secondary to the complication of the transplant itself [29]. Therefore, the mainstay of therapy is treatment and prevention of clinical complications.

Surgery

Individuals with SCD often require surgery for many of the complications of the disease such as cholelithiasis, recurrent splenic sequestration, avascular necrosis, vitreous hemorrhage, retinal detachment, and nocturnal hypoxemia secondary to obstructive sleep apnea. However, patients are at increased risk of complications before, during and after surgery because of their anemia, the tendency of the red blood cells to sickle and occlude the microvasculature especially during times of stress, and the risk of hypoxia [35]. The morbidity and mortality can be significantly increased surrounding surgery, especially post-operatively. Pre-operative, peri-operative and post-operative complications include ACS, stroke, vaso-occlusive pain, renal dysfunction/failure, infection, and even death [35-37]. Therefore, many hematologists prepare SCD patients for surgery with blood transfusions (as well as other supportive measures such as hydration and good oxygenation) in hopes of reducing their risk of post-operative complications [9]. Buck et al suggested that the risk of post-operative complications has more to do with the risk of the surgical procedure itself than having or not having pre-transfusion [37], whereas other authors debate the type of transfusion to be given (no transfusion, simple transfusion, or exchange transfusion) [35,36]. Current recommendations from the National Institute of Health (NIH) monograph on the management of SCD include simple transfusion to increase the hemoglobin to no more then ten grams per deciliter prior to all but the lowest risk procedures in HbSS and HbSβ-Thal^0 and exchange transfusion may be warranted for HbSC to avoid hyperviscosity [9].

Hematopoietic Stem Cell Transplant

In the US, over 200 patients with severe SCD have been transplanted using matched sibling donors and conventional myeloablative therapy with an 83% event free survival [29]. The limiting factors are still the availability of a suitable matched sibling donor for the individual with SCD, and the risk of short-term and long-term toxicities are still present. Several reports demonstrate less favorable outcomes with reduced intensity regimens [29]. In adults, morbidity and mortality risks may be even higher so very few transplants are performed in adults [38]. Current studies are exploring partially matched relatives and matched unrelated donors using umbilical cord transplants with promising results [39].

Hydroxyurea

Hydroxyurea (HU) is the only pharmacologic agent FDA-approved for preventing complications of SCD. HU has been shown to significantly decrease the number of painful sickle cell episodes, hospitalizations for painful episodes, acute chest syndrome and the total number of blood transfusions [40]. Increased painful episodes are associated with increased mortality in SCD [6]. If the numbers of painful episodes are reduced with a drug such as HU, it stands to reason that the mortality rate will also decrease.

HU offers a very important option to improve healthcare in SCD patients. Yet, HU remains underused [41]. The concern about the potential carcinogenic effects of HU likely contributes to the underuse [41]. However, follow up on patients in the original Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), three malignancies were noted in the HU group: one carcinoma in situ of the cervix, one multi-focal carcinoma in situ of the breast and one endometrial carcinoma. There were no leukemias or lymphomas in the cohort [42]. All three patients died but the first two died of complications unrelated to their cancers [42].

HU is a ribonucleotide reductase inhibitor, which prevents DNA synthesis [1]. The benefit to SCD patients is that it increases fetal hemoglobin levels which inhibit polymerization of HbS [40]. Therefore, the amount of sickled red blood cells is decreased. High levels of HbF as a result of HU may reduce SCD complications [40, 42]. HU has other possible mechanisms as well, which include increasing nitric oxide, decreasing expression of red cell and endothelial adhesion, slight neutropenia (therefore less leukocyte adhesion) and diminished reticulocytes (which are the cells with the greatest adhesiveness) [4, 42].

Blood Transfusions

Acute and chronic blood transfusions are important in the management of SCD complications. Along with the drug HU, transfusions are the only other widely available treatment for SCD complications at this time. Transfusions are useful under certain circumstances of SCD such as splenic sequestration, aplastic crisis, prevention of primary or secondary strokes, hypoxia with acute chest syndrome, complicated pregnancy, recurrent priapism, surgeries, and any acute central nervous system injury such as seizure or central nervous system infarction [9]. Transfusions raise the oxygen-carrying capacity of blood and decrease the proportion of sickle RBCs. When used properly, transfusions are beneficial and often save lives of SCD patients on a daily basis. When they are improperly performed, more problems are created that can be life-threatening. Pre-operative transfusions are often given for the prevention of potential intra-operative and post-operative complications in SCD patients [35-37]. Also, transfusions greatly reduce recurrent stroke in children with SCD [25, 26], and the risk of first stroke in children with SCD who have abnormal results on TCD [30]. In light of the increasing number of transfusion indications, transfusions remain the mainstay of SCD therapy.

Despite the proven benefits of transfusions, there are limitations. Transfusions are associated with adverse effects which include but are not limited to transmission of infectious

diseases (such as HIV, CMV, hepatitis B & C), volume overload, hyperviscosity, hemolytic reactions, alloimmunization (development of antibodies or proteins that attack/destroy donated RBCs), and iron overload [15, 43-45].

