TELEPHONE EDUCATION AND FOLLOW-UP IMPROVE ADHERENCE TO COMPREHENSIVE CARE IN SICKLE CELL DISEASE

by

Meredith Suzann Patik

B.S., Biopsychology, Russell Sage College, 2002

Submitted to the Graduate Faculty of

Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Meredith Suzann Patik

It was defended on

April 7, 2005

and approved by

Thesis Advisor:
Lakshmanan Krishnamurti, MD
Assistant Professor
Pediatrics
School of Medicine
University of Pittsburgh

Committee Member:
James Butler, PhD
Assistant Professor
Behavioral and Community Health Sciences
Graduate School of Public Health
University of Pittsburgh

Committee Member:
Elizabeth Gettig, MS, CGC
Associate Professor
Human Genetics
Graduate School of Public Health
University of Pittsburgh

Lakshmanan Krishnamurti, MD

TELEPHONE EDUCATION AND FOLLOW-UP IMPROVE ADHERENCE TO COMPREHENSIVE CARE IN SICKLE CELL DISEASE

Meredith Suzann Patik, MS

University of Pittsburgh, 2005

Programs such as routine follow-up phone calls are an important part of public health. These programs are developed as a means to enhance the medical care offered by physicians. It brings many services to the public, making them more accessible for everyone. Integrating outreach programs in order to provide services to help meet the needs of a chronically ill population is of great importance to the field of public health.

It is vital for patients with sickle cell disease to adhere to comprehensive care in order to decrease the morbidity and mortality of the disease. Patients who do not adhere to the recommended routine of care set forth by their physicians run the risk of developing serious complications or even death. The Comprehensive Sickle Cell Center at Children's Hospital of Pittsburgh has established an outreach program that is aimed at increasing attendance to comprehensive care clinic, as well as educating patients and their families about sickle cell disease. All active patients were routinely contacted via phone in order to remind them to schedule an appointment in the clinic and to provide a range of services over the phone, such as prescription refills, answering questions about sickle cell disease, and psychosocial support. The patients were also asked questions about their home care routine so as to follow-up with them. This outreach program has been successful in increasing attendance to comprehensive clinic and in increasing the number of patients who are compliant with annual screenings.

TABLE OF CONTENTS

LIST OF FIGURES

PREFACE

The Comprehensive Sickle Cell Clinic at Children's Hospital of Pittsburgh has an on-going outreach program that aims to improve the outcome of sickle cell disease. I wanted to be a part of a public health program that included patient education as well as programming for the patients. I took on this project because I was interested in working with a specific population which shares a common genetic disorder. The program works with an electronic database that was established in 1995 to track cohorts of patients with sickle cell disease. From this work, we are in the process of creating a nation-wide database that can be used by each hospital to hold patients' medical records as well as provide a large patient base for research studies.

This is an on-going outreach program that is a part of a HRSA Grant, #6H46MC 00255-01-01. It is designed to measure the effectiveness of integrating phone calls into traditional medical care as well as improve upon the services provided by comprehensive care.

1.0 INTRODUCTION

Public health is a vital part of healthcare. It provides services and programs to the public that help to improve the quality of their health. One of its focuses is healthcare services and programs outside of a traditional doctor's visit. These programs round out patients' total healthcare experience. The Comprehensive Sickle Cell Center at Children's Hospital has one such program that involves calling all patients and their caregivers between clinic visits to follow-up with them. Pediatric comprehensive care programs for sickle cell disease have been a model for chronic illness management and have had a substantial impact on the morbidity and mortality from this disease [1]. The patients receive medical care, counseling, and education through face-to-face contact with the multi-disciplinary members of the sickle cell care team during a routine clinic visit. There is a need to follow-up with the home care routine of families dealing with sickle cell disease to ensure they are following their physician's orders and performing positive health behaviors. In addition, the importance of routine clinic visits can be re-enforced during the phone calls. Poor attendance at the comprehensive care clinic has been a major obstacle to providing proper health care for sickle cell disease, so as to improve the outcome for these patients.

Besides routine comprehensive clinic visits every six months, a large part of treating sickle cell disease includes daily home care. It is important for the patients to take their medications daily and to follow the home care routine outlined by their sickle cell care team. This helps to prevent complications such as infections, pain crises, and strokes. Phone calls provide a means to deliver the positive health messages and suggestions for positive health

behaviors that are emphasized by the sickle cell care team. By involving the patients and their families in the healthcare process, the patients' quality of life can be greatly improved.

This program has two specific aims: 1) to re-enforce positive health messages and suggestions for positive health behavior regarding sickle cell disease and 2) to increase patients' adherence to comprehensive care. We hypothesize that delivering positive health messages and suggesting positive health behaviors to families via phone calls is feasible and will result in improved adherence to comprehensive care.

2.0 BACKGROUND

Sickle cell disease is a genetic hemoglobinopathy that involved red bloods cells and manifests in chronic tissue ischemia, chronic organ damage, and dysfunction. It is the result of a point mutation on the β globin gene on chromosome 11 [30]. Normal hemoglobin is Hemoglobin A and carries oxygen within the red blood cells around the body. The mutation of the β globin gene causes the development of Hemoglobin S. Hemoglobin S is unable to hold on to oxygen adequately. It becomes deoxygenated and polymerizes, thus changing the shape of the red blood cell. Instead of being a round, concave shape, and flexible, the red blood cell becomes hard and rigid, and takes the form of a banana or sickle. It has sharp edges that cause it to get stuck in blood vessels. This results in vaso-occulsions, which lead to vascular obstruction, organ damage and hemolytic anemia [32]

The mutation in the β globin gene is common among people with African, Mediterranean, Middle Eastern, Indian, Caribbean, and Central and South American ancestry. It is inherited in an autosomal recessive pattern, meaning that both parents must have the mutation in order for their child to have the disease. This is called homozygous Hemoglobin SS disease, where both β globin genes are mutated. If just one β globin gene is mutated, then the person is considered heterozygous and has no clinical complications. These people have the sickle cell trait and are carriers; they can pass the mutation on to their children. There are other mutations in the β globin gene that cause sickle cell disease. The most common genotypes include Hemoglobin SS, Hemoglobin SC, Hemoglobin Sβ+ thalassemia and Hemoglobin $S\beta^0$

thalassemia. Overall, the most severe phenotypes are associated with Hemoglobin SS and Hemoglobin $S\beta^0$ thalassemia [30].

Thirty years ago, the average life-span for someone with sickle cell disease was 14 years. Today, the average life-span has increased significantly to 50 years [33]. Approximately 2000 infants are born each year affected with sickle cell disease. The incidence of sickle cell disease exceeds the incidence of other serious genetic disorders, such as cystic fibrosis and hemophilia. Sickle cell disease is the most prevalent genetic disorder identified by routine newborn screening [33].

Initially, infants with sickle cell disease had an extremely high mortality rate, especially within the first three years of life [21]. Babies were born seemingly healthy, but their health began to deteriorate after several months. They would become ill rather suddenly, and then die, mostly because no one knew what was wrong and consequently, proper treatment could not be administered in a timely fashion. Once these babies were studied, it was concluded that they all had a genetic mutation that resulted in sickle cell disease. In 1987, the highest mortality rate was among children between 1 and 3 years old. A fair number of these children had enlarged spleens and internal infections in their spleens, lungs and even brains. Early detection of organ malfunction allows for early intervention, thus reducing the risk of further damage. This is especially the case with the lungs and brain [20, 21]. In more recent years, the mortality rate is declining. This can be attributed to newborn screening, early diagnosis, early initiation of comprehensive care, parental education and daily penicillin prophylaxis [29].

2.1 NEWBORN SCREENING AND DIAGNOSIS

Early detection of sickle cell disease leads to early intervention so as to prevent complications. Newborn screening identifies infants affected by sickle cell disease and allows for proper comprehensive care to begin immediately, thus reducing morbidity and mortality from sickle cell disease in infants and children. Newborn screening also identifies other hemoglobinopathies that are in need of medical attention, such as α-thalassemia and the β-thalassemias, and identifies who are hemoglobinopathy trait carriers. In 1986, the Prophylactic Penicillin Studies I and II demonstrated the greatly reduced incidence of pneumococcal sepsis in children with sickle cell disease who began taking penicillin as a part of their daily health care routine. In order to administer the penicillin from birth, newborn screening was necessary to identify those babies who had sickle cell disease [20].

Newborn screening should be performed 48 hours after birth to test for genetic and metabolic defects like sickle cell disease. Hemoglobin electrophoresis is the standard test when determining the hemoglobin genotype. Solubility tests, like Sickledex, are not reliable tests. They do not distinguish between sickle cell trait and other forms of sickle cell disease. Also, the elevated levels of fetal hemoglobin at that age can produce false negative results [20]. Abnormal results should be confirmed via DNA analysis [24]. DNA analysis is the best way of determining an accurate and correct hemoglobin genotype [20]. This is especially important when determining the presence of β^S haplotypes and α-thalassemia [25].

2.2 SYMPTOMS

No one knows exactly how the course of sickle cell disease will affect them. The phenotype cannot be consistently correlated with the genotype, though being homozygous for Hemoglobin S is associated with the most severe complications while heterozygosity for Hemoglobin S and Hemoglobin C is associated with a milder course of the disease. There are some predictors of clinical severity [20]. They include: dactylitis in the first year of life, average hemoglobin level <7g/dL in the 2nd year of life, and elevated leukocyte count (13,700/μL) before age 10 years [23].

Fever is one of the most common signs of illness in children with sickle cell disease. Children can die from a fever – it can precipitate a pain crisis or be an indicator of infection. Fever is a very serious complication in children with sickle cell disease. Even low-grade fevers, 99º-100ºF, are very important to monitor since they can rise to 101ºF, the temperature at which physicians recommend seeking emergency care. If a child with a minimal fever is brought to the emergency room, they should still be observed for several hours in case any additional symptoms develop. Detecting even the subtlest hint of a symptom is especially important in younger children [20].

Sepsis is a major cause of infant mortality. Sickled cells block blood flow to the spleen. Due to their inflexibility, they are unable to fit through smaller diameter vessels and get stuck, creating a blockage. If the spleen is not getting adequate blood flow, then splenic sequestration can occur. This infection can be fatal within 3-4 hours of onset and emergency care is needed. Also, the spleen has B-cells for antibody production which is lost when the spleen is damaged due to an infarct. This leaves the infant susceptible to infections. Because the physical

symptoms are more noticeable than some other complications, sepsis may go unchecked. A child may look happy, be content, or sleeping when they are really sick internally. This can make it difficult to convince caregivers that the infant is in danger of dying from infection. It is vital for the health of their children that parents are educated about the signs and dangers of infection. Parents should be taught physical assessment skills, like spleen palpation, temperature-taking, and behavior assessment so that they can judge when a non-verbal child is not feeling well; methods to avoid vaso-occlusion complications, which can lead to a pain crisis; how to treat a pain crisis at home; and when to notify the sickle cell care team in the event of a more serious problem [20].

Pulmonary problems that children with sickle cell disease encounter include acute chest syndrome and low oxygen saturation levels. Early acute chest syndrome in young children may not show signs of pulmonary problems. Lung function deteriorates with age, so it is important to identify patients who are prone to these problems from the start and to continually monitor their pulmonary function [2].

Pain crises, or painful events, are common in children with sickle cell disease. The episodes begin in several ways. The onset can be sudden, or it can develop slowly, usually following an illness with decreased activity, loss of appetite, and increased jaundice. Dactylitis, or hand-foot syndrome, is often the initial complication observed clinically. This usually begins within the first year of life. The pain is usually due to vaso-occlusion of the blood vessels. Typically, these pain events occur in the limbs, abdomen, ribs, sternum, vertebrae, and sometimes skull bones. Most pain crises begin without warning. It is important to identify exactly where the pain is to rule out any other causes, like a sprain or broken bone [20].

