RACE AS A FUNDAMENTAL CAUSE OF DISPARITIES IN THE CONSEQUENCES OF INECTION IN CHILDREN WITH LEUKEMIA

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ABSTRACT OF THE DISSERTATION

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Despite gains in overall survival following the diagnosis of leukemia, disparities persist between children belonging to White and non-White racial groups. Infectious complications are the second leading cause of death after the leukemia itself, yet few studies have sought to determine if there are racial differences in these complications that can explain some of the disparities that exist. The purpose of this study was to investigate race as a risk factor for infectious complications in hospitalized children, and when infection is present, if there are racial differences in the progression to severe sepsis and utilization of healthcare resources.

This was a secondary analysis of cross-sectional data compiled from the 2016 Healthcare Cost and Utilization Project Kids' Inpatient Database that tested hypotheses guided by the conceptual framework of the Fundamental Cause Theory. There were two separate samples analyzed representing the common forms of childhood leukemia: the sample of lymphoblastic leukemia consisted of 28914 cases, and the sample of acute myeloid leukemia consisted of 2902 cases. Each case represented a pediatric hospitalization that took place in the United States in the year 2016. Logistic regression analyses revealed the risk for severe sepsis in Hispanic children was significantly greater than that of White children in both the acute lymphoid leukemia and the acute myeloid leukemia groups. Asian and Black children with acute lymphoid leukemia were found to

be at significantly increased risk for high-cost hospitalizations, compared to White children.

This study provided evidence that the occurrence of life-threatening infections in hospitalized children with leukemia is a potential contributor to the disparate rates of survival and worthy of further investigation. Additional research should be conducted with the goal of developing an explanatory model for these disparities that can be used to improve nursing care of this vulnerable population.

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Chapter 1: The Problem

Childhood Leukemia in the United States

Leukemia is the most common form of cancer accounting for 29% of the malignancies in children (Siegel, Miller, & Jemal, 2017). Leukemia is a malignancy of the hematopoietic tissues and is characterized by the uncontrolled proliferation of immature blood cells. As these cells multiple they compete with normal cells in the marrow and interfere with hematopoiesis (Baggott, Fochtman, & Patterson Kelly, 2011). Leukemic disorders are categorized by the affected cell line and the stage at which hematopoiesis is disrupted. Acute lymphoblastic leukemia (ALL) is the result of abnormal proliferation of cells along the lymphoid lineage in either the B-cell or T-cell pathway. It is the most common form of cancer in children less than 15 years of age representing approximately 3000 new cases per year (Baggott et al., 2011; Pui, Robinson, & Look, 2008; Siegel et al., 2017). The incidence of ALL is highest in Hispanic children with 42.9 diagnoses per one million and lowest in non-Hispanic Black children with an incidence of 18.7 per one million (Siegel et al., 2017). Children between the ages of one and nine years are most commonly affected and have the greatest survivorship as the result of higher rates of favorable prognostic factors (Baggott et al., 2011; Pui et al., 2008; Siegel et al., 2017). Infants and adolescents are more likely to be diagnosed with less favorable subtypes of ALL and have higher rates of mortality. Children with Down syndrome have worse outcomes due to the tendency to develop greater treatment-related toxicity including severe myelosuppression, mucositis, and infections (Baggott et al., 2011).

The second most common form of childhood leukemia is acute myeloid leukemia (AML) affecting the myeloid, erythroid, megakaryocytic, and monocytic cell lines (Baggott et al., 2011; Rubnitz, Gibson, & Smith, 2010). Although only 15 to 20% of all childhood leukemia cases are AML, it accounts for 30% of all leukemia deaths due to high rates of treatment failure and treatment-related mortality (Rubnitz et al., 2010). Children younger than two years of age have the highest incidence of AML. Following a decrease in early childhood, the rate of diagnosis increases again in adolescence. Although there are no differences between the incidence rate in White and Black children, Hispanic children are more likely to be diagnosed with the less common subtype acute promyelocytic leukemia. Previous treatment for another childhood malignancy and certain inherited syndromes including Down syndrome, Noonan syndrome, and Fanconi anemia predispose children to AML (Baggott et al., 2011; Rubnitz et al., 2010). In contrast to ALL, the diagnosis of Down syndrome is a favorable prognostic factor in AML and these children have superior outcomes (Rubnitz et al., 2010).