Many of the transfusion complications may be minimized by appropriate administration techniques, selection, and modification of RBC products. RBC products are often modified prior to a transfusion in SCD. The RBC product is leukocyte reduced to decrease the risk of alloimmunization. The RBC product is also usually specified to be sickle cell trait negative and fresh (obtained within the last five days of transfusion). Other modifications of RBCs are usually not standard for SCD unless they have had a prior reaction to RBC during infusion (which require the product is washed before a transfusion), or they have had a bone marrow transplant (which would require an irradiated and leukocyte reduced product).

In one report, 60% of chronically transfused adults become alloimmunized [45]. Alloimunization leads to increase delayed hemolytic reactions and life threatening events. However, performing limited RBC phenotypic matching with C, E, and Kell (since these antigens account for 60-98% of antibody detected previously in SCD) can reduce the rate of alloimmunization [45, 46]. Vinchinsky et al. demonstrated a reduction in the rate of alloimmunization from three percent to half a percent per unit and a reduction in hemolytic transfusion reactions by 90% by using limited phenotypic RBC matching in a study for stroke prevention in SCD [45]. Josephson et al have provided a set of guidelines for the transfusion management of SCD and recommend the practice of limited phenotypic RBC matching as a standard of care for all transfused SCD patients [47].

The toxicity of iron overload may be reduced with iron chelation therapy [15, 48-50]. Regular transfusions lead to the accumulation of iron in multiple organs with resultant

irreversible damage if left untreated [15, 50]. Iron overload is monitored using measurements such as serum ferritin levels, number of RBC units transfused, magnetic resonance imaging of the liver or heart, and liver biopsy [15, 48, 50]. Iron overload can be effectively managed with iron chelation therapies such as deferoxamine and deferasirox. Deferoxamine requires eight to twelve hours of continuous subcutaneous infusion five to seven times a week resulting in many limitations of its use by the patient [48, 49, 51]. Deferasirox is an oral chelator now available for the treatment of transfusional iron overload [48, 49]. Our study was conducted prior to the FDA approval of deferasirox to evaluate the issues surrounding transfusional iron overload and chelation therapy.

CHAPTER 2
RESEARCH STUDY

Rationale

The application of evidence-based medicine for the transfusion management of sickle cell disease (SCD) is based on observational studies and the opinions of experts in SCD with just a few randomized controlled trials (RCTs) to guide decision making [11]. The few RCTs available support the use of prophylactic chronic transfusions for primary stroke prevention in high risk children identified by abnormal transcranial Doppler (TCD) and prevention of recurrent stroke in children or adults who have already experienced a stroke [26, 27, 30]. One of the RCTs also recommends that all SCD patients be antigen matched for E, C, and Kell [45]. Another provides evidence that a conservative transfusion program (simple transfusions that increase the hemoglobin to ten grams per deciliter) is just as effective as an aggressive transfusion program (exchange transfusion to reduce sickle hemoglobin (HbS) levels to below 30%) in preventing SCD complications in patients requiring major surgery [35]. A RCT also demonstrated that transfusions to maintain a hematocrit of more than 30% do not reduce complications of pregnancy [34]. Therefore, chronic transfusions are not recommended for the management of uncomplicated pregnancy.

Although a recent critical review of the literature and transfusion guidelines provided some insight into transfusion management of the patients with SCD [47] and the National Institute of Health (NIH) monograph provides a thorough and comprehensive outline for the management of SCD [9], limited data exist on actual hematologist prescribing practices in either academic or community-based settings. In this study, we set out to evaluate the physician prescribing practices in these settings for the transfusion management of SCD. Evaluating the current practices of physicians with respect to the transfusion management of SCD, providing a

universal set of practice guidelines, and finally, actively making physicians aware of the information based on the best scientific evidence are all necessary steps to improve healthcare management of SCD patients. The objective of this study was to examine current Florida hematologist/oncologist transfusion practices in the management of SCD. We tested the hypothesis that the transfusion prescribing practices vary among Florida physicians in the management of SCD.

Methods and Materials

A literature search was performed to obtain references addressing current recommendations for transfusion management and to catalog items to be considered for inclusion in the survey. Basic survey development was pursued [37, 52-54] and basic transfusion and sickle cell research were explored [27, 30, 35-37, 43, 45, 55]. A draft of the survey was developed and reviewed by a health service researcher with expertise in physician surveys, blood bank specialists, and a highly regarded hematologist with expertise in transfusion medicine for SCD. The survey was refined with the input from a group of academic hematologists in other regions of the US with particular interest in SCD. Face and content validity were evaluated by pilot testing the survey with current and previous trainees (residing out of state of Florida) of the University of Florida hematology/oncology fellowship programs. Feedback was obtained and revisions were implemented accordingly, with input from two other healthcare provider survey experts. The survey and accompanying cover letter were submitted and approved by the Institutional Review Board.