Cerebrovascular disease is the most serious complication in homozygous sickle cell disease. However, the pathophysiology of strokes in sickle cell disease is poorly understood. Occlusion of the blood vessels or an increase in the cerebral blood flow in the major intracranial arteries leads to cerebral infarction, or stroke, and other neurologic damage. The risk of stroke increases significantly with increased velocity of the blood flow in the intracranial arteries. The Cooperative Study of Sickle Cell Disease found that patients have an 11% chance of an initial cerebrovascular accident by age 20 years, a 15% chance by age 30 years, and a 24% chance by age 45 years [2-7]. There is a sub-group of sickle cell disease patients who are at higher risk for stroke than the rest based on their age and genotype. These patients are 2-10 years old with a genotype of either Hemoglobin SS, Hemoglobin Sβ^0-Thalassema, or Hemoglobin S-O^{Arab} [8, 9]

2.3 TREATMENT

The main goal of pain management is pain relief. Most pain episodes can be treated at home by the parent. Parental education on proper analgesic use can provide prompt care to the child in pain as well as decrease the demand on the emergency room staff. Medications given to the parents for home care include acetaminophen (Tylenol), nonsteroidal anti-inflammatory drugs (NSAIDs like ibuprofen), and mild opioids (codeine) [2]. Parent education should include information about drug addiction as well as drug side-effects. If the patient's pain is not eased by homecare, or gets worse, then the caregivers are encouraged to call their sickle cell team or go to the hospital.

In the emergency room, broad-spectrum antibiotics are given to treat infections, especially since bacterial infection is the major concern with a febrile child with sickle cell disease [22]. Survival beyond age 5 years is due largely to the prevention of bacterial infections. Splenic sequestration and erythroid aplasia (aplastic crisis) are also commonly found with a fever [20].

Previously, stroke treatment was reactive, not preventative. Blood transfusions were found to be highly effective in decreasing the risk of recurrent strokes. Patients who had already had a stroke were put on transfusion so as to prevent subsequent strokes [10-12]. However, it would be best to prevent the first stroke, especially if the high-risk patients were known. By not preventing the initial stroke, the chance of death from a cerebral accident increases, as well as the possibility of the patient suffering permanent neurologic damage. Unfortunately, putting all of these high-risk patients on transfusion is not only risky and expensive, but also unnecessary. Not all children who are at high-risk for stroke will develop one [2]. A method was needed to determine which of the high-risk patients were most likely to develop a cerebral infarction so that only those patients could be transfused [10, 13]. This would prevent transfusing patients who would not have had a stroke anyway, but are a part of the high-risk group because of their age and genotype. At the same time, it is important to identify those patients at high-risk for stroke so that they can begin red blood cell transfusion [9]. Cerebral angiography was previously used to study blood vessels involved in strokes, however this method is invasive and risky for patients. Measuring the intracranial arterial blood flow velocity needed a non-invasive method in order to screen for candidates for transfusion [8]. Transcranial Doppler ultrasonography (TCD) is a non-invasive tool that allows for widespread screening to identify sickle cell disease patients who are at risk for stroke [9]. It is the optimal tool for screening for stroke [8].

TCD is used to measure the blood flow velocity in the intracranial arteries of the circle of Willis, specifically the internal carotid artery (ICA) and the middle cerebral artery (MCA). Elevated velocity levels indicate arterial stenosis and cerebrovascular disease, both of which have an increased risk for stroke [2, 5]. Young age, lower baseline hemoglobin level, increased white blood cell count and an increased reticulocyte count are all correlated with higher cerebral blood flow velocities [2, 14]. One problem that is encountered while testing is getting the youngest patients, those under the age of 5 years, to sit still long enough for the exam. Using anesthesia or letting them sleep is not an option since it will create inaccurate TCD results. Cerebral blood flow velocity naturally increases during sleep. [2]. Very high cerebral blood velocities are associated with cerebrovascular disease and are highly predictive of stroke [2, 8]. MCA or ICA velocities greater than 200 cm/sec are considered an abnormal result and show strong support for the use of transfusion in the prevention of the initial stroke. Sickle cell disease patients with an MCA or ICA velocity greater than 200 cm/sec have a 40% chance of a stroke in a 40 month period. Sickle cell disease patients who have an MCA or ICA velocity from 170 to 199 cm/sec have approximately a 7% chance of stroke in a 40 month period and are considered conditional results. MCA or ICA velocities less than 170 cm/sec are normal results and have a 2% chance of stroke in a 40 month period [5]. The optimal frequency for TCD screening is unknown, but most studies stated that they screened annually per their institutional standard of care. These studies did state that if a TCD result was normal, then the screening could be performed every 12-15 months [4]. High-risk patients may benefit from more frequent screenings [2]. Patients should begin the screening at 2 years of age, then annually thereafter if the results come back normal. If the results are conditional, a repeat TCD should be administered in 4 months. Abnormal results should be retested within 2-4 weeks [2, 9][20]. It is

unknown how long transfusions should continue as a preventative measure of stroke in children with sickle cell disease [4]. Unfortunately, some children with an MCA velocity below 170 cm/sec still can have a stroke. There is a small group of patients who are at risk for stroke even with normal, low, or unmeasurable velocities. The velocities may seem to be low because stenosis might be high enough to reach critical level or might disappear because of total vessel closure [5]. Stenosis of blood vessels occurs when the cerebral blood velocity is several times the normal velocity [8].

The Stroke Prevention Trail, known as the STOP study, was aimed at decreasing the occurrence of initial strokes in children with sickle cell disease. The researchers hypothesized that lowering the total Hemoglobin S concentration would reduce the risk of stroke by 70%, as compared to the standard of care at the time. The researchers tested the efficacy of administering transfusions to patients with abnormal TCD results as a means to decrease the risk of stroke. Before this study, patients were treated with transfusions in order to prevent subsequent strokes, meaning they only got preventative treatment once they had a stroke. The STOP Study used TCD screening to identify the patients with dangerously high MCA velocities so that they could begin transfusions to prevent a stroke. For the study, the patients with abnormal TCD results were put into two groups. The first group was observed, as was the standard of care at the time, for clinical signs of a cerebral infarction such as high white blood cell count, low hemoglobin levels, and recent acute chest syndrome episodes. The other group was put on transfusions, with the goal being to decrease the concentration of Hemoglobin S to less than 30% of the total hemoglobin concentration. After 10 months of the study, there were 11 total strokes: 10 cerebral infarcts in the standard care group and 1 in the transfusion group. The risk for stroke was 92% lower in the transfusion group. The success of transfusion was so evident that the trial was

stopped early so that transfusions could be offered to all children with high blood flow velocities [2, 4, 8, 9].

There is evidence of a familial predisposition to cerebral vasculopathy [2]. Sibling studies have identified the need to closely monitor the siblings of a patient who has positive TCD results even if that sibling had a negative TCD result. Research shows there is an increased risk of stroke in these patients. The study showed that within one year, four children with prior negative TCD results and who had a sibling with a positive TCD results all developed a positive TCD result on their next exam. Also, patients with abnormal TCD results indicated a greatly increased risk of abnormal TCD results in their siblings. Children who had a sibling with a positive TCD result had significantly higher TCD velocities than children without a sibling with sickle cell disease matched for age, sex, genotype, and hemoglobin level. Conversely, siblings with a negative TCD result had siblings who also had negative TCD results [2]. Age is not a factor within these families – neither the younger or older sibling is more likely to develop a stroke first.

2.4 MANAGEMENT

The successful management of sickle cell disease is due to the vigilant effort of parents and healthcare workers. There are very serious complications associated with sickle cell disease that can lead to death if not treated properly and in a timely fashion. Public health programs have greatly decreased the mortality rate among children with sickle cell disease. As a result, death from pneumococcal infection is very rare in the United States [20]. Comprehensive care

programs have been established in many developed countries, thus leading to a longer and healthier life for people with sickle cell disease.

Parental education is an ongoing process. It should occur at each clinic visit, with the information being updated as the child ages and the clinical needs change. Parents should be educated about what symptoms to look for when they care for their child at home. A spleen stick is used to measure the spleen size and is taught to parents in the first few clinic visits. An enlarged spleen is an indicator of sepsis. Parents should look for changes in skin tone and color, like jaundice. Also, fevers should be closely monitored; a child with a fever $\geq$101ºF should be seen in the emergency room [20].

It is extremely important to educate parents about the level of medical care needed for sickle cell patients. Proper education about sickle cell disease leads to a better understanding of the care needed and can help healthcare professionals provide the best care possible. The sickle cell care team members work together to provide comprehensive care for sickle cell patients. The team is often made up of doctors (hematologists), nurses, genetic counselors, social workers, and health educators. This team receives the results of the newborn screenings and initiates contact with the family to begin comprehensive care [20]. It is important to notify the parents immediately if there are positive newborn screening results. Then education about sickle cell disease can begin. Parents need to be made aware of their child's health care needs, including the immediate initiation of prophylactic penicillin [26, 27, 28]. It is important for parents to be taught to understand laboratory results, physical findings, and how to navigate through the health care system in case they need to go to a medical facility other than their primary one, especially in an emergency situation [20]. Patients of sickle cell disease must adhere to routine comprehensive care, but it is also just as important to continue with general health maintenance

with a primary care physician. Patients should attend comprehensive clinic every 2-3 months in the first 2 years of life. After the age of 2 years, patients should attend clinic every 6 months, or as needed as discussed with the physician [20].

Penicillin prophylaxis for the prevention of pneumococcal infection is the most important intervention in the comprehensive management of sickle cell disease. The success of the Penicillin Prophylaxis Studies of the 1980s justifies newborn screening to identify these children [15]. As a part of today's standard care practices, penicillin prophylaxis, especially in children under the age of 5 years, and pneumococcal vaccine are administered to children to prevent death from pneumococcal infection [2]. Beginning shortly after birth, penicillin is given twice daily, 125 mg twice daily orally for children <3 years old, and 250 mg twice daily orally for children >3 years old [15]. Pill form is an advantage because they are viable for years, whereas liquid forms must be replaced every 2 weeks. Using the pill form can be lucrative because a 12 month prescription can be given to patients. Since the liquid form requires a lot of maintenance, it may not be the best option for someone of limited resources. Pneumococcal vaccinations are also administered [20]. Both have greatly reduced the risk of mortality for children with sickle cell disease.

A study conducted to evaluate the efficacy of penicillin prophylaxis for children over the age of 5 years found no clinical benefit when compared to a control group on placebo. Thus penicillin prophylaxis is not indicated after 5 years of age [16]. However, it is important to note that if the splenic function is absent, the patients are very prone to infection and may still want to continue penicillin [20].

One group studied the efficacy of including MRIs in image screenings like TCDs to make the results more sensitive to predicting strokes. Patients with normal TCD velocities who later

had a stroke may have had an abnormality that was detectable via an magnetic resonance image (MRI) but not TCD [8]. MRI screening has found that 34% of homozygous sickle cell disease patients did in fact have a silent cerebral infarct, even though they were not clinically diagnosed with having had a neurologic event [5]. Lesions from advanced arterial disease with occlusion, stenosis, or previous silent cerebral infarct can make TCD results uninterpretable. MRI is able to detect previous lesions from silent cerebral infarcts that may have caused damage that is either undetectable via TCD screenings, or caused the TCD results to be inaccurate. This would help those who have a normal TCD result but still have a stroke, or have had a silent stroke between readings. Patients who had abnormal MRI results were also found to have significantly higher cerebral blood velocities via TCD testing. It could not be determined if abnormal MRI findings are independent enough to use as the sole predictor of stroke. The study showed that MRI did not find high velocity results that were different than TCD results. MRI may be good as a supplemental tool, but it does not appear to be a good independent predictive tool for stroke. MRI might be best for children whose risk for stroke cannot be determined via TCD screening. It can serve as a back-up for interpreting the imaging results in cases where the TCD indicates a smaller risk of stroke, for example a conditional result, or when the results are inconclusive. MRI may also be best suited for chronically transfused patients, especially when looking for neurologic damage like a silent cerebral accident [8].

