MEASURING CARE QUALITY AND HEALTH OUTCOMES IN PATIENTS WITH SICKLE CELL DISEASE

By

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This work is dedicated to my parents, Kenneth and Kathleen Mayhew, who truly exemplify selfless giving. I love you both.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abstract of Dissertation Presented to the Graduate School
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Background: Pain is the leading cause of morbidity for patients with sickle cell disease (SCD). Hydroxyurea is the first therapy proven in clinical trial to reduce pain episodes, as well as acute chest syndrome and the number of hospitalizations for patients with SCD. Since its approval, many eligible patients are not treated with hydroxyurea. This dissertation explores factors that are related to the prescribing of hydroxyurea and assesses the outcome of treatment when given in usual care settings.

Objectives: Two main objectives were set for this study: (1) to create a risk-adjusted predictive model of disease-related morbidity with regards to treatment with hydroxyurea, and (2) to explore the health outcomes of patients with SCD in relation to the structure and process of health care.

Methods: Florida Medicaid data were used to meet the goals of this project. For objective 1, principal components analysis was used to create a composite measure of morbidity which was based on the number of emergency department visits and

hospitalizations for SCD complications. Stepwise multiple regression was applied to predict morbidity before HU initiation and again after therapy was initiated. Creating the two predictive models allowed post-treatment reductions in morbidity to be measured. For objective 2, physician specialty and provider practice location were examined as structural factors related to prescribing hydroxyurea. Instrumental variable analysis was used to estimate these associations and subsequent outcomes.

Results: Hydroxyurea was associated with a reduction in morbidity by greater than 20% from pretreatment to post-treatment. Significant predictors of morbidity were decreasing age, comorbid diseases, and increasing number of prescriptions for opiate drugs. SCD-specialists were more likely than non-specialists to prescribe hydroxyurea. When compared to patients not treated with hydroxyurea, morbidity was lower for treatment patients. This difference was not statistically significant.

Conclusion: SCD patients can experience a reduction in disease-related complications with hydroxyurea, though not all patients will have a positive treatment response. Efforts to improve prescribing of hydroxyurea should be targeted towards non-specialists as well as SCD-specialists.

CHAPTER 1
INTRODUCTION

The Need for the Study

Problem of Sickle Cell Disease

Sickle cell disease (SCD) is a genetic condition that results from a defect in the gene that produces hemoglobin. The origin of SCD traces back to people of African, Mediterranean, Middle Eastern, and Indian descent. Today approximately 72,000 Americans are affected with the disorder [1]. Sickle cell disease is most common among African Americans, occurring in 1 in every 350-500 African American births [1, 2]. The estimated prevalence of SCD among blacks, Hispanics, and whites is 289, 5.28, and 1.72 persons per 100,000 population, respectively [3]. The life expectancy of patients with sickle cell disease is reduced by 25-30 years compared to that of the general population [4]. Death for patients with SCD often occurs unexpectedly, with 33 percent of patients dying while hospitalized for disease-related complications [5]. The epidemiology of this illness and the magnitude of its sequelae have made SCD a disease of public health importance.

The public health implication of SCD is confounded by the unpredictable morbid states associated with the disease. Some patients with SCD may experience a mild disease course with minimal morbidity, while others repeatedly exhibit very severe symptoms. The variability in disease expression is not exclusive to patient-to-patient differences. Patients often present with altering disease patterns within themselves, precluding consistent treatment regimens. The unpredictability of SCD makes treating

and managing the disease difficult for patients and their caregivers; hence the effect of SCD on the burden of health care is accentuated by the inability to provide uncomplicated care to patients.

Although the clinical course of SCD does not follow a pre-specified, uniform pattern, symptoms of chronic pain, acute anemia, infection, and other potentially debilitating complications are characteristic of the disease. Unlike normal red blood cells (RBC's), sickle shaped cells can not move freely through small blood vessels. This leads to the cells becoming stacked up and forming blockages that preempt oxygenated blood from reaching surrounding tissue and organs, fostering pain as well as organ or tissue damage. The truncated life span of sickled cells further induces acute phases of morbidity. Sickled red blood cells generally do not survive beyond 20 days, whereas the life cycle of a normal red blood cell lasts about 120 days. The rapid breakdown of the blood cells and the inability of the body to quickly replenish the loss of cells promote anemia in SCD patients. The breakdown of cells may also lead to excessive levels of bilirubin in the blood system, resulting in jaundice. Other acute events such as infection are often associated with SCD. Deprivation of oxygenated blood to the spleen creates a likelihood for splenic damage, rendering patients with a decreased capacity to destroy bacteria, thereby increasing their susceptibility to infection. When infection occurs in the lungs, patients are subject to develop a pneumonia-like condition known as acute chest syndrome (ACS), which is potentially life threatening. Of the numerous complications, vaso-occulsive pain is the primary cause of morbidity among sickle cell patients. Pain can occur spontaneously or in association with hypoxia, infection, or anxiety, and most often settles in the back, chest or extremities [6].

Treatment Options

Understanding the experiences of sickle cell patients helps to shape assessment and management of the disease, and plays a critical role in mollifying suffering [7]. Timely, aggressive treatment is an important factor in reducing morbidity. Conventional treatment includes nonpharmacological as well as pharmacotherapeutic interventions such as analgesics and folic acid. Folic acid has been recommended for all SCD patients for the purpose of reducing bone marrow aplasia and to aid in the proliferation of normal red blood cells [8]. Blood transfusions are often incorporated as a nonpharmacological proactive measure in averting sickle cell complications such as stroke and ACS [9]. Stroke is a frequent cause of death among adult sickle cell patients [4, 9]. In a study of 3,764 patients with SCD between the ages of 0 and 66 years, stroke was one of the highest known causes of death, second to pain crises. Among the 38 percent of deaths in otherwise healthy patients, 22% were due to stroke [4]. Patients on transfusion programs have been found to have a reduced incidence of stroke [8, 10, 11]. Pegelow et al. [10] observed the risk of recurrent stroke in children with SCD who were placed on transfusion therapy to be reduced to one recurrence for each 24 patient-years of observation. Another study demonstrated prolonged transfusion dramatically slowed the progression of cerebral arteriostenosis. Before beginning the transfusion program, 90 percent of patients experienced recurrent stroke. This number was drastically reduced to 10 percent upon initiation of transfusion therapy [11]. Transfusions are also instrumental in correcting anemia by increasing the oxygen carrying capacity of the blood and maximizing the number of normal red blood cells in circulation [9]. Although blood transfusions are a critical component of care for many patients, iron overload,

transmission of infectious agents, and alloimmunization resulting from frequent transfusions are of concern.

Much SCD related therapy is targeted towards remedying pain. Uncontrolled pain could produce further exacerbations that may require hospitalization. Basic pain management involves heavy reliance on analgesic therapies, oral and intravenous fluids, rest, and avoidance of circumstances that may precipitate a painful episode, such as extreme temperatures, high elevations, and poor nutrition [12, 13].

Until recent years, no therapies had been successful at averting pain episodes. Achievements in increasing the number of normal red blood cells had been noted with the use of folic acid and blood transfusions, and pain amelioration could be seen with the use of analgesics such as ibuprofen, aspirin, or acetaminophen, yet none of these interventions prevent the occurrence of future pain. Further, pain relief provided by analgesic therapies sometimes requires large doses of treatment, and is often only temporary. It was during a landmark multicenter clinical trial (Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)) that the chemotherapeutic agent hydroxyurea was found to demonstrate remarkable outcomes in patients with SCD [14]. The MSH trial was a randomized double-blind placebo controlled trial designed to test whether hydroxyurea (HU) could reduce the rate of pain in adult patients with SCD. Two hundred ninety-nine patients age 18 years and older were recruited from 21 medical clinics across the United States and Canada. Study results indicated that patients who received HU during the trial presented with less frequent pain episodes, required fewer blood transfusions, and were hospitalized less often than patients receiving placebo drug therapy. The incidence of ACS was also lower among patients in the treatment group.

Participants were anticipated to be followed for a minimum of two years; however the trial was ended early due to the overwhelming results. Based on the outcome of the MSH trial, a clinical alert was issued in 1995 and HU was subsequently approved in 1998 by the Food and Drug Administration (FDA) for use in adult patients with sickle cell disease. Follow-up studies to the MSH trial have shown significant implications for reductions in health care costs and increased survival rates associated with hydroxyurea use [15, 16]. Utilizing data from the MSH trial along with cost data obtained from an administrative database, hospital charges, and professional fees, Moore et al. were able to show a substantial difference in total health care costs between the HU and placebo treatment groups [15]. Data from a nine-year follow-up study of mortality on 233 of the 299 MSH trial participants indicated that patients taking HU have reduced mortality. Deaths occurring during the follow-up period (n = 75) were due to non-SCD-related causes [16]. The value of hydroxyurea to the sickle cell community can be appreciated by its propensity to reduce overall morbidity while creating a potential for improvements in quality of life.

Problem Statement

Inequalities in health care have long been realized, yet conciliating resolution has yet to be seen. Systematic breakdowns in the structure of health care have contributed to the disproportionate rendering of quality health-related services, with certain population groups receiving less than adequate care. Populations that have historically been considered underserved due to race, socioeconomic status, place of residence, or other demographic characteristics remain a focus as health outcomes researchers seek methods to measure and improve the quality of today's health care.

Many patients with sickle cell disease dwell in underserved populations, have limited income, and do not have regular access to specialized care [17, 18]. They are faced with the challenge of identifying qualified practitioners to provide coordinated services and who could offer to them the latest advancements in the treatment of their disease. The most recent advancement in drug therapy is hydroxyurea. Despite its proven success, many patients who will benefit from this therapy do not receive the treatment. During a survey of community hematologists/oncologists, 45 percent of responding physicians reported treating fewer than ten percent of their SCD patients with HU. Only ten percent indicated that 60-90 percent of their patients receive treatment with HU [19].

Hydroxyurea is indicated for adult patients with moderately severe to severe SCD, qualified as three or more episodes of pain in a year, recurrent hospitalizations, or frequent episodes of ACS [20]. Patients who have mild disease symptoms typically do not receive HU treatment; however other factors that have been unmeasured may also contribute to not being treated with HU. Hydroxyurea requires intensive supervision with frequent laboratory monitoring, multiple patient visits, and possible dose changes. Additional efforts are required from the physician to ensure that patients receive the maximum benefit of the drug in the safest manner. A study of prescribing influences among a group of Australian general practitioners has suggested that the level of monitoring required for a drug is a determinant towards it being prescribed. Sixty-three percent of the participating physicians indicated they are less likely to prescribe a drug requiring frequent monitoring [21]. Physicians who do not specialize in treating patients with SCD may not fully appreciate the benefits of treatment with HU, and may be

adverse to the additional constraints imposed by the drug, deterring them from prescribing it to their patients. The absence of medical specialization may also reflect a lack of comprehensive knowledge and understanding of SCD as well as a lack of familiarity with available treatments, which too may obviate the use of HU. Additionally, the scarcity of specialized sickle cell treatment facilities is often associated with a disconnect between adult sickle cell patients and the medical community. Health care for these patients is provided in large tertiary care medical centers and emergency departments where the emphasis is on diagnosis and treatment of acute exacerbations rather than continuous, coordinated care [7]. What is more, a considerable proportion of SCD patients reside in areas where access to specialized clinicians, major medical centers, and other health care resources is limited. Studies conducted in Alabama and Illinois revealed that 45 percent and 10 percent of participants, respectively, reside in such counties [18, 22]. In Florida, more than 15 percent of the sickle cell population resides in counties where there are only a few practicing SCD specialists. With a disease where resources are scarce and access to comprehensive care is limited, these numbers reflect individuals who may experience even greater distress with obtaining needed care. Under such constraints, patients' abilities to receive and benefit from treatment advances such as hydroxyurea are hindered.

Purpose and Significance

The quality of health care services has been widely examined by Donabedian, who has established the paradigm of structure, process, and outcome to measure quality in health care [23]. Under this framework, the structural components of the health care system (staff, facilities, or provider characteristics) can be linked with the process of health care delivery to assess patient outcomes. As treatment advances lead to increased

life expectancy for patients with SCD, the structures and processes that facilitate the delivery of health care will require continual assessments and expansions to accommodate patients and their needs.

Though the MSH trial has provided empirical evidence of the efficacy of HU in patients with SCD, the trial does not lend itself to examining the relationship between structural and process measures, and their inherent influence on disease-related morbidity in these patients. Moreover, retrospective database studies such as that employed here can complement the findings of randomized controlled trials by capturing the health-related experiences of patients in usual care settings. Hence, to provide a retrospective account of the use of HU in a general sickle cell population and further advance our understanding of the associations between the structural and process measures of health care delivered to patients with SCD, this dissertation aimed to examine the quality of care provided to patients with SCD and subsequent patient outcomes. The specific objectives of this project were (1) to establish a risk-adjusted predictive model of disease-related morbidity with regards to treatment with HU; and (2) to explore the health outcomes of patients with SCD in relation to the structure and process of health care. In so doing, factors that increase a patient's risk for morbid outcomes were controlled, and attempts at uncovering previously unmeasured factors that may lead to a patient's receipt of HU were undertaken. The variables examined were based upon known influences on health as well as factors deemed important for the population understudy. Specific variables included disease-related morbidity, patient age, patient gender, comorbidity, disease severity, treatment, treatment supply, treatment initiating physician, treatment/disease managing physician, and patient/provider location. Variables treated as structural

measures are treatment initiating physician, treatment/disease managing physician, and patient/provider location. The treatment variable served as the process measure, and disease-related morbidity as the outcome measure. All variables are further defined in a later chapter.

Research Questions

Florida Medicaid data from fiscal years (FY) 1997-2002 was used to meet the objectives of this dissertation. In meeting these objectives, the following research questions were addressed:

1. Controlling for underlying health status, where health status is measured by disease severity and comorbidity, does use of HU reduce the disease-related morbidity of SCD patients in usual care settings?

2. To what extent do treatment initiating physician, treatment/disease managing physician, and patient/provider location, influence prescribing of HU to SCD patients in usual care settings?

3. Controlling for health status, where health status is measured by disease severity and comorbidity, what is the combined association of the measures of treatment initiating physician, treatment/disease managing physician, patient/provider location, and receipt of HU on the disease-related morbidity of SCD patients in usual care settings?

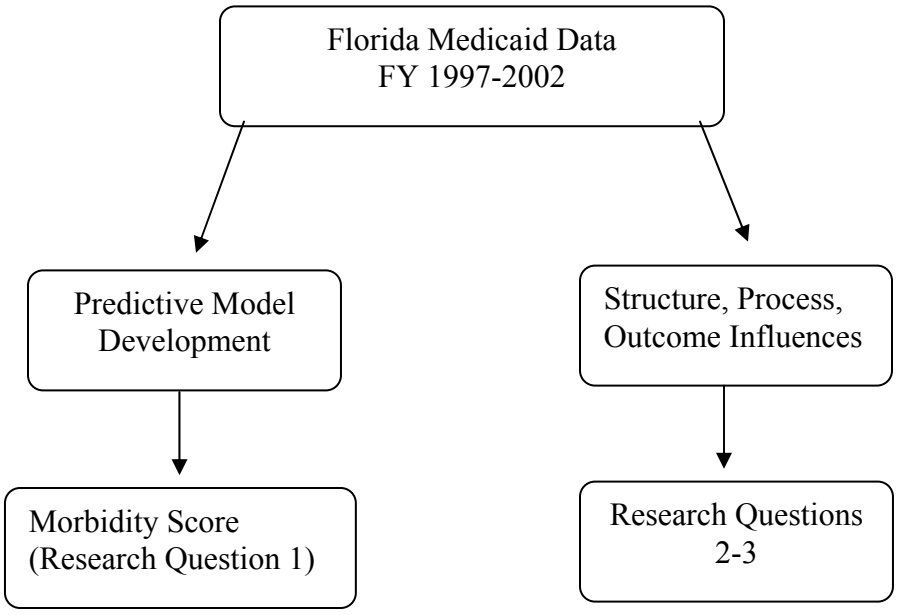

Figure 1-1. Overview of Study

CHAPTER 2
LITERATURE REVIEW

This literature review is divided into four sections. The first two sections specifically relate to sickle cell disease. The third section discusses health care quality. In the final section, concepts on measuring morbidity will be detailed.

Pain Crises

The most common complication associated with sickle cell disease is pain. Patients with SCD experience unpredictable pain episodes that vary in frequency, intensity, and duration. The terminology that is often used to refer to a pain episode is "pain crisis", which has been defined as an acute dystrophic episode experienced by patients with sickle cell disease [24]. Acute pain crises have been described by some patients as throbbing, sharp, gnawing sensations that may persist for several hours or several days [25]. Others have likened the pain experience to breaking all of one's bones at the same time [2]. In any case, unresolved pain may lead to further affliction [26]. In addition to acute pain, patients may also experience chronic pain crises in which the pain is associated with unremitting suffering. Chronic pain syndromes may be precipitated by severe damage to bones, nerves, and other tissues [2], and include complications such as avascular necrosis of the hip or shoulder, vertebral collapse, leg ulcers, or arthropathy [26]. Most patients with SCD have mild pain of short duration that can be managed at home, with only a small percent enduring severe, constant pain [2, 27].

A typical pain crisis in adults progresses in two phases: an evolving phase and a resolving phase. The evolving phase is characterized by an escalating painful experience,

an increase in dense cells, a decrease in erythrocyte distribution width (RDW) and an increase in hemoglobin distribution width (HDW). Erythrocytic changes may precede the onset of pain by one to three days. It is during the evolving phase that pain reaches its maximum intensity and anemic exacerbations occur. Decreases in the hemoglobin levels and increased reticulocyte counts are also typical during this phase of the crisis, and may be indicative of hemolysis. During pain resolution, patients experience a decrease in pain severity, a decrease in dense cells, an increase in erythrocyte deformability, and RDW and HDW are restored to steady state. Hemoglobin levels and reticulocyte counts also return to the pre-crisis level [7, 24]. The increase in erythrocyte deformability and the decrease in dense cells that occur at the end of the cycle incites a recurrent pain episode within a one month period in nearly half of all pain crises [24].

Reportedly, an estimated 18 percent of SCD patients experience recurrent pain, with approximately five percent exhibiting greater than three pain crises per year [28]. Though unpredictable in nature, the frequency of pain crises has been found to be related to biophysical and social influences. The presence of concurrent illness, a patient's physical condition, and psychological factors have all been associated with recurrent pain episodes[2]. Genetic factors such as hemoglobin phenotype, hematocrit, and level of fetal hemoglobin (HbF) are also key influences on the expression of pain [2, 26, 28]. Findings from the Cooperative Study of Sickle Cell Disease (CSSCD) suggest that patients with higher levels of HbF present with lower incidences of pain, and the frequency of pain varies directly with hematocrit [28]. The CSSCD was a longitudinal, multicenter clinical study which explored the natural history of SCD in patients of all ages [29]. The study further indicated that pain rates tend to increase as patients grow

older, peaking between ages 20-29. Male patients were found to experience more frequent crises than their female counterparts. Another important finding from the CSSCD study was the positive correlation between pain rate and death. Patients who experienced three or more pain crises per year were at greater risk for mortality than patients with fewer episodes of pain [28].

The lack of an objective diagnosis and the absence of overt disability preclude timely, effective treatment for many patients with SCD. Diagnosis of pain is typically based on patients' subjective report, though clinical signs of a painful episode may include localized swelling, tachypnea, tachycardia, and nausea and vomiting. However, not all patients will exhibit obvious symptoms and clinical signs are not specific and can be due to other conditions which are unrelated to sickle cell disease [7]. Health care providers who are not adept to treating SCD fail to appreciate the different types of pain and pain expression, supporting the misconception that all pain is the same and can be treated in the same manner [26]. Pain research has posited that the pathophysiology of pain in sickle cell disease is different from that of other pain syndromes [26], and, as such, should be regarded as a unique experience deserving of careful, specialized attention.

The paradoxical presentation of SCD contributes to the mismanagement of the disease. There are days when patients may experience life threatening complications, yet patients are relatively healthy when sickling episodes are dormant [12]. The lack of physical or laboratory manifestations during uncomplicated episodes of pain makes pain diagnosis difficult [2], and seemingly uncomplicated pain crises could evolve into acute chest syndrome or multiorgan failure, leading to hospitalization or death [30]. Most

hospitalizations for SCD patients occur in the context of pain [13, 31], and typically lasts four to ten days [25]. Patients who present to the hospital generally have failed to control pain with oral therapy, or exhibit symptoms that suggest a serious complication [2, 25]. The responsibilities of health care providers concerning pain management may vary among providers and institutions, [32] but there needs to be a generalized realization of the magnitude and seriousness of the pain experiences of SCD patients.

Hydroxyurea

The potential benefits of HU were first realized in the early 1980's when it was discovered that anemic monkeys responded to treatment with HU with increases in HbF levels [33]. It was this development that led to the initial investigation of HU in two patients with HbSS disease [34]. As with the anemic monkeys, HU demonstrated a desirable effect on HbF production in these two patients.

Since this discovery HU has been considered as a drug that could significantly impact the HbF levels of patients with SCD. HU is a small molecule that blocks DNA synthesis by inhibiting ribonucleotide reductase and is commonly used for the management of neoplastic diseases, such as chronic myeloid leukemia [35]. It is the least toxic of most chemotherapeutic agents previously tested in SCD patients, and offers administration ease to its users [34].