A thirty-one item, five page self administered questionnaire was created to collect information about the background and professional practice characteristics of physicians, their SCD patient population, and their transfusion practices. Questions regarding transfusion practices included the settings used for non-emergent transfusions, the use of practice site

defined criteria/guidelines, the use of phenotypically matched red blood cells (RBCs), and how RBCs were modified. We asked about the availability and frequency of automated exchange transfusion, transfusion recommendations for acute and chronic transfusions, and experience with iron overload and deferoxamine. We also asked about the availability of educational resources such as information on transfusions of SCD patients, the attendance of at least one conference or presentation on the management of SCD in the past two years and the use of the Management of Sickle Cell Disease monograph published by the National Institutes of Health [9]. Four clinical vignettes were presented and physicians were asked to choose the single most likely treatment recommendation (based on their experience with SCD patients). There were several other forms of questions, including simple binary questions requiring a yes or no answer, multiple choice questions with the ability to circle all that apply, and open-ended questions. Likert scaling was used for several questions in which the respondent was asked to rate their level of agreement as never, rarely, sometimes, or always or as very important, somewhat important or not important.

Study Design

The survey was mailed to hematologists/oncologists in the state of Florida from fall 2005 through spring 2006. A list of possible participants was compiled from membership directories of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO) and the Florida Association of Pediatric Tumor Programs (FAPTP). Surveys were mailed to physicians via three mailing attempts, with telephone and email follow-up for non-responders.

Survey Analysis

Data were processed by checking for item non-response, distributional forms (e.g., normality of continuous data elements), and creating derived variables. SAS Version 9.1 (SAS

Institute Inc., Cary, N.C.) statistical software was used for all statistical analyses. Frequencies and percents were calculated for categorical data and means and standard deviations were calculated for numerical data. Associations between numerical measures were tested using Spearman correlations. Chi-square and Fisher's exact tests were used to test relationships between bivariate categorical data. Groups were compared using Wilcoxon rank sum tests. P-values < 0.05 were considered significant. We focused on comparing differences between pediatric and adult practice responses as analysis factors since these are the two major practice types that care for SCD patients and would likely exhibit the most important aspects of variation if it existed. Also, physician-specialists are generally either in an academic or private practice location and would also demonstrate variation if it existed. We set out to determine if major differences existed in SCD management between pediatric and adult practices and also between academic and private practices.

Results

One hundred fifty five hematologist/oncologists completed the survey out of 474 requested (33% response rate). Twenty-five percent were pediatric and 75% were adult physicians. An academic setting was reported as the location for 23% of the practices and 77% were in private practice. The majority of the respondents were adult providers in private practice. The highest numbers of SCD patients were reported in the pediatric practice respondents; whereas the majority of adult practice respondents reported fewer SCD patients (Table 2-1). When comparing private and academic practice respondents, 49% of the academic respondents had 51 or more patients in comparison to only 17% of the private practice respondents.

The highest numbers of stroke patients were noted in the pediatric practice respondents with 87% having six or more overt stroke patients in comparison to 90% of the adult practice respondents having five or fewer overt stroke patients. Sixty-four percent of the adult practice

respondents had no stroke patients. Fifty-four percent of the private practice respondents had no stroke patients in comparison to 23% of the academic practice respondents.

The majority of the academic and pediatric practice respondents had higher numbers of patients receiving hydroxyurea (HU). For instance, 95% of the pediatric practice respondents had three or more patients receiving HU with 38% having 16 or more patients receiving HU. In contrast, 71% of the adult practice respondents had two or fewer patients on HU with 32% of the adult practices having no patients receiving HU. Sixty-one percent of academic practice respondents had three or more receiving HU while 57% of the private practice respondents had two or fewer patients receiving HU.

Use of Transfusion Guidelines

There was a statistically significant difference between adult and pediatric practice respondents with respect to practice guidelines and the use of the monograph (Figure 2-1). Physicians were asked if their practice had specific transfusion guidelines and 61% of pediatric practice respondents answered yes whereas 8% of adult practice respondents answered yes. Fifty-six percent of pediatric practice respondents reported usage of the 2002 management of SCD monograph published by the NIH while only 26% of adult practice respondents reported they used the monograph for the management of SCD. Sixty-three percent of the academic practices and 83% of the private practices reported they did have defined criteria/guidelines for the transfusion management of SCD patients. Forty-six percent of the academic practices and 72% of the private practices reported they did not use the NIH monograph. Several physicians were not aware of the monograph and were pleased to learn of its existence by means of completing the survey.