It is very important for patients to adhere to the recommended health care guidelines for sickle cell disease. Regular comprehensive clinic visits, along with TCD screenings, can really decrease the morbidity and mortality of the disease. Helping the patients to follow these protocols is just as important as the protocols themselves.

3.0 METHODOLOGY

The Comprehensive Sickle Cell Care Program at Children's Hospital takes care of roughly 230 patients with sickle cell disease from birth to age 21 years. CHP provides specialized hemoglobinopathy care to the patients. The patients' medical and demographic information is kept in a paper chart as well as recorded in an electronic comprehensive database (Microsoft Access, Microsoft Corporation, Redmond, WA). This database allowed for easy and expedient access to the patients' medical information, which was especially helpful when they had a question. The database was also able to generate queries that notified the sickle cell care team as to who was due for a clinic visit, who needed a TCD, and who needed to be called for follow-up.

A semi-structured script was designed for the telephone follow-up survey which included a series of questions relating to the patient's well-being and health-related behaviors, as well as open-ended questions which enabled families to ask questions and request services. The script was reviewed and evaluated by the physicians, nurse practitioners, and genetic counselors of the sickle cell program for content, relevance, and cultural sensitivity. This study was approved by the Institutional Review Board of the Children's Hospital of Pittsburgh and the University of Pittsburgh in 2002.

All telephone surveys were administered by a graduate student researcher in genetics. This eliminated time being taken away from physicians and nurses. The caller was trained in sickle cell disease through didactic education sessions and sickle cell team meetings. There was no prior or ongoing direct contact with the patients. The patients were unaware they were being called for the surveys.

To begin the telephone study, there was an initial survey that evaluated the patients' home care routines at great length. All active patients were attempted to be contacted for this survey. Subsequent phone calls were made for follow-up surveys every three months after the last contact between the patient and the clinic. The follow-up survey consisted of approximately eight questions. The call-back list was based on a list of patients that was generated using a database query. The criteria for this list included patients who had not been seen in the clinic or talked to on the phone for at least three months. The To-Call-List and Call-Back-Lists were queries generated upon the caller's request and updated daily in the CHP database. All patients for whom we had good phone numbers were called up to five times in an attempt to reach them. It was ideal to speak with the patients themselves so as to promote self-responsibility and positive health behaviors that would last a lifetime. However, we did speak to the primary caregiver if the patient was under 16 years old. If no contact was made after five attempts, their survey was marked as "No Response to Multiple Calls" and they would appear on the To-Call-List three months later. Patients who had incorrect or disconnected phone numbers were pursued along with the help of the sickle cell disease social worker to find a good number.

For all calls, the time of the call, the call response, and the phone number that was used were noted in each survey. The name of the person talked to was recorded as well as their relation to the patient. All phone numbers (cell, home, work, additional family members) were checked for accuracy and updated during the call. Phone survey responses were recorded in the CHP database, with the caller typing the responses as the patient or primary caregiver spoke. Database queries indicated each patient's last clinic visit and TCD exam. The caller was thus able to provide the family with reminders regarding clinic visits and TCD exams. When a clinic

visit was needed to be scheduled they were transferred to a scheduler's phone number. Patients were called throughout the weekday, from 10 am until 8 pm.

A database query was designed to perform a cross-sectional survey on a given date to determine the time elapsed since the last clinic visit for all of the active patients. This calculation was performed prior to the initiation of the telephone survey and repeated one year later. Patients were stratified according to the time since the last clinic visit on the date of the survey.

A list of patients who had not received comprehensive care for prolonged periods as indicated by the lack of a clinic visit for two years or longer was generated. These patients were also contacted over the telephone, with an extra emphasis on finding them if they had no contact numbers. When it was determined that a family had not been adhering to comprehensive clinic visits for prolonged periods of time and was unable to be reached by telephone, the sickle cell social worker implemented a protocol of sending certified letters to the families through case management cells of third party payers, public welfare departments and when appropriate, contacting children and youth services.

The database was also used to generate lists of patients according to hemoglobin type, birthdates, TCD exam eligibility, TCD exam dates and results, clinic dates, and phone survey dates with call response. From these lists, it was determined who needed to be called, who was due in the clinic, and which patients were due for a TCD.

4.0 RESULTS

Overall, the phone calls had a positive effect on the health care of sickle cell patients. The feasibility and effectiveness of the phone calls were evaluated at periodic intervals.

All patients were attempted to be called for the initial survey. However, not all patients were eligible to be called for the follow-up surveys. Figure 1 shows that approximately 80% of the patient population was attempted to be contacted for follow-up surveys.

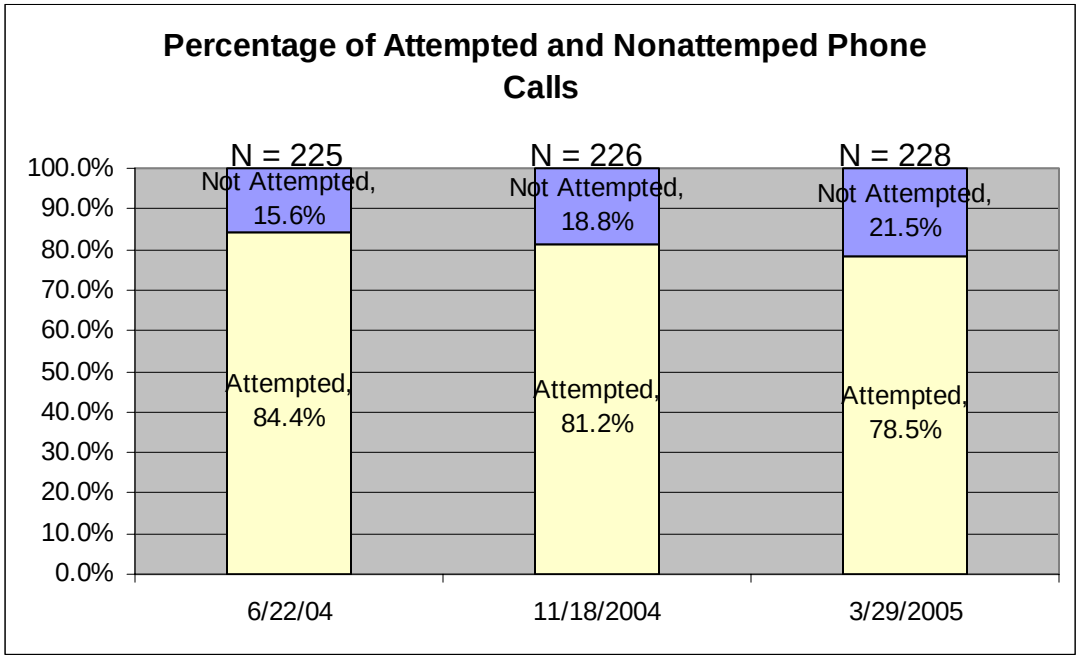

Figure 1. Summary of Call Attempts to the Patient Population

There are several reasons patients were not attempted to be contacted for follow-up (Figures 2-3).

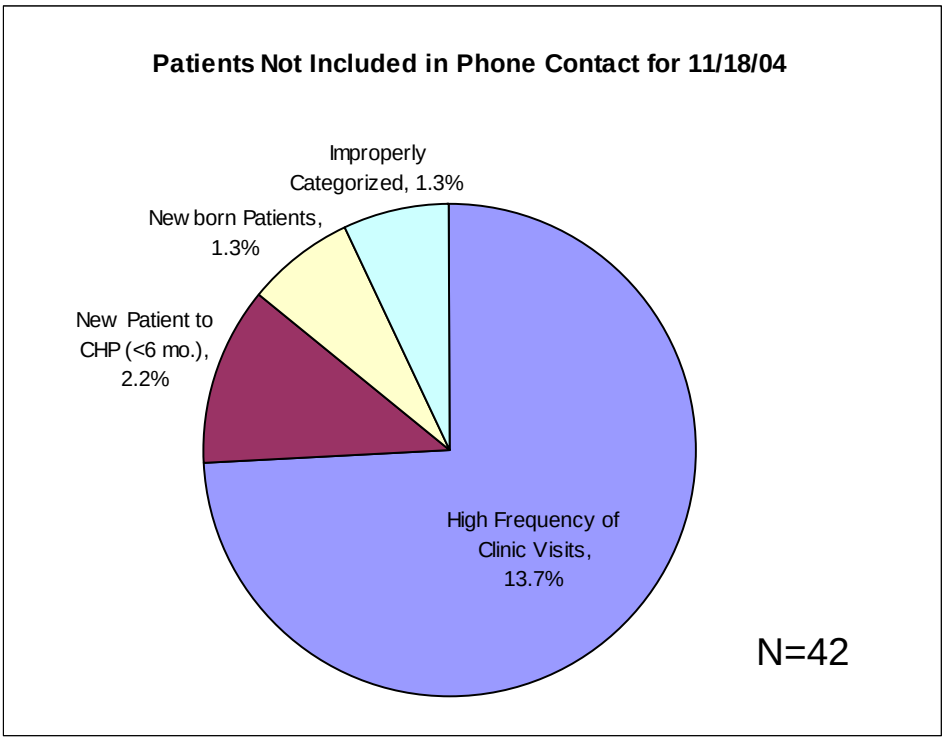

Figure 2. Summary of Reasons for Not Contacting Patients within Population

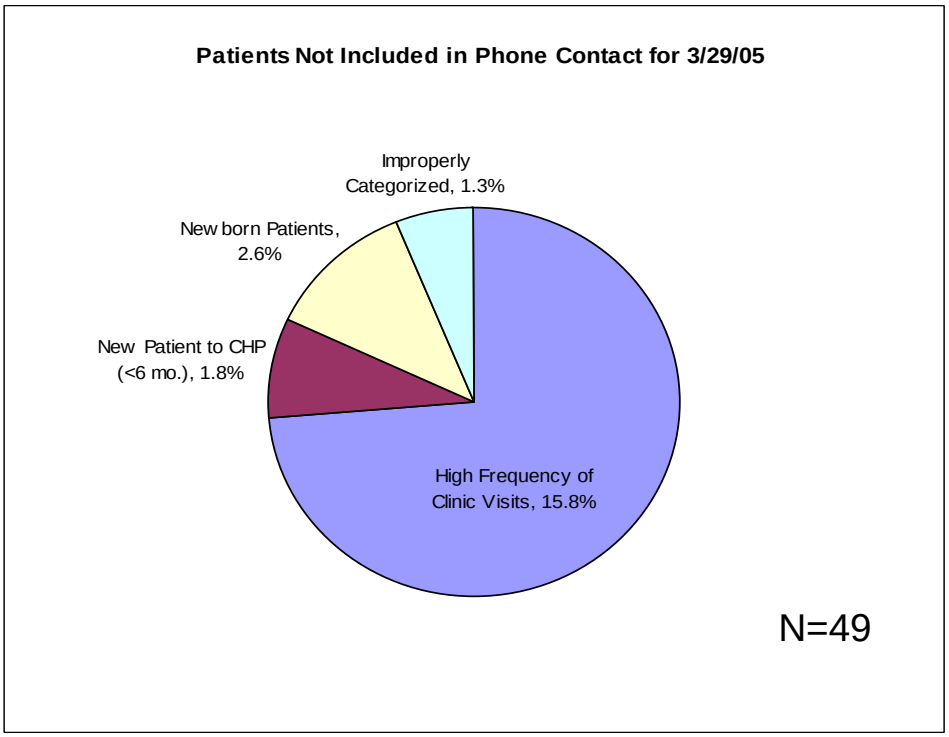

Figure 3 Summary of Reasons for Not Contacting Patients within Population

About 15% of the patient population attends clinic more often than every three months, so they do not qualify for a follow-up call. Approximately 2% of the patients are new to the clinic and are not established in the database until they are seen in the clinic; consequently, they do not qualify for a follow-up call. An additional 2% are newborns that have not been established in the database for the same reason as above. A few patients (1.3%) were improperly categorized in the database and were unable to be pulled on the To-Call List.