Alterations in red blood cells as a result of treatment with HU promote increases in total Hb and hematocrit; increases in mean corpuscle volume (MCV), and increases in the water content of RBC's, yielding an antisickling effect [35]. The increase in HbF noted with use of HU results from its interference with normal erythropoiesis, causing adult Hb to revert to HbF [20, 36].

Speculations that newborns were protected from the clinical manifestations of SCD by the presence of HbF were first reported several decades ago when Janet Watson realized that RBC's of infants failed to sickle in vitro. The sickling of blood cells is caused by polymerization of molecules of deoxygenated sickle hemoglobin (hemoglobin S) into rigid, rod-like polymers. Fetal hemoglobin inhibits sickling in vitro by interfering with the polymerization of hemoglobin S, thereby preventing the formation of the rigid structures [14]. Higher levels of HbF have been associated with amelioration of the clinical problems of SCD [4], with patients with low HbF concentrations experiencing more frequent painful events and episodes of acute chest syndrome, as well as increased mortality rates [4, 28].

Hydroxyurea is the first approved drug clinically proven to modulate the production of HbF in adult patients with SCD, and no other drug has been found to be as efficacious at reducing morbidity as HU. In clinical trial, there was a 44 percent difference in crisis rate between the HU treatment and control group, and the median time to first and second pain crisis was longer for the treatment group [14]. Others have reported a decline in hospital admissions and a decline in the number of red cell units required for transfusion as a result of HU treatment [36]. Ferguson et al. noticed a 24 percent reduction in hospital admissions and a 25 percent reduction in transfusions in the 60 patients they followed [36]. These findings did not reach significance, possibly due to low statistical power resulting from a small sample size. Physiologic changes leading to clinical improvements may appear within eight weeks of initiating therapy [14]; however the clinical response to HU varies among individuals and depends on the capacity of the bone marrow to withstand moderate doses of treatment [30]. Thus, the cited findings

may not be demonstrated in all patients. The National Institutes of Health (NIH) recommends a standard dosing regimen for all patients, suggesting that therapy be initiated at a single daily dose of 10-15 mg/kg/day and titrated upward until the maximum tolerated dose is reached (i.e. until marrow suppression occurs) [8].

Hydroxyurea has been indicated for patients with moderately severe to severe disease symptomatology. This includes patients with frequent episodes of pain, history of acute chest syndrome, or severe symptomatic anemia [8]. The remarkable potential of HU in patients with SCD has incited concerns about its underuse in this population. Concerns about side effects and toxic properties of HU may contribute to the conservative approach to its use; however treatment and control patients in clinical trial presented equally with non-threatening side effects [14]. Thus, fears of serious adverse events associated with HU should be assuaged. Other factors believed to influence the decision to start treatment with HU include age, patient motivation, compliance, and access to laboratory facilities for monitoring [27, 30]. For reasons such as lack of immediate reduction in symptoms, the reluctance to have frequent blood tests, financial strains, and the fear of departure of routine treatment, prescribers are concerned that patients may not adhere to treatment, and therefore are less likely to recommend it [30]. Compliance, however, was found to be adequate when HU was tested in clinical trial. During the study period 75 percent of patients took more than 80 percent of the treatment, as measured by pill count [14]. In light of the promising potential of HU, reservations about treating SCD patients with the treatment should be revisited and physicians should make HU available to all patients who meet the approved criteria [37].

Quality in Health Care

One approach to examining the factors that have led to restricted use of HU is through quality improvement efforts, the basis of which is to ensure that the needs and expectations of patients are met [38]. As a reflection of the values and goals of the health care system [23], quality in health care is demonstrated by the effectiveness and outcomes of care, and is judged by how the delivery of care conforms to a set of expectations or standards [39].

Quality of health care has been defined as the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge [40]. In his description of quality, Donabedian [39] has declared seven attributes that contribute to quality in health care. 'Efficacy', accordingly, refers to the ability of science and the art of health care to bring about improvements in health and well-being. It is rooted in the premise that under the most favorable conditions, the best possible care will be provided. Similar to efficacy is the concept of 'effectiveness', which is also concerned with improvements in health. Effectiveness, however, is measured in terms of ordinary circumstances in daily practice, where conditions may not always be ideal. In defining and assessing quality, effectiveness can be measured as the degree to which care attains the level of health improvement that studies of efficacy (e.g. randomized controlled trials) have achieved. Along with health improvements, considerations of costs are pivotal to assessing quality. Donabedian has adopted the terms 'efficiency', which refers to achieving the greatest improvements at the lowest costs, and 'optimality', which relates the cost of care to its benefits, to reflect this idea. Quality of care is also reflected by the perceptions held by patients themselves as well as the community as a whole. The attribute 'acceptability'

encompasses a patient's subjective valuation of effectiveness, efficiency, and optimality as well as the relationship between the patient and provider, and the accessibility and amenities of health care. 'Legitimacy' can be thought of as acceptability of care by the general community. This includes concerns at the individual level as well as a responsibility for the well-being of all. As mentioned in chapter 1 of this dissertation, inequalities in health care have long been of concern. The final attribute of quality, 'equity', addresses this by promoting care that is not only acceptable to individuals but also socially legitimate. Equity is concerned with just and fair distribution of health care services and the benefits of care to the population. The above attributes represent the aspects of health care that help to determine its degree of quality with regards to improving health, conserving cost, and meeting the needs and expectations of individuals and society at large. Though these attributes alone do not provide a definitive solution to the problems in health care, they offer a perspective by which to evaluate and align quality in health services.

When assessing quality in health care, one must look beyond the actual delivery of services and incorporate into the assessment those factors that facilitate delivery and the inherent consequences. These have come to be known as the structure, process, and outcome of care.

The structural capacity of the health care system is the cumulative of the resources and relationships necessary to facilitate the provisions of health care [41]. Hence, an assessment of structure is a judgment on whether care is being provided under conditions that are conducive to supplying good care [42]. This entails assessing the setting in which care takes place and the means by which it is delivered [23]. Structural assessment

involves the study of system factors, staffing patterns, and characteristics of care providers [43]. It is concerned with the adequacy of facilities and equipment, the qualifications of medical staff and their organization, and the administrative structure and operations of programs and institutions providing care [23]. The variables considered in a measure of structure may describe the physical office or hospital environment, organizational resources, or the training, experience, and specialization of providers [41, 44, 45]. In this respect, structural attributes become indirect measures of the quality of care as well as indicators of where the quality of care is likely to be deficient [44].

An examination into whether or not medicine is properly practiced speaks to the process of health care [23]. Assessment of process involves the study of what the care provider does and describes the care patients actually receive [42]. Efforts to assess process often focus on the patient's exposure to medical interventions, thereby connecting the process of care to patient outcomes. Under the process of health care, attention to overuse, underuse, and misuse of medical resources such as drug products is appropriate. Factors like reimbursement incentives or pressure from patients and pharmaceutical advertisements may lead physicians to generate a high volume of prescriptions for certain drugs [46]. Overuse of a drug may also occur when patients are prescribed doses higher than necessary to treat their condition. Low volume prescribing despite the presence of approved indication and proven efficacy, or prescribing doses that are insufficient for patient needs describes drug underuse. Misuse of drugs results when prescriptions are given for the wrong indication, when drugs are used for purposes other than which they were intended, or when drug use deviates from recommended dosing or instructions. Drug misuse may encompass both overuse and underuse.

Patient outcomes reflect the effect of care processes on health and well-being [42]. Outcomes are states of health or events that follow care, and may be expressed as death (mortality), disease (morbidity), discomfort, disability, or dissatisfaction [40, 42]. They can be used to provide valuable information about the overall performance of the health care system [41]. Outcomes are seldom fallible, thus, as concrete measures of health care, outcomes serve as validators of the effectiveness and quality of care [23]. However, while outcomes may imply good or inadequate care, they alone do not point to the nature and location of deficiencies or strengths of the system [23].

Understanding the relation of structure and process to outcomes is important for the ultimate goal of assessing the quality of the health care system [47]. As a part of this understanding, the limitations of these measures and their relationships should be recognized. Often times, the triadic relationship between structure, process, and outcome is not well established [23]. Not all structural variables are amenable [45] and only process measures can be manipulated directly [47]. What is more, structural variables tend to reflect average results for large groups of providers, not individuals [45]. As for outcome assessments, outcomes reflect the power of medical science to achieve certain results, however many factors, including nonmedical attributes and patient behaviors, can influence outcomes and must be considered when forming conclusions [23].

Quality in Prescribing

Included in the delivery of quality health care is the aspect of prescribing. Prescribing refers to a process in which recommendations are made and written directions for therapeutic agents are provided to patients for treatment of a medical condition. These recommendations and instructions are based on the information that is available to

the prescribing provider. When the information is incomplete or inaccurate, inappropriate prescribing may result [48].

As elicited from a delphi study on quality assessment, one of the indicators of quality of care most favored by general practitioners is appropriate prescribing [49]. Appropriate prescribing depends on just allocation of resources as defined by care that meets the needs of patients [48]. Prescribing is therefore appropriate when a rational thought process leads to a favorable drug selection for any patient who would benefit from therapy, given the availability of the drug. From this perspective, prescribing providers should strive to strike a balance between maximizing patient well-being and distributing resources to promote individual health gains [48].

Along this continuum, quality in prescribing implies that treatment is not only suitable for the patient, but also safe and effective. A population-based assessment on maximizing effectiveness and minimizing risks of drug therapy can be conducted using administrative databases. This provide a quick and efficient appraisal of prescribing to a large number of patients [50]. By creating prescribing indicators, which typically focus on the proportion of patients prescribed a particular drug, examination of the database can reveal when patients are receiving sub-optimal care [51]. Developing valid and meaningful indicators, however, can be difficult for conditions that require complex treatment regimen [51], as with SCD.

A number of studies have been conducted to examine prescribing patterns. Factor studies, adoption studies, and decision-making studies are three primary methods of investigating patients' receipt of particular drugs [52]. Though different by approach, each type of study offers an assessment of physician, patient, and/or environmental

attributes influencing treatment selection. Factor studies are typically interested in exploring the relationship(s) between variables such as physician specialization or practice setting and prescribing; whereas adoption studies focus on the ways in which physicians are exposed to medical information and innovations, and how this exposure influences the adoption of new treatments. Decision-making studies address the cognitive processes and physician values important to prescribing [53]. In a likeness to factor studies, the current research presents a test of patient and provider characteristics believed to have a role in patients receiving HU for treatment of SCD.

The literature reports on a number of factors that have been correlated with prescribing. Many of these factors are structural influences that include provider and practice characteristics such as formulary restrictions, medical management protocols, type of board certification, and demographics [54, 55].

Supporting the link between provider characteristics and prescribing, Blanc et al. [56] have asserted that specialty training has a role in prescribing decisions. These authors report that pulmonary specialists have a greater likelihood of prescribing asthma-related drugs when compared to other physicians. It has also been suggested that prescribing may be associated with physician's age, practice setting, and organizational structure [50, 54, 55]. Younger physicians have been found to select optimal treatment for chronic pain more often than their older counterparts [57]. Lexchin [50] reports that physicians in practices with higher mortality and morbidity rates prescribe differently than physicians who practice in settings where mortality and morbidity is lower. The same has been said of physicians who practice in rural settings [55]. This observation coupled with the limited access to care in rural environments led to the speculation in this

dissertation that patients' residential location and physician practice location may influence access to treatment. Organizational influences on prescribing have been described by Avorn [46], who explains that physicians' selection of drugs are aligned with the goals of the health care system in which they practice. When the goals of the system are cost containment, pharmaceuticals are the likely target, where cheaper alternatives are desired. In the absence of a comparable alternative with respect to safety and efficacy (e.g. the case with HU), under-use of the drug may result from efforts to control costs. If, however, improvements in patient outcomes can be demonstrated, the value of that drug is better appreciated and the drug becomes more appealing [46].

Quality in Pain Management

Despite the publication of evidence-based pain guidelines, proof that these guidelines result in improvements in clinical practice is lacking, as reports of inadequate pain management continue to surface [58, 59]. This may be partly explained by the focus of guidelines on the current state of scientific knowledge and the difficulty some physicians face with applying these guidelines to certain patients. Other reasons may include physicians' disagreement or distrust with the guidelines, thus choosing to ignore them [50]. Whatever the reason, quality in pain management still suffers.

Utilizing hypothetical clinical vignettes of different pain types, Green et al. [57] sought to investigate the issue of pain management. Pain due to SCD was considered as chronic pain in one of the vignettes. Findings from this study indicate that there is variability between primary care and specialty physicians in the way pain is managed. Their findings also demonstrated that physicians had lower pain relief goals for chronic pain than other pain types, and optimal treatment choices were less likely to be selected for chronic pain. The authors suggest physician attitudes and physician demographics

may contribute to these findings. One other explanation, as commonly reported with SCD, may be related to the trepidation of health care providers to prescribe optimal treatment for chronic pain due to fears of patients developing an addiction to the medications. Patients with chronic pain seek relief in narcotic drugs such as opiates. The negative attitudes and fears of providers towards narcotics may dissuade the use of opiates, resulting in a failure to appropriately respond to and manage pain [26]. This phenomenon provides an example of the underuse of therapies proven to be effective for an approved indication of chronic pain. As the fears are well respected, true addiction is uncommon with the use of opiates to control chronic pain [60].

Though barriers to quality pain management have been mentioned to include factors associated with patients and the health care system [61, 62], the relationship between structure, process, and outcome of pain management remains obscure. The reluctance of patients to assertively report pain and take medications as prescribed along with the health care system's low priority to pain control and the insufficient knowledge of medical professionals as well as their reluctance to prescribe certain drugs [62] has hindered progress towards quality improvement. An interdisciplinary approach to improve quality in pain management that identifies system breakdowns is needed [63]. Merely measuring the outcomes of pain is not a sufficient assessment of quality because it does not take into account the activities or provisions taken to prevent pain, and does not assess appropriateness of treatment [58]. In the context of structure, process, and outcome, evaluation of pain management should be multidimensional and include assessments of the factors that led to a particular outcome.

Structural areas that have been used previously in quality improvement efforts include an evaluation of institutional policies that support staff's expectation of providing satisfactory pain relief, innovations that indicate institutional commitment to prioritize pain management, and the availability of resources across settings [58, 63]. Process measures include consistency in pain assessments, prompt and appropriate treatment of pain, collaborative approaches to care, and access to specialty care [58, 59]. Structure, process, and outcome measures in pain management are summarized in Table 2-1.

Table 2-1. Structure, Process, and Outcome Measures in Pain Management

Structure	Process	Outcome
Range and appropriateness of options available within a particular setting	Pain assessment	Patient comfort (pain intensity and duration)
Quality of pain management across settings	Preventing and treating pain	Impact of pain on function
Institutional policies on pain relief	Collaborative care	Satisfaction with management
Innovations for pain management	Access to specialty care	Effectiveness of pain management options used Prevalence of complications associated with pain management

Morbidity Scores

To date, no objective scoring of outcomes in patients with SCD has been presented in the literature; particularly in association with treatments. Hence, measurements of disease-related morbidity in SCD have not been fully defined in terms of adjusting for the mix of risks that affect outcomes.

The factors that promote use of the health care system are variable among patients and may be dependent upon geographic location, expectations for health care services, health care needs, and illness severity [64]. Complex illnesses and coexisting conditions

make treating some patients more difficult than others, creating an imbalance when comparing outcomes. If we assume that outcomes are a function of patient-related risk factors, treatment effectiveness, quality of care, and random chance, the goals of outcomes research should be directed towards facilitating assessments of quality or effectiveness of care by adjusting for the influence of patient-level risk factors [64].

One approach to risk-adjustment is use of morbidity scores. Risk-adjusted morbidity scores provide a means for quantifying patient data to enable direct comparison of outcomes by incorporating a combination of factors into the prediction of outcomes [65]. This is particularly useful with retrospective data where the lack of randomization creates a mix of risks unevenly distributed across patient groups. Nevertheless, because the data contained in administrative databases is not as enriched as clinical data obtained at the time care is given, the inferences produced from retrospective data may be affected by the quality of the data itself (ex. the validity of coding and reporting) [65].

Application of risk-adjusted scores has been seen in various research studies aimed at predicting outcomes. Folsom et al. [66] created a coronary heart disease risk score to predict the probability of in CHD diabetic patients. Development of the score was based on regression modeling, taking into account those variables believed to influence the risk of CHD, such as blood pressure, cholesterol level, and smoking status. The authors concluded that most people with diabetes are at increased risk of CHD of at least one percent per year as compared to non-diabetic patients. A diabetes risk score was developed by Griffin et al. [67] for the purpose of assisting physicians in identifying patients at high risk for diabetes. Variables believed to contribute to the score were tested by regression modeling, with only those that reached significance being retained.

Hypothetical scenarios were used in this study to estimate the effects of employing a high or low risk threshold, as depicted by the receiver operating characteristic (ROC) curve, in predicting diabetes. It was predicted that approximately 11 to 12 percent of patients undergoing diagnostic testing would have diabetes. The authors concluded that a score like the one used in this study can identify patients at risk of diabetes just as effectively as screening tests. Another study incorporated a risk score in their prediction of survival after cardiopulmonary resuscitation (CPR). George et al. [68] created a score (the pre-arrest morbidity score (PAM)) to measure morbidity and mortality in hospitalized patients who had cardiopulmonary arrest and were resuscitated. Score development was based on weighted clinical variables and regression modeling. An inverse correlation was found between frequency of successful resuscitation and the probability of survival. Patients with a score equal to or greater than seven were reported to have low probability of survival, and the morbidity score was the only independent variable to significantly predict mortality. In summary, when medical testing is not feasible, risk-adjusted morbidity scores can be used to supplement clinical judgment and identify patients who are most likely to experience poor outcomes.

Important decisions can be made from risk-adjusted patient outcomes [69]. In addition to creating a foundation for future research, morbidity scores can be used to evaluate hospitals and physicians, can serve as a teaching aid for some physicians, and can be used by physicians in discussing treatment options with patients, thus allowing for informed decision-making [65, 69].

CHAPTER 3
CONCEPTUALIZATION

Chapter 2 introduced several variables previously explored in the literature as correlates of prescribing. Of those mentioned, a few have been selected for examination in this study. Mainly, variables reflecting demographics and type of board certification have been chosen, as these variables are also key elements in patients' access to health services.

Unpublished patient accounts highlight concerns over patients with SCD finding qualified professionals to help manage their condition [70]. Several focus groups eliciting the life experiences of patients with SCD were held with patients who had recently entered into an adult-oriented care system (see Appendix A). The focus groups took place in three north-central Florida cities. Data from the focus groups indicate that participants were troubled by the lack of SCD specialists, suggesting that, from their experience, generalists were not adept in managing SCD. Participants reported having to travel outside of their home cities to find qualified physicians. Distance to specialty care has been reported by McClellan et al. to be an important predictor of the type of treatment received [71]. These authors found patients living closest to catheterization hospitals to be more likely to undergo catheterization for treatment of acute myocardial infarction than patients living further away. These accounts underscore the importance of demographics with regards to where health services are located in relation to patients' residential location, and physician specialization in influencing patients' access to treatments. Recognizably, these variables are only a small representation of a myriad of

factors that contribute to patients' access to and receipt of particular treatments. Table 3-1 defines these and all other variables to be used in this study.

Figure 3-1 represents the conceptual framework guiding one of the objectives of this research. Following the Donabedian model of structure, process, and outcome, inferences about the quality of care provided to patients with SCD were attempted. Giving thought to the premise of good structure increasing the likelihood of good processes, and good processes promoting good outcomes induces a logical argument for evaluating quality under these triadic relationships [72].

Quality assessment studies can be used to illustrate that patient/provider attributes, when considered as determinants of a performance, indicate the likelihood of certain care components being delivered [44]. Most states and accrediting bodies require physicians to adhere to specific structures of health care (e.g. credentialing) [73]; however the linkages between the structures and processes or structures and outcomes of care are often not well defined. Possible explanations of the associations between structure and process or structure and outcome may lie within procedure-specific processes [45]. As an example, documentation of pain is a different process from prescribing a drug to treat or avert pain. Each of these processes is connected to a set of structural influences that may or may not be common to both, and each process may also hold its own respective set of outcomes. Given this and the realization that there are no single, universal measures of structure, process, or outcome, flexibility in the approach to quality assessment needs to be appreciated [45].