Administration Techniques, Selections and Modifications of RBCs

In spite of the evidence that limited/extended phenotypic matching reduces alloimmunization, a minority of respondents requested limited (16%) or extended/complete (23%) phenotypic matching of RBCs on a routine basis when compared to not matching until antibodies were identified (61%). An automated exchange transfusion on an emergent basis is often vital to saving the lives of individuals with SCD, especially acutely when acute chest syndrome (ACS), stroke, sepsis and multi-system organ failure occurs. Emergent automated exchange transfusion was available in the majority of pediatric (94%) and adult practice respondents (71%) as well as academic (97%) and private practice respondents (71%). Noticeably, the academic and pediatric practice respondents had much higher percentages in comparison to the adult and private practice respondents. Ten physicians reported from one to ten patients on chronic transfusion programs using automated exchange transfusion. Six were in pediatric practices (five were academic and one private) and four were in adult practices (two academic and two private).

We asked respondents how often certain RBC products are requested for a sickle cell patient who has not had a bone marrow transplant. Choices were always, sometimes, rarely or never. RBC products listed were leukocyte reduced, non-leukocyte reduced, irradiated, washed, sickle cell negative and other products (please specify). Overall, respondents "always" requested leukocyte reduced products (83%). There was variability in the request for sickle negative, irradiated, and washed blood products (Figure 2-2).

Acute and Chronic Transfusion Indications

We asked respondents when they considered certain indications for acute (episodic) transfusion for sickle cell anemia (HbSS) patients. Choices were always, sometimes, rarely or never. The indications for acute transfusions listed for the respondents included: acute painful

episodes, ACS, acute priapism, acute stroke, pre-operative for general anesthesia, and vitreoretinal surgery. Other acute indications were specified by respondents as a write-in and included aplastic crisis, bone marrow transplant, severe symptomatic anemia, multi-organ system failure, hepatic sequestration, hospitalization for infection in a non-acute pain crisis, pregnancy with and without complications, non-healing ulcers, and hypoxia with pneumonia. Seventy-eight percent of the respondents thought that acute transfusion was "always" indicated for acute stroke. Fifty-five percent of respondents would "always" transfuse acutely for ACS. Fifty-two percent would "always" transfuse for acute priapism, and 49% would "always" transfuse for pre-operative general anesthesia. Forty-one percent of respondents thought acute transfusion was "sometimes" indicated for acute painful episodes, and 44% thought vitreoretinal surgery was "sometimes" an indication for acute transfusion.

There were statistically significant differences among pediatric and adult practice respondents with respect to acute transfusion indications, most notably with acute painful episodes, acute stroke and preoperative general anesthesia. The majority of pediatric practice respondents "rarely" considered acute painful episodes an indication for acute transfusion in comparison to adult practice respondents (76% versus 25%). In contrast, 53% of adult practice respondents "sometimes" consider acute painful episodes as an indication for acute transfusion compared to 3% of pediatric practice respondents. Pediatric practice respondents were more likely to view an acute stroke as an indication for acute transfusion with 95% reporting "always" in comparison to 72% of adult practice respondents. Pre-operative for general anesthesia was "always" an indication for acute transfusion in 71% of pediatric practices and 42% of adult practices.

There were statistically significant differences between academic and private practice respondents with respect to acute transfusion indications, most notably with acute painful episodes and acute priapism. Academic practice respondents were less likely to transfuse for acute pain and priapism when compared to their adult practice respondents. Sixty percent of academic practice respondents reported they "rarely" transfused acutely for pain whereas 51% of private practice respondents reported they "sometimes" did. Priapism was "sometimes" an indication for acute transfusion in 62% of the academic practices and "always" an indication for 58% of the private practices.

We queried chronic transfusion indications in the same manner we approached the acute indications. We asked respondents when they considered certain indications for chronic transfusion for SCD patients. The chronic transfusion indications listed for the respondents were primary prevention of stroke, prevention of recurrence of stroke, history of ACS, renal failure, congestive heart failure, pulmonary hypertension, recurrent debilitating painful episodes, non-healing leg ulcers, prevention of recurrence of priapism, uncomplicated pregnancy. Other indications were specified by respondents such as an abnormal TCD.

Pediatric practice respondents were more likely to use chronic transfusions for primary stroke prevention than adult practice respondents. Forty-one percent of pediatric providers "always" use chronic transfusions for primary stroke prevention. In contrast, only seven percent of adult providers "always" transfuse. However, there was as many pediatric practice respondents (22%) as adult practice respondents (30%) who "never" use chronic transfusion for primary stroke prevention. Prevention of stroke recurrence was "always" an indication for chronic transfusion in 95% of pediatric practice respondents, compared to only 27% of the adult practice respondents.

A history of ACS was "always" or "sometimes" an indication for chronic transfusion in 77% of pediatric and 42% of adult practice respondents. Fifty-seven percent of pediatric practice respondents thought that renal failure was "always" or "sometimes" an indication for chronic transfusion compared to 30% of the adult practice respondents. Recurrent debilitating painful episodes were "always" or "sometimes" an indication for chronic transfusion in 64% of pediatric and 50% of adult practice respondents. There was not a statistically significant difference between pediatric and adult practice respondents for congestive heart failure, pulmonary hypertension, non-healing ulcers, or recurrent priapism.