Improved Outcomes in Childhood Leukemia

Over the past 40 years, there have been extraordinary improvements in the treatment of many childhood cancers and the current survival rate is 83%, compared to 58% in the mid-1970s. In 2012, the 5-year overall survival for children less than 15 years of age diagnosed with ALL was 90.2% and 64.2% for children diagnosed with the more severe form, AML. Survival in older adolescents was 74.7% for ALL and 59.7% for AML (Siegel et al., 2017). Improvements in survival following the diagnosis of ALL can be attributed to the addition of central nervous system prophylaxis, stratification of

patients into risk groups, and an increased understanding of genetic determinants of drug resistance and toxicities resulting in targeted therapies (Pui et al., 2015). Although the therapies used to treat AML have not varied greatly over the years, individual patient risk is now stratified and supportive care of side effects has greatly improved allowing for the delivery of intensive therapy with less treatment-related mortality. Additionally, prudent use of stem cell transplant and improved treatment in the event of relapse have contributed to the overall success for both leukemia types (Pui et al., 2015; Rubnitz et al., 2010).

In 1986, the American Academy of Pediatrics (AAP) issued the recommendation that a child diagnosed with cancer be promptly referred to a comprehensive pediatric cancer center that meets the defined requirements for programs with this designation. According to these recommendations "early detection, accurate diagnosis, and appropriate treatment depend on a multidisciplinary treatment approach to children and adolescents with cancer, and that approach is uniquely available at a pediatric cancer center" (Corrigan et al., 2004). More than 90% of affected children in the U.S. receive care in the setting of pediatric cancer centers and this trend has contributed to dramatically improved rates of survival through knowledge gained in large, consortium-based clinical trials that take place in these institutions. The Children's Oncology Group (COG) is the largest of these research consortiums in the United States and 50 to 60% of all children seen in COG institutions are enrolled in therapeutic clinical trials (O'Leary, Krailo, Anderson, & Reaman, 2008). Large multi-center clinical trials allow researchers to pool together patients for the study of genetic features of the disease and response to treatment resulting in improved outcomes (Pui et al., 2015).

One study that examined access to specialized cancer care and survival outcomes of 1751 children treated in the state of Georgia found that those who were not treated at a COG center had lower 5-year overall survival compared to children who received care in COG-affiliated programs (53.3% versus 86.3%, $p<.05$) (Howell, Ward, Austin, Young, & Woods, 2007). The adolescent and young adult age group (AYA) has had historically poor survival rates in comparison to younger children. An analysis of 1870 AYA patients diagnosed with ALL and AML in California was performed to compare outcomes between those receiving treatment in designated research institutions and those who were treated elsewhere. The researchers found that patients with ALL between the ages of 15 and 21 years whose treatment took place in an institution without a COG or National Cancer Institute (NCI) affiliation were at greater risk for mortality compared to younger children ($p=.005$). However, when treated in COG or NCI centers, this age group had comparable outcomes to younger children ($p=.8$). Similarly, patients with AML between the ages of 15 and 21 had higher rates of mortality if treatment did not take place in a COG or NCI center ($p=.02$) (Wolfson, Sun, Wyatt, Stock, & Bhatia, 2017).

Leukemia and Infectious Complications

Children diagnosed with leukemia are at increased risk for infection and the reasons for this are multifactorial. In addition to the primary risk of immunosuppression caused by the therapy, other risk factors include prolonged hospitalization, antibiotic use, loss of the intact mucosal barrier, and the need for indwelling venous catheters to deliver treatment and supportive care. Viruses are the most common cause of infection in children with leukemia. Bacterial and invasive fungal infections are responsible for the

most life-threatening infectious complications (Baggott et al., 2011; Bailey, Reilly, & Rheingold, 2009).

Following mortality as a result of the malignancy itself, infection is the second leading cause of death in children diagnosed with cancer (Bailey et al., 2009). A retrospective study of children in the United Kingdom treated for ALL found a 2.4% infection-related mortality rate between 2003 and 2011 accounting for 30% of all clinical trial deaths (O'Connor et al., 2014). With the increasing success of leukemia therapies resulting in less relapse and greater overall survival from the disease itself, death from infectious complications becomes less acceptable (Alexander et al., 2015; Bailey et al., 2009; Hunger et al., 2012; Smits-Seemann, Pettit, Li, Kirchhoff, & Fluchel, 2017).