Table 3-1. Description of Variables

Variable	Definition
Disease-related morbidity (O)	Health care encounter (emergency department visit or hospitalization) generated for treatment of SCD or SCD-related complication (see Appendix B for list of complications)
Patient age (age)	Age of patient at the beginning of the observation period
Patient gender (gender)	Male or female gender
Comorbidity	Presence of hypertension, hepatitis C, diabetes, and/or HIV
Disease severity	Measured by the following variables: ➢ opiate use: continuous measure of the number of opiate prescriptions received throughout the observation period ➢ pulmonary infections ➢ chronic transfusion: patients who receive repeat transfusions as well as deferoxamine therapy
Treatment (P)	3 or more prescriptions for HU throughout the observation period
Treatment Supply	Total day supply of HU throughout observation period
Treatment initiating physician (S)	Type of board certification (specialist vs. nonspecialist) of physician initiating HU therapy ➢ Specialists: hematology/oncology, pediatric hematology/oncology ➢ Nonspecialists: internal medicine, family practice, general practice and general pediatrics
Treatment/disease managing physician (S)	Type of board certification (specialist vs. nonspecialist) of physician managing HU therapy ➢ Specialists: hematology/oncology, pediatric hematology/oncology ➢ Nonspecialists: internal medicine, family practice, general practice and general pediatrics
Patient/provider location (S)	County in which patients and providers resides

(S) = structure; **(P)** = process; **(O)** = outcome measures

Application of the structure, process, and outcome model has been seen across various settings and medical conditions. Lee et al. applied the model to their assessment of clinical integration in a hospital setting. The researchers sought to investigate the relationships between clinical integration (structure), average total charge per discharge (process), and surgical complications and in-hospital mortality (outcome). They found a significant association between the structure and process measures (although in an opposite direction than expected), and reported a significant direct relationship between the process and outcome measures [74]. Their results corroborated the triadic association proposed by Donabedian. Also in support of this model were the findings of Hoenig et al. [75], who evaluated stroke outcomes in patients in a VA medical center. Among other variables, system characteristics, adoption of guidelines, and post-stroke disability were used to examine the quality of care offered to stroke victims. The researchers observed that the structure of care independently predicted process of care, and improved processes led to better outcomes. A direct relationship between the structure and outcome of care was not established, maintaining that outcomes are indirectly affected by structure, and that the effect of structure on outcome is mediated by structure's influence of the process of care. In a study of the quality of diabetes care for black patients, Heisler and colleagues [76] concluded that deficiencies in medical care could contribute to poor outcomes. Standards from the Diabetes Quality Improvement Project (DQIP) and the Health Plan Employer Data and Information Set (HEDIS) were applied in their assessment. Patients for whom there were low performances on the process indicators used in the assessment experienced worst outcomes than patients for whom the process measures specific to diabetes care were adequately performed.

These studies offer a preview of how the Donabedian model can be used in outcomes research, and support the stability of the model across various study types. The integrity of the structure, process, and outcome paradigm conveys its usefulness in quality assessment and its suitability in the present research. The relationships to be modeled under this framework are hypothesized below:

H_{o1}: Type of board certification of treatment initiating physician has no effect on prescribing HU to SCD patients in usual care settings.

H_{a1}: SCD specialists are more likely to initiate treatment with HU than are nonspecialists, when treating SCD patients in usual care.

H_{o2}: Type of board certification of treatment/disease managing physician has no effect on subsequent prescribing of HU to SCD patients in usual care settings.

H_{a2}: SCD specialists are more likely to provide subsequent HU prescriptions than are nonspecialists, when treating SCD patients in usual care.

H_{o3}: Patient/provider location has no effect on prescribing HU to SCD patients in usual care settings.

H_{a3}: Usual care SCD patients who reside in the same county as their physician's practice location have easier access to care and are therefore more likely to receive treatment with HU than patients residing in a county other than that in which their physician practices.

H_{o4}: Controlling for health status, where health status is measured by disease severity and comorbidity, disease-related morbidity of SCD patients in usual care settings is independent of treatment initiating physician, treatment/disease managing physician, patient/provider location, and prescribing of HU.

H_{a4}: Controlling for health status, where health status is measured by disease severity and comorbidity, there is an association between treatment initiating physician, treatment/disease managing physician, patient/provider location, receipt of HU, and disease-related morbidity of SCD patients in usual care settings.

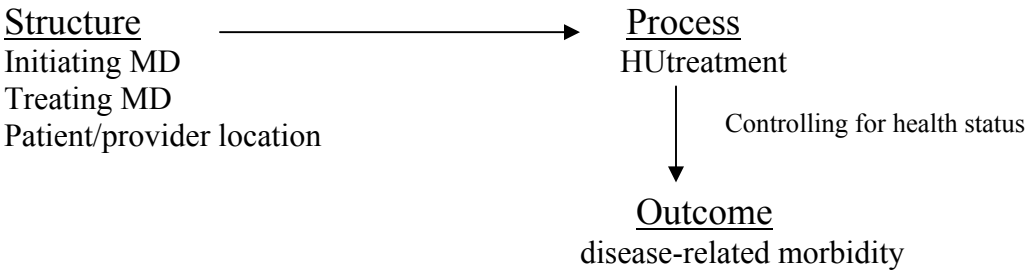

Figure 3-1. Conceptual Framework

A second object of this dissertation was to estimate the disease-related morbidity of SCD patients with regards to treatment with HU. For patients with SCD, one of the most promising advances in the management of this condition was the acceptance of HU as an important drug in SCD therapy. Support of decreasing clinical manifestations of SCD has been found in the efficacy study of HU [14], yet lacking are reports from studies of effectiveness. Effectiveness studies that are also able to demonstrate positive treatment outcomes will further substantiate what is already suspected, and will serve as a critical addition to the current body of knowledge. As an assessment of effectiveness, this dissertation provides a risk-adjusted model of disease-related morbidity associated with use of HU in patients with SCD. Based on what is known about the efficacy of HU and the existing gaps in the literature, the following hypothesis has been formulated:

H_0: Controlling for health status, where health status is measured by disease severity and comorbidity, use of HU has no effect on the disease-related morbidity of SCD patients in usual care settings.

H_a: Controlling for health status, where health status is measured by disease severity and comorbidity, SCD patients in usual care will experience reduced disease-related morbidity with the use of HU.

CHAPTER 4
METHODS

This dissertation presents application of a framework that evaluates the triadic relationship between structure, process, and outcome measures in health care. The objectives of this study were to develop a predictive model of disease-related morbidity of patients with SCD, and to examine the health outcomes of SCD patients with regards to the structure and process of health care. To investigate these relationships, a retrospective cohort analysis of observational data was employed.

Data Source

Medicaid Data

This project utilized administrative claims data generated by the Florida Medicaid system during fiscal years 1997-2002. Medicaid is a governmental program funded at the federal and state level that has been designed to provide health care coverage for populations who would otherwise go without coverage. The Medicaid program was established in Florida in 1970, and has since provided health care services for indigent and medically needy individuals.

Eligibility to receive Medicaid services is based on disability, annual earnings, and medical need. The three basic groups that are eligible under Florida's Medicaid plans include supplemental security income (SSI) recipients, low income children and families, and aged, blind, and disabled individuals. Health care services that are covered by Medicaid include but are not limited to prescription drug coverage, outpatient physician

visits, hospital care, laboratory and x-ray services, and visits to rural health and ambulatory clinics.

To be reimbursed for services, health care providers are responsible for submitting claims to the Medicaid program, noting the type of service provided. Medicaid reimbursement for pharmacy claims is in most cases based on a 30-day supply of prescription drugs. The claims are entered into separate files (ex. inpatient, outpatient, medical, pharmacy, long-term care, and transportation) which can be linked together for analysis. There is an additional file, eligibility, which contains useful information regarding the time periods in which a patient was covered under Medicaid. For the purpose of this dissertation, the eligibility, inpatient, outpatient, pharmacy, emergency department, and medical files were used.

Selection of subjects

This study only included Florida Medicaid recipients with a diagnosis of sickle cell disease. When a narrow definition of SCD was applied to the initial selection of subjects, it was observed that some patients who were found in the eligibility file one year were not captured in other years. To increase the sensitivity of the selection criterion and ensure the loss of patients was not due to changes in eligibility status, a broader definition of SCD that was based on a combination of three different algorithms was adopted. Under the first algorithm, Medicaid recipients were identified as having SCD if they had a primary, secondary, or tertiary ICD-9 diagnosis indicative of a blood disorder, as denoted by the codes 282.4, 282.5, 282.6, 282.60, 282.61, 282.62, 282.63, 282.69, 282.7, 282.8, and/or 282.9. Of those recipients who were not selected from this step, the second algorithm identified patients under the age of 45 with a primary, secondary, or tertiary ICD-9 diagnosis coded as 362.1, 362.16, 362.2, 430, 431, 431.1, 432, 434, 434.0, 434.9,

436, 437.1, 437.5, 707.1, 707.10, 707.19, 733.4, 733.40, 733.41, and/or 733.42; and/or a CPT code of 83020 or 36455. These codes reflect medical procedures or likely complications related to SCD, possibly due to stroke. The final algorithm identified patients with a NDC code reflecting a prescription for hydroxyurea attached to the pharmacy record. Realizing that this approach lacked specificity, true cases were then identified as recipients eligible for services in 2001 with an ICD-9 diagnosis of 282.61 (sickle cell disease without mention of crisis) and/or 282.62 (sickle cell disease with crisis) and/or 282.63 (sickle cell SC disease without crisis) in any year. The year 2001 was chosen because it was the most recent calendar year in the database for which there was complete data (data was available for only part of 2002, due to fiscal year reporting). Those not meeting this requirement as well as patients with an ICD-9 code for hemophilia or acute leukemia were eliminated.

As patients are initially enrolled to receive Medicaid coverage, they are assigned a unique identification number that can be used to track them throughout the system. Though this number should be retained as changes in eligibility occur it is possible that patients are re-assigned to other identifications numbers as they leave and re-enter the system. Of those patients who met database inclusion based on the selection criteria presented above, only those for whom there was a single unique identification number were retained. These patients were identified by examining the date of birth and address fields included in the eligibility file. Cases with different identification numbers but identical address and date of birth were assumed to be the same patient. Attempts at consolidating the observations for the cases assumed to be the same patient failed due to

incongruence in the data. These cases were therefore excluded from further analyses (n=10).

Because this study was designed from a longitudinal perspective, only those patients with continuous eligibility (i.e., maintained eligibility 80% of the time), during FY1997- FY2002 were desired. To identify these patients, the number of months between the beginning eligibility and ending eligibility dates was calculated for each patient. Patients who had a cumulative eligibility of at least 48 months out of the 60 month observation period were retained for the final cohort (n = 2,258). This method takes into account the fluctuations in enrollment without making assumptions regarding periods of inactivity.

Validation of database

Administrative databases have been reported to be a reliable compilation of information for outcome research studies [77, 78], and various techniques have been employed to validate these data sources. McKenzie and colleagues relied on Oregon Medicaid pharmacy claims to assess prescription drug use in an elderly population. To determine the accuracy of the Medicaid files, the authors compared the claims data to that contained in the patients' medical charts. They found overall agreement between the claims data and chart data to be greater than 95 percent [77]. Quam et al. reported on the utility of claims data in identifying patients with specific medical conditions. These authors used patient surveys and medical records to validate medical and pharmacy claims that came from two independent health plan organizations managed by United HealthCare Corporation, and were able to demonstrate a high level of agreement between the sources [78].

Whereas the above studies in common incorporated medical chart review into validation of the databases used, logistical constraints obviated the review of medical records for this dissertation. Other validation techniques (cross-validation and clinical judgment) were therefore employed. Florida hospital discharge data was used as a secondary database to make comparisons with the Medicaid claims. This database was obtained from the Florida Hospital Association (FHA) and consisted of inpatient charges generated at 225 Florida hospitals by patients with an ICD-9 diagnosis of 282.61, 282.62, 282.63, or 282.69 between 1997 and 2002. Because the discharge data file only contained hospital data, only the inpatient Medicaid claims were cross-examined, with the assumption that the other Medicaid files (outpatient, pharmacy, and medical) reflected similar validity. Comparisons were made by way of descriptive statistics, assessing similarities in race and gender distributions, and patient and provider locations. It should be noted that because unique patients could not be identified in the hospital discharge file, comparisons were based on individual hospital claims and not unique patients. As an additional measure of validation of the Medicaid database, judgments based on clinical knowledge and experiences of a practicing hematologist/oncologist were imposed on the data. Data from the medical, outpatient, emergency, and inpatient files were partitioned and examined for clinical plausibility. Questionable records were further investigated and reconciled where possible.

Data Analysis

This section describes the statistical techniques utilized for each specific objective outlined for this dissertation. Recalling from chapter 1, the objectives for this project were to (1) create a risk-adjusted predictive model of disease-related morbidity; and (2)

provide a quality assessment of health care by examining the relationships between the structure, process, and outcome measures of care.

Variable Descriptions

This section presents a detailed description of the variables studied in this dissertation.

Disease-related morbidity. Disease-related morbidity was expressed as the number of emergency department visits (ED) and/or hospitalizations (INPT), (collectively referred to as health care encounters), for SCD or complications of SCD. Emergency department visits that led to an inpatient stay were counted as a hospitalization only, and not as an ED visit. This morbidity variable was designed to reflect the extent of illness experienced by SCD patients, and how illness is modified with HU treatment. Patients with more ED and INPT encounters were assumed to have greater morbidity. Based on this assumption, outpatient visits were not considered here, as it is expected that patients properly managed on HU treatment will have recurrent follow-up physician visits, increasing their use of the outpatient clinic. In this sense, increased outpatient visits are a reflection of care and not necessarily of morbidity.

Patient age. This variable describes the age (in years) of the patient at the beginning of the observation period. Patients tend to experience more pain and become more susceptible to the onset of other chronic conditions as they age, calling for its inclusion in the risk adjustment procedures.

Patient gender. Another important variable in the risk adjustment is gender. Aside from the disparity between males and females in their use of the health care system, male patients with SCD have been reported to experience more pain than female patients.

Reasons for this trend may be due to the expression of HbF being greater in females than in males [79].

Comorbidity. Comorbidity was measured by the presence of one or more of the following conditions: hypertension (HTN), HIV, hepatitis C (HEP), and diabetes (DIA). Each condition was coded as 0 (not present) or 1 (present), and summed for a composite measure of comorbidity. The maximum score achievable was four. Hypertension and diabetes were controlled as comorbid disease states because of their high prevalence in blacks. Additionally, since HU is indicated for HIV as well as SCD, and because blood transfusions increase the risk of hepatitis C, it was necessary to account for the influence of these conditions in predicting morbidity.

Disease severity. Three variables were selected as independent indicators of disease severity: opiate use (opiate), pulmonary infection (PI), and chronic transfusion (TRANS). The opiate variable were represented a continuous measure of the number of opiate prescriptions received by patients. This is a reflection of the degree of pain experienced. As pain rate and intensity increases, so does opiate use. The presence of pneumococcal infections was used to reflect pulmonary infections. Based on prior research, diagnoses meeting this purpose include pneumonias due to adnovirus (480.0), respiratory syncytial virus (480.1), streptococcus (482.30, 482.31), staphylococcus (482.4), legionella (482.84), klebsiella (482.0), hemophilus influenzae (482.2), mycoplasma (483.0), and bacterial pneumonia (482.9) [80]. Patients who experience frequent pain episodes or who have had a stroke are often placed on chronic transfusion programs. Transfusions were identified by the procedure codes 9901, 9903, 9904, 9905, 9907, 9909, 36430, and 36455. The accumulation of iron in the body as a result of the

repeat transfusions is treated with iron chelation therapies such as deferoxamine, when the iron reaches a level associated with toxicity. While patients with mild disease may require episodic transfusions, they typically are not on chronic transfusion programs and are thus unlikely candidates for deferoxamine. Hence, transfusions plus desferal was used a third indicator of severity, where patients receiving both therapies were coded as '1' and all other patients '0'.

Treatment. The treatment variable (TRT) represents receipt of hydroxyurea. TRT=1 means patients received three or more prescriptions for the drugs. Since it takes approximately three months of treatment for clinical changes to appear, using a definition of three or more prescriptions seems appropriate. This definition assumes that patients were treated on a continuous basis with a 30-day treatment supply of HU. Only patients age 16 or older were considered, as current indication for HU in SCD is in older patients. TRT= 0 denotes patients who received fewer than three prescriptions, or who were not treated at all.

Treatment supply. Treatment supply (TS) is the total day supply of HU pills received throughout the observation period. This variable was created to take into account the variability in the amount of medication received by the patients.

Treatment initiating physician. This variable (initiate) reflects one of the structural influences on patients' access to HU treatment. Treatment initiating physician represents the medical specialty of the physician who provided the first prescription for HU. Because specialists have greater awareness of specific treatment advances, it was assumed that SCD specialists would be more likely to initiate HU therapy than non-specialists.

Treatment/disease managing physician. Similar to the 'initiate' variable, the management variable was developed to indicate the type of medical specialty of the physician who provided subsequent prescriptions for HU, after the initial prescription. Specialists again were thought to be more likely to maintain treatment with HU than are non-specialists.

Patient/provider location. A common challenge for patients with SCD is locating a physician who is knowledgeable about SCD and able to properly manage the disease. In Florida, there are not many physicians specialized in treating SCD, and patients sometimes find themselves traveling far distances to receive care. This prompted the hypothesis that residing in the same county as the physician's practice location (coded as location =1) increases access to health services and therefore the likelihood of treatment with HU.

Statistical Analysis.

This section of the chapter describes the statistical techniques to be used to in this dissertation. Each statistical test is presented under the objective to which it was applied. All tests of significance were conducted at a type I error (α) of 0.05 and type II error (β) of 0.20. Objectives, research questions and hypotheses, and statistical tests are summarized in Table 4-1.

Objective 1: To create a risk-adjusted predictive model of disease-related morbidity in patients with SCD, with regards to treatment with HU.

1. Controlling for underlying health status, where health status is measured by disease severity and comorbidity, does use of HU reduce disease-related morbidity in SCD patients in usual care settings?

H_0: Controlling for health status, where health status is measured by disease severity and comorbidity, use of HU has no effect on the disease-related morbidity of SCD patients in usual care settings.

H_a: Controlling for health status, where health status is measured by disease severity and comorbidity, SCD patients in usual care will experience reduced disease-related morbidity with the use of HU.

The morbidity score is important for assessing health outcomes while adjusting for extraneous risk factors. Although no risk-adjustment approach can control for every factor that affects the outcome of care [81], morbidity scores offer a more precise estimate of the effect of a particular variable on the outcome of interest when other factors are considered. No objective measure of morbidity is provided in the database used in this study, thus, as a proxy measure, disease-related morbidity was measured by a composite of ED and INPT health care encounters.

The predictive model was estimated in two phases. Phase one involved creating the composite of ED visits and hospitalizations. Since there is a hierarchy between these measures, where a hospitalization is obviously more serious than a visit to the emergency department, simply adding the counts of ED visits to the counts of hospitalizations did not fully capture the hierarchy. Rather, this was handled by the statistical procedure principal components analysis (PCA). In applying PCA, number of ED and INPT encounters was summarized into one meaningful measure. PCA works best when there is correlation between the variables, making it ideal for the present application.

In PCA, the variables are treated equally and each principal component is a linear combination of the original variables. The first principal component is the most informative and accounts for most of the covariance shared by the original variables. It is this component that was adapted for the composite measure of disease-related morbidity.

The second phase of the model development was the prediction phase. So as to gain a more efficient estimate of treatment effect, only patients meeting the requirement of three or more prescriptions of HU were included, and the disease-related morbidity of

these patients was estimated by two stepwise multiple regression equations. The first equation (EQ 1) was developed to predict morbidity before the initiation of HU. This represents the pretreatment model. To estimate pretreatment morbidity, only ED and INPT claims generated before the HU startdate were included in the calculation of the pretreatment morbidity scores. This provided a measure of SCD-related complications prior to treatment with HU. The model is illustrated by

EQ1. $\text{morbidity}_{\text{pretrt}} = \alpha + \beta_1\text{age} + \beta_2\text{gender} + \beta_3\text{comorbidity} + \beta_4\text{opiates} + \beta_5\text{pi} + \beta_6\text{trans}$,

where trt = 0.

For the second prediction equation (the post-treatment model), ED and INPT claims generated after the HU startdate were used to form post-treatment morbidity scores, providing a measure of SCD-related complications after treatment with HU. This equation is depicted as

EQ2. $\text{morbidity}_{\text{posttrt}} = \alpha + \beta_1\text{ts} + \beta_2\text{age} + \beta_3\text{gender} + \beta_4\text{comorbidity} + B_5\text{opiates} + \beta_6\text{pi} + \beta_7\text{trans}$,

where trt = 1.

The pretreatment morbidity score was compared to the post-treatment score and the effect of treatment was determined. Estimating morbidity in this way provided a pre/post treatment assessment and allowed patients to serve as their own control group.

Stepwise multiple regression was used to estimate the prediction models. This procedure maximizes prediction accuracy by applying statistical criteria to eliminate those variables not contributing to model prediction. The purpose was to identify and retain only those variables that significantly added to the model, making the model more precise. Stepwise regression evaluates the meaningfulness of each of the independent variables in a sequential manner. All of the variables are initially correlated with the

dependent variable, and the one with the highest correlation enters first into the equation. This process is repeated, with variables being examined at each step for inclusion and added to the model if the partial correlation is highest of all of the remaining variables. The process ends when the addition of variables will not significantly improve the predictive abilities of the model.

Objective 2: To explore the health outcomes of patients with SCD in relation to the structure and process of health care.

2. To what extent do treatment initiating physician, treatment/disease managing physician, and patient/provider location, influence patients' receipt of HU among SCD patients in usual care settings?

H_{o1}: Type of board certification of treatment initiating physician has no effect on prescribing HU to SCD patients in usual care settings.

H_{a1}: SCD specialists are more likely to initiate treatment with HU than are nonspecialists, when treating SCD patients in usual care.