Uncomplicated pregnancy was "never" an indication for chronic transfusion in 37% of all adult respondents and "sometimes" in 37%. The majority (59%) did transfuse on a regular basis. There was not a statistically significant difference between pediatric and adult practices or academic and private practices with respect to uncomplicated pregnancy indications for transfusions. There was not a statistically significant difference between the academic and private for any of the chronic transfusion indications.

Iron Overload and Iron Chelation therapy

Iron overload and chelation therapy, specifically deferoxamine, were explored in the survey. There were no statistically significant differences in other measures used to assess iron levels when starting deferoxamine therapy between pediatric and adult or private and academic practices, except between pediatric (36%) and adult (11%) respondents in terms of percentage that used liver biopsy as a measure to assess iron overload. Liver biopsy is considered the most accurate measurement [9]. Other measures used by physicians included steady state ferritin levels, radiologic imaging (MRI, CT), and number of RBC units transfused. Despite having an indication for deferoxamine, many patients are not receiving it. Therefore, we investigated the reasons why physicians felt deferoxamine was not being used. Physicians were asked to evaluate

the importance of each reason listed for not using deferoxamine as very important, somewhat important or not important. The results of the reasons are displayed in Figure 2-3. Noncompliance and patient's refusal were cited most frequently as very important reasons for not using deferoxamine. Fear of side effects, poor understanding of iron overload and iron chelation by patient/family, lack of healthcare providers to supervise treatment, and cost were cited most frequently as somewhat important reasons.

Clinical Vignettes

The vignettes revealed statistically significant differences between pediatric and adult (Table 2-2). In clinical vignette one, a sixteen year old male with HbSS is scheduled for elective laparoscopic cholecystectomy with a baseline hematocrit (hct) of 22% and hemoglobin (hb) of 7.2. The treatment options were (1) perform an exchange transfusion to reduce the HbS fraction to 30%, (2) transfusion of RBCs to an hct of 30%, (3) transfusion of RBCs to an hct of 36%, or (4) no pre-operative transfusion is indicated. Ninety-two percent of pediatric and 56% adult practice respondents indicated transfusion to hct of 30% was the treatment of choice. However, seventeen percent of adult practice respondents indicated no pre-operative transfusion. Sixty-nine percent of academic and 64% private practice respondents chose transfusion to an hct of 30%.

In vignette two, a four year old girl with splenic sequestration presents to the emergency room with an hct of 12% and transfusion recommendations are requested. The treatment options were (1) transfusion of packed red blood cells (PRBCs), (2) transfusion of whole blood, (3) performing an exchange transfusion, or (4) transfusion is not indicated. Ninety-two percent of the pediatric practice respondents recommended transfusion of PRBCs in comparison to 43% of adult practice respondents. Thirty-five percent of adult practice respondents recommended perform an exchange transfusion in comparison to five percent of the pediatric practices. Sixty

percent of academic and 55% of the private practice respondents also recommended transfusion of PRBCs for this vignette. Forty percent of the academic practices recommended exchange transfusion in comparison to 24% of the private practices.

In vignette three, a twenty-eight year old woman has ACS with progressive hypoxemia, despite oxygen supplementation. Treatment options were (1) transfusion of two units PRBCs, (2) exchange transfusion with target hct 30%, (3) exchange transfusion to hct 38% or (4) transfusion is not indicated. Sixty-nine percent of pediatric and 64% of adult practice respondents indicated exchange transfusion to hct of 30% was the treatment of choice. Eighty-two percent of academic and 60% of private practices also recommended exchange transfusion to hct of 30% for the vignette. Eighteen percent of pediatric and 23% of adult practices recommended transfusion of two units of PRBCs for the scenario.

In the fourth vignette, we queried recommendations for a twenty-one year old male who had undergone chronic transfusion for nine years for secondary stroke prevention. Continuation treatment options were (1) continue transfusions at four week intervals, (2) begin automated exchange transfusions at four week intervals, (3) discontinue transfusions and begin HU therapy or (4) discontinue transfusions. Overall for all respondents, both "discontinuation of transfusions and beginning HU" and "continuation of transfusions at four week intervals" were considered treatments of choice with 37% for each option and few indicating no further therapy or beginning automated exchange transfusion at four week intervals. The private and academic practices' responses essentially mirrored the pediatric and adult practices for this vignette.

Educational Resources

Educational resources were also investigated. Physicians were asked if information was readily available on transfusion of SCD patients. Eighty-two percent of the pediatric and 64% of the adult practice respondents answered yes. Eighty-nine percent of academic and 62% of

private practices answered yes. Physicians were also asked if they had attended at least one conference or presentation on the management of SCD in the past two years. Twenty-eight percent of the pediatric and 18% of the adult practices answered yes. Sixty percent of the academic and 24% of the private practices responded yes. In response to an open-ended question about materials that would be helpful, 35% of physicians that requested materials wanted specific transfusion guidelines for the management of SCD.