A serious concern in this population is the development of severe sepsis. Severe sepsis is a systemic clinical situation that occurs in the presence of a suspected or proven infection. As the body fails to initiate an adequate immune response to the infectious pathogen decreased tissue perfusion occurs, resulting in life-threatening organ damage (Baggott et al., 2011; Conway, 2018; Singer et al., 2016). Severe sepsis represents an oncologic emergency and the prognosis is dependent upon the nature of the infectious organism, the promptness of the initiation of treatment, and the child's response to the treatment (Baggott et al., 2011). Severe sepsis in children hospitalized with an underlying diagnosis of cancer results in a higher risk of mortality than in children who had been previously healthy and develop sepsis (Prout et al., 2018; Ruth et al., 2014). In a cohort of 12,466 children hospitalized between 1995 and 2002 with cancer complicated by neutropenia, those who developed sepsis had an 9.93-fold increase in the odds of death (Basu, Fernandez, Fisher, Asselin, & Lyman, 2005).

Infectious complications also result in prolonged hospitalizations and increased healthcare costs. In an analysis of admissions from three separate years, Russell et al. (2014) determined in a cohort of 202,995 hospitalizations for the diagnosis of childhood cancer in the U.S. that 15% of the hospitalizations were for the complication of infection. A nation-wide analysis from the year 2012 determined that chemotherapy-induced neutropenia, a risk factor for infection, accounted for 16,859 pediatric hospitalizations accompanied by a financial burden of $439 million. Neutropenia was attributed as the cause of 5.2% of all childhood cancer-related hospital admissions and 8.3% of all cancer-related hospital costs in 2012 with a mean length of stay of 8.5 days (Tai, Guy, Dunbar, & Richardson, 2017). The impact of healthcare utilization increases in the presence of more severe infections in children with cancer. Length of hospitalization and expenses rise significantly when admissions are complicated by sepsis, bacterial infections, fungal infections, and pneumonia (Alvarez, Chamberlain, Aftandilian, Saynina, & Wise, 2017; Mueller, Croop, & Carroll, 2016).

Racial Disparities in Childhood Leukemia Outcomes

Race and Mortality. Despite tremendous gains in survivorship for children diagnosed with both ALL and AML, evidence exists that these triumphs have not been universal and disparate outcomes have persisted over time with non-Hispanic White children experiencing superior rates of survival compared to children belonging to other races and ethnicities. In a population-based study of 9,295 children diagnosed with ALL in the state of California between 1988 and 2011, Abraháo et al. (2015) found 5-year overall survival had improved during the timeframe from 76.9% to 85.7%. However, there were racial and ethnic differences in survival. Compared to 85% survival by non-

Hispanic White children, this number was 74.5% for African American, 79% for Hispanic, and 81.4% for Asian children. After adjusting for demographic and prognostic risk factors, African American children had a 57% increased risk of death compared to non-Hispanic White children. Hispanic and Asian children were also found to have significantly increased rate of mortality, 38% and 33% respectively, compared to non-Hispanic White children (Abraháo et al., 2015).

A larger population study of the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER) conducted by Goggins and Lo (2012) examined childhood leukemia survivorship in 19 states between the years 1998 and 2008. Again, while there was improvement during the timeframe, there were persistent disparities in 5-year overall survival and African American, Hispanic, Native American, and Asian children had significantly lower rates of survivorship when compared to non-Hispanic White children (Goggins & Lo, 2012).

A separate analysis of SEER data compared mortality rates in the time periods between 1992 and 2000 with 2001 and 2007. Despite improved survival for all children in the recent era, Black children had significantly higher rates of mortality when diagnosed with ALL ($p<.01$) and AML ($p<.01$) compared to White children (Pui et al., 2012). In a similar cohort comparison study of SEER data, Kadan-Lottick et al. (2003) found that overall survival for children with ALL increased from 56% between 1973 and 1982 to 81% between 1990-1999. However, the adjusted risk of death for Black and Hispanic children was greater than White children regardless of the era. Black children had a 1.49-fold increased risk of death compared to White children between 1973 and 1982 ($p<.001$) and Hispanic children had a 1.39-fold increase during that period

($p<.001$). Between 1990 and 1999, Black children had a 1.50-fold risk ($p=.03$) and Hispanic children a 1.83-fold risk of death ($p<.001$) compared to White children (Kadan-Lottick et al., 2003).