The number of patients able to be reached increased over time as the calls were made (Figure 4).

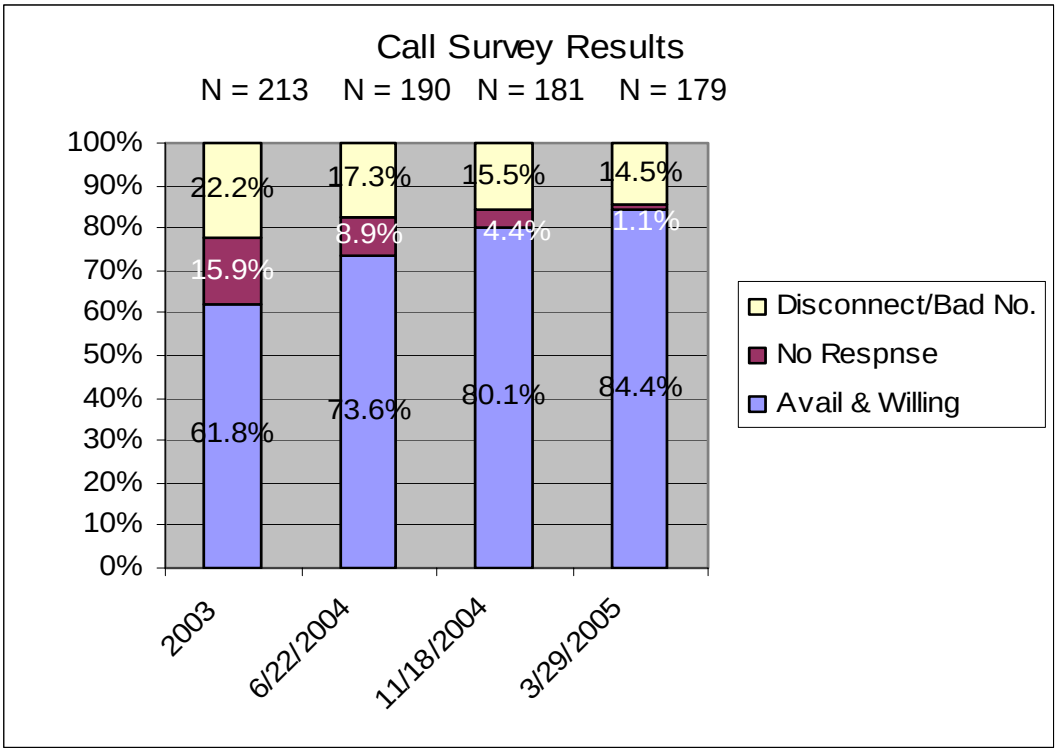

Figure 4. Results of Phone Call Attempts to Patient Population

84.4% of the patients contacted were available and willing to talk. No patient that was reached was unwilling to talk. There was a decrease in the number of patients who had no numbers to call due to numbers being disconnected or incorrect in the database. The number of patients who did not respond to multiple call attempts also decreased.

The following services were offered and requested during the phone calls. (Figures 5-7).

Prescription refills (penicillin, folic acid, pain medications)

Letters about sickle cell disease sent to schools, jobs, or insurance companies

Psychosocial support

Questions answered about sickle cell disease

Assistance with making a comprehensive clinic appointment

Figures 5-7 show a comparison of the frequency of these requests.

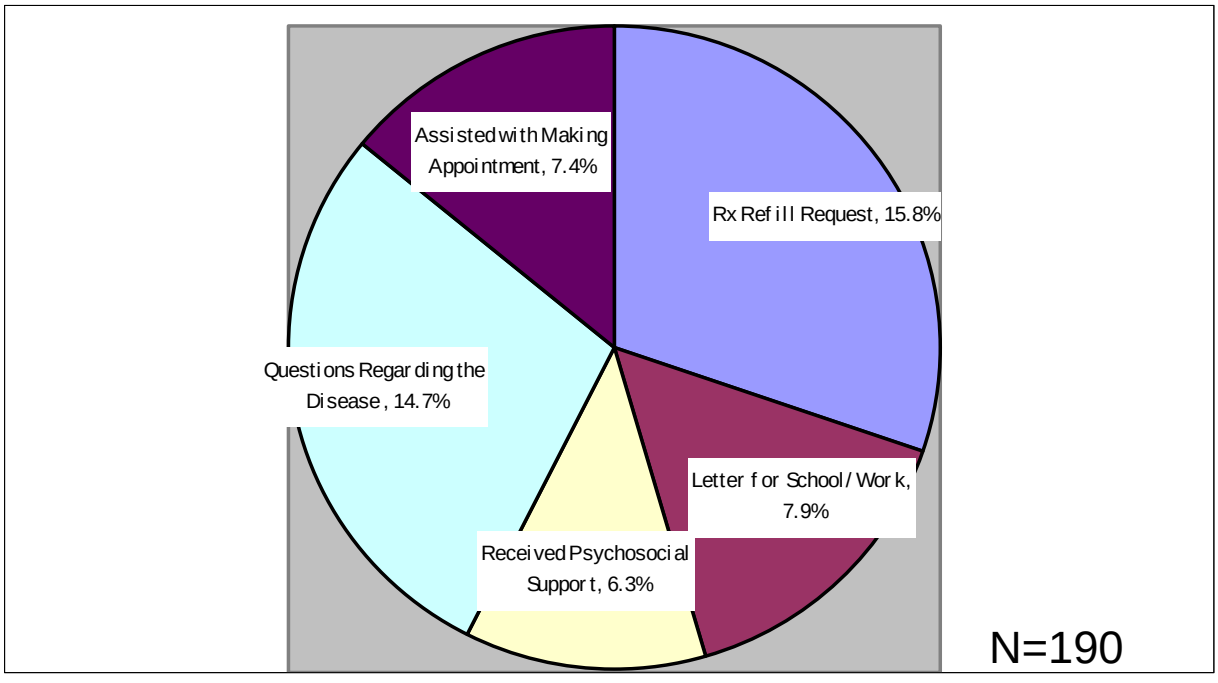

Figure 5. Survey Results from Patient Phone Calls as of 6/22/2004

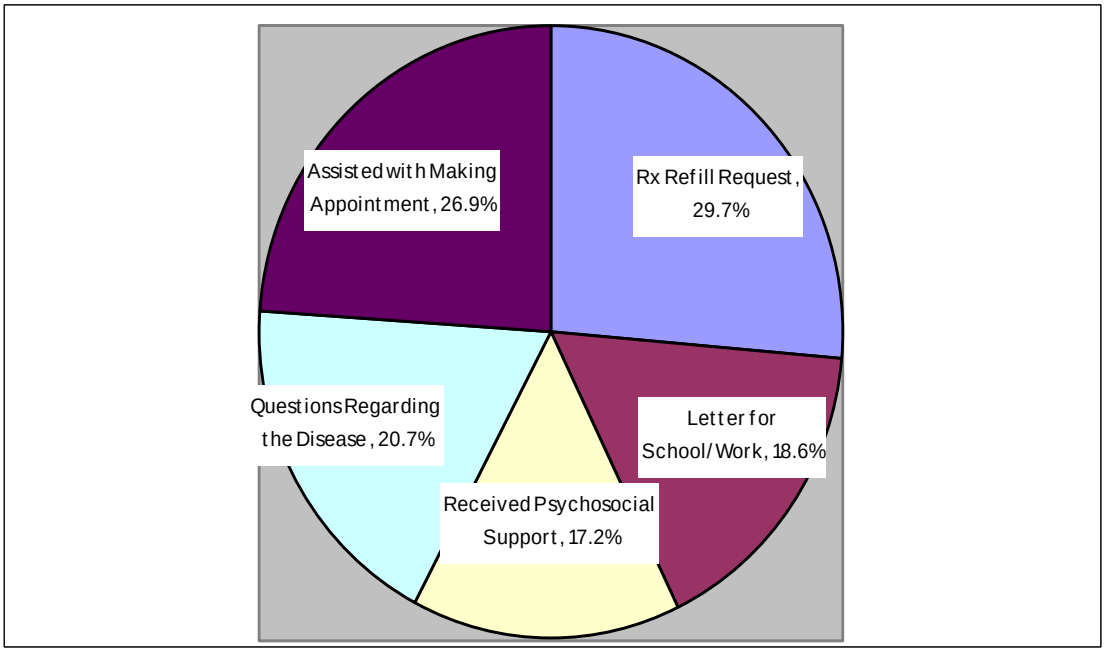

Figure 6. Survey Results from Patient Phone Calls as of 11/18/04

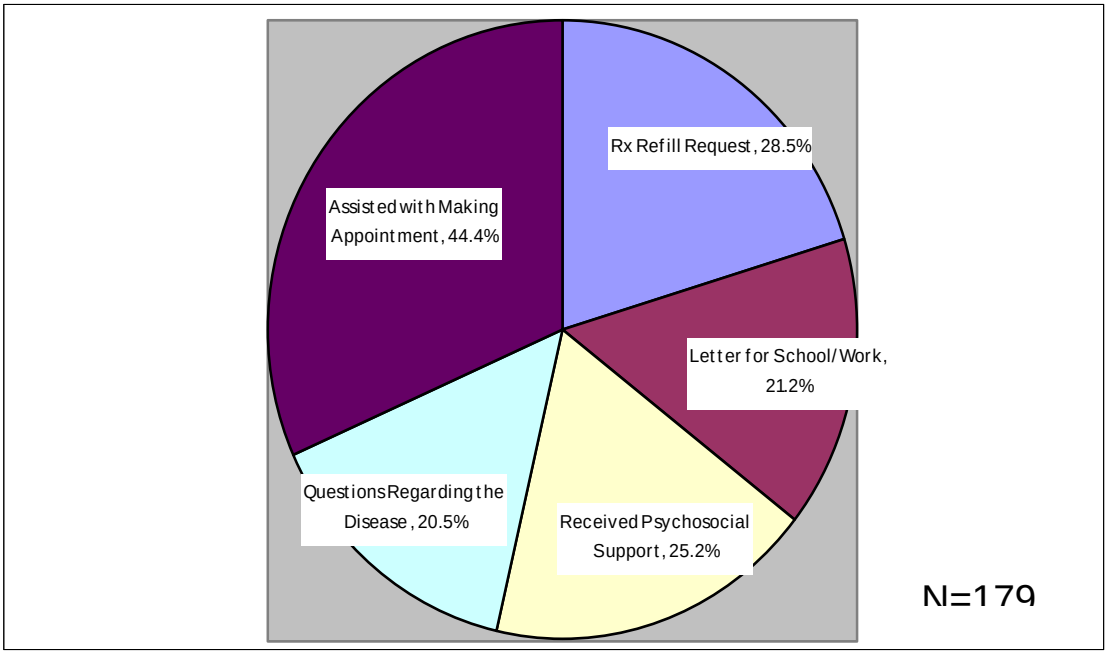

Figure 7. Survey Results from Patient Phone Calls as of 3/29/05

There was a significant increase in the requests for services over time during the phone calls (Figure 8). Of note, the prescription refill requests nearly doubled (15.8% to 29.7%). The number of patients who were assisted with making an appointment at the clinic increased dramatically, from 7.4% to 44.4%.