Table 2-1. SCD patients according to practice type

Number of SCD patients	Pediatrics (%)	Adult (%)	P-value
0-15	2	94	< 0.0001
16 or more	98	6	

Table 2-2. Clinical vignettes according to practice type

Case 1: A 16 year old boy with sickle cell anemia (Hb SS) is scheduled for elective laparoscopic cholecystectomy. The baseline labs reveal Hct is 22% and Hb is 7.2.

Responses	Adult (%)	Pediatric (%)
Perform an exchange transfusion to reduce the Hb S to 30%	15	5
Transfuse RBCs to a Hct of 30%	56	92
Transfuse RBCs to a Hct of 36%	10	0
No pre-operative transfusion is indicated	17	3

Case 2: A 4 year old girl with known sickle cell anemia (Hb SS) presents to the Emergency Department with a 12 hour history of abdominal pain, nausea, vomiting, and lethargy. Physical examination reveals an easily palpable and tender spleen. The CBC shows WBC 29,000/μL with 80% neutrophils and 12% bands, Hct 12%, platelets 88,000/μL. The physician in charge requests assistance in transfusion recommendations.

Responses	Adult (%)	Pediatric (%)
Transfusion of packed RBCs	43	92
Transfusion of whole blood	3	0
Perform an exchange transfusion	35	5
Transfusion is not indicated	5	3

Case 3: A 28 year old woman with Hb SC disease has acute chest syndrome with progressive hypoxemia, despite oxygen supplementation. Review of the CBC reveals WBC 22,000/μL, Hct 28%, platelets 530,000/μL.

Responses	Adult (%)	Pediatric (%)
Transfusion of 2 units packed RBCs	23	18
Exchange transfusion with target Hct 30%	64	69
Exchange transfusion with target Hct 38%	9	3
Transfusion is not indicated	4	3

Case 4: A 21 year old male with sickle cell anemia (Hb SS) would like to enter your practice. The patient has been undergoing transfusions of 2 units packed RBCs, every 4 weeks since a stroke at age 12 with a goal to maintain his Hb S level at ~50%. He has been on deferoxamine therapy over the past 7 years.

Responses	Adult (%)	Pediatric (%)
Continue transfusion at 4 week intervals	36	39
Begin automated exchange transfusion at 4 week intervals	14	15
Discontinue transfusions and begin hydroxyurea therapy	40	28
Discontinue transfusions	8	0

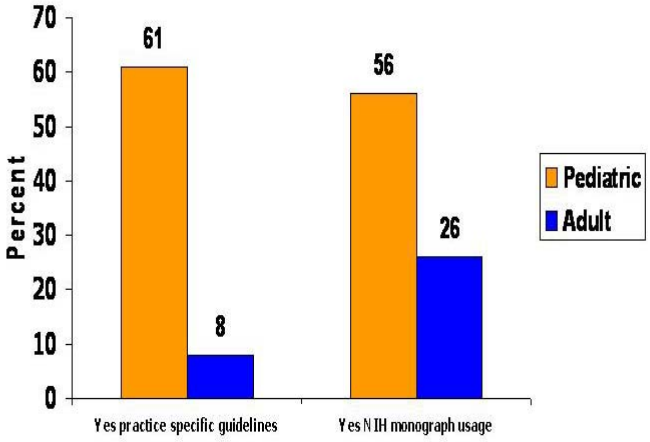

Figure 2-1. Use of practice specific guidelines and NIH monograph by respondents, p-values <0.0001 and <0.001 respectively.

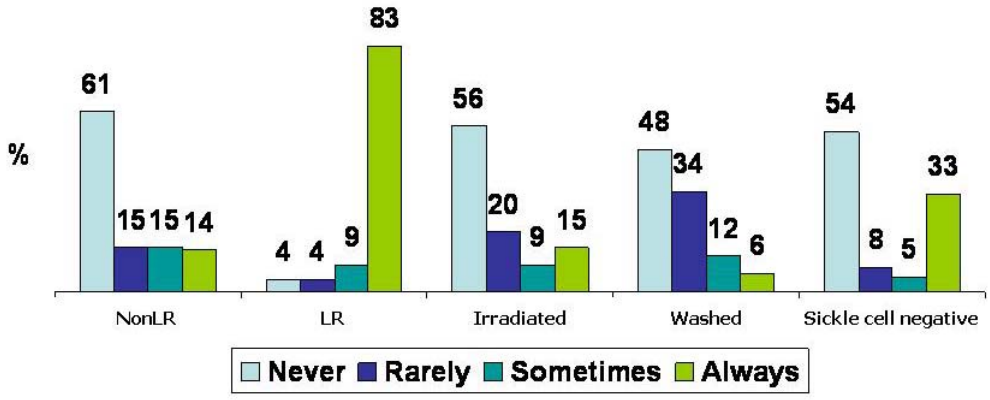

Figure 2-2. Frequency of RBC modifications requested by respondents. LR, leukocyte reduced.