Persistent racial disparities in leukemia survivorship are also apparent when care is provided in the controlled setting of clinical trials and despite taking place in COG-affiliated institutions. Hunger et al. (2012) reported the findings of two consecutive ALL trials conducted by COG between 1990 and 2005. There were 21,626 enrollees, representing 55.8% of all U.S. children diagnosed with ALL during this timeframe. Five-year overall survival increased significantly from 83.7% in 1990 to 90.4% in 2005. These favorable findings included improved outcomes for all ages, with the exception of infants, as well as all races, ethnicities, immunophenotypic subtypes, and those children presenting with clinical high-risk features at diagnosis. African American children were found to have significantly higher rates of poor prognostic disease features than non-Hispanic White children. However, multivariate analysis showed a persistence of inequitable outcomes after adjusting for these clinical factors. The relative risk of death, compared to non-Hispanic White children, in the more recent treatment era was 1.37 for African American children and 1.47; both were significant findings (Hunger et al., 2012).

Acute myeloid leukemia survivorship has also increased as demonstrated in a report of outcomes of two consecutive COG trials conducted between 1989 and 2002 (Aplenc et al., 2006). Eight hundred thirty-six children were treated in the first trial spanning the years 1989 to 1995 and 900 children were treated between 1996 and 2000. Remission was achieved in 77.9% of non-Hispanic White children in the first study and 85.6% in the second. Rates of remission for African American, Hispanic, and Asian

children did not differ significantly from this in either treatment era. However, long term survival was significantly less for African American and Hispanic children in the earlier era. In the more recent treatment era, African American children continued to have significantly worse long-term survival when compared to non-Hispanic White children (Aplenc et al., 2006). Similarly, in a retrospective review of the medical records of 129 patients under the age of 18 years diagnosed with AML treated at Texas Children's Cancer Center, Hispanic children were more likely to have cytogenetic disease features associated with a favorable prognosis ($p=.04$), yet there was not a superior survival rate when compared to non-Hispanic White children ($p=.64$) (Gramatges et al., 2017).

Race and Infectious Complications. While advancements in treatment and supportive care have allowed for improved outcomes for children with leukemia by increasing survival and decreasing the likelihood of recurrent disease, infection remains a contributor to mortality (Alexander et al., 2015; Basu, Fernandez, Fisher, Asselin, & Lyman, 2005; Hunger et al., 2012). There is evidence that inequities exist in the rates and consequences of infectious complications experienced by children with leukemia and the burden is upon children belonging to groups other than the non-Hispanic White group. Basu et al. (2005) found that, compared to non-Hispanic White children, African American children had 1.95-fold increased odds of death when admitted with neutropenia and for Hispanic and Asian children this risk was 2.12-fold and 2.53-fold, respectively. African American children diagnosed with AML and treated between 1996 and 2000 in a clinical trial conducted by COG had a 13% risk of infection-related death and Hispanic children had a 16% risk. This was significantly greater than non-Hispanic White children who had a nine percent risk (Aplenc et al., 2006).

Study Purpose

Despite increasing rates of survival following the diagnosis of childhood leukemia, disparate rates of mortality persist for children who do not belong to the non-Hispanic White group (Abraháo et al., 2015; Aplenc et al., 2006; Goggins & Lo, 2012; Gramatges et al., 2017; Hunger et al., 2012; Kadan-Lottick et al., 2003; Pui et al., 2012). The immunosuppressive therapy required for the successful treatment of childhood leukemia leaves all children vulnerable to infection (Baggott et al., 2011; Bailey et al., 2009; Hakim & Gaur, 2011). Yet, evidence exists that despite universal exposure to these risk factors non-White children develop invasive bacterial infections at higher rates than White children (Doganis, Yankelevich, Ravindranath, Asmar, & Thomas, 2013; Hakim et al., 2010). African American, Hispanic, and Asian children are at greater risk of death from infectious complications when undergoing treatment of leukemia (Aplenc et al., 2006; Basu et al., 2005). African American, Asian, and Hispanic children with leukemia require longer hospitalizations for the treatment of infectious complications (Alvarez et al., 2017; Basu et al., 2005; Mueller et al., 2016). Still, there is a paucity of research focused on these potential racial and ethnic disparities in children with cancer who develop infectious complications (Smits-Seemann et al., 2017).

This study was a secondary analysis of a nationally representative database of children hospitalized in the year 2016 in the U.S. The purpose was to examine the relationship between race and the risk of infection in children hospitalized with the diagnosis of leukemia. Additionally, this study explored racial differences in the development of the complication of severe sepsis in children hospitalized with infection. A secondary aim of this study was to analyze the association between race and healthcare

utilization in the form of extended hospitalization and increased cost when infectious complications occur.