H_{o2}: Type of board certification of treatment/disease managing physician has no effect on subsequent prescribing of HU to SCD patients in usual care settings.

H_{a2}: SCD specialists are more likely to provide subsequent HU prescriptions than are nonspecialists, when treating SCD patients in usual care.

H_{o3}: Patient/provider location has no effect on prescribing HU to SCD patients in usual care settings.

H_{a3}: Usual care SCD patients who reside in the same county as their physician's practice location have easier access to care and are therefore more likely to receive treatment with HU than patients residing in a county other than that in which their physician practices.

3. Controlling for health status, where health status is measured by disease severity and comorbidity, what is the combined association of the measures of treatment initiating physician, treatment/disease managing physician, patient/provider location, and receipt of HU on the disease-related morbidity of SCD patients in usual care settings?

H_{o4}: Controlling for health status, where health status is measured by disease severity and comorbidity, disease-related morbidity of SCD patients in usual care settings is

independent of treatment initiating physician, treatment/disease managing physician, patient/provider location, and prescribing of HU.

H_{a4}: Controlling for health status, where health status is measured by disease severity and comorbidity, there is an association between treatment initiating physician, treatment/disease managing physician, patient/provider location, receipt of HU, and disease-related morbidity of SCD patients in usual care settings.

Instrumental variable (IV) analysis was used to assess the relationships presented in the above hypotheses. The associations that were tested are depicted by Figure 4-1. A common concern with the analysis of observational data is the presence of selection bias. Due to the lack of randomization in observational studies, patients have an unequal probability of receiving treatment for their health condition. In usual care settings, treatment decisions typically depend on unobserved characteristics such as health status and comorbid illnesses [82]. From an epidemiological point of view, treatment becomes confounded by indication, as only patients demonstrating certain disease characteristics are likely to receive treatment. Thus, it is these unobservable factors, and not the process of randomization, that influences treatment assignment in observational studies.

Another concern with observational data is reverse causality, in which the association between the independent and outcome variable is bidirectional ($X \leftrightarrow Y$). For example, the likelihood of treatment with HU (X) is dependent on the degree of disease-related morbidity, where disease-related morbidity is also the outcome of interest (Y). Using methods of instrumental variable estimation to control for the presence of reverse causality and counter selection bias, a pseudo-randomization that stratifies patients to different likelihoods of receiving treatment and isolates the variation of the effect of X on Y is created, facilitating estimation of the marginal treatment effect.

Unlike in clinical trials, where the treatment effect can be estimated by the difference between the group means (assuming the randomization worked and there are no baseline differences between the groups) the lack of randomization in observational studies, and consequential unequal treatment groups, does not allow for the interpretation of average treatment effects [82]. Instead, the marginal effect of treatment (i.e., the effect of treatment taking into account the differential risks in receiving treatment) can be determined. The marginal treatment effect presents a treatment effect of patients who receive treatment only because they belong to a certain group. An illustration of this concept follows. Consider two groups of patients, one residing in a rural city and the other group in a non-rural city. These groups will be referred to as R and NR, respectively. Now consider a hypothetical value of 5.2 on the outcome measure of pain episodes/year for R and 2.1 for NR; and that 10.3 percent of patients in R received treatment with HU, compared to 17.5 percent in NR. A marginal treatment effect can be estimated by the equation:

$$\text{EQ3.}\quad \text{marginal effect} = \frac{\text{difference in outcome}}{\text{difference in treatment}}$$

Substituting the numbers into the equation,

$$\text{EQ4.}\quad \text{marginal effect} = \frac{5.2 - 2.1}{10.3 - 17.5} = -0.43$$

This shows us (1) that there is an additional 7.2 percent of patients who received treatment because they reside in a non-rural city (17.5 – 10.3), referred to as the marginal patients; and (2) the 7.2 percent of patients who received HU because they reside in a non-rural city had a 43 percent reduction in pain.

A two stage least square regression (2SLS) technique was applied for the instrumental variable estimation. This method consisted of two regression equations, one in which the instrumental variables were used to predict treatment (EQ5) and another using the predicted value of treatment from the first equation to explain the outcome (EQ6). For this stage of analysis, treatment patients were identified as patients age 16 or older with three or more prescriptions for HU. Non-treatment patients were those with three or more ED visits and/or hospitalizations for pain in any year who were never prescribed HU.

$$\text{EQ5.}\quad T_i = \alpha + \beta_1 X_i + \beta_2 A_i + \theta_i + \varepsilon$$

$$\text{EQ6.}\quad O_i = \delta + \gamma_1 X_i + \gamma_2 T_i + \theta_i + \varepsilon,$$

where T_i represents the treatment variable, O_i the outcome variable, X_i the set of independent variables, A_i is the set of instrument variables, and θ_i represents the unobserved variables that affect treatment assignment and outcome. This analysis assumes that the instrumental variables are directly related to treatment, and are unrelated to the unobservable factors confounding treatment and outcome. This process yields unbiased estimates of marginal treatment effect that are attributable to treatment differences based on how patients are distributed across the instrumental variables.

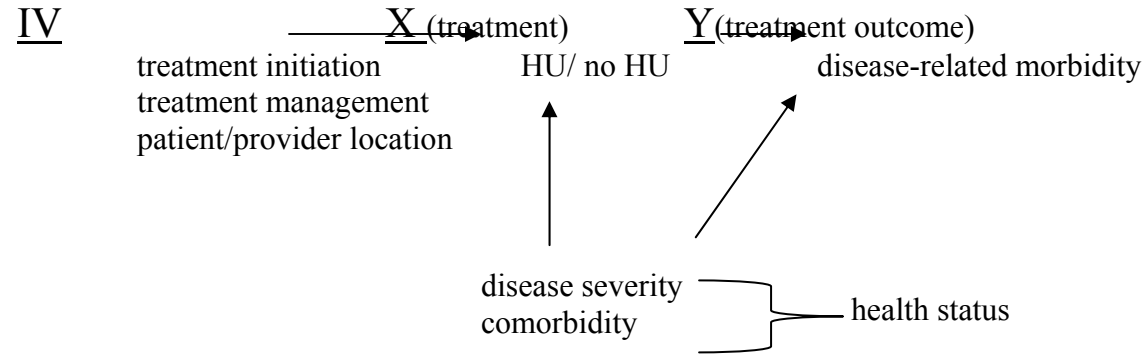

Figure 4-1. Model for Instrumental Variable Analysis

Table 4-1. Summary of Objectives, Research Questions, Hypotheses, and Statistics

OBJECTIVE	RESEARCH QUESTION	HYPOTHESIS	STATISTICAL TEST
Predictive model of disease-related morbidity	Controlling for health status, does use of HU reduce disease-related morbidity in usual care settings?	Controlling for health status, SCD patients will experience reduced disease-related morbidity with the use of HU.	PCA Stepwise regression
Assess structural and process influences on health outcomes	To what extent does treatment initiating MD, treatment managing MD, and pt/provider location influence patient's receipt of HU?	SCD specialists are more likely to initiate treatment with HU than are nonspecialists.	IVA (2SLS)
		SCD specialists are more likely to provide subsequent HU prescriptions than are nonspecialists.	IVA (2SLS)
		SCD patients who reside in the same county as their physician's practice location are more likely to receive treatment with HU than patients residing in a county other than that in which their physician practices.	IVA (2SLS)
	Controlling for health status, what is the combined association of initiating MD, managing MD, location, and treatment on the disease-related morbidity?	There is an association between treatment initiating physician, treatment/disease managing physician, patient/provider location, receipt of HU, and disease-related morbidity of SCD patients.	IVA (2SLS)

Limitations

The wealth of information provided by administrative claims makes claims database a suitable source of data for outcomes research. The benefits of use, however, are not without limitations. Since there is no uniform method of data collection and entry, there is great potential for administrative errors, such as errors in coding, incomplete data files and information gaps. Misclassification due to these errors is likely to result. With specific reference to Medicaid, because the data is reported in separate files according to the type of service provided, it is likely that information reported for a variable in one file may differ from that reported for the same variable in another file. For example, it was observed in the current database that for a particular patient, the outpatient file reported a date of birth different than that in the eligibility file. To resolve this and other like incidences, all other files (i.e. pharmacy and inpatient) were examined to identify the correct information, and the data was recoded accordingly.

Also with Medicaid databases, generalizability of the results is limited by the inherent skewness of the data due to the overrepresentation of disadvantaged children, females and nonwhites [83]. The risks associated with disadvantaged populations may differ from those of advantaged populations [81]. What is more, patients cycle through the Medicaid system with varying eligibility and may not be enrolled on a continuous basis. This complicates methods for using Medicaid data for population-based longitudinal analysis. The method used here to identify continually eligible patients captured patients who were eligible for Medicaid at least 80 percent of the observation period. Different findings may result from patients with a different threshold for eligibility.

The lack of laboratory and/or patient-reported data to supplement the database complicated defining some of the variables used in this study. The database does not contain a true measure of morbidity so a surrogate measure based on health care utilization was adopted. Recognizing that increased utilization of outpatient services is associated with best practice guidelines, and so as to not compromise the integrity of the disease-related morbidity measure, outpatient resource utilization was not included. Further, patients who use the emergency department and who are hospitalized have failed to control their symptoms at home, and their use of these services becomes an indication of disease exacerbation. These things considered, emergency department and hospital health care encounters are suitable measures of morbidity. A surrogate measure was also used to define acute chest syndrome. There is no standard ICD-9 code for this condition, and multiple codes for pneumonia are contained within the database. The diagnoses selected to represent pulmonary infections were based on clinical findings reported from previous research, upholding their use here [80]. Hydroxyurea use as defined in this study was based on generation of a prescription claim. The claim itself does not guarantee that the drug will be taken as prescribed, if taken at all, thus findings of better treatment outcomes may be biased. As another limitation, many variables that are important to health outcomes of SCD patients (e.g. patient compliance, genetic factors, hemoglobin levels, hematocrit, and mean corpuscle volume) are not contained in the Medicaid database, restricting the analysis.

Lastly, there are no NIH funded comprehensive SCD treatment centers in Florida that coordinates the care for adult patients. The results of this study may differ from those of states where a comprehensive treatment center exists.

CHAPTER 5
RESULTS

This chapter presents the study findings. First, validation of the database will be discussed, followed by a section detailing descriptive characteristics of the study population. Findings that are specific to the goals of this project are presented under their respective objective.

Database Validation

As a means of validation, the inpatient file from the Medicaid database used in this study was compared to an external database file (Florida hospital discharge) and the similarities between the two were determined. Patients in both files were reported to have sickle cell disease, to receive Florida Medicaid, and to be hospitalized at some point between 1997 and 2002.

The files were compared on location of providers and patients, patient gender and patient race (Table 5-1). The distribution of patients across the Florida counties was nearly identical in both files, with most inpatients residing in Dade County. Dade County was also where the majority of providers were located and where most hospitalizations occurred. As with the external file, females were more prevalent than males in the inpatient Medicaid file, and were equally represented in both files (56%). As expected, 'black' was the most popular ethnic group represented in the files. Given the comparisons of the files and the similarities between the two, and assuming that all of the files in the Medicaid database have validity comparable to that of the inpatient file, the validity of the Medicaid data is acceptable.

Table 5-1. Database Comparisons

	Medicaid (*%)	Hospital Discharge (*%)
Gender		
Female	56.2	56.4
Male	43.8	43.6
Race		
Black	71.1	93.9
Hispanic	0.82	3.8
White	0.87	1.02
Other	27.1	0.63
Patient County		
Dade	28.1	25.8
Broward	9.1	11
Hillsborough	7.4	7.1
Duval	5.8	7.4
Orange	5.5	6
Other	44.1	42.7

*represents percentage of claims

Descriptive Findings

The subject selection criteria described in the previous chapter yielded 2,258 patients who were eligible for analysis. Of those, approximately 69% were black and 52% were female. Twenty-six percent of the patients had their race reported as 'other', and there was one patient for whom no gender was reported. The mean age at the start of the observation period (1997) was 14.3 years and the mean ending age (2002) was 19.1 years. Since SCD is a disease detected at infancy and the risk for mortality increases with age, it is understandable that adults are underrepresented in the database. As presented in Table 5-2, the majority of the patients meeting the eligibility requirements were located in metropolitan Florida counties, with the highest proportion residing in Dade County.

Figure 5-1 shows the distribution of the patients across the separate Medicaid files. There were 1,773 of the 2,258 patients who had at least one visit to the emergency

department and 1,742 who had at least one inpatient stay. Of the 2,214 patients that presented with a prescription claim, only 306 were prescribed at least one month of HU at any time during the observation period. These patients were between the ages of 3 and 58 years at the time treatment was initiated.

To be considered for analysis according to treatment, patients had to have been prescribed at least three prescriptions for hydroxyurea. Figure 5-2 illustrates the number of patients who received at least three prescriptions for HU for each year of the observation period. Also shown is the total number of patients who received at least one prescription per year. The incidence of new prescriptions (i.e., number of patients not prescribed HU in the previous years) is given in Table 5-3. The proportion of the total number of patients prescribed HU each year that were new recipients ranged from 25% to 53%.

Although HU is FDA approved for patients aged 18 years and older, it is not uncommon for patients who are at least 16 years of age to be prescribed HU in usual care. For this reason, the analysis was further restricted to patients aged 16 and older. There were 153 patients who were at least 16 years of age and had at least three prescriptions for HU. It was initially assumed in defining treatment that patients would be prescribed a 30-day supply of HU on a continuous basis, given treatment tolerability. When continuity of therapy was assessed, the data indicated that 39% of the 153 patients had an average time between HU prescriptions of one month, and that 41% had an average time between prescriptions of greater than two months. This suggests that there were many patients for whom therapy was non-continuous. Whereas most patients were prescribed a 30-day supply of treatment as suspected, there were some patients who received less and

a few patients who received more. Five patients were prescribed a 90-day supply and there were seven patients for whom a 100-day supply of HU was prescribed.

Table 5-2. Demographic Characteristics of Continuously Eligible Patients

Characteristic	*n (%) (N= 2,258)
Months eligible	57.6 (± 6.9)
Age	
Beginning age	14.3 (±13.2)
Race	
Black	1,554 (68.8)
White	63 (2.8)
Hispanic	60 (2.7)
Other	581 (25.7)
Gender	
Female	1,181 (52.3)
Male	1,076 (47.7)
Top Counties	
Dade	540 (23.9)
Broward	214 (9.5)
Duval	181 (8.0)
Palm Beach	154 (6.8)
Hillsborough	140 (6.2)
Orange	137 (6.1)
Lowest Counties	
Calhoun	1 (0.04)
Hardee	1 (0.04)
Liberty	1 (0.04)
Baker	2 (0.09)
Citrus	2 (0.09)
Dixie	2 (0.09)

*Means (standard deviations) presented for age and months eligible

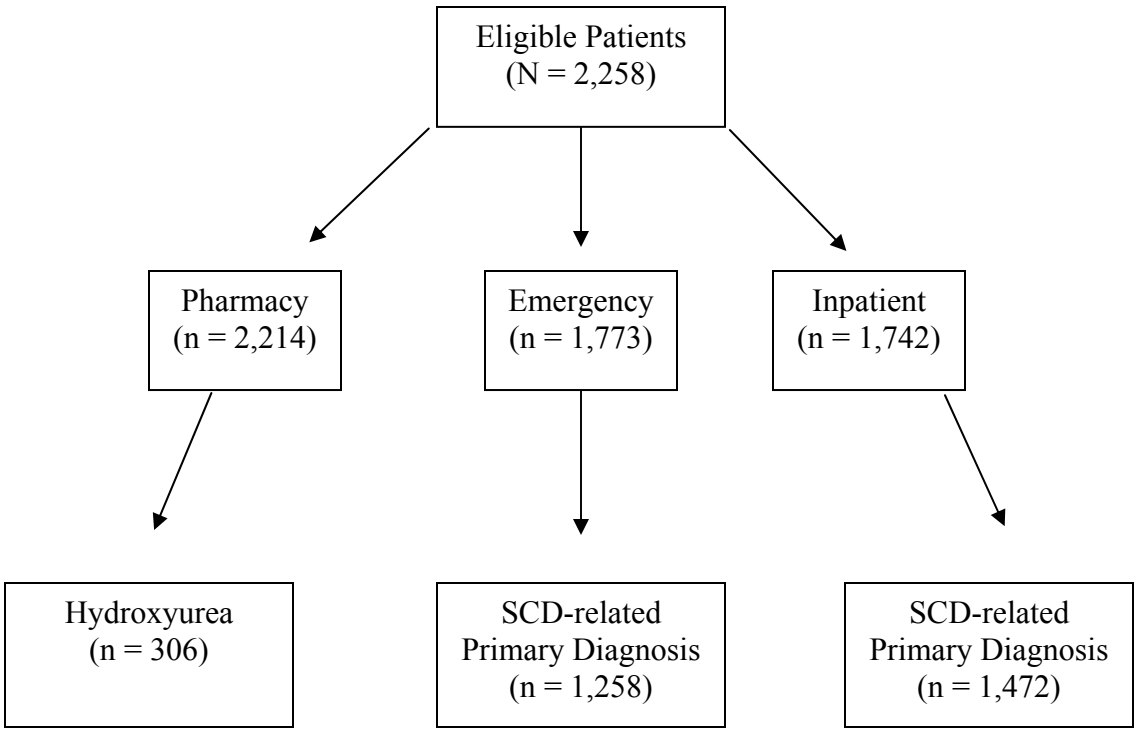

Figure 5-1. Distribution of Patients Retained in the Database

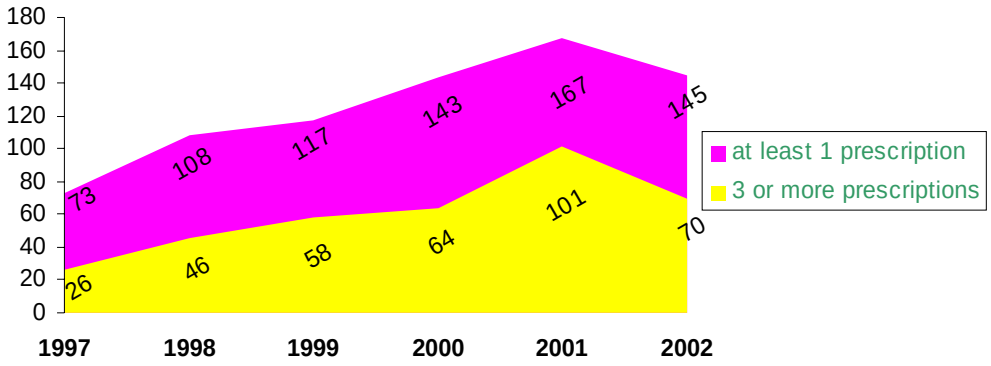

Figure 5-2. Number of Patients Prescribed Hydroxyurea

Table 5-3. Number of New Hydroxyurea Recipients per Year

Year	Total Number of Recipients	Number of New Recipients
1998	108	57
1999	117	39
2000	143	56
2001	167	45
2002	145	36

Objective 1: Predictive Model of Morbidity

Principal Component Analysis

To form a composite measure of disease-related morbidity on the basis of health care encounters (emergency department visits and hospitalizations), principal component variables were computed. The variance-covariance matrix was used in the computation of the principal component variables. Social science researchers often resort to extracting components from the correlation matrix due to the arbitrary scaling of tests used in social science research, yet when the scales of the original variables are comparable, as is the present case, extractions based on the covariance matrix are recommended [84]. Pretreatment and post-treatment estimates were calculated separately, and were used in the calculation of pretreatment and post-treatment morbidity scores.

The total variance of the original health care encounter variables increased from pretreatment to post-treatment (45.16 and 178.39, respectively). In the pretreatment estimation, 89% of the total variance was explained by the first principal component (PRIN1), and 74% was explained by PRIN1 in the post-treatment estimate. The components indicated a decrease in morbidity as the number of ED visits and hospitalizations decreased, and an increase in morbidity with increasing health care

encounters. A composite morbidity score was calculated for each patient based on the coefficients provided by the principal components.

Morbidity Scores

Pretreatment and post-treatment morbidity scores were calculated for the 153 patients who were at least 16 years of age and had three or more prescriptions for HU. These scores represent a weighted sum of the number of ED visits and hospitalizations for a SCD-related complication. The mean (median) pretreatment score was 4.11 (0.34) compared to 7.80 (2.86) post-treatment. The unexpected higher post-treatment score was influenced by the lack of data from previous years for patients who began HU therapy in 1997. Without this data, no pretreatment measures were available, thus only health care encounters occurring after HU initiation was provided. Given this, and to approximate equal lengths of pre/post observation, patients who began HU prior to 1999 were removed from the analysis and subsequent modeling was based on the remaining patients (n=67). The smaller sample size did not affect statistical power. The mean (median) of the adjusted pretreatment morbidity scores was 6.67 (4.67) and the mean for the adjusted post-treatment scores was 4.92 (1.43). Hence, hydroxyurea was associated with a 26% reduction in morbidity in these patients. Figures 5-3 and 5-4 portray these comparisons. Figure 5-3 displays the range of pretreatment and post-treatment morbidity scores of the original 153 patients. Figure 5-4 shows the range of morbidity scores for the adjusted cohort. As seen in Figure 5-4, the range of morbidity scores was smaller post-treatment.