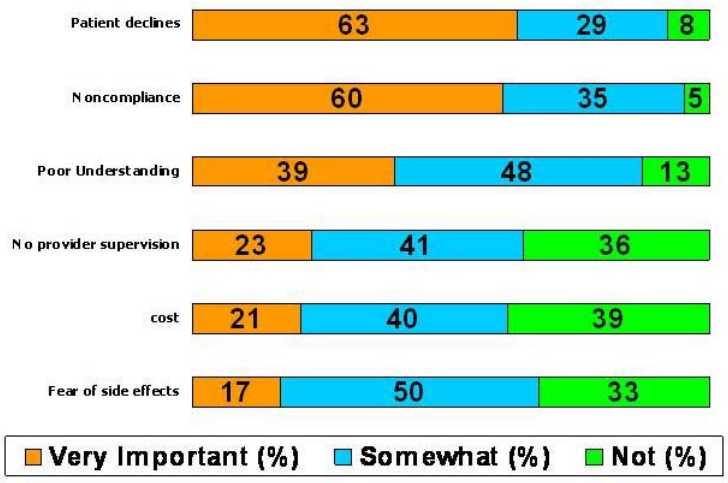

Figure 2-3. Importance of reasons for not using deferoxamine.

CHAPTER 3
DISCUSSION

The results support the hypothesis that there is variation in the transfusion management of SCD among Florida hematologists/oncologists. Although the private and adult practices are largest in number, the academic and pediatric practices have the most SCD patients and readily use the resources available for SCD management. As noted in a brief review of evidence-based approaches for the treatment of SCD, the application of evidence based medicine to the transfusion management of SCD patients is based on a few RCTs. However, comparison of evidence-based recommendations and transfusion practices of respondents revealed variability between what is actually suggested based on the best evidence and what is actually practiced.

In a survey of 1182 North American laboratories, the majority did not determine the red cell antigen phenotype of non-alloimmunized SCD patients beyond ABO and D, even with evidence to support phenotype matching for C, E and K to drastically prevent alloimmunization and delayed hemolytic transfusion reactions [46]. In our study, just as the study noted above, the majority of the respondents did not routinely request phenotypically matched RBCs for SCD patients until the patient makes an antibody. The majority of respondents used leukocyte reduced products, consistent with current recommendations [45]. There was variability in the request of sickle negative product, which is consistent with the local blood bank practices [46]. The indications for washed and irradiated RBC product are limited to specific situations such as previous anaphylactic transfusion reactions or bone marrow transplant, respectively. Of note, we specified the request was for a SCD patient who had not had a bone marrow transplant. Even with this information provided, 15% of physicians responded they “always” request irradiated blood and six percent responded that they “always” request washed blood, which is not necessary.

Our study results are consistent with current literature on iron overload and chelation therapy. Most providers use multiple measures to assess iron levels as was the case in our study. Deferoxamine is an effective treatment of chelation therapy. However, many factors contribute to the discrepancy between the number of SCD patients with indications and the number of patients prescribed deferoxamine with patient compliance being the most frequently cited reason in our study as well as others [51]. Deferasirox shows great promise as an oral iron chelator with less compliance issues since it is an once a day oral medication compared to deferoxamine's nightly ritual of subcutaneous infusions. Deferasirox has similar efficacy as deferoxamine in the treatment of iron overload in SCD patients [49]. The survey data may serve as a point of reference in future discussions comparing the use of deferoxamine and deferasirox in chelation therapy.

A randomized clinical trial (RCT) demonstrated no benefit of prophylactic transfusion in pregnancy in terms of maternal and perinatal complications [34]. In concordance with these findings, the majority of respondents do not routinely transfuse for uncomplicated pregnancy. A RCT comparing conservative to aggressive transfusion in elective surgery demonstrated equivalent efficacy [35]. Cholecystectomy is a commonly performed surgery for SCD patients [9]. The majority of adult and pediatric as well as private and academic practice respondents indicated conservative transfusion management of laparoscopic cholecystectomy. However, this approach was more prevalent among pediatric practices.

Randomized clinical trials support chronic transfusions for the primary prevention of stroke in high risk children [30-32]. There was variability in adherence to this recommendation with only 41% of pediatric practice respondents indicating they "always" transfuse and 22% indicating "never" transfusing for primary stroke prevention in children. A higher number of

pediatric practice respondents were expected to "always" use chronic transfusion for primary stroke prevention given the significant reduction of strokes observed in the Cooperative Study of Sickle Cell Disease (CSSCD) group of participants with abnormal TCDs. However, in our study, the terms primary prevention of stroke does not specify high risk children due to an abnormal TCD and may represent the source of such a low number for "always" and the high percentage for "never".