Research Question

A series of statistical analyses were conducted on nationally representative administrative data to address the research question: *Are there racial disparities in infectious complications and healthcare burden experienced by hospitalized children with leukemia?*

Sub-questions

1. Is race associated with the risk of infection in children hospitalized with the diagnosis of leukemia?
2. When infection is present, is race associated with the risk of severe sepsis in children hospitalized with the diagnosis of leukemia?
3. Are there racial differences in the likelihood of an extended hospital stay when an infectious complication is documented in a child with leukemia?
4. Are there racial differences in the likelihood of a high cost hospital stay when an infectious complication is documented in a child with leukemia?

Significance of the Study

There have been significant improvements in the overall survival rates for children diagnosed with leukemia in the U.S. (Siegel et al., 2017). Unfortunately, not all children have benefited from the medical advances that have led to improved survival resulting in the persistence of racial differences in rates of mortality (Bhatia, 2011). Death from infection persists as an unacceptable cause of mortality, second only to treatment-resistant disease (Alexander et al., 2015; Bailey et al., 2009; Hunger et al.,

2012; Pole et al., 2017). There is evidence that racial differences exist in the experience of infectious complication in children with leukemia (Alvarez et al., 2017; Aplenc et al., 2006; Basu et al., 2005; Doganis et al., 2013; Hakim et al., 2010). According to Smits-Seemann et al. (2017), "infections during cancer therapy may be an underappreciated potential contributor to disparities in survival among pediatric cancer patients." This study sought to add to the current body of evidence by examining the associations between race and the rate of infectious complications, the threat of severe sepsis, and healthcare utilization in children hospitalized with leukemia.

This study is a secondary analysis of a large national database of pediatric hospitalizations that took place in the year 2016 in the U.S. Much of the research mentioned in this summary of the current evidence was discovered in the course of pediatric cancer clinical trials. In comparison, the hospital-based data in this study allows the findings to be inclusive of all children with leukemia, regardless of where they were treated and whether or not they were enrolled in a trial. Clinical trial research does not capture other areas of interest to nursing that this analysis is capable of addressing, including complications experienced, length of stay, and cost of hospitalization (Rice et al., 2015). The other lens through which much of the previously mentioned findings were obtained was that of population science. While helpful in capturing outcomes of all children affected by leukemia, regardless of clinical trial enrollment status, this research failed to provide information other than survivorship.

The present study is unique in that it is the application of nursing science to previously collected administrative hospital data. As the field of data science evolves, nursing will emerge as a leader due to the discipline's tradition of theory-driven research

that will lend itself to meaningful discoveries in populations of interest that can be used to direct interventions, improve outcomes, and reduce disparities (Brennan & Bakken, 2015). This study provides a unique pathway to knowledge acquisition about the relationship between race and infectious complication in children hospitalized with leukemia with the benefit of the application of a conceptual framework.

Chapter 2: Theoretical Framework and Literature Review

Chapter two introduces the Fundamental Cause Theory, which served as the conceptual framework that guided this study of the influence of race on infectious complications of childhood leukemia. Following the description of the framework, a review of current empirical literature in which the Fundamental Cause Theory was applied to race and cancer outcomes in adult populations is presented. The potential application of the framework to childhood leukemia is supported by a summation of the current findings in the field that demonstrate the disparate outcomes of children belonging to racial groups other than the non-Hispanic White group. A summary of the gaps in literature is presented with the hypotheses that were developed for this study using the Fundamental Cause Theory as a guide. In conclusion, theoretical and operational definitions of the variables and relationships tested in the hypotheses will be described.

Conceptual Framework

The Fundamental Cause Theory. The Fundamental Cause Theory was developed to provide an explanation for the social conditions that underlie health disparities, even as advancements in the prevention, detection, and treatment of disease result in improved population health. Risks to health that are the result of socioeconomic

status, race, ethnicity, and any other factor that is closely affiliated with one's position in society are not amenable to interventions implemented at the level of the individual (Link & Phelan, 1995). Rather, to minimize these risks, interventions must be focused on altering the social condition that created the risk (Link & Phelan, 1995; Ward, 2007). Link and Phelan (1995) demonstrate the theory by citing the example of recommending a nutritious diet to an impoverished person. Providing advice on healthy dietary choices to this individual in the absence of contextualizing the social, cultural, and economic forces at work is unlikely to minimize the risk of inadequate nutrition on health outcomes because the social conditions underpinning this risk are being ignored (Link & Phelan, 1995). That is, to attempt to draw a direct line between a social condition and an adverse health outcome will lead to an oversimplification of the relationship and thus, a failure to eliminate the health disparity (Link & Phelan, 1995; Phelan & Link, 2015; Phelan, Link, Diez-Roux, Kawachi, & Levin, 2004). In this conceptual framework, these social conditions are referred to as "fundamental causes" (Link, 2005; Link, Northridge, Phelan, & Ganz, 1998; Phelan, Link, & Tehranifar, 2010; Phelan et al., 2004).