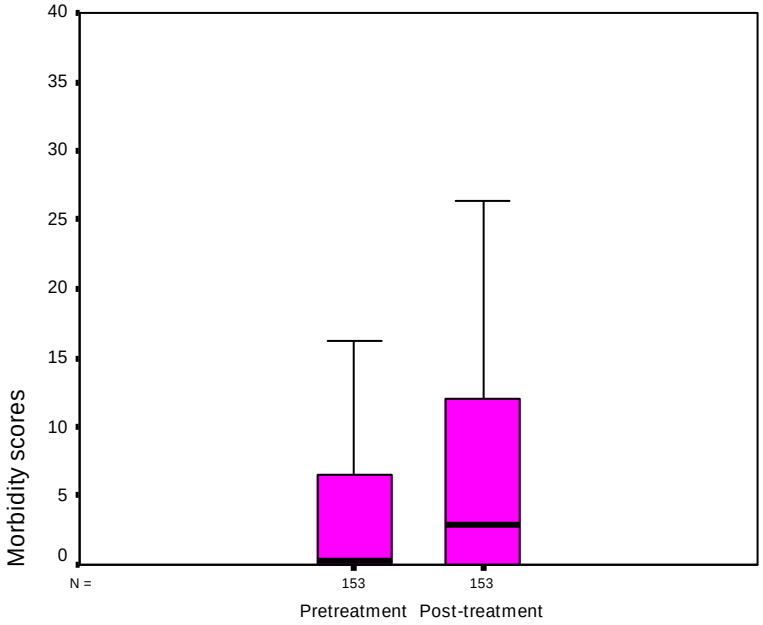

Figure 5-3. Distribution of Morbidity Scores

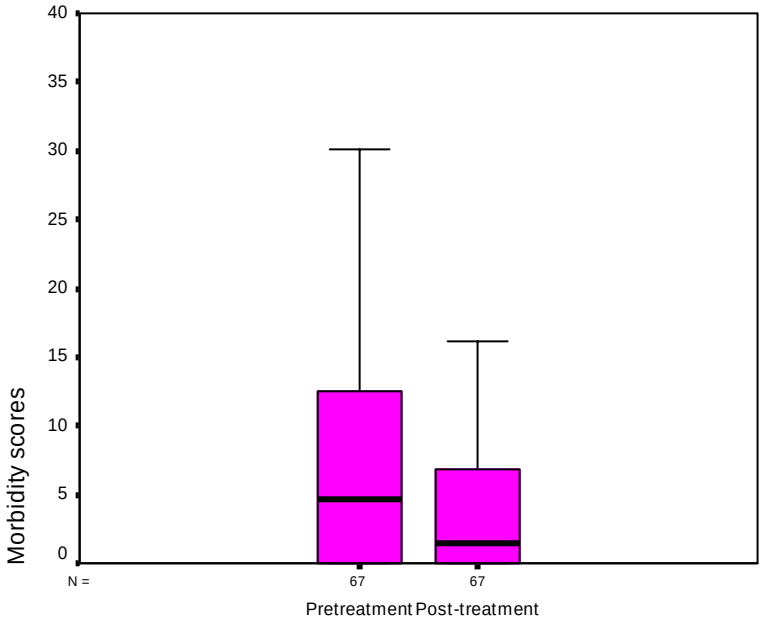

Figure 5-4. Adjusted Morbidity Scores

Additional comparisons were made on patients with six or more prescriptions for HU to further evaluate treatment effect (n=30). In these 30 patients, a 22% reduction in

morbidity was detected. The mean (median) morbidity score was 7.0 (5.60) and 5.44 (2.49) pre- and post-treatment, respectively.

A positive treatment response was not seen in all patients. As indicated by Figures 5-5 and 5-6, there was individual variation in the response to treatment, with some patients exhibiting an increase in morbidity despite treatment with HU. The histogram in Figure 5-7 represents the total day supply of treatment from 1999 to 2002 of the 67 retained patients. The majority of the patients received a total day supply between 90 and 150 days and one patient received nearly 800 days supply.

Predictive Model of Morbidity

Two stepwise regression models were constructed to predict pretreatment and post-treatment morbidity. Variables retained from the stepwise selection process were significant at the 0.15 level. Significant risk factors for morbidity did not change with the initiation of HU. The factors that significantly predicted morbidity prior to treatment with HU were also significant risk factors for morbidity after treatment initiation. Younger patients experienced more frequent disease-related complications than older patients, and patients with HIV, hypertension, hepatitis C, and/or diabetes were nearly five times as likely to exhibit complications as patients without comorbid conditions. Increasing use of opiate drugs was also predictive of morbidity. For every increase in the number of opiate prescriptions, morbidity increased by 0.06 pretreatment and by 0.13 post-treatment. These findings are summarized in Table 5-4. Twenty-three percent of the variance in morbidity was explained by the variables retained in the pretreatment model, while identical risk factors were responsible for 55% of the variance in post-treatment morbidity.

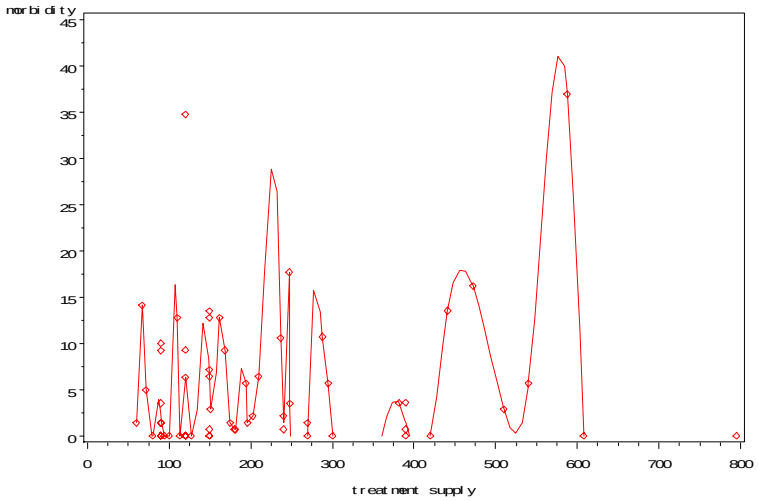

Figure 5-5. Morbidity by Treatment Supply

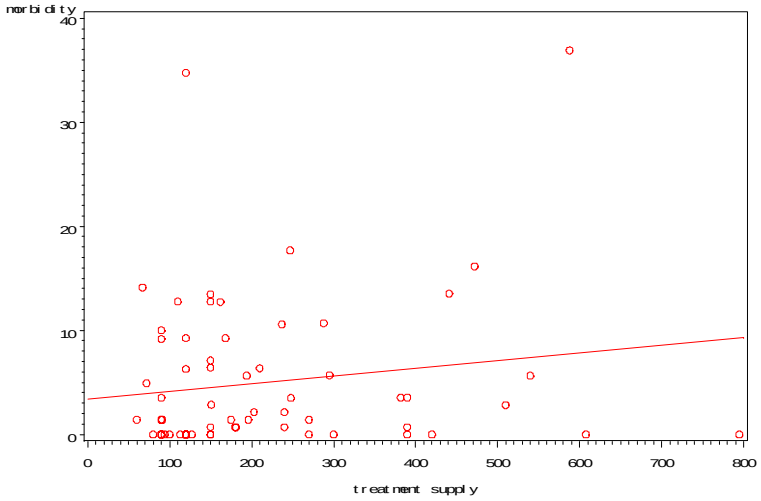

Figure 5-6. Scatterplot of Morbidity by Treatment Supply

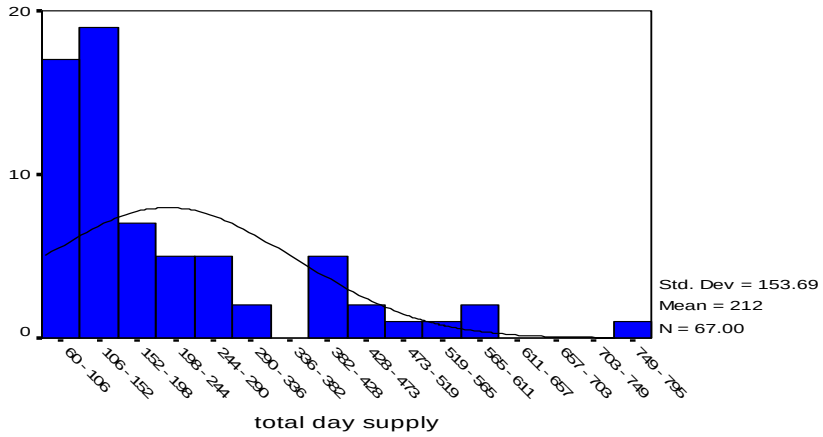

Figure 5-7. Histogram of Treatment Supply

Table 5-4. Summary of Stepwise Regression Analysis

(n=67)	**Variable**	**b**[†]	**P-value**[‡]	**Partial R^2**
Pretreatment				
	Comorbidity	4.79	0.001	0.03
	Age	-0.31	0.106	0.10
	Opiate	0.06	0.008	0.10
Model Summary			0.0008 (F=6.34)	Adj. R^2=0.20
Post-treatment				
	Comorbidity	4.68	0.007	0.06
	Age	-0.30	<0.0001	0.11
	Opiate	0.13	<0.0001	0.38
Model Summary			<0.0001 (F=25.54)	Adj. R^2=0.53

[†]parameter estimate, beta [‡]significant at the 0.15 level

Objective 2: Structure, Process, and Outcome Assessment

The relationships between physician specialty, patient/provider location, prescribing of HU and disease-related morbidity were assessed under objective 2. The comparison groups were made of 154 non-treatment patients and 153 treatment patients.

The data used for this analysis consisted of peculiarities with regards to medical specialty, in that some patients were purportedly exposed to HU treatment by physicians who would not typically recommend drug therapy for SCD (e.g. ophthalmologists, obstetrician/ gynecologists). To handle this and maintain the fidelity of the specialty variables, medical specialty was defined for each patient by the specialty of the prescribing physician most represented for that patient; and patients who were only treated by physicians who would not typically prescribe HU were excluded.

After the exclusions there were 141 treatment patients and 144 non-treatment patients who were retained for analysis. Non-treatment patients were 54% female, had a mean age of 25.7 years, and a mean morbidity score of 13.91 (median: 10.4; range of score: 2.07 – 79.85). The mean morbidity score for treatment patients was 11.04

(median: 7.6; range of score: 0 – 80.97). Hypertension was the most prevalent comorbidity for both groups of patients. Overall, 52% of all patients were treated by non-SCD specialists (internal medicine, family practice, general practice, or general pediatric physicians), and non-specialists provided most of the care to patients not treated with HU. The care for patients who were treated with HU was mostly managed by hematologists or oncologists. Table 5-5 summarizes the characteristics of the patients. Aside from who manages their care, the two groups were not significantly different based on demographic characteristics.

Table 5-5. Characteristics of Treated vs. Non-treated Patients

Characteristic	†HU (N =141) *n (%)	‡No HU (N=144) *n (%)	**P-value
Age	27.8 (±10.4)	25.7 (±8.9)	0.07
Gender			0.69
Female	73 (52)	78 (54)	
Male	68 (48)	66 (46)	
Managed by SCD specialist	92 (65)	45 (31)	< 0.0001
Comorbidities			
Diabetes	4 (3)	7 (5)	0.36
Hypertension	12 (8)	15 (10)	0.58
HIV	1 (.71)	3 (2)	0.62
Hepatitis C	3 (2)	5 (3)	0.49
Morbidity Score	11.04 (±13.18)	13.91 (±12.64)	0.06

†indicates patients who were treated with hydroxyurea; ‡indicates patients not treated with hydroxyurea; *mean (standard deviation) given for age and morbidity score;
** tests of significance at $\alpha < 0.05$

Instrumental Variable Analysis

The IVA technique assumes that (1) changes in the instruments will produce changes in X, and (2) there is no direct effect of the instruments on Y. To test the first assumption, cross-tabulations of each instrumental variable with the treatment variable

(X) were produced. When only one of the specialty variables was considered at a time, SCD specialists were more likely to initiate and more likely to manage HU therapy than non-specialists. However, when the two specialty variables were considered together, the interpretation of the effect of physician specialty on prescribing HU changed, suggesting that non-specialists were more likely to initiate therapy. This signified an interaction between the two variables. Because the 'initiating physician' and 'managing physician' variables essentially measure the same concept (physician specialty), the two variables were combined to handle the collinearity between them. This was accomplished by selecting the specialty of the provider who did most of the prescribing, regardless of who initiated the prescribing. This single physician specialty variable replaced 'initiating physician' and 'managing physician' as instrumental variables. For the instrument 'patient/provider location', 35% of patients who reside in counties other than their physician's practice location were prescribed HU, and 53% of patients residing in the same county as their physician's practice location were treated with HU, giving a marginal difference of 18% of treated patients. For the instrument 'physician medical specialty', non-SCD specialists provided treatment with HU in 33% of their patients, compared to SCD specialists, who provided HU prescriptions to 67% of their patients. This represents a marginal difference of 34% of patients being prescribed HU. The variability in prescribing across the groups that make up the instrumental variables support the assumption that changes in the instruments will produce changes in prescribing.

By testing the correlation between the instrumental variables and the variables that represent the unobservable characteristic of health status, the association between the

instrumental variables and disease-related morbidity can be assessed. Non-significant correlations were found between patient/provider location and health status (disease severity and comorbidity) as well as between the specialty variable and health status, suggesting that the instrumental variables are uncorrelated with disease-related morbidity. This confirms the second assumption.

Two stage least squares regression was applied to the execution of the instrumental variable analysis. In stage one, the factors chosen to represent the structure of health care were regressed on the process measure, treatment. Patient/provider location and physician specialty exhibited mixed contributions to the prescribing of HU. Provider practice location in relation to patient's residence did not have a significant influence on the process of prescribing HU ($p = 0.06$), while the prescribing of HU was significantly associated with physician specialty ($p < 0.0001$). When compared to non-specialists and after adjusting for comorbidities and disease severity, SCD specialists prescribed HU 30% more often. This finding substantiate the hypothesis that physicians who specialize in treating SCD are more inclined to recommend therapy with HU. Of the health status variables controlled in the analysis, only increasing opiate use as a measure of disease severity was [minimally] associated with hydroxyurea use (Table 5-6).

Stage two of the analysis consisted of using the predicted values of treatment to predict disease-related morbidity (Table 5-7). After taking into account disease severity and comorbidities, combined with the effect that patient/provider location and provider medical specialty had on prescribing, patients for whom HU was prescribed were less likely to experience a complication leading to a visit to the emergency department or a hospitalization than non-treated patients. On average, morbidity was lower by 5.25 in

treatment patients. While this reduction in morbidity holds clinical precedence, statistical significance was not established (p=0.25).

The presumption that the outcome of health care is not directly influenced by the structure of health care was upheld by this study. Neither patient/provider location nor physician medical specialty had a significant bearing on the disease-related morbidity of patients with SCD. Though medical specialty was significantly related to the use of HU, the 34% difference between SCD specialists and non-specialists in prescribing HU was not associated with a difference in SCD-related complications between patients treated by specialists and those treated by non-specialists. This is evidenced in Table 5-8. The two patient groups were comparable on several other characteristics.

Table 5-6. Instrumental Variable Analysis - Step 1: Predicting Prescribing

Predictor	Coefficient (b)	t value	*P-value	(N =285)
Location	0.13	1.85	0.06	
Physician specialty	0.30	5.33	<0.0001	
Comorbidity	-0.06	-1.03	0.31	
Pulmonary infection	0.11	0.85	0.39	
Opiate	0.001	2.72	0.007	
Transfusion	0.15	1.09	0.28	

*significant at 0.05 level

Table 5-7. Instrumental Variable Analysis - Step 2: Predicting Morbidity

Predictor	Coefficient (b)	t value	*P-value	(N = 285)
HU	-5.25	-1.14	0.25	
Comorbidity	0.79	0.49	0.63	
Pulmonary infection	9.46	2.70	0.007	
Opiate	0.06	4.38	<0.0001	
Transfusion	2.87	0.77	0.44	

*significant at 0.05 level

Table 5-8. Characteristics of Patients Treated by SCD Specialists vs Non-specialists

Characteristic	Specialist (N=137) n (%)	Non-specialist (N=148) n (%)
*Age	26.1 (±10.11)	27.3 (±9.45)
Female gender	67 (48.9)	84 (56.8)
HU treatment	92 (67.1)	49 (33.1)
Comorbidities		
Diabetes	3 (2.2)	8 (5.4)
Hypertension	13 (9.5)	14 (9.5)
HIV	1 (0.7)	3 (2.0)
Hepatitis C	4 (2.9)	4 (2.7)
*Morbidity Score	12.59 (±13.35)	12.40 (±12.64)

*means (standard deviation) given for age and morbidity score

Ordinary Least Squares Regression vs. Instrumental Variable Analysis

Estimates produced by IVA were compared to the values given by ordinary least squares regression (OLS). When applying OLS to observational data in which case the underlying characteristics of the treatment and non-treatment groups are dissimilar, biased estimates are likely to result. Unlike IVA, OLS allows treatment to be correlated with the error term in the prediction of morbidity, yielding a biased treatment effect.

Instrumental variable analysis breaks up the correlation by using the predicted treatment values in place of the actual data, thereby removing the bias from the estimated effect of treatment.

When OLS was applied to the present data (Table 5-9), SCD patients treated with HU were suggested to have lower morbidity than patients not treated with HU (b_{HU} = -4.7, p=0.004). Contrasting this observation with the estimates given by IVA (b_{HU} = -5.3, p=0.25), the consequence of not controlling the bias in the data is made obvious. Whereas the magnitude of effect is noticeably similar, one method of analysis [OLS] yielded a significant treatment effect while the other method [IVA] resulted in a non-significant treatment effect. Considering that the mean difference in morbidity scores between treatment and non-treatment patients was not very large (13.91 -11.04 = 2.87), the finding of a significant difference in morbidity between the groups appears to be overestimated, implicating the IVA results as being more probable. This demonstrates the appropriateness of IVA to analyzing observational data.

Table 5-9. Regression Analysis: Predicting Morbidity

Predictor	Coefficient (b)	t value	*P-value	(N = 285)
HU	-4.68	-2.95	0.004	
Location	-2.19	-1.18	0.24	
Physician specialty	0.53	0.33	0.74	
Comorbidity	0.87	0.55	0.58	
Pulmonary infection	9.14	2.67	0.008	
Opiate	0.06	5.04	<0.0001	
Transfusion	3.73	0.76	0.45	

*significant at 0.05 level

CHAPTER 6
DISCUSSION AND CONCLUSION

This study has demonstrated the utility of administrative databases in assessing health outcomes and care quality. Administrative databases are legitimate sources of information concerning patients' use of the health care system. Outcome assessments are made feasible by administrative databases in that the databases are readily available, inexpensive to acquire, and encompass defined sub-populations of patients [85]. Patient sub-populations for study can be identified within the database by demographic features, insurance payer, disease diagnosis, or prescription drug use.

Florida Medicaid recipients with a diagnosis of sickle cell disease were the focus of this study. Health outcome and quality assessments with respect to the drug hydroxyurea were made. Following the MSH trial, in 1995 the National Heart, Lung, and Blood Institute (NHLBI) issued a clinical alert that announced the study's findings and that stated physicians could prescribe HU to patients with SCD [86]. Hydroxyurea gained FDA approval in 1998 for use in adult patients with SCD.

Using Medicaid data to identify drug exposure gave the added benefit to this research of being more comprehensive than patient recall and physician prescribing records [77]. As an initial evaluation of prescribing hydroxyurea to SCD patients, the utilization rate of hydroxyurea among the population studied in this dissertation was investigated. It was determined from this inquiry that hydroxyurea has been under-prescribed to patients with SCD. The numbers presented in Figure 5-2 imply that only a small percentage of the sickle cell population was prescribed treatment with hydroxyurea.

In spite of this, it is important to consider that reasons for non-prescribing or under-prescribing HU can not be derived directly from this database. Aside from being ineligible to receive treatment, patients may have rejected a physician's recommendation for HU, may have discontinued therapy due to intolerability, or may have received treatment through means not captured by this database. Nevertheless, as a drug demonstrating superiority in treating SCD, prescribing HU to eligible patients is vital to the management of this disease.

Albeit a significant advancement in SCD therapies, it has been indicated by other studies and also seen in this study that not all patients will respond to treatment with HU in the same way, and some patients will not respond at all. Ferster et al. reported that 27% of the patients they studied had no clinically meaningful response to HU [87], and a number of participants in the MSH trial maintained high crises rates despite high doses of HU [20]. In the present research, the variability in treatment response was reflected in two ways. The findings from the principal component analysis suggest that among the patients evaluated, variation in health care encounters was greatest after HU was initiated. The lower pretreatment variance may be related to disease expression, and, consequently, health care utilization being similar among the patients. Considering the notion that, as patients meeting indication for HU, these patients share the likeness of representing the proportion of the SCD population with severe (or moderately severe) disease symptomatology; it is reasonable to assume that there is not much variation between these patients in how they use the health care system and the number of health care encounters they incur before beginning HU therapy. Conversely, after therapy initiation patients with a positive response to treatment should experience a reduction in health care

encounters in the form of ED visits and hospitalizations resulting from disease complications, while patients for whom HU therapy was ineffective will continue to frequent the emergency department and will be hospitalized often; hence the increase in post-treatment variance. The variability in treatment response can also be appreciated by the dose-response relationship plotted in Figures 5-5 and 5-6. The plots illustrate that morbid complications did not always decline as the total day supply of HU increased. In the efficacy trial of HU, patients with the lowest rate of pain were those who received the lowest dose of treatment [14]. A similar trend is reported here. Data on how the medication was actually taken by the patients was not retrievable, thus non-compliance can not be eliminated as justification for this trend. This trend may also be a product of biological factors like the inability of a patient's bone marrow to withstand HU. Unfortunately, it is not yet possible to predetermine which patients will have success with treatment.