Observational data supports indefinite transfusion for secondary stroke prevention in children [27]. Ninety-five percent of pediatric practices "always" adhere to this recommendation, while only 26% of adult practices follow this recommendation. There are currently no standard of care guidelines or supportive studies for adults for secondary stroke prevention. So it is not unexpected that as many physicians opted to "discontinue transfusions and begin HU" as there were to "continue transfusions". Clearly, there is no one option for the clinical vignette scenario especially in light of studies such as the stroke with transfusions changing to HU (SWITCH) trial that is currently underway to compare treatments for the prevention of a recurrent stroke and the treatments of iron overload in children with sickle cell anemia [24]. The standard chronic transfusions for stroke prevention and iron chelation for the prevention of iron overload will be compared with HU to prevent recurrent stroke and phlebotomy to treat iron overload.

Limitations

As a result of non-response bias, the completed responses may not be a true representation of a larger sample. Although we attempted to specifically contact only hematologists/ oncologists prescribing transfusions to SCD patients, our sample size of 474 represents all physicians listed in the directories and not actually the number of hematologists/oncologists managing SCD patients with transfusions. Therefore, the response rate calculation based on our denominator is likely inaccurate. Florida Medicaid population data identified 265 unique

providers that prescribed transfusions for the management of SCD. Although primary care providers are included in the Medicaid data, the data suggest as we speculate that our sample requested is an overestimate of hematologists that actually prescribe transfusions in the management of SCD. One solution to this problem we are exploring is conducting follow-up phone calls to the non-respondents to find out if they actually care for SCD patients and if so, to ask if they have transfused a SCD patient in the past year. Therefore, non-respondents can be determined to be the same or different from the sampled population that completed the survey and conclusions drawn will be stronger.

Generalization of the results is also limited by the fact that only one state (Florida) was sampled. It may be useful to survey physicians from other states and investigate if the practices observed are universal. Also, evidence-based medicine recommendations do not represent a definitive standard of care. Therefore, comparing results to evidence-based medicine recommendations may not be a true point of reference for intervention. A few survey questions were specific for pediatric practice providers such as the questions about primary stroke prevention and splenic sequestration. Therefore, adult practices may not be as familiar with current recommendations as their pediatric practice colleagues.

Conclusion

The data indicate variability in the incorporation of evidence-based approaches, use of routine clinical guidelines, and availability of emergent exchange transfusion when comparing pediatric and adult physician practices and academic and private practices. The high variation may relate to the fact that there are no standard of care guidelines established and there is a lack of experience in managing SCD patients in many provider populations. The differences in transfusion practices for stroke prevention in this study indicate a need to explore the challenges that exist in adequately providing these services. There exist opportunities to provide educational

materials based on evidence-based medicine to all physicians caring for SCD patients. The differences in characteristics of pediatric and adult practices in the state of Florida indicate a need for tailoring the available materials for individual practice needs.

In a recent literature review of transfusion management of patients with SCD, Josephson et al. recommended a set of transfusion guidelines which offer an excellent resource for physicians in the transfusion management of patients with SCD [47]. One of the most valuable lessons learned from this study was that many physicians who care for patients with SCD are not aware of the useful resources that are available to guide physicians in the management of SCD. A great starting point to reduce the variation in the transfusion management of the SCD is to come up with an efficient and effective way to disseminate the current information to those caring for patients with SCD. Many points of reference for SCD treatments are considered controversial and therefore many different approaches are acceptable. However, if there is less variation in the care of SCD, there will be less unnecessary transfusions and fewer complications from improper transfusions and therefore more effective treatment of SCD complications and ultimately better quality of care and life for individuals with SCD. Removing controversy surrounding treatments and having an agreed upon approach is extremely important for future research and universal guidelines. Fortunately, many who care for patients with SCD recognize the need to provide universal transfusion guidelines not only in the literature but also among the Florida hematologist/oncologist who completed the survey. Given that there are so many acute and chronic complications associated with transfusions and that transfusions are so important in the treatment of almost every SCD complications, many studies are not only looking for effective alternatives to transfusion therapy, but also acceptable ways to improve the current use of transfusions.

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BIOGRAPHICAL SKETCH

Levette Nicole Dunbar was born in Augusta, Georgia. She graduated from Augustus Richard Johnson High School and then pursued her undergraduate degree at Tuskegee University (TU), in Tuskegee, Alabama. After completing her B.S. in biology at TU in 1991, she completed her Master of Public Health (MPH) at the University of Michigan School of Public Health in Ann Arbor, Michigan in 1993. Levette was an eighth grade science teacher after completing her MPH from the fall 1993 until spring 1994 at East Augusta Middle School in Augusta, Georgia. After teaching for 1 year, Levette earned a certificate of completion from the Southern Illinois University School of Medicine medical education preparatory program in Carbondale, Illinois in 1997. Levette entered medical school in 1997 and earned her medical degree from the University of South Carolina School of Medicine in May 2001. After completing three years of a pediatric residency and three years of a pediatric hematology/oncology fellowship at the University of Florida, Levette accepted a faculty position at the University of Florida Department of Pediatric Hematology/Oncology as a Clinical Lecturer in July 2007.