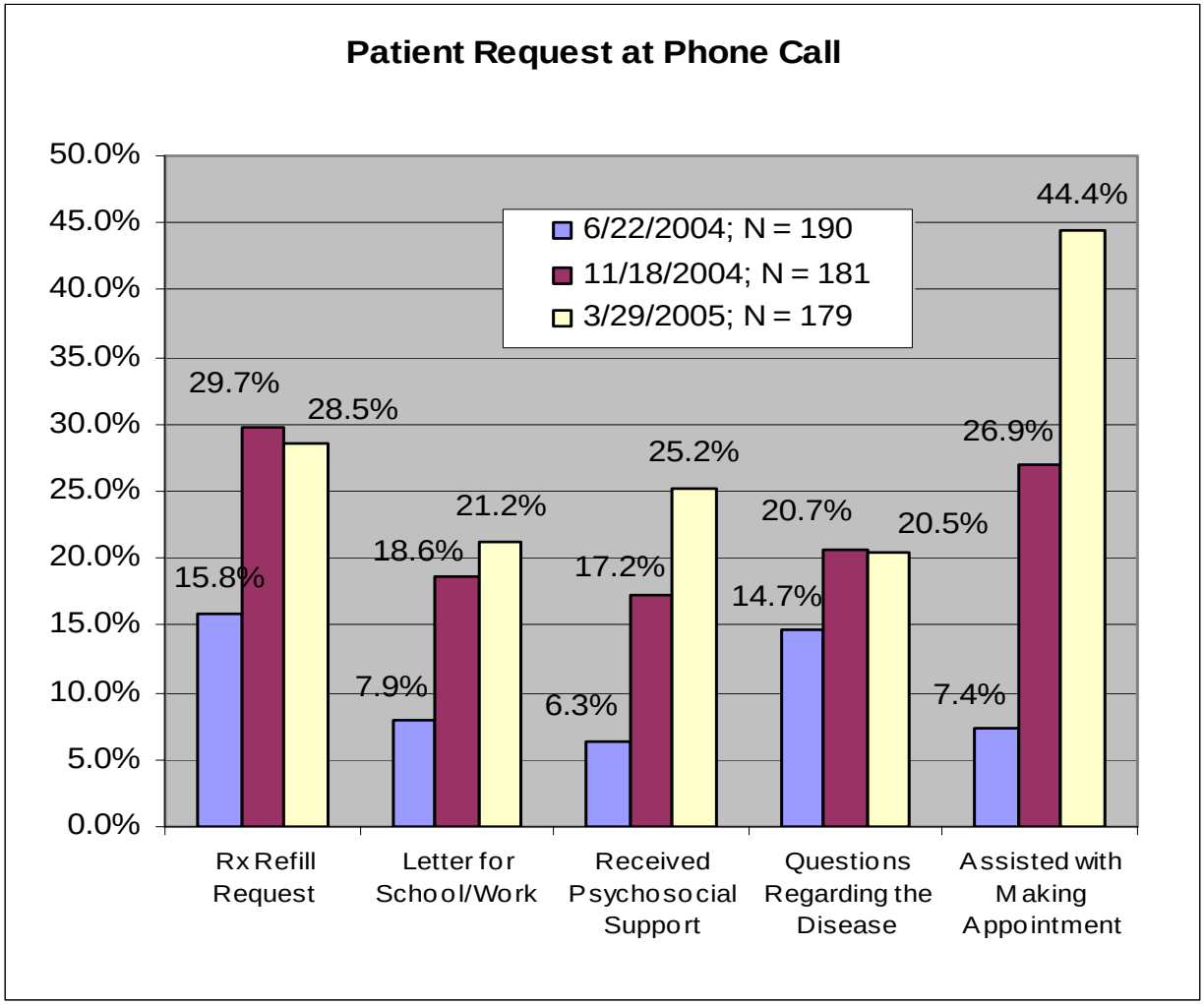

Figure 8. Comparison of Phone Call Item Requests

The phone calls had a positive effect on the interval between clinic visits. They decreased the interval between the clinic visits. The mean interval between visits was reduced by 25 days, from 160 to 135 days. The maximum interval between visits was reduced by 158 days, from 753 to 591 days (Figures 9-10).

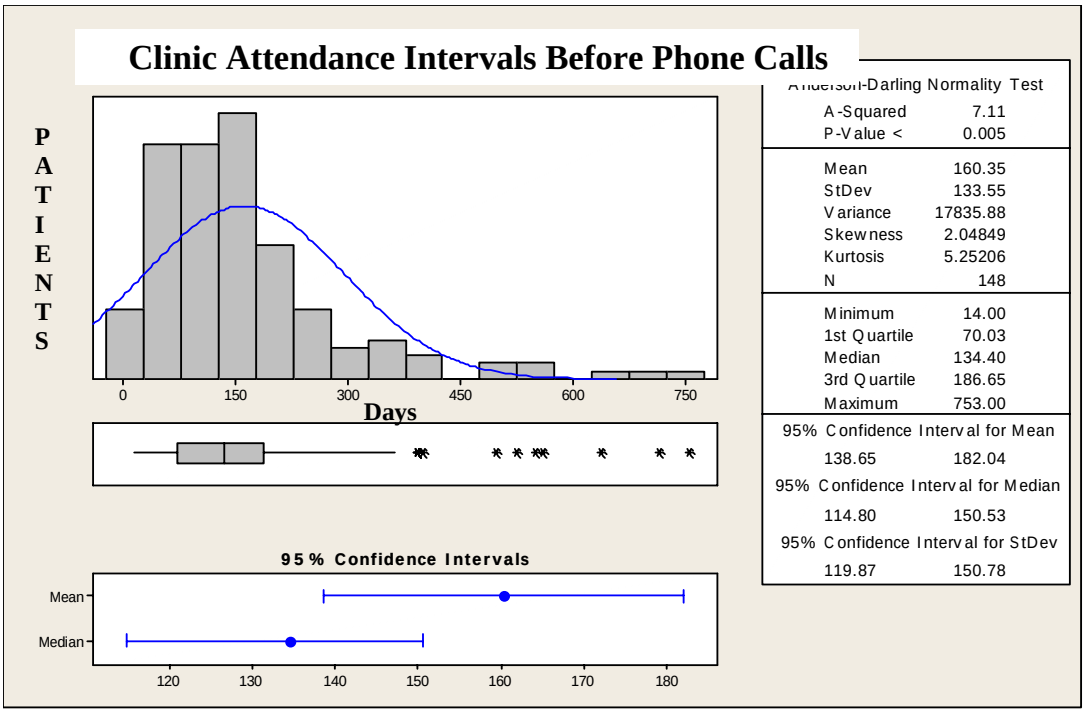

Figure 9. Average Time in Days Between Clinical Visits Before Phone Call Initiation

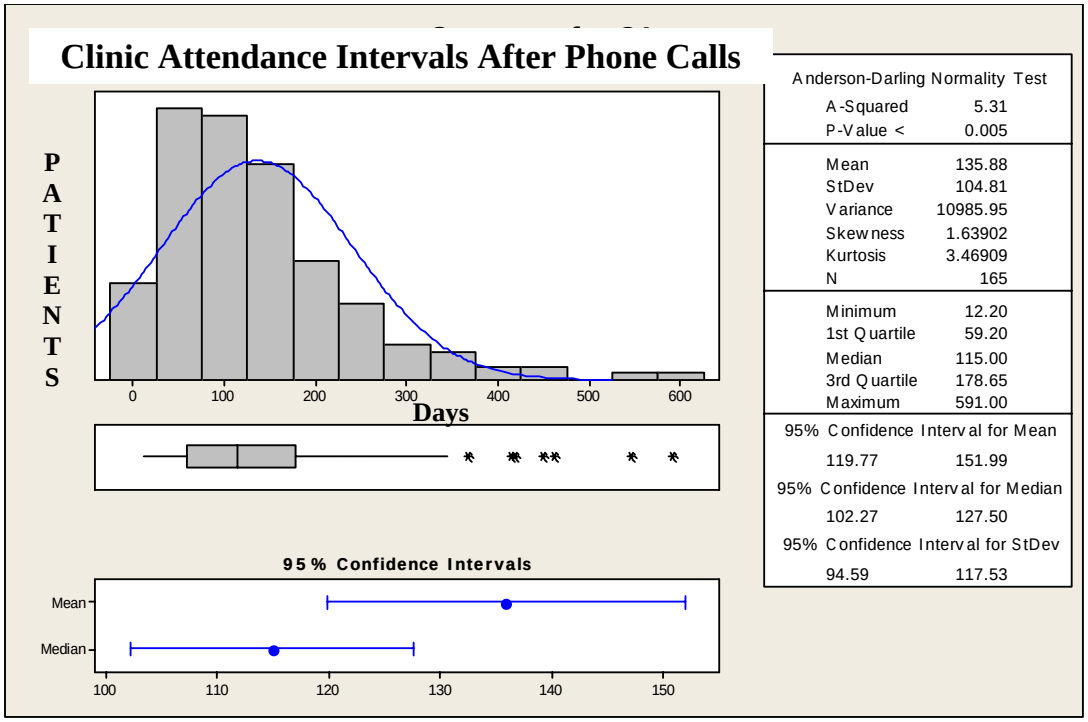

Figure 10. Average Time in Days Between Clinical Visits After Phone Call Initiation

There is a noticeable increase in the number of patients who are adhering to regular comprehensive clinic visits. 64% of the population has been seen in the clinic in the last 6 months (Figure 11). The increase in this number can be attributed to the increase in the number of patients requesting help with scheduling an appointment.

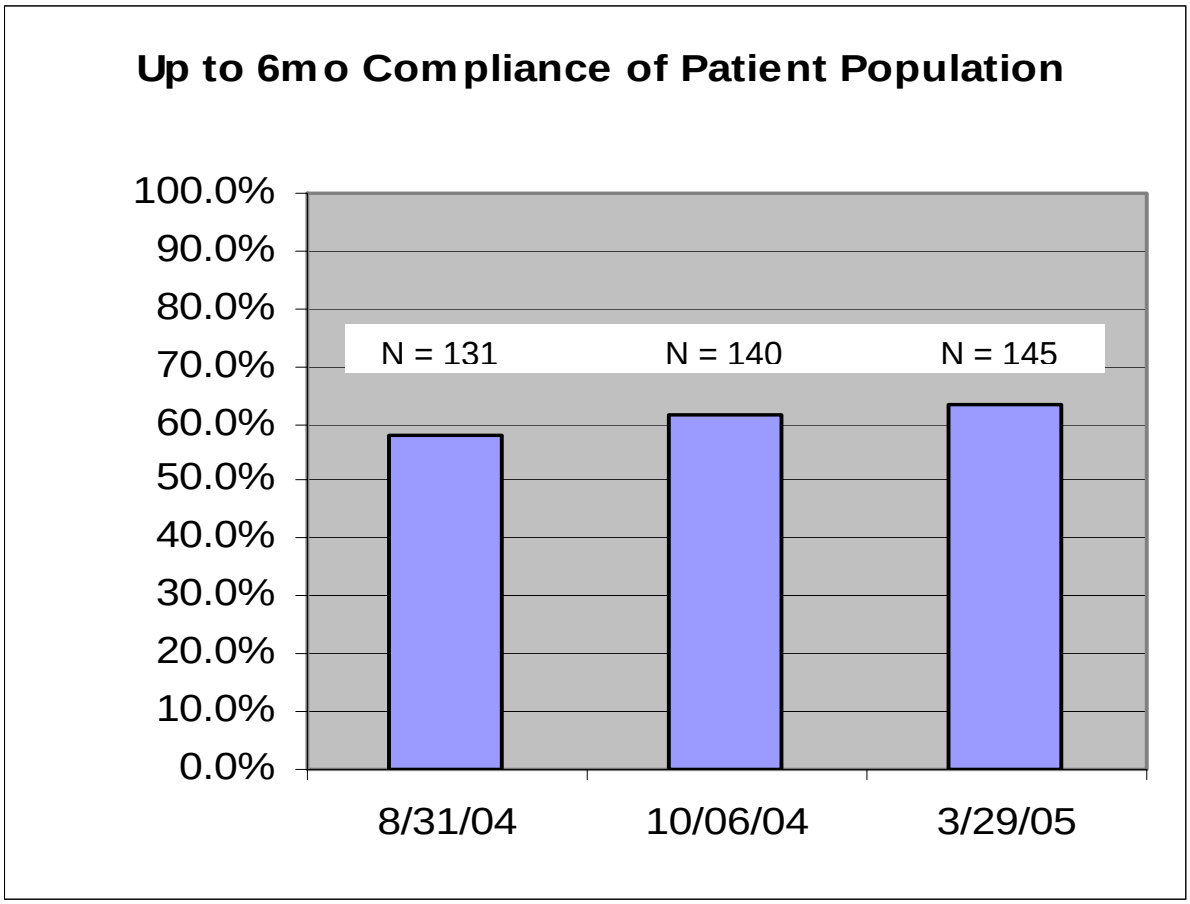

Figure 11. Percentage of Compliant Patients Over the Last 6 months

Figure 12 demonstrates the proportion of patients who have not been seen in the clinic for 6-12 months.