The claim that HU is associated with a reduction in morbidity in patients with SCD finds support from this study. It was demonstrated that on average, disease-related morbidity was lower after initiation of HU than before therapy. It was further determined that patients who were prescribed HU generated less frequent health care encounters as a result of morbidity than patients who were never prescribed HU. These observations are both clinically and economically meaningful. Though not yet proven, the fact that patients can experience a reduction in morbidity with HU suggests that use of HU could afford patients with a more productive, less restrained way of life. Preliminary research has indicated that in the absence of pain and other disease complications, patients' functional abilities increase (still, over-exertion should be avoided) [70]. Improved

clinical well-being can also promote fewer days of lost employment and decreases in the burden of family members serving as caretakers. It is suspected that HU could foster patients' abilities to function more like non-diseased individuals; however more research is needed to confirm this speculation. The economic advantage to treating patients with HU is inherent in the reduction in the number of visits to the emergency department and the number of hospitalizations, which leads to lower health care costs. Moore et al. [15] found this to be so when they compared health care costs of treated patients to costs for non-treated patients.

Pre/post treatment comparisons were made on patients with three or more prescriptions for HU as well as patients with six or more prescriptions. This provided indication of how morbidity changed with treatment duration. Both groups experienced a more than 20% reduction in morbidity; however the reduction was greater for the three or more treatment group. One reason for this may be non-compliance. Compliance with prescribed medications has been known to suffer with increased treatment duration [88], implying that patients taking HU long-term may begin to feel burdened by the therapy and fail to take it as prescribed. The greater reduction in morbidity for the three or more group could also be attributed to treatment effect being greatest nearer the start of therapy. Steinberg et al. [89] showed physiological changes resulting from HU to be greatest in the early part of therapy, prior to reaching plateau. Since it is these changes that facilitate treatment effect, reductions in morbidity are best noticed during peak physiological improvements.

There were three variables identified as significant predictors of morbidity: age, comorbidity, and opiate use. Contrary to the findings of Platt et al. [28], this study found

morbidity to decline with increasing age. Platt et al. reported an increase in morbidity as patients grew older. One reason for the discrepancy between the findings may lie within the definition of morbidity used in each study. The measure of morbidity used by Platt et al. was defined as 'pain in the extremities, back, abdomen, chest, or head lasting at least 2 hours and leading to a clinic visit'. Specific assessments of pain such as that detailed in the Platt study were not available in the data used for this study, thus a proxy measure was adopted. Morbidity in the present case was based on a broader perspective of health care encounters resulting from any disease-related complication, not just pain. In this sense, morbidity becomes a reflection of health care utilization. It is possible that as patients grow older and become more autonomous, they decidedly refrain from frequenting the health care system and opt to self-treat their symptoms at home. The observation of older patients experiencing fewer morbid episodes may therefore be representative of diminishing use of the health care system with increasing age. The observed relationship may also be due to the decreased life span of patients with severe disease manifestation. Patients who experience severe disease complications while young may not survive long enough to belong to the cohort of older SCD patients. Sickle cell patients who do reach middle to late adulthood are thus likely to be patients with a mild disease course. This too explains the lower morbidity amongst older patients.

It seems obvious that the presence of other illnesses in addition to SCD perpetuates morbidity. Even amongst the general population, individuals with multiple health conditions are at increased risk for poor health status [90]. As for opiate use, high consumption of opiate drugs is generally indicative of patients who experience unrelenting, severe pain crises. Considering this, and given the significance of opiate use

in predicting morbidity, the amount of opiates a patient uses is a reasonable measure for providers in forming recommendations for adjuvant therapies.

Although 'pulmonary infection' did not enter into the model as a significant predictor of morbidity, its importance should not be discounted. The purpose of this variable was to serve as a surrogate measure of ACS, which poses great infliction to patients with SCD. Acute chest syndrome is a leading cause of mortality in patients with SCD and therefore should be considered as an important factor in patients' well-being.

Judging from the modest R^2 values, it is evident that there are other factors contributing to morbidity that were not considered in the predictive models. The following rationale is offered to explain the shift in R^2 from the pretreatment model to the post-treatment model. Physiological contributions to sickle cell pain are known to include hematocrit, HbF levels, mean corpuscle volume, and neutrophil count [14, 28]. The lack of laboratory data prevented the inclusion of these measures in the predictive models, yet it is suspected that their effects were manifested through the shift in R^2. Prior to treatment with HU the occurrence of pain can be associated with decreased HbF levels and elevated neutrophil counts. Hydroxyurea is suspected to exert its effects through modulation of these parameters. Treatment with HU has been associated with increases in HbF levels and MCV (which is directly related to HbF), and decreases in neutrophil counts [14, 35]. In the pretreatment predictive model of morbidity, these parameters have not yet been altered by HU and thus remain contributors to morbidity. Upon HU initiation, alterations begin to occur and the effect of these variables on morbidity is attenuated [4, 14, 89]. Their influence is naturally controlled in the post-treatment predictive model; hence the increased post-treatment R^2.

Although the literature acknowledges deficits in providing optimal therapy to patients with SCD [12] there is little empirical work citing the nature of these deficits and identifying targets for improvements. This study differs from other quality assessments made in SCD by examining the role of physician characteristics in prescribing, and by moving the traditional focus away from children to giving attention to young and older adults affected by the disease. Because patients are living longer with SCD, identifying ways to promote quality care for these patients is essential.

The physician attributes of medical specialty and practice location were evaluated as structural influences on the prescribing of HU. The non-significant relationship between physician practice location and prescribing suggests that a patient's access to treatment with HU is not determined by proximity to the patient's health care provider. Even though reports have indicated that patients sometimes travel long distances to obtain care from competent professionals [70], the county in which the provider practices does not appear to be an important factor in the receipt of treatments related to the patient's care. A central detail related to this finding is the observation in this data that the counties most saturated with physicians who prescribe HU were also the counties most populated with sickle cell patients, signifying that county demographics may play a part in the detected relationship.

Other studies examining a similar concept report associations disparate from that noted here. McClellan et al. [71] considered distance to specialty hospitals in determining the likelihood of catheterization post-acute myocardial infarction and found patients living closer to specialty hospitals to be more likely to undergo catheterization procedures. Another study demonstrated the effect of distance on the utilization of

Veteran's Administration (VA) hospitals by American veterans and reported the use of VA hospitals to decline as travel distance increased [91]. These authors did notice a cut-off at which distance became negligible; however the prevailing conclusion was that the majority of veterans were unlikely to use VA services unless the distance was short. Both of these studies measured proximity by calculating the actual distance a patient would have to travel to obtain health care. It is plausible that examining proximity by county as done in the current study is too broad a measure, and a more precise measure like physical distance would provide greater insight and lead to alternate findings.

The finding that SCD specialists (hematologists/oncologists) are more likely to prescribe HU (a chemotherapeutic drug) is consistent with the viewpoint that specialists are more aggressive treatment providers for patients with SCD. Physicians who specialize in treating SCD have an advanced knowledge of the disease and are more informed about related medical progress. This is not to imply that non-specialists are incapable of effectively treating sickle cell patients. Although specialists were most likely to prescribe HU, the data indicated that more patients received care from family practitioners, general practitioners, internal medicine physicians, or pediatricians than from hematologists or oncologists. In Florida, there's a scarcity of physicians who specialize in SCD, and access to available specialists is limited for most patients. This being so, it can be theorized that routine patient care is most likely to be managed by non-specialists. It is evident that specialists play an important role in prescribing; however the role of non-specialists is equally critical. Since care for SCD patients appears to be more likely to be managed by non-specialists as suggested by data, efforts to improve the prescribing of HU should not be restricted to targeting hematologists and oncologists, but

should be extended to include family practice, general practice, internal medicine, and pediatric physicians who also care for patients with SCD.

The results indicated that increased number of opiate prescriptions was significantly related to prescribing HU; however the effect was not substantial. The observed relationship may be due to other factors aside from actual opiate use. Chronic opiate use is indicative of patients who are more symptomatic, thus it could be that the association between opiate use and HU reflects a pattern in prescribing in which there is correlation between prescribing treatments for pain. Physicians who prescribe opiates in high quantities may also be more inclined to prescribe HU.

As with the findings of others [75], structural factors of care did not have a significant direct influence on health outcomes. There was no difference in morbidity with respect to patient/provider location; and despite the difference in prescribing HU, there was no real difference in morbidity between patients treated by SCD-specialists and those treated by non-specialists.

Care should be taken when making inferences regarding the physician specialty data, such that it is not assumed that patients were treated exclusively by a particular provider. The physician specialty variable was defined as the physician who did most of the prescribing for a patient, while other providers may have at times been involved in the patient's care. Some patients may have visited the specialist for the sole purpose of HU management but were followed by non-specialists for routine care; and prescribing that appeared to be done by a non-specialist may have been prompted by a recommendation from a specialist. These points should be considered when deducing conclusions about physician specialty.

By using IVA, the average effect of treatment over the marginal probabilities of treatment was estimated. In contrast to the OLS results, the IVA estimates indicated no significant effect of HU on morbidity. After taking into account the influence of patient/provider location and physician specialty on prescribing HU, and controlling for unobservable health characteristics, the trend towards clinical improvement was not statistically significant. Looking beyond statistical significance, the value of HU can be found in the five-fold decrease in disease complications seen amongst the treatment patients.

Several limitations should be considered when interpreting the results of this study. First, the definition of treatment used in this study included patients who may not have been on continuous therapy. Additionally, the time period between prescriptions for HU was not considered. For instance, a patient who received three prescriptions in the same year was treated the same as a patient who received three prescriptions over 2-years. Both these patients were treated the same as a patient who received 24 prescriptions in a 2-year period. Thus, the definition of treatment and the inclusion of patients on non-continuous therapy may have contributed to the non-significant treatment effect.

Next, the confines of the administrative database inhibited the ability to fully capture other important measures of disease severity, such as hemoglobin levels, pain history, and history of acute chest syndrome. Any outpatient visit, visit to the emergency department, or hospitalization coded as ‘sickle cell crisis with pain’ was incorporated to quantify pain; however it is likely that this estimate was underestimated. Patients may have reported to the physician’s office or emergency department with a complaint of

pain, but the provider may have failed to use the appropriate ICD-9 code indicative of a pain crisis, and may have used a non-specific ICD-9 code instead.

There is indication in the results that the proxy 'pulmonary infection' may have been a weak measure to represent ACS. Given the non-significance of 'pulmonary infection' in the predictive model of morbidity and the implication that 'pulmonary infection' has no significant influence on HU prescribing (when history of ACS is indication for treatment), 'pulmonary infection' may have been too broad to target the actual impact of ACS, suggesting that ACS was not effectively observed. Radiological results or a specific diagnosis confirming ACS is desirable.

One other limitation of the study findings should be noted. Prescription claims provide evidence that a prescription for HU was filled, not that it was taken as prescribed. The results reported here assume that patients were compliant with HU therapy; however no compliance measures were applied. Irrespective of this and the aforementioned limitations, important findings have emerged from this research.

This study shows that promising outcomes are attainable when patients in usual care settings are prescribed HU. The hypothesis that patients prescribed HU will have a reduction in morbidity has been supported. This finding can be used to influence patients, physicians, and policy makers in promoting HU therapy. Also as hypothesized, SCD-specialists were more likely to prescribe HU, reinforcing the structure-process relationship. A significant link between process and outcome of health care was not established. Possible reasons for this have been stated above.

In generalizing the presented findings, it should be understood that HU is not a cure for SCD; and use of HU will not lead to complete eradication of symptoms and

complications. It should be further understood that not every SCD patient is a candidate for HU therapy, and not all patients who are candidates for treatment will benefit. This research supports the prescribing of HU to eligible patients, but maintains that patients treated with HU should be followed closely.

APPENDIX A
TRANSITION FOCUS GROUP GUIDE

Today we want to talk about your transition from pediatric to adult care, that's the process that transferred your health care from the people that took care of you when you were a child to the people that are providing care for you now that you are older. We believe that we can make this transition better but need more information from you about your process, how good or bad it was, and how much more or less control you have of your sickle cell disease. Please be open and honest because your comments will hopefully help us create a better program.

- When you think back about your transition from pediatrics to adult care, what comes to mind first?
  - ⇒ Transition difficult or smooth?
  - ⇒ Compare your feelings of control of your SCD now compared to before transition
  - ⇒ Do you feel you are better treated now or before?

- What were the main problems you faced before your transition?
  - ⇒ Were they addressed during the transition?
  - ⇒ Have they become better?

- What are the main problems you are facing now?

- What are the major things about your sickle cell disease that have changed throughout your transition?

Now I want to talk about how your family, friends and other people you know are involved with your sickle cell disease.

- Who did you rely on the most prior to transitioning? And now?
- Prior to transition, describe your family's involvement in the day-to-day management of your sickle cell disease.
  - How has their involvement changed since your transition to adult care?

- Prior to transition, describe your friends' involvement in the day-to-day management of your sickle cell disease.
  - How has their involvement changed since your transition to adult care?

- How do the following people treat you now compared to how they treated you before transitioning into adult care? How were the following people involved in your transition?
  - ⇒ Family
  - ⇒ Friends
  - ⇒ Church members
  - ⇒ Employers
  - ⇒ Coworkers
  - ⇒ Other

Now I want to talk about similar issues - how your experiences with people in your social network have changed since transitioning into adult care- but instead of your friends and family, I want you to now talk about your experiences with your health care providers - your doctors, the nurses you see, everyone at the clinic that you deal with.

- Compare your experiences with the following people before and after transition.
  - ⇒ Regular doctor
  - ⇒ Sickle cell disease specialist
  - ⇒ Emergency room doctors and staff
  - ⇒ Other health care workers

Next I want us to talk about how sickle cell disease affects your school and work life.

- *How has your ability to work changed throughout the transitioning period?*
  - ⇒ Compare your experiences concerning work before and after transition.

- *How has your ability to go to school changed throughout the transitioning period?*
  - ⇒ Compare your experiences concerning school before and after transition.

One problem we see with the transition to adult care is the sudden shift of financial responsibility for health care costs on to your shoulders. Let's take a few minutes to talk about this.

- Who pays for your health care bills now?
- Who paid for them when you were in the pediatric system?
- What strains does this new financial responsibility put on you?
- How has your usage of the emergency room and clinics changed throughout transition?

Next, I want us to talk about your management of your sickle cell disease before, during and after transitioning to adult care, and your ideas on when and how the transition to adult care should occur.

- At what age did you assume more responsibility for the management of SCD?
  - ⇒ Would you have liked more control or responsibility earlier in your life?
  - ⇒ At what age would you like to have started having more responsibility for managing your disease?
  - ⇒ Would it have been desirable to transfer to adult care at an earlier age, for example, when you were 16-18 years old? Why or why not?

- What things do you do to manage your sickle cell disease now?
- How has your responsibility for managing your sickle cell disease changed since transition?

- Compare the ease of managing your disease yourself in adult care compared to pediatric care. Is it easier to manage your disease yourself in pediatric care or in adult care? Why? What are the differences between the two systems that impact your ability to self-manage your sickle cell disease?

- What in the system could be changed to make it easier for you to better manage your sickle cell disease?

Last, I want to ask you to talk about your ideas that would make the transition to adult care better, easier and smoother for you and for other patients at the clinic.

- *What things would you change about your transition to the adult health care system that would make it better?*
- *If a program were in place at the clinic aimed at making the transition to adult care easier for you, a program that was designed just the way you would want it, with all the traits and characteristics that you would want and that would be meaningful to you, what would that program be like?*
    - ⇒ *Topics - what do you want to know, learn or talk about?*
        - ⇒ *the disease*
        - ⇒ *Disease management*
        - ⇒ *Psychosocial effects of the disease*
        - ⇒ *Economic/financial issues*
        - ⇒ *Work or school life*
        - ⇒ *Long term goals/life plans*
    - ⇒ *Who is involved (patients, providers, family, friends, advocate, others)*
    - ⇒ *Individual or in groups*
    - ⇒ *When (in pediatric care, during the transition phase, or after transition occurred)*
    - ⇒ *Where (at the clinic, at home, at school, at work)*
    - ⇒ *How long (brief before or after transition, extended throughout transition period, as needed)*

APPENDIX B
SCD COMPLICATIONS LIST

ICD-9 code	Diagnosis
038.9	Unspecified Septicemia
275.0	Disorders Of Iron Metabolism
276.5	Volume Depletion
282.4	Thalassemias
282.5	Sickle-cell Trait
282.6	Sickle-cell Anemia
282.60	Unspecified Sickle-cell Anemia
282.61	Hb-s Disease Without Mention Crisis
282.62	Hb-s Disease With Mention Of Crisis
282.63	Sickle-cell/hb-c Disease
282.69	Other Sickle-cell Anemia
284.8	Other Specified Aplastic Anemias
289.4	Hypersplenism
289.51	Chronic Congestive Splenomegaly
289.59	Other Diseases Of Spleen
320.1	Pneumococcal Meningitis
320.2	Streptococcal Meningitis
322.9	Unspecified Meningitis
428.0	Congestive Heart Failure
430	Subarachnoid Hemorrhage
431	Intracerebral Hemorrhage
434.91	Unspec Cerbrl Art Occl W/infarct
435.9	Unspec Transient Cerebral Ischemia
436	Acut But Ill-defined Cerebrvasc Dz
453.8	Embolism&thrombosis Oth Spec Veins
481	Pneumococcal Pneumonia
485	Bronchopneumonia Organism Unspec
486	Pneumonia, Organism Unspecified
518.81	Acute Respiratory Failure
518.82	Other Pulmonary Insufficiency Nec
574.00	Calculus Gb W/acut Cholcyst W/o Obst

574.01	Calcu Gb W/acut Cholcyst&obst
574.10	Calcu Gb W/oth Cholcyst W/o Obst
574.11	Calcu Gallbladd W/oth Cholcyst&obst
574.20	Calcu Gb W/o Mention Cholcyst/obst
574.21	Calcu Gb W/o Cholcyst W/obst
574.31	Calcu Bd W/acut Cholecyst&obst
574.60	Calcu Gb&bd W/ac Cholcyst W/o Obst
574.70	Calcu Gb&bd W/oth Cholcyst W/o Obst
574.71	Calcu Gb&bd W/oth Cholcyst W/obst
574.81	Calcu Gb&bd-acut&chrn Cholcyst-obst
574.90	Calcu Gb&bd W/o Cholcyst W/o Obst
574.91	Calcu Gb&bd W/o Cholcyst W/obst
575.0	Acute Cholecystitis
575.10	Cholecystitis, Unspecified
575.11	Chronic Cholecystitis
575.12	Acute And Chronic Cholecystitis
575.9	Unspecified Disorder Of Gallbladder
576.1	Cholangitis
576.2	Obstruction Of Bile Duct
581.0	Nephrotic Synd W/les Proliferat Gln
584.9	Unspecified Acute Renal Failure
585	Chronic Renal Failure
607.3	Priapism
707.1	Ulcer Lower Limbs Except Decubitus
707.10	Ulcer Of Lower Limb, Unspecified
707.13	Ulcer Of Ankle
707.14	Ulcer Of Heel And Midfoot
707.15	Ulcer Of Other Part Of Foot

711.02	Pyogenic Arthritis, Upper Arm
711.03	Pyogenic Arthritis, Forearm
711.05	Pyogenic Arthrit Pelv Region&thigh
711.06	Pyogenic Arthritis, Lower Leg
719.40	Pain In Joint, Site Unspecified
719.41	Pain In Joint Involving Shoulder Region
719.42	Pain In Joint Involving Upper Arm
719.43	Pain In Joint Involving Forearm
719.44	Pain In Joint Involving Hand
719.45	Pain In Joint Pelvic Region&thigh
719.46	Pain In Joint Involving Lower Leg
719.47	Pain In Joint Involving Ankle And Foot
719.49	Pain In Joint, Multiple Sites
724.1	Pain In Thoracic Spine
724.2	Lumbago (lower back pain)
724.5	Unspecified Backache
729.1	Unspecified Myalgia And Myositis
729.5	Pain In Soft Tissues Of Limb
730.02	Acute Osteomyelitis, Upper Arm
730.05	Acute Osteomyel Pelvic Region&thigh
730.06	Acute Osteomyelitis, Lower Leg
730.07	Acute Osteomyelitis, Ankle And Foot
730.08	Acute Osteomyelitis Other Spec Site
730.12	Chronic Osteomyelitis, Upper Arm
730.14	Chronic Osteomyelitis, Hand
730.15	Chronic Osteomyel Pelv Region&thigh
730.16	Chronic Osteomyelitis, Lower Leg
730.20	Unspec Osteomyelitis Site Unspec
730.21	Unspec Osteomyel Shoulder

	Region
730.24	Unspecified Osteomyelitis, Hand
730.25	Unspec Osteomyel Pelv Region&thigh
730.26	Unspecified Osteomyelitis Lower Leg
730.27	Unspec Osteomyelitis Ankle&foot
730.28	Unspec Osteomyelitis Oth Spec Sites
733.41	Aseptic Necrosis Of Head Of Humerus
733.42	Aseptic Necrosis Head&neck Femur
733.49	Aseptic Necrosis Of Other Bone Site
789.00	Abdominal Pain, Unspecified Site
789.01	Abdominal Pain Right Upper Quadrant
789.07	Abdominal Pain, Generalized
789.1	Hepatomegaly
789.2	Splenomegaly
789.60	Abdominal tenderness, unspecified site
790.7	Bacteremia
999.8	Other Transfusion Reaction Nec
V43.64	Hip Joint Replacement Other Means

APPENDIX C
CLINICAL MONOGRAPH FOR HYDROXYUREA

Hydroxyurea
Droxia®, Hydrea®, Mylocel™

Indications

- acute myelogenous leukemia (AML)†
- astrocytoma†
- chronic myelogenous leukemia (CML)
- head and neck cancer
- human immunodeficiency virus (HIV) infection†
- lung cancer†
- malignant glioma†
- malignant melanoma
- ovarian cancer
- polycythemia vera†
- psoriasis†
- sickle cell disease
- thrombocytosis†

†non-FDA-approved indication

Dosage

For the treatment of chronic myelogenous leukemia (CML):
Oral dosage:
Adults: For a white blood cell count (WBC) > 100,000/m[3], give 50—75 mg/kg/day PO once daily to cause a rapid decline in the WBC. For WBC < 100,000/mm^3, a dose between 10—30 mg/kg PO once daily may be given for maintenance therapy, adjusted for WBC count.
Children: 10—20 mg/kg/day PO once daily; adjust dose according to hematologic response.