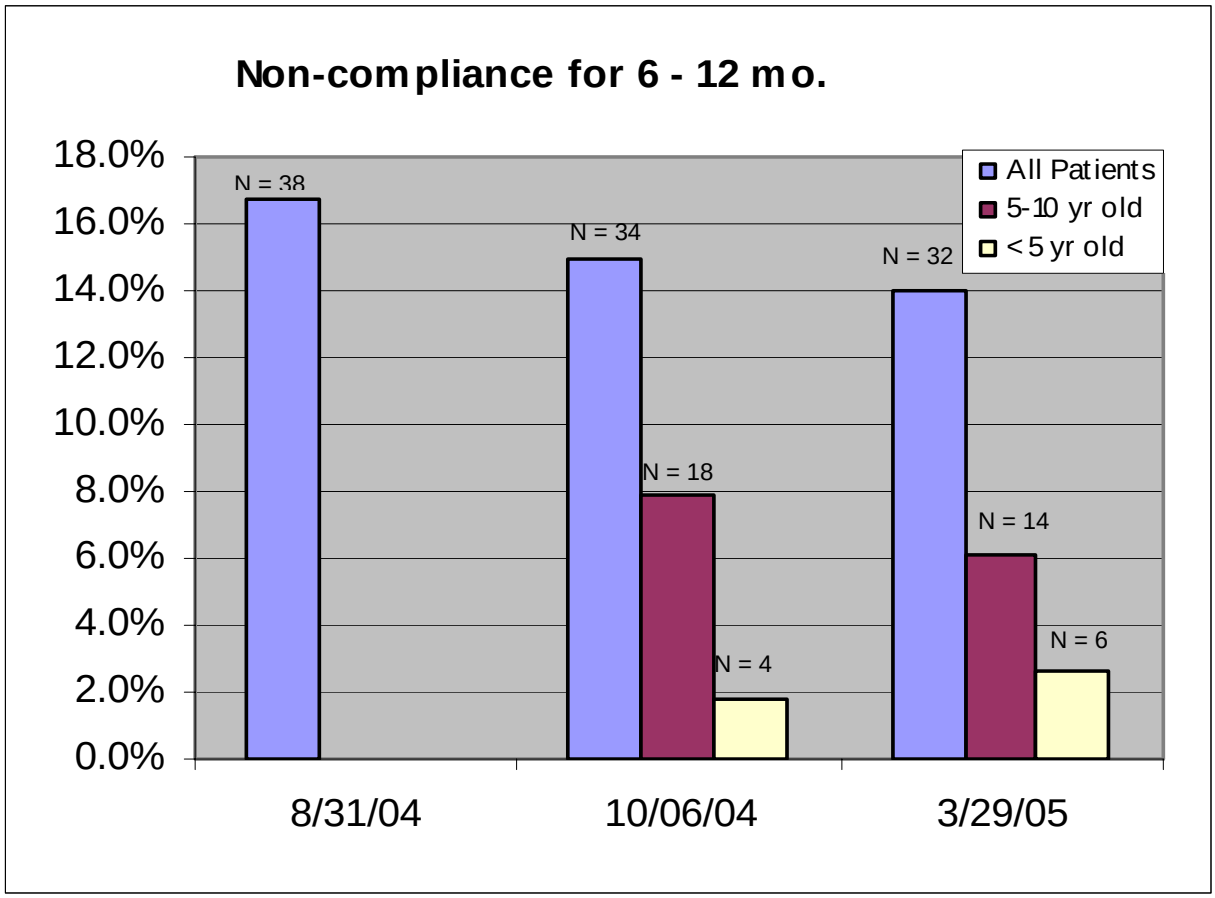

Figure 12. Percentage of patients who have not been to the clinic for 6 – 12 months
Data for 8/31/04 was not stratified by age at that time.

In August 2004, 16.7% of the population had not been seen for 6-12 months. In October 2004, that statistic was broken down to determine the non-compliance among the younger patients, those more susceptible to sepsis. There was a decrease in the number of non-compliant patients between the ages of 5-10 years old. The number of patients under 5 years old who were not compliant with comprehensive clinic remains low at approximately 1%. Overall, there was a steady decline in the number of patients in this category.

There is a significant decline in the number of patients who have not been seen for 12-24 months (Figure 13).

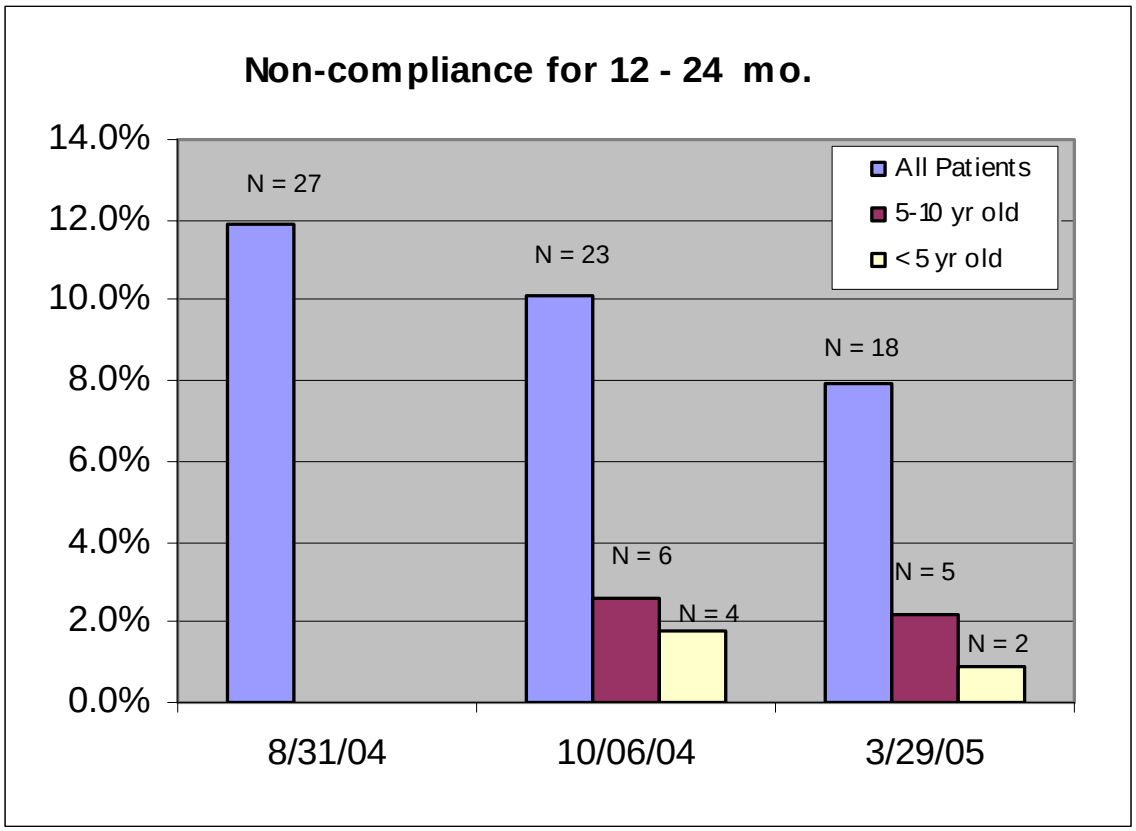

Figure 13. Percentage of patients who have not been to the clinic for 12 - 24 months Data for 8/31/04 was not stratified by age at that time.

Of importance, there are less than 3% of the patients between 5-10 years old who have not been seen at the clinic for 12-24 months, and only 2% of for those patients less than 5 years old are not compliant to comprehensive care.

One of the most significant accomplishments of the phone calls has been to locate patients who have not been seen in the clinic for 2 years or more. At the initial survey, 25% of the population that had not been seen at clinic for over 2 years. That has decreased significantly to 10%, p=0.0019 (Figure 14).

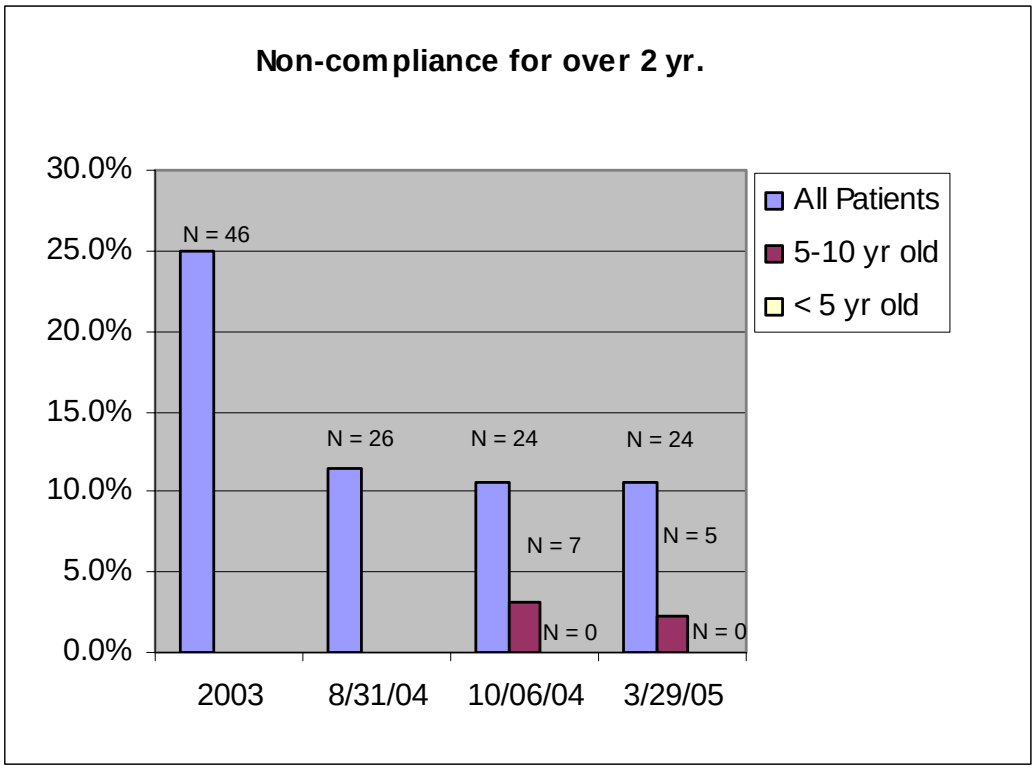

Figure 14. Percentage of patients that have not been to the clinic in over 2 years
Data for 2003 and 8/31/04 was not stratified at that time.
There was 100% compliance among all patients <5 years old for 10/06/04 and 3/29/05.

Also of important note, all patients under the age of 5 years have been seen at the clinic in the last 18 months and are on prophylactic penicillin. This age group is most at risk for stroke and pneumococcal sepsis.

Adherence to yearly TCD screening has also significantly increased. There are 75 patients who meet the criteria for TCD screening. At the time of the initial survey, 34% of the patient population was compliant with yearly TCD exams. After 18 months of calling, 49% of the population was compliant with yearly TCD exams, p=0.0501 (Figure 15).