For the treatment of acute myelogenous leukemia (AML)†:
Oral dosage:
Adults and children: For a white blood cell count (WBC) over 100,000/mm^3, a dose of 50—75 mg/kg/day PO will cause a rapid decline in the WBC. Once the patient is beyond the crisis stage, conventional antileukemia therapy should be given.

For the treatment of lung cancer†:
Oral dosage:
Adults: 500 mg/m^2/day PO for 3 days per month in combination with doxorubicin, mechlorethamine, methotrexate, fluorouracil, and procarbazine.[1332]

For the treatment of malignant melanoma:
Oral dosage:
Adults: 20—80 mg/kg/day PO in 1—3 divided doses.

For the treatment of ovarian cancer:
Oral dosage:
Adults: 80 mg/kg PO every third day or 20-30 mg/kg/day. If radiation therapy is being

used concurrently, then administer 80 mg/kg PO every third day.

For the treatment of head and neck cancer:
Oral dosage:
Adults: 80 mg/kg PO every third day in combination with radiation therapy.

For the treatment of polycythemia vera†:
Oral dosage:
Adults: 1000—2000 mg PO per day divided into 1—3 doses initially. The dose is adjusted as needed to normalize the blood counts of red cells, neutrophils, and platelets.

For the prevention of thrombosis in patients with essential thrombocytosis†:
Oral dosage:
Adults: In one study, 114 elderly patients with a platelet count of 1,500,000/mm^3 or less and a history of thrombosis were randomly assigned to receive hydroxyurea or no treatment. Both groups were followed for a median of 27 months. The starting dose of hydroxyurea was 15 mg/kg/day PO and was adjusted to maintain the platelet count below 600,000/mm^3 without causing a WBC count < 4000/mm^3. Patients were allowed to continue taking aspirin or ticlopidine. All patients assigned to receive hydroxyurea demonstrated a platelet count < 600,000/mm^3 within 2—8 weeks and this value was maintained for the duration of therapy. Two patients in the hydroxyurea group and 14 patients in the control group had thrombotic episodes.[951]

For the treatment of sickle cell disease (i.e., to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with recurrent moderate to severe painful crises):
NOTE: Droxia™ has been designated an orphan drug by the FDA for this indication.
NOTE: The decision to titrate the dosage of hydroxyurea should be based on the patient's blood counts. The dosage may be titrated if blood counts are within an 'acceptable' range defined as: neutrophils >= 2500/mm^3, platelets >= 95,000/mm^3, hemoglobin > 5.3 g/dl, and reticulocytes >= 95,000/mm^3 if the hemoglobin concentration < 9 g/dl. 'Toxic' blood counts are defined as: neutrophils < 2000/mm^3, platelets < 80,000/mm^3, hemoglobin < 4.5 g/dl, and reticulocytes < 80,000/mm^3 if the hemoglobin concentration < 9 g/dl.

Oral dosage:
Adults: The recommended starting dose is 15 mg/kg PO once daily. If blood counts are in an 'acceptable' range, the dosage may be increased by 5 mg/kg/day PO every 12 weeks until a maximum tolerated dose (i.e., the highest dose that does not produce 'toxic' blood counts over 24 consecutive weeks), or 35 mg/kg/day PO is reached. If blood counts are between the 'acceptable' and 'toxic' range, the dose is not increased. If blood counts are considered 'toxic,' hydroxyurea should be discontinued until hematologic recovery. Treatment can then be resumed after reducing the dose by 2.5 mg/kg/day PO from the dose associated with hematologic toxicity. Hydroxyurea may then be titrated up or down, every 12 weeks in 2.5 mg/kg/day increments, until the patient is at a stable dose that does not result in hematologic toxicity for 24 weeks. Any dosage on which a patient develops hematologic toxicity twice should not be tried again. A study begun in January 1992 by

the National Heart, Lung, and Blood Institute was terminated early because of an obvious demonstrated benefit from hydroxyurea. There was a median rate of 2.5 crises/year in the hydroxyurea group and 4.5 crises/year in the placebo group. The median time to first vaso-occlusive crisis was longer in patients treated with hydroxyurea. All patients also received folic acid 1 mg/day.[616]

Children†: In a randomized, crossover trial, 25 children received either hydroxyurea at an initial dosage of 20 mg/kg/day PO or placebo for 6 months and were then switched to the other arm for the next 6 months. Significant increases in HbF and mean corpuscular volume were observed during treatment with hydroxyurea. Compared with placebo, treatment with hydroxyurea was associated with a reduce number of hospitalizations.[1873] Several uncontrolled studies have also been conducted in children. In one study (n=15), hydroxyurea was initiated at a dosage of 10—20 mg/kg/day and doses were titrated as tolerated (mean dose 21.4 plus or minus 5.2 mg/kg/day).[1874]

For the treatment of psoriasis†:
Oral dosage:
Adults: 500—1500 mg PO daily based on clinical response.

For the treatment of malignant glioma†, including astrocytoma†, medulloblastoma†, and primitive neuroectodermal tumors:
Oral dosage:
Children: Dosages of 1500—3000 mg/m^2 PO as a single dose administered every 4—6 weeks have been given in combination with other chemotherapeutic agents.

For the treatment of human immunodeficiency virus (HIV) infection†:
Oral dosage:
Adults: Safe and effective use is not established; current guidelines do not recommend the use of hydroxyurea for the treatment of HIV infection.[1800] Hydroxyurea is associated with decreased CD4 cell counts and inconsistent evidence of viral suppression. Clinicians considering use of hydroxyurea in a treatment regimen for HIV should be fully aware of the limited and conflicting data in support of its efficacy, and should be familiar with HIV treatment guidelines.[1800] A trial of didanosine, stavudine and indinavir in previously-treated HIV patients showed no difference in viral load suppression in patients receiving hydroxyurea 600 mg PO bid as compared to patients not receiving hydroxyurea. This study was prematurely closed due to a higher risk of toxicities, including fatal and non-fatal pancreatitis, in the treatment group receiving hydroxyurea.

Patients with hepatic impairment:
Dosage should be modified depending on clinical response and degree of hepatic impairment, but no quantitative recommendations are available.

Patients with renal impairment:

Dosage should be modified depending on clinical response and degree of renal impairment, but no quantitative recommendations are available.

†non-FDA-approved indication

Administration Guidelines

NOTE: The correct dose of hydroxyurea will vary from protocol to protocol. Clinicians should consult the appropriate references to verify the dose.

Oral Administration
•Hydroxyurea is administered orally.
•If capsules are unable to be swallowed, empty contents into a glass of water and administer immediately.

†non-FDA approved

†non-FDA-approved indication

Contraindications/Precautions

- *anemia*
- *bone marrow suppression*
- *breast-feeding*
- dental disease
- dental work
- elderly
- females
- herpes infection
- human immunodeficiency virus (HIV) infection
- hyperkalemia
- hyperphosphatemia
- hyperuricemia
- hypocalcemia
- infection
- infertility
- *intramuscular injections*
- *neutropenia*
- pregnancy
- radiation therapy
- renal failure
- renal impairment
- *thrombocytopenia*
- tumor lysis syndrome (TLS)
- vaccination
- varicella
- viral infection

• Absolute contraindications are in italics.

Hydroxyurea is a potent mutagenic and teratogenic agent and could cause fetal harm when administered during pregnancy (FDA pregnancy risk category D). Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs and monkeys at doses within 1-fold of the human dose on a mg/m^2 basis. Hydroxyurea causes fetal malformations (partially ossified

cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a mg/m^2 basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of >= 375 mg/kg (about 1.7 times the maximum recommended human daily dose on a mg/m^2 basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or it the patient becomes pregnant while taking hydroxyurea, the patient should be counseled regarding the potential harm to the fetus. Females of childbearing potential who are taking this drug or whose spouse is taking this drug should avoid becoming pregnant. There are many reports in the literature describing the use of hydroxyurea in pregnant women with acute or chronic myelogenous leukemia, primary thrombocythemia, or sickle cell disease. Several women electively terminated their pregnancies; one developed eclampsia and delivered a phenotypically normal still born infant. All others delivered live, healthy infants without congenital anomalies. However, further studies and longer follow-up with careful assessment of fetotoxic effects are required to determine the safety of hydroxyurea during pregnancy.[2755]

Hydroxyurea passes into breast milk. Women should not continue *breast-feeding* their infants while receiving hydroxyurea because of potential harm to the infant.

In males, reversible germ cell toxicity and infertility have been reported following hydroxyurea therapy.

Hydroxyurea should be used cautiously in patients with preexisting bone marrow suppression, such as those who have recently received radiation therapy or cytotoxic therapy, because the drug could exacerbate myelosuppression. Hematologic toxicity, including *neutropenia*, *thrombocytopenia*, and *anemia*, often occur during hydroxyurea therapy, and hematologic status should be closely monitored. If the leukocyte count is $<2500/mm^3$, or the platelet count is below $100{,}000/mm^3$, therapy should not be initiated. When hydroxyurea is used to treat a malignancy, complete blood counts should be determined every 3—7 days. In patients with sickle cell disease, the manufacturer recommends monitoring of complete blood counts every 2 weeks; if leukocyte or platelet counts fall during hydroxyurea therapy, the drug should be discontinued and resumed when the values return to normal. In all patients, anemia should be corrected with whole blood replacement both before and during therapy, if necessary. Severe *bone marrow suppression* is a contraindication to hydroxyurea. Therefore, this drug should be used only by clinicians experienced in chemotherapy. Patients with active infection should be treated prior to receiving hydroxyurea, the dose should be reduced or discontinued in patients who develop such infections. Patients with a history of varicella zoster, other herpes infections (e.g., herpes simplex), or other viral infections are at risk for reactivation of the infection when treated with chemotherapy.

Myelosuppressive effects of hydroxyurea can increase the risk of infection or bleeding;

therefore, dental work should be delayed until blood counts have returned to normal. Patients, especially those with dental disease, should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss, and toothpicks.

Intramuscular injections should not be administered to patients with platelet counts < 50,000/mm^3 who are receiving hydroxyurea. IM injections may cause bleeding, bruising, or hematomas due to hydroxyurea-induced thrombocytopenia.

Hydroxyurea should be used cautiously in patients with renal impairment because the drug can accumulate rapidly, resulting in visual hallucinations, auditory hallucinations, and hematologic toxicity. Hydroxyurea is eliminated extensively through the kidneys, so renal impairment or renal failure can delay clearance and increase the risk of toxicity. Elderly patients are more likely to have age-related impaired renal function. Elderly patients may be more sensitive to the effects of hydroxyurea and require lower doses.

Hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and decreased urine output may be indicative of hydroxyurea-induced tumor lysis syndrome (TLS). Appropriate measures (e.g. aggressive hydration and allopurinol) must be taken to prevent severe electrolyte imbalances and renal toxicity during and following chemotherapy administration in patients with large chemosensitive tumors.

Vaccination during chemotherapy or radiation therapy should be avoided because the antibody response is suboptimal. When chemotherapy is being planned, vaccination should precede the initiation of chemotherapy by >= 2 weeks. Those undergoing chemotherapy should not be exposed to others who have recently received the oral poliovirus vaccine (OPV). Measles-mumps-rubella (MMR) vaccination is not contraindicated for the close contacts, including health care professionals, of immunocompromised patients. Passive immunoprophylaxis with immune globulins may be indicated for immunocompromised persons instead of, or in addition to, vaccination. When exposed to a vaccine-preventable disease such as measles, severely immunocompromised children should be considered susceptible regardless of their vaccination history.

The use of hydroxyurea in the treatment of human immunodeficiency virus (HIV) infection is not recommended. Hydroxyurea is associated with a decreased CD4 cell count and inconsistent evidence of improved viral suppression.[1800] Limited studies have shown the addition of hydroxyurea to a regimen of didanosine, ddI, and stavudine, d4T, or didanosine alone appeared to result in moderately enhanced antiretroviral activity. However, one clinical trial (ACTG 5025) was stopped prematurely due to an increased frequency of fatal pancreatitis in patients receiving hydroxyurea in combination with didanosine, stavudine, and indinavir as compared to those patients receiving the anti-retroviral agents alone. Hepatotoxicity and hepatic failure resulting in death have been reported during clinical use of hydroxyurea and anti-retroviral agents, especially didanosine and stavudine. Additional concerns with the use of hydroxyurea in HIV infection include an increased risk of persistent cytopenias, teratogenic potential, and the increased risk of neuropathy.[1800]

Drug Interactions

- Anticoagulants
  - Cytarabine, ARA-C
  - Didanosine, ddI
  - Digoxin
  - Filgrastim, G-CSF
  - Fluorouracil, 5-FU
- Immunosuppressives
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Platelet Inhibitors
- Salicylates
  - Sargramostim, GM-CSF
  - Stavudine, d4T
  - Strontium-89 Chloride
  - Tenofovir, PMPA
- Thrombolytic Agents
- Vaccines

Due to the inhibitory effects of hydroxyurea on the formation of deoxyribonucleotides, hydroxyurea can modulate the effects of many antimetabolites. High levels of deoxyuridine monophosphate (dUMP) have been associated with resistance to fluorouracil, 5-FU. Hydroxyurea may inhibit the formation of dUMP and lead to increased efficacy of 5-FU when administered after 5-FU.[5126]

Hydroxyurea potentiates the activity of cytarabine, ARA-C by depleting the cell of another nucleoside, deoxycytidine triphosphate, which would otherwise compete with cytarabine for activity in the cell.[5127] Some clinicians have recommended decreasing the dose of cytarabine when it is given concurrently with hydroxyurea.[5128]

Hydroxyurea exhibits significant myelosuppression [5129] that may be additive to other myelosuppressive antineoplastic agents and may lead to additive effects with immunosuppressives. While therapy is designed to take advantage of this effect, clinicians should be alert for possible combined drug actions, desirable or undesirable, and the potential need for dosage adjustment. Over-immunosuppression or myelosuppression may result in an increased risk for the development of severe infections, malignancies including lymphoma and leukemia, myelodysplastic syndromes, and lymphoproliferative disorders.

The immune response of the immunocompromised patient to vaccines is decreased and higher doses or more frequent boosters may be required. Despite these dose increases, the immune response may still be suboptimal. Live virus vaccines are contraindicated during therapy with antineoplastic agents due to the potentiation of virus replication, adverse reactions to the virus, and the immunocompromised status of the patient.[3957] Those undergoing antineoplastic therapy should not be exposed to others who have recently received the oral poliovirus vaccine (OPV).[3957] Estimates for postponing vaccination vary from 3 months to 1 year following discontinuation of treatment depending of the type of antineoplastic agent used and the disease state of the patient.

Due to the thrombocytopenic effects of hydroxyurea [5129], an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. Large doses

of salicylates (>= 6 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.

Because antineoplastic agents exert their toxic effects against rapidly growing cells, such as hematopoietic progenitor cells, sargramostim, GM-CSF[4669], and filgrastim, G-CSF[4670], are contraindicated for use in patients in the period 24 hours before through 24 hours after treatment with cytotoxic chemotherapy.

The combined use of hydroxyurea and didanosine, ddI, with or without stavudine, d4T, is associated with an increased incidence of didanosine-associated adverse effects, including pancreatitis and peripheral neuropathy. In addition, it is recommended that hydroxyurea not be used in patients with HIV; hydroxyurea has been associated with decreased CD4 counts, and, while there have been reports of hydroxyurea improving viral suppression, specifically when used in combination with didanosine, ddI or stavudine, d4T, overall reports of viral suppression are inconsistent.[1800] Hepatotoxicity, including hepatic failure leading to death, has been reported with the combination of hydroxyurea and other anti-retrovirals. Fatal hepatic events were reported most often in patients treated with the combination of hydroxyurea, didanosine, and stavudine.[1800]

Some antineoplastic agents have been reported to decrease the absorption of digoxin tablets due to their adverse effects on the GI mucosa; no significant change was seen with digoxin capsules, and the effect on digoxin liquid is not known.[4668] The reduction in digoxin tablet absorption has resulted in plasma concentrations that are 50% of pretreatment levels and has been clinically significant in some patients. Digoxin capsules (Lanoxicaps®) may be utilized to avoid this interaction in patients receiving antineoplastic agents and digoxin tablets. It is prudent to closely monitor patients for loss of clinical efficacy of digoxin while receiving antineoplastic therapy.

In vitro, HIV isolates with reverse transcriptase mutations associated with slightly decreased susceptibility to tenofovir demonstrated hypersusceptibility to tenofovir, PMPA in the presence of hydroxyurea; although, this synergy was not demonstrated in clinical trials. Hydroxyurea decreases dATP pools in exposed cells. This favors the binding of the active tenofovir analog to the reverse transcriptase enzyme. Hydroxyurea reduced IC_{50} of tenofovir against HIV-1 isolates 8- to > 26-fold.[3373] However, it is recommended that hydroxyurea not be used in patients with HIV; hydroxyurea has been associated with decreased CD4 counts, and, while there have been reports of hydroxyurea improving viral suppression, overall reports of viral suppression are inconsistent.[1800]

Adverse Reactions

- anemia
- constipation
- diarrhea
- dizziness
- drowsiness
- erythema
- esophagitis
- fever
- hallucinations
- headache
- hepatic failure
- hyperkalemia
- hyperphosphatemia
- hyperuricemia
- hypocalcemia
- infertility
- leukopenia
- macrocytosis
- maculopapular rash
- metabolic acidosis
- nausea/vomiting
- nephrolithiasis
- neutropenia
- oral ulceration
- pancreatitis
- pancytopenia
- peripheral neuropathy
- polycythemia
- rash (unspecified)
- renal tubular obstruction
- secondary malignancy
- seizures
- skin ulcer
- stomatitis
- thrombocytopenia
- tumor lysis syndrome (TLS)

Hydroxyurea is mutagenic and clastogenic in animal models and is presumed to cause secondary malignancy in humans. In patients receiving long-term hydroxyurea for myeloproliferative disorders, (e.g., polycythemia vera and thrombocythemia), leukemia and skin cancer has been reported. However, it is not known whether the leukemogenic effect is secondary to hydroxyurea or the patient's underlying disease. Conventional long-term human studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. In animal studies, administration of hydroxyurea (about 0.6—1.2 times the maximum human dose on a mg/m^2 basis) increased the incidence of mammary tumors in rats.

In animal models, hydroxyurea causes teratogenesis and may decrease fertility. There are no well controlled studies in women, but hydroxyurea may cause fetal harm when administered to a pregnant woman. Case reports have not indicated fetotoxicity; however, large numbers of patients, careful assessment, and long-term follow-up are lacking. Reversible germ cell toxicity and infertility have been reported following hydroxyurea therapy in men.

Hydroxyurea can cause bone marrow suppression including pancytopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; hematologic status should be evaluated regularly. When used to treat blast crisis of chronic myelogenous leukemia or acute myelogenous leukemia, the WBC count will fall in 1—3 days. When lower doses are used, neutropenia, thrombocytopenia, and anemia all occur by day 10 after therapy. Thrombocytopenia and anemia are much less common than neutropenia and are often preceded by the development of leukopenia. In patients treated with hydroxyurea for

sickle cell anemia, the development of neutropenia, and low reticulocyte and platelet counts, require temporary discontinuation of therapy in almost all patients. In patients with sickle cell disease, hematologic recovery usually occurs within two weeks.