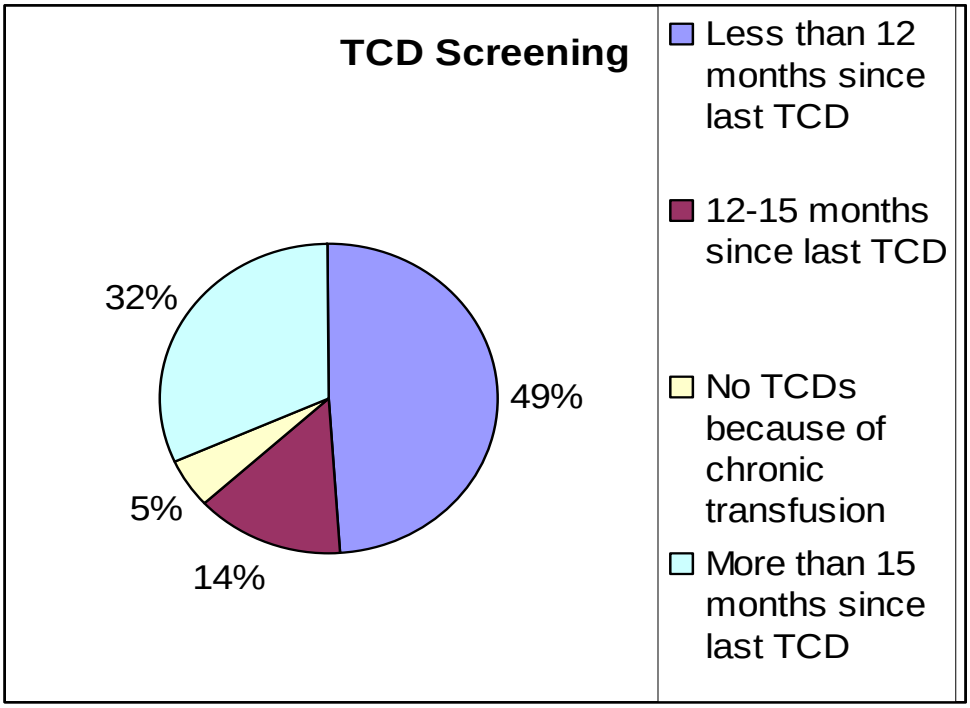

Figure 15. The number of Patients adhering to recommended annual TCD screenings N=75

Another 14% were 12-15 months from their last TCD exam. This makes 63% of the population compliant to annual TCD exams.

In addition to the objective evidence of acceptability of phone contact, 17.2% of those talked to made subjective comments indicating their positive views of being contacted. No one who was talked to indicated any negative views or reservations about speaking to a member of the sickle cell care whom they had not met.

5.0 DISCUSSION

A modified telephone based outreach program was implemented to further improve adherence to comprehensive care. Telephone based health education interventions have used a wide variety of individuals to provide health education [17]. Nurses have been used in these outreach programs to call the patients. This has been relatively easy to implement and maintain in comprehensive clinics. The downside of using nurses to make the phone calls is the cost – nurses already have a full work load with clinical duties that could limit the amount of time given to calling patients. In this project, a trained graduate student, using a structured script, guided by a computerized clinical database, calling patients at times convenient to them, was able to reach a substantial proportion of families. This allowed for the program to be implemented at a substantially lower cost and allowed nurses to focus on other clinical duties and serve as a backup to the student caller. The phone calls were well-received by the patients and their families and resulted in the delivery of education, support, and improvement of adherence to comprehensive care in a relatively short period of time, 18-months. The fact that the calls were well-received even though they were being made by a person unfamiliar to the family is suggestive of the importance of training, the use of a structured script as well as the readily available backup from medical personnel. In fact, 17.2% of the patients available to talk made unsolicited subjective comments expressing their gratefulness for being called and checked-up on.

Other studies that have used phone calls as a part of their patients' medical care have reported that they have been well-received and useful for both the medical team and the patient. The calls were usually shorter in duration than a clinic visit, and more convenient for the patients

since there was no travel time involved. Phone calls can be a good setting for the Sickle Cell Comprehensive Care Team to answer questions about medications and homecare that the patient does not need to be in the clinic to have answered [31] Another benefit to the phone calls is that a graduate student can perform these calls. Then nurses and physicians are not stretched even further in their duties and the patients are still able to get the additional care. Studies involving diabetes home care showed a greater compliance rate among the group that was followed-up routinely with phone calls versus just being given a packet to read on their own. Using phones in medical care is not a new method, however, the recent increase in its involvement in the health care process has shown to be beneficial in treating chronically ill patients. Patients liked the idea of incorporating telephone calls into their medical care. They have stated that it allows them more access to their physician, and that they are highly satisfied with this mode of communication. Telephone use in medical care is also beneficial for the physicians and healthcare team. It keeps costs low while increasing the frequency of patient contact. This can be especially helpful for patients who cannot easily come in to the clinic. In addition, one study found it decreased the number of emergency room admissions they had [31]

Contacting patients on the phone every three months also served as means of regular communication with families, informing them of upcoming events and updating demographic and medical information. Approximately 80% of the patient population was attempted to be contacted (Figure 1). Though fewer patients were attempted to be contacted for the follow-up survey as time went on, there are some plausible reasons for this decline. This was partially due to patients attending clinic more frequently, thus they did not show up on the To-Call-List as often. Another reason is the larger-than-normal influx of newborns and new patients. They were usually seen in the clinic and then were entered into the database. It would then be three months

until they were attempted to be contacted. It is also not unusual for newborns to attend clinic quite frequently in the first few months of life.

All active patients were attempted to be contacted for the initial survey in 2003. Since the next phone call was scheduled for three months after the last contact with the clinic, those patients who attend clinic several times a month for chronic transfusions or Hydroxyurea treatments would not appear on the To-Call-List for follow-up phone calls and consequently were not called. This occurred in approximately 15% of the active patients (Figures 2-3). It was concluded that contacting the patients who attended clinic so frequently would be redundant. They can be educated about sickle cell disease at each clinic visit and are not likely to go prolonged periods between clinic visits. The other patients not contacted were new to the clinic, either as newborns or because of relocation to Children's geographic area. It took some time to get these new patients into the database and established into the system.

With each round of calling, more patients were able to be reached (Figure 4). The number of patients for whom there were good phone numbers but were hard to reach (no response to multiple phone calls for 5 tries) showed a dramatic decrease from 15.9% to 1.1%. Also, the number of patients who had a bad phone number decreased. This was caused by two actions. First, each time a family was able to be reached, they were asked for all contact information, such as home, work, and cell numbers, as well as phone numbers for local family members in the event that none of the other numbers were functioning. This was very helpful since there are an increasing number of people who use cell phones as their main home number. In the event that they get a new phone or phone number, their extended family members usually had the new number to use to reach them. Their home address was also checked in each phone call. Second, the patients were called every three months from their last contact with the clinic.

It was hoped that the frequent calling would help to retain contact and good information for each patient. In the event a phone was disconnected, the patient's chart would be flagged so that the next time they came to clinic, a new phone number could be obtained. Being able to reach more patients with each round of calling, either by locating a good phone number for them or by reaching them, allowed for more follow-up of their home care routine to ensure that they were getting proper care.

Figures 5-7 show the services that were requested during the phone calls. In June 2004, the major services requested were prescription refills and answers for their questions about sickle cell disease. In November 2004, the services requested were spread a bit more evenly, but there is a noticeable increase in those assisted with making a comprehensive clinic appointment, from 7.4% to 26.9%. In March 2005, a large proportion of the patients requested help with scheduling an appointment (44.4%). The number of letters about sickle cell disease being sent to schools and employers also increased from 7.9% to 21.2%.

As the follow-up phone calls continued, more and more patients took advantage of the services that were being offered over the phone (Figure 8). There was a dramatic increase in the number of patients who requested prescription refills, 15.8% to 29.7%. The prescription refills were mostly for penicillin, but a few were for more folic acid or pain medication. It was interesting to have so many requests for penicillin since the prescription is filled at clinic visits and is good for a year. Some of the parents did mention that they got their penicillin from their primary care physician. The phone calls did allow for follow-up of penicillin compliance if the patients were getting the penicillin from their primary care physician. Adherence to penicillin prophylaxis has been used as a marker of adherence to comprehensive care [18, 19]. In our experience, information regarding penicillin prescription refills was difficult to obtain because of

concerns about HIPAA compliance. However clinic visits are directly associated with improved compliance with penicillin prophylaxis [18]. In each phone call, the patients and their families were asked if they need more penicillin. The response to this question can be a good barometer for their compliance with it.

An increasing number of patients (7.4% to 44.4%) were assisted with making an appointment for comprehensive care. Accordingly, the number of patients adhering to comprehensive care increased. It can be surmised that since the patients were given the number to the scheduling line or directly connected to it, they were more likely to make an appointment. Most patients did not have the scheduling number accessible, so they were thankful to be given the phone number again or to be transferred over to the scheduling line if it was still open. Psychosocial support was also offered during these phone calls. If patients needed help coping with the complications of sickle cell disease, or needed help understanding insurance coverage, they were connected with the sickle cell disease social worker. The number of patients and parents who asked questions about sickle cell disease also increased. The phone calls allowed the patients an additional venue to ask questions. Educating themselves is a very important part of sickle cell care. Asking for letters to be sent to the children's schools showed that the parents realized the importance of educating others who spend time around their children about sickle cell disease. The more knowledgeable patients can make themselves about the disease, the better care then can obtain for themselves.

Lack of clinic attendance for prolonged periods is easily determined by measuring the adherence to comprehensive care. Since Children's Hospital of Pittsburgh is the sole provider of care for sickle cell disease patients in the Western Pennsylvania region, it is unlikely that patients not attending comprehensive care clinic at Children's were receiving care elsewhere. Figures 9

and 10 show the effect of phone calls on the time interval between the clinic visits. Before the phone calls began, the largest interval between clinic visits was 753 days (Figure 9). After the phone calls began, the largest interval between clinic visits decreased to 591 days (Figure 10). The best-fit-curve got taller and narrower after the phone calls. This means more patients attended clinic more frequently than before the phone calls began. There was a marked improvement in clinic attendance among patients who had not been to comprehensive clinic for over 2 years. Figure 14 demonstrates the significant decrease in non-compliant patients over the last 18 months. At the time of the initial survey, 25% of the population that had not been seen at clinic for over 2 years. That has decreased significantly to 10%, p=0.0019. Also of important note, all patients under the age of 5 years have been seen at the clinic in the last 18 months and are on prophylactic penicillin. This age group is most at risk for stroke and pneumococcal sepsis. Patients in this category were attempted to be contacted in several ways to ensure that they were able to get proper sickle cell disease health care. Patients who could not be reached by telephone were either contacted by letter or, in a handful of cases, through public welfare agencies. This may have contributed to their return to clinic. Further study is in progress to determine the long long-term effect of this intervention on clinic attendance.

TCD screening is an integral part of stroke prevention in comprehensive care. At the start of the initial survey, 34% of the TCD-eligible population adhered to the recommended yearly TCD screenings. After 18 months of phone calls, that number increased to 49% compliance. Notice there are 14% who are just beyond the recommended time frame for TCD screenings, but still within a range that was deemed acceptable providing the previous results were normal. Limited periods of compliance did not negate the benefits of prior treatment, so

this is encouraging as far as reducing the overall risk of stroke [4]. Currently, there are patients who are past due for their next TCD who have scheduled an appointment to have one.

The first aim of the phone calls is to re-enforce the positive health messages and positive health behaviors that were discussed at the clinic visit. The phone calls allow the Sickle Cell Care Team to ensure the patients are doing well and following the recommended healthcare routine. This project was appealing because it was a way to enhance the health care that patients with sickle cell disease were receiving. It supplemented the care that they received while at a doctor's visit in that if they had questions after their appointment or before they could get another one, they still had someone to answer their questions. The caller was familiar with their case and with the system in which they were treated. Patients receive a great deal of information while at a doctor's visit. It can be overwhelming to remember or to even fully understand all of the information. Not everyone writes down or remembers questions they want to ask their doctor at their visits. Therefore the phone calls are an advantage because it allows patients the time and opportunity to ask their questions. Questions may come up at home while they are following the recommended routine. It may be a relief for the parents to be able to ask someone these questions at a later date. The patients do not know exactly when they would be called so they are not always prepared to ask questions. The phone calls are made mainly between 4pm and 8pm, a time when families are home for the evening. This increases the response rate, but it may distract from other family activities. The phone calls are needed to impress upon the patients and their families the importance of health messages. The calls stress the importance of taking penicillin everyday, and the consequences if this regime is not followed.