Hydroxyurea can cause macrocytosis, which may mask the incidental development of folic acid deficiency. Therefore, administration of folic acid is recommended during hydroxyurea therapy.

With hydroxyurea doses over 60 mg/kg, nausea/vomiting, diarrhea, or constipation can occur in more than 80% of patients.

A number of mucocutaneous reactions can occur during therapy with hydroxyurea. Hydroxyurea can cause radiation recall, which consists of burning, pain, erythema, and desquamation at the site of prior radiation. Stomatitis, esophagitis, and oral ulcerations can be severe when hydroxyurea and radiation therapy are given concurrently. Erythema on the face, hands, and soles has been reported, as has a maculopapular rash. Hydroxyurea has also been associated with the development of painful skin ulcers in patients receiving the drug for the treatment of myeloproliferative disorders. The most common ulcer site was the malleoli. These skin ulcers can be difficult to treat and usually require cessation of hydroxyurea therapy.[1549]

Hydroxyurea-induced cellular destruction can result in tumor lysis syndrome (TLS) which includes hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia. Uric acid nephropathy, acute renal failure due renal tubular obstruction, metabolic acidosis, and nephrolithiasis can also occur. These problems are more severe when a highly chemosensitive disease is treated (i.e., leukemia or lymphoma). Aggressive alkalinization of the urine and use of allopurinol can prevent urate nephropathy; close monitoring of serum electrolytes and renal function is recommended.

Drug fever secondary to hydroxyurea confirmed by rechallenge has been documented in three cases. The mechanism of hydroxyurea-induced fever in unknown, but may be due to direct toxicity or an idiosyncratic reaction.[635]

In patients with sickle cell disease, non-hematologic adverse events possibly associated with treatment included alopecia, skin rash (unspecified), fever, gastrointestinal disturbances, weight gain, bleeding, and parvovirus B-19 infection; however, these events occurred with similar frequencies in both the hydroxyurea and placebo treatment groups.

Large doses may produce moderate drowsiness. Neurological disturbances have occurred rarely and were limitited to headache, dizziness, disorientation, hallucinations, and seizures.

Fatal and nonfatal pancreatitis, severe hepatotoxicity, including hepatic failure, and severe peripheral neuropathy have been reported in HIV-infected patients during therapy with hydroxyurea in combination with anti-retrovirals, in particular didanosine plus stavudine.

Product Information

More information about the following products is available:

• Droxia®
• Hydrea®
• Hydroxyurea
• Mylocel™

References

3. Phillips RE, Warrell DA, White NJ et al. Intravenous quinidine for the treatment of severe Falciparum malaria. N Engl J Med 1985;312:1273—8.

616. Charache S, Terrin ML, Moore RD et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 1995;332:1317—22.

635. Lossos IS, Matzner Y. Hydroxyurea-induced fever: case report and review of the literature. Ann Pharmacother 1995;29:132—3.

951. Cortelazzo S, Finazzi G, Ruggeri M et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995;332:1132—6.

1332. Bonadonna G, Tancini G, Bajetta E. Chemotherapy of lung cancer: the experience of the National Cancer Institute of Milan. Cancer Chemother Rep 1973;4;231—7.

1549. Best PJ, Daoud MS, Pittelkow MR et al. Hydroxyurea-induced leg ulceration in 14 patients. Ann Intern Med 1998;128:29—32.

1800. US Department of Health and Human Services (DHHS) and National Institutes of Health (NIH). The Living Document: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Retrieved April 14, 2004. Available on the World Wide Web at www.aidsinfo.nih.gov.

1873. Ferster A, Vermylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 1996;88:1960—4.

1874. Scott JP, Hillery CA, Brown ER, et al. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr 1996;128:820—8.

2755. Byrd DC, Pitts SR, Alexander CK. Hydroxyurea in two pregnant women with sickle cell anemia. Pharmacotherapy 1999;19:1459—62.

3373. Palmer S, Shafer RW, Merigan TC. Hydroxyurea enhances the activities of didanosine 9-

3957. Centers for Disease Control and Prevention (CDC). General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002;51(RR-2):1—35.

4668. Bjornsson TD, Huang AT, Roth P, et al. Effects of high-dose cancer chemotherapy on the absorption of digoxin in two different formulations. *Clin Pharmacol Ther* 1986;39:25—8.

4669. Leukine® (sargramostim, GM-CSF) package insert. Richmond, CA: Berlex, Inc.; 2002 Jun.

4670. Neupogen®(filgrastim, G-CSF) package insert. Thousand Oaks, CA: Amgen Inc.; 2002 May.

5126. Muggia FM, Moran RG. Treatment of colon cancer based on biochemical modulation of fluoropyrimidines by hydroxyurea. *Semin Oncol* 1992;19 (3 Suppl 9):90—3.

5127. Kubota M, Takimoto T, Tanizawa A, et al. Differential modulation of of 1-beta-d-arinofuranosylcytosine metabolism by hydroxyurea in human leukemic cell lines. *Biochem Pharmacol* 1988;37:1745—9.

5128. Zittoun R, Marie JP, Zittoun J, et al. Modulation of cytosine arabinoside (ara-c) and high-dose ara-c in acute leukemia. *Semin Oncol* 1985;12:139—43.

5129. Hydrea® (hydroxyurea) package insert. Princeton, NJ: Bristol-Meyers Squibb Company; March 2001.

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LIST OF REFERENCES

1. Facts about sickle cell anemia. 1996, National Institutes of Health: Bethesda, MD.

2. Platt A, Eckman JR, Beasley J, and Miller G. (2002). Treating sickle cell pain: An update from the Georgia comprehensive sickle cell center. J Emerg Nurs, 28:297-303.

3. Hughes MH. Sickle cell disease. http://www.pitt.edu/~mahst51. July 7,2003.

4. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, and Klug PP. (1994). Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med, 330:1639-1644.

5. Charache S, Natural history of disease: Adults, in Sickle cell disease: Basic principles and clinical practice, H.R. Embury SH, Mohandas N, Steinberg MH, Editor, Raven Press, Ltd: New York. 1994

6. Zimmerman S, Ware R, and Kinney TR. (1997). Gaining ground in the fight against sickle cell disease. Contemp Pediatr, 14:154 -177.

7. Shapiro B and Ballas S, The acute painful episode., in Sickle cell disease: Basic priniciples and clinical practice, H.R. Embury SH, Mohandas N, Steinberg MH, Editor, Raven Press, Ltd: New York. 1994

8. The management of sickle cell disease. 2002, National Institutes of Health: Bethesda, MD.

9. Reed W and Vichinsky E. (1998). New considerations in the treatment of sickle cell disease. Annu Rev Med, 49:461-474.

10. Pegelow CH, Adams RJ, McKie V, Abboud M, Berman B, Miller ST, Olivieri N, Vichinsky E, Wang W, and Brambilla D. (1995). Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr, 126:896-899.

11. Russell MO, Goldberg HI, Hodson A, Kim HC, Halus J, Reivich M, and Schwartz E. (1984). Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood, 63:162-169.

12. Elander J and Midence K. (1996). A review of evidence about factors affecting quality of pain management in sickle cell disease. Clin J Pain, 12:180-193.

13. Davies SC and Oni L. (1997). Fortnightly review: Management of patients with sickle cell disease. BMJ, 315:656-660.

14. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, and Bonds DR. (1995). Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med, 332:1317-1322.

15. Moore RD, Charache S, Terrin ML, Barton FB, and Ballas SK. (2000). Cost-effectiveness of hydroxyurea in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. Am J Hematol, 64:26-31.

16. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Saunthararajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, and Terrin M. (2003). Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: Risks and benefits up to 9 years of treatment. JAMA, 289:1645-1651.

17. Haque A and Telfair J. (2000). Socioeconomic distress and health status: The urban-rural dichotomy of services utilization for people with sickle cell disorder in North Carolina. J Rural Health, 16:43-55.

18. Telfair J, Haque A, Etienne M, Tang S, and Strasser S. (2003). Rural/urban differences in access to and utilization of services among people in Alabama with sickle cell disease. Public Health Rep, 118:27-36.

19. Lottenberg R, Reddy S, Boyette R, Schwartz R, and Konrad T. (2002). Hydroxyurea therapy for sickle cell disease in community based practices: A survey of Florida and North Carolina hematologists/oncologists. Blood, 100:186a.

20. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, Ballas SK, McMahon RP, Castro O, and Orringer EP. (1996). Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The multicenter study of hydroxyurea in sickle cell anemia. Medicine (Baltimore), 75:300-326.

21. Cutts C and Tett SE. (2003). Influences on doctors' prescribing: Is geographical remoteness a factor? Aust J Rural Health, 11:124-130.

22. Woods K, Karrison T, Koshy M, Patel A, Friedmann P, and Cassel C. (1997). Hospital utilization patterns and costs for adult sickle cell patients in Illinois. Public Health Rep, 112:44-51.

23. Donabedian A. (1966). Evaluating the quality of medical care. Milbank Mem Fund Q, 44:Suppl:166-206.

24. Ballas SK and Smith ED. (1992). Red blood cell changes during the evolution of the sickle cell painful crisis. Blood, 79:2154-2163.

25. Rees DC, Olujohungbe AD, Parker NE, Stephens AD, Telfer P, and Wright J. (2003). Guidelines for the management of the acute painful crisis in sickle cell disease. Br J Haematol, 120:744-752.

26. Sutton M, Atweh GF, Cashman TD, and Davis WT. (1999). Resolving conflicts: Misconceptions and myths in the care of the patient with sickle cell disease. Mt Sinai J Med, 66:282-285.

27. Steinberg MH. (1999). Management of sickle cell disease. N Engl J Med, 340:1021-1030.

28. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, and Kinney TR. (1991). Pain in sickle cell disease. Rates and risk factors. N Engl J Med, 325:11-16.

29. Gaston M and Rosse WF. (1982). The cooperative study of sickle cell disease: Review of study design and objectives. Am J Pediatr Hematol Oncol, 4:197-201.

30. Steinberg MH. (1996). Review: Sickle cell disease: Present and future treatment. Am J Med Sci, 312:166-174.

31. Brozovic M and Davies S. (1987). Management of sickle cell disease. Postgrad Med J, 63:605-609.

32. Ballas SK. (2001). Ethical issues in the management of sickle cell pain. Am J Hematol, 68:127-132.

33. Letvin NL, Linch DC, Beardsley GP, McIntyre KW, and Nathan DG. (1984). Augmentation of fetal-hemoglobin production in anemic monkeys by hydroxyurea. N Engl J Med, 310:869-873.

34. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, and Nathan DG. (1984). Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. J Clin Invest, 74:652-656.

35. Davies SC and Gilmore A. (2003). The role of hydroxyurea in the management of sickle cell disease. Blood Rev, 17:99-109.

36. Ferguson RP, Arun A, Carter C, Walker SD, and Castro O. (2002). Hydroxyurea treatment of sickle cell anemia in hospital-based practices. Am J Hematol, 70:326-328.

37. Weiner DL and Brugnara C. (2003). Hydroxyurea and sickle cell disease: A chance for every patient. JAMA, 289:1692-1694.

38. Blumenthal D and Kilo CM. (1998). A report card on continuous quality improvement. Milbank Q, 76:625-648, 511.

39. Donabedian A. (1990). The seven pillars of quality. Arch Pathol Lab Med, 114:1115-1118.

40. Lohr K, ed. Medicare: A strategy for quality assurance. National Academy Press: Washington, D.C. 1990

41. Handler A, Issel M, and Turnock B. (2001). A conceptual framework to measure performance of the public health system. Am J Public Health, 91:1235-1239.

42. Mainz J. (2003). Defining and classifying clinical indicators for quality improvement. Int J Qual Health Care, 15:523-530.

43. Lee T and Mills ME. (2000). Analysis of patient profile in predicting home care resource utilization and outcomes. J Nurs Adm, 30:67-75.

44. Donabedian A. (1985). The epidemiology of quality. Inquiry, 22:282-292.

45. Birkmeyer JD, Dimick JB, and Birkmeyer NJ. (2004). Measuring the quality of surgical care: Structure, process, or outcomes? J Am Coll Surg, 198:626-632.

46. Avorn J. (2002). Balancing the cost and value of medications: The dilemma facing clinicians. Pharmacoeconomics, 20 Suppl 3:67-72.

47. Perrin EB. (2002). Some thoughts on outcomes research, quality improvement, and performance measurement. Med Care, 40:III89-91.

48. Buetow SA, Sibbald B, Cantrill JA, and Halliwell S. (1997). Appropriateness in health care: Application to prescribing. Soc Sci Med, 45:261-271.

49. Moussa A and Bridges-Webb C. (1994). Quality of care in general practice. A delphi study of indicators and methods. Aust Fam Physician, 23:465-468, 472-463.

50. Lexchin J. (1998). Improving the appropriateness of physician prescribing. Int J Health Serv, 28:253-267.

51. Pont LG, Denig P, van der Molen T, van der Veen WJ, and Haaijer-Ruskamp FM. (2004). Validity of performance indicators for assessing prescribing quality: The case of asthma. Eur J Clin Pharmacol, 59:833-840.

52. Segal R and Wang F. (1999). Influencing physician prescribing. Pharm Pract Manag Q, 19:30-50.

53. Raisch DW. (1990). A model of methods for influencing prescribing: Part I. A review of prescribing models, persuasion theories, and administrative and educational methods. DICP, 24:417-421.

54. Raisch DW. (1990). A model of methods for influencing prescribing: Part II. A review of educational methods, theories of human inference, and delineation of the model. DICP, 24:537-542.

55. Becker MH, Stolley PD, Lasagna L, McEvilla JD, and Sloane LM. (1972). Correlates of physicians' prescribing behavior. Inquiry, 9:30-42.

56. Blanc PD, Trupin L, Earnest G, San Pedro M, Katz PP, Yelin EH, and Eisner MD. (2003). Effects of physician-related factors on adult asthma care, health status, and quality of life. Am J Med, 114:581-587.

57. Green CR, Wheeler JR, and LaPorte F. (2003). Clinical decision making in pain management: Contributions of physician and patient characteristics to variations in practice. J Pain, 4:29-39.

58. Gordon DB, Pellino TA, Miaskowski C, McNeill JA, Paice JA, Laferriere D, and Bookbinder M. (2002). A 10-year review of quality improvement monitoring in pain management: Recommendations for standardized outcome measures. Pain Manag Nurs, 3:116-130.

59. Gordon DB and Dahl JL. (2004). Quality improvement challenges in pain management. Pain, 107:1-4.

60. Marcus DA. (2000). Treatment of nonmalignant chronic pain. Am Fam Physician, 61:1331-1338, 1345-1336.

61. Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, and Pandya KJ. (1993). Physician attitudes and practice in cancer pain management. A survey from the eastern cooperative oncology group. Ann Intern Med, 119:121-126.

62. Cleeland CS, Reyes-Gibby CC, Schall M, Nolan K, Paice J, Rosenberg JM, Tollett JH, and Kerns RD. (2003). Rapid improvement in pain management: The veterans health administration and the institute for healthcare improvement collaborative. Clin J Pain, 19:298-305.

63. Brown ST. (2000). Outcomes analysis of a pain management project for two rural hospitals. J Nurs Care Qual, 14:28-34.

64. Iezzoni LI. (2004). Risk adjusting rehabilitation outcomes: An overview of methodologic issues. Am J Phys Med Rehabil, 83:316-326.

65. Bowker L and Stewart K. (1999). Predicting unsuccessful cardiopulmonary resuscitation (cpr): A comparison of three morbidity scores. Resuscitation, 40:89-95.

66. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, and Pankow JS. (2003). Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care, 26:2777-2784.

67. Griffin SJ, Little PS, Hales CN, Kinmonth AL, and Wareham NJ. (2000). Diabetes risk score: Towards earlier detection of type 2 diabetes in general practice. Diabetes Metab Res Rev, 16:164-171.

68. George AL, Jr., Folk BP, 3rd, Crecelius PL, and Campbell WB. (1989). Pre-arrest morbidity and other correlates of survival after in-hospital cardiopulmonary arrest. Am J Med, 87:28-34.

69. Iezzoni LI, Ash AS, Shwartz M, Daley J, Hughes JS, and Mackiernan YD. (1995). Predicting who dies depends on how severity is measured: Implications for evaluating patient outcomes. Ann Intern Med, 123:763-770.

70. Mehta SR, Mayhew DY, De Leon JM, Hartzema AG, Lottenberg R, and Boyette R, [The health-related quality of life and health care transition experiences of young adults with sickle cell disease]. 2003, Unpublished raw data.

71. McClellan M, McNeil BJ, and Newhouse JP. (1994). Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. JAMA, 272:859-866.

72. Donabedian A. (1988). The quality of care. How can it be assessed? JAMA, 260:1743-1748.

73. Hammermeister KE, Shroyer AL, Sethi GK, and Grover FL. (1995). Why it is important to demonstrate linkages between outcomes of care and processes and structures of care. Med Care, 33:OS5-16.

74. Lee K and Wan TT. (2002). Effects of hospitals' structural clinical integration on efficiency and patient outcome. Health Serv Manage Res, 15:234-244.

75. Hoenig H, Duncan PW, Horner RD, Reker DM, Samsa GP, Dudley TK, and Hamilton BB. (2002). Structure, process, and outcomes in stroke rehabilitation. Med Care, 40:1036-1047.

76. Heisler M, Smith DM, Hayward RA, Krein SL, and Kerr EA. (2003). Racial disparities in diabetes care processes, outcomes, and treatment intensity. Med Care, 41:1221-1232.

77. McKenzie DA, Semradek J, McFarland BH, Mullooly JP, and McCamant LE. (2000). The validity of medicaid pharmacy claims for estimating drug use among elderly nursing home residents: The Oregon experience. J Clin Epidemiol, 53:1248-1257.

78. Quam L, Ellis LB, Venus P, Clouse J, Taylor CG, and Leatherman S. (1993). Using claims data for epidemiologic research. The concordance of claims-based criteria with the medical record and patient survey for identifying a hypertensive population. Med Care, 31:498-507.

79. el-Hazmi MA, Warsy AS, Addar MH, and Babae Z. (1994). Fetal haemoglobin level--effect of gender, age and haemoglobin disorders. Mol Cell Biochem, 135:181-186.

80. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, Nickerson B, Orringer E, McKie V, Bellevue R, Daeschner C, and Manci EA. (2000). Causes and outcomes of the acute chest syndrome in sickle cell disease. National acute chest syndrome study group. N Engl J Med, 342:1855-1865.

81. Iezzoni LI, ed. Risk adjustment for measuring healthcare outcomes. 2nd ed., Health Administration Press: Chicago, IL. 1997

82. Harris KM and Remler DK. (1998). Who is the marginal patient? Understanding instrumental variables estimates of treatment effects. Health Serv Res, 33:1337-1360.

83. Carson J and Strom B, Medicaid databases, in Pharmacoepidemiology, B. Strom, Editor, John Wiley and Sons, Ltd: Chichester, England. 1994

84. Stevens JP. (2002). Applied multivariate statistics for the social sciences. 4th ed. Mahwah: Lawrence Erlbaum Associates, Inc.

85. Iezzoni LI. (1997). Assessing quality using administrative data. Ann Intern Med, 127:666-674.

86. Bonds D. Clinical alert: Drug treatment for sickle cell anemia. http://www.nlm.nih.gov/databases/alerts/sickle_cell.html. November 17,2004.

87. Ferster A, Vermylen C, Cornu G, Buyse M, Corazza F, Devalck C, Fondu P, Toppet M, and Sariban E. (1996). Hydroxyurea for treatment of severe sickle cell anemia: A pediatric clinical trial. Blood, 88:1960-1964.

88. Vermeire E, Hearnshaw H, Van Royen P, and Denekens J. (2001). Patient adherence to treatment: Three decades of research. A comprehensive review. J Clin Pharm Ther, 26:331-342.

89. Steinberg MH, Lu ZH, Barton FB, Terrin ML, Charache S, and Dover GJ. (1997). Fetal hemoglobin in sickle cell anemia: Determinants of response to hydroxyurea. Multicenter study of hydroxyurea. Blood, 89:1078-1088.

90. Selim AJ, Fincke G, Ren XS, Lee A, Rogers WH, Miller DR, Skinner KM, Linzer M, and Kazis LE. (2004). Comorbidity assessments based on patient report: Results from the veterans health study. J Ambul Care Manage, 27:281-295.

91. Mooney C, Zwanziger J, Phibbs CS, and Schmitt S. (2000). Is travel distance a barrier to veterans' use of VA hospitals for medical surgical care? Soc Sci Med, 50:1743-1755.

BIOGRAPHICAL SKETCH

Dionne is a Florida native who has a passion for studying minority health issues. Her interest in pharmacoepidemiology and health outcomes research was realized after working as a research coordinator for the Department of Family Medicine at the University of South Florida.

Prior to enrolling at the University of Florida, Dionne attended Florida State University where she received her bachelor's degree in chemical science, and the University of South Florida, where she earned a master's degree in public health. Throughout her graduate career, Dionne has received such honors as induction into the Pi Kappa Phi Honor Society, membership into the McKnight Doctoral Fellowship program; also she was a University of Florida Minority Fellowship recipient. She is grateful for the guidance she received while at UF, and is excited to embark on a career in health outcomes research.