The second aim of the phone calls is to increase adherence to routine comprehensive care. Patients who regularly attend comprehensive care clinics are less likely to use emergency

services [1]. Regular attendance of comprehensive clinic also lends to the improvement of their condition [30]. During the phone call, patients were reminded to schedule an appointment in the clinic. Simply writing a self-reminder on a calendar may not be enough to make someone call a doctor's office for an appointment. If someone calls from that doctor's office and is willing to connect you directly at that moment to a clinic scheduler, then it is much more likely that an appointment will be scheduled. Also, the patients were reminded when they were due for an ultrasound for stroke risk assessment. This is an annual exam that is very important in stroke prevention, but it is easy to forget when the last exam occurred.

Phone calls allow for additional services to be provided to the patients and their parents. Questions about sickle cell disease, such as complications to expect as the child grew and about sickle cell disease inheritance patterns, were asked by the patients during the phone call. By answering these questions, the patients may realize that if they follow a few daily guidelines, this may result in a positive and productive life. It is important to realize that the disease does not define life. It was encouraging that parents wanted to know more about the disease and what they could do to help their child lead a healthy life. However, some parents did not seem as interested in their child's care as others. Healthcare that goes into treating sickle cell disease is preventative and this prevention mostly occurs at home. Parental involvement at home is vital for a positive outcome. Sepsis and strokes are complications that can develop without warning, and once they occur, they can create a lot of damage. The damage is often irreversible. This is why prevention in sickle cell disease is very crucial. The penicillin prevents sepsis and the ultrasounds help in preventing strokes. The parents who do not comply with the recommended comprehensive care say the reason is they do not see their child as being sick. Their child plays or studies or acts like a typical child. This is very dangerous for their child. The parents say that

if their child gets an infection or a fever, then they will take them to the hospital. By then it can be too late. This is why it is important to remind families that once sepsis sets in, it can be lethal in 3-4 hours, and that it may take that long to realize there is a problem and decide to go to the hospital to get treated. The same goes for fevers. Fevers are sometimes the only symptom for several serious complications like acute chest syndrome, splenic sequestration, a pain crisis, or pneumococcal sepsis. If parents are not educated on how to recognize these symptoms or what to do if they find one, then they are not providing their child with proper health care. The phone calls are a positive reminder for what proper health care entails. They reinforce the positive health messages and health behaviors that they were introduced to at clinic visits. This encourages parents to bring their child in for clinic visits, if they do not already do so, on a regular basis. Nothing new or different is introduced in these phones calls – they simply re-iterate the important health messages that were relayed to them by the sickle cell care team.

I learned that genuine kindness and caring go a long way. When parents answered the phone, they had a neutral tone, but once I identified myself and that I was calling to check up on their child, they were more enthusiastic and appreciative of the call. Dealing with the patients in a positive manner allows for work to be accomplished to help their child. Plus, it helps to reinforce a positive relationship between the clinic and the patients. Calling over 200 people has really enhanced my phone communication skills. As time went on, I became more relaxed when making the calls. I also learned that education of the disease is very important. Parents who did not bring their child to clinic at recommended intervals did not understand the multiple reasons for attending. Besides checking the child's medical status, it was also a time to educate the caregivers about the next group of complications they had to deal with as the child aged. Some parents intimated that they thought there was nothing new to learn about sickle cell disease after

the first few years of life. I was able to tell them about delays in the onset of puberty and eye problems, such as retinopathy, that affect teenagers that they would have learned about at a clinic visit. After explaining these items to the parents, they were much more inclined to attend clinic on a regular basis. Reminding patients to attend clinic on a regular basis really reinforced the importance of the clinic visits, not just for the patients, but also for the caregiver.

I really felt like I was making a positive impact on the patients' lives. I enjoyed working with a population that shared a common genetic disease because I was able to focus on one disease, sickle cell disease, and learn as much as I could about it so that I could be a useful resource for the patients. This outreach program is very beneficial, especially for chronic illnesses, and should be incorporated in all medical practices as a part of their total health care services.

6.0 CONCLUSION

Structured telephone based follow-up, support and education for families with a child with sickle cell disease using non-medical personnel is a simple, relatively inexpensive, intervention which can lead to improved adherence to comprehensive care measures. This approach was both feasible for the comprehensive clinic and accepted by families with a child with sickle cell disease. It was an effective means of maintaining communication and providing essential services to patients. Continuing the use of phones in health care will benefit patients by decreasing the morbidity and mortality of the disease and help them improve their ability to adhere to comprehensive care.

The routine phone calls allowed the sickle cell care team to fulfill the first aim by re-enforcing positive health messages and suggesting positive health behaviors. Additionally, the phone calls were an effective means to increase adherence to comprehensive care. Increased attendance at the comprehensive clinic was the second aim and the data demonstrated that clinic attendance improved after the phone calls were implemented.

Long-term studies need to be done to measure the efficacy of continuing the phone calls. It would be interesting to observe if the current levels of clinic attendance are at least maintained and do not decline significantly. It is possible that some patients may be so accustomed to getting a phone call that they would wait until they were called again to schedule an appointment or fill a prescription.

Providing a complete healthcare package for the patients benefits more than just the physical health of the patient. The phone calls open another channel for the patients to connect

with the sickle cell care team. This increased contact can help to relax the patients when the go to the clinic for a visit. The added personal attention from the clinic demonstrates their genuine care for the patients and the patients are more trusting of the team. This increased trust allows for a closer doctor-patient relationship that is able to provide the best care possible. Trust between a medical care team and patients is a significant part of public health. Patients must feel comfortable and safe when pursuing health care services, otherwise the services will not be effective. Putting the patients first not only makes for happy and healthier patients, but also an enjoyable work environment. Each team member has an undisputable common goal: to help the patients.

7.0 BIBLIOGRAPHY

1. Yang, Y.M., et al., *Comparison of costs to the health sector of comprehensive and episodic health care for sickle cell disease patients.* Public Health Rep, 1995. **110**(1): p. 80-6.

2. Kwiatkowski, J.L., et al., *Transcranial Doppler ultrasonography in siblings with sickle cell disease.* Br J Haematol, 2003. **121**(6): p. 932-7.

3. Rothman, S.M., K.H. Fulling, and J.S. Nelson, *Sickle cell anemia and central nervous system infarction: a neuropathological study.* Ann Neurol, 1986. **20**(6): p. 684-90.

4. Adams, R.J., et al., *Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography.* N Engl J Med, 1998. **339**(1): p. 5-11.

5. Cheung, A.T., et al., *Correlation of abnormal intracranial vessel velocity, measured by transcranial Doppler ultrasonography, with abnormal conjunctival vessel velocity, measured by computer-assisted intravital microscopy, in sickle cell disease.* Blood, 2001. **97**(11): p. 3401-4.

6. Powars, D., et al., *The natural history of stroke in sickle cell disease.* Am J Med, 1978. **65**(3): p. 461-71.

7. Ohene-Frempong, K., et al., *Cerebrovascular accidents in sickle cell disease: rates and risk factors.* Blood, 1998. **91**(1): p. 288-94.

8. Abboud, M.R., et al., *Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study.* Blood, 2004. **103**(7): p. 2822-6.

9. Adams, R.J., et al., *Stroke prevention trial in sickle cell anemia.* Control Clin Trials, 1998. **19**(1): p. 110-29.

10. Pegelow, C.H., et al., *Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions.* J Pediatr, 1995. **126**(6): p. 896-9.

11. Russell, M.O., et al., *Transfusion therapy for cerebrovascular abnormalities in sickle cell disease.* J Pediatr, 1976. **88**(3): p. 382-7.

12. Sarnaik, S., et al., *Periodic transfusions for sickle cell anemia and CNS infarction.* Am J Dis Child, 1979. **133**(12): p. 1254-7.

13. Russell, M.O., et al., *Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease.* Blood, 1984. **63**(1): p. 162-9.

14. Adams, R.J., et al., *Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler.* Ann Neurol, 1997. **42**(5): p. 699-704.

15. Gaston, M.H., et al., *Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial.* N Engl J Med, 1986. **314**(25): p. 1593-9.

16. Falletta, J.M., et al., *Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II.* J Pediatr, 1995. **127**(5): p. 685-90.

17. Soet, J.E. and C.E. Basch, *The telephone as a communication medium for health education.* Health Educ Behav, 1997. **24**(6): p. 759-72.

18. Sox, C.M., et al., *Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease.* Jama, 2003. **290**(8): p. 1057-61.

19. Teach, S.J., K.A. Lillis, and M. Grossi, *Compliance with penicillin prophylaxis in patients with sickle cell disease.* Arch Pediatr Adolesc Med, 1998. **152**(3): p. 274-8.

20. National Institutes of Health. National Heart, Lung, and Blood INstitute. Division of Blood Diseases and Resources: *The Management of Sickle Cell Disease.* Revised 2002, 4th ed. NIH Publication No. 02-2117.

21. Leiken SL, Gallagher D, Kinney TR et al. Mortality in children and adolescents with sickle cell disease. The Cooperative Study of Sickle Cell Disease. Pediatrics 84(3): 500-508 (1989).

22. Pearson, H.A., Gallagher, D., Chilcote, R., et al., *Developmental pattern of splenic dysfunction in sickle cell disorders.* Pediatrics, 1985. **76:** p. 392-7.

23. Miller, S.T., Sleeper, L.A., Pegelow, C.H., et al., *Prediction of adverse outcomes in children with sickle cell disease.* N Engl J Med, 2000. **342:** p. 83-9.

24. Sickle Cell Disease Guideline Panel. *Sickle Cell Disease: Screening, Diagnosis, Management, Counseling in Newborns and Infants.* Clinical Practice Guideline No. 6. Rockville, Maryland: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. 1993. AHCPR Pub. No. 93-0562.

25. Brown, A.K., Speeler, L.A., Miller, S.T., et al., *Reference values and hematological changes from birth to five years in patients with sickle cell disease.*b Arch Pediatr Adolesc Med, 1994. **48:** p.796-804.

26. Lessing, S., Vichinsky, E., eds. *A Parents' Handbook for Sickle Cell Disease. Part I, Birth to Six Years of Age.* Children's Hospital, Oakland Sickle Cell Center. Copyright 1990. State of California, Department of Health Services Genetic Disease Branch, Revised 1991.

27. Sickle Cell Disease Guideline Panel. *Sickle Cell Disease in Newborns and Infants. A Guide for Parents.* Consumer Version, Clinical Practice Guideline No. 6. Rockville, Maryland: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. 1993. AHCPR Pub. No. 93-0562.

28. Day, S., *Your Child and Sickle Cell Disease.* Biomedical Communications Department, St. Jude Children's Research Hospital, Memphis, Tennessee. Mid-South Sickle Cell Center. P.O. Box Suite 235, 1 Children Plaza, Memphis, Tennessee 38103.

29. *Mortality among children with sickle cell disease identified by newborn screening during 1990-1994-California, Illinois and New York.* MMWR, 1998. **47**(9): 169-172

30. Wilson, R. E., L. Krishnamurti, et al. *Management of sickle cell disease in primary care.* Clin Pediatr (Phila), 2003. **42**(9): 753-61

31. Car, J. and Sheikh, A. *Telephone consultations*. BMJ, 2003. **326**(7396): 966-9.

32. Bunn, H. F. *Pathogenesis and treatment of sickle cell disease.* New Eng J Med, 1997. **337**(11): p. 762-9.

33. Claster, S., and Vichinsky, E. P. *Managing sickle cell disease*. BMJ, 2003. **327**: 1151-5.