A fundamental cause makes a population vulnerable to more than one disease or health outcome (Link & Phelan, 1995; Phelan et al., 2010; Phelan & Link, 2015; Phelan et al., 2004). Again, examining the role of socioeconomic status as a fundamental cause illustrates this feature of the theory. People living in poverty have historically been at greater risk of communicable diseases, injuries, and the development of chronic conditions (Phelan et al., 2004). A fundamental cause affects disease outcomes through multiple risk factors (Link & Phelan, 1995; Phelan et al., 2010; Phelan et al., 2004). Chronic health problems may be linked to lower socioeconomic status through a number

of different pathways including occupation and environmental exposures, stress, sedentary lifestyle, poor nutrition, and limited access to health care providers (Phelan et al., 2004).

Embodied within fundamental causes of health outcomes are resources in one's possession that allow for either the avoidance or minimization of a health threat. In the framework, these resources are identified as money, knowledge, power, prestige, and social connections. Resources work on two levels. One can take advantage of available resources through independent actions. When knowledge about a disease and effective treatments are available, those with access to greater resources are in a better position to avail themselves of these and experience improved health and less mortality than those who are not in possession of the resources (Link & Phelan, 1995). A person can also experience contextual advantage by being situated in a circumstance in which he or she benefits from available resources as a result of social position, even in the absence of actions intentionally taken (Link, 2005; Link & Phelan, 1995). Health advantage can be the consequence of broader levels of connectedness through neighborhoods, social circles, schools, places of employment, and the healthcare system as these settings have the potential for both protective and deleterious health effects (Link, 2005).

When new circumstances of a health threat emerge, for instance knowledge about prevention or advancements in treatment, those with greater resources will have an advantage in accessing these innovations resulting in the persistence of health inequality. That is, there is transportability of resources to minimize new health threats or take advantage of new discoveries. It is this deployment of flexible resources in the face of emerging health threats that results in an enduring association between social position

and risk of mortality (Link & Phelan, 1995; Phelan et al., 2010; Phelan & Link, 2015; Phelan et al., 2004).

The present study examined race as a fundamental cause of health disparities experienced by children with leukemia, specifically the consequences of infection. The concept of race as a fundamental cause has been attributed to pathways that are inextricably linked to the unequal availability of resources for members of different racial groups, even when socioeconomic status is controlled. Examples of these pathways include the constructs of racism, employment discrimination, residential segregation, and stigma (Hatzenbuehler, Phelan, & Link, 2013; Phelan & Link, 2015; Williams & Collins, 2001). Systemic racism limits employment opportunities and thus, access to the flexible resources of money and prestige (Phelan & Link, 2015). Racial segregation enhances or limits access to the resource of beneficial social connections (Acevedo-Garcia, Osypuk, McArdle, & Williams, 2008; Phelan & Link, 2015; Williams & Collins, 2001). Another pathway by which race is a fundamental cause of health outcomes is stigma. Stigma results from the labeling or stereotyping of a group of people creating a power differential in which one group loses status, power, and prestige. Stigma overlaps with discrimination through multiple mechanisms including language mastery and immigration status (Hatzenbuehler et al., 2013).

Literature Review

This review of English language literature took place in the Medline, Google Scholar, CINAHL, and PubMed databases and, due to rapid advancements in the treatment of cancer, was almost exclusively limited to studies published between 2007 and 2018. Studies that took place outside of the U.S. were excluded because of potential

variation that exists in social policies between countries that could alter the influence of risks posed by fundamental causes. Finally, single institution studies were excluded due to the potential for biased results. Literature will be presented here to address the applicability of the Fundamental Cause Theory to the present study of the association between race and infectious complications of childhood leukemia.

Race as a fundamental cause of cancer outcomes. This section will address the theorized relationship between race, as a fundamental cause, and cancer outcomes. The search of the current literature yielded three studies in adult cancer populations that specified the Fundamental Cause Theory as a guiding framework in assessing the role of race, as a fundamental cause, in cancer outcomes. In each of these studies, racial inequities are demonstrated with members of the White race having superior outcomes following the diagnosis of cancer. For each study the sample under study, the variables measured that pertain to the current study, and relevant outcomes are summarized in Appendix A, Table A1.

Inherent in a fundamental cause are resources in the form of money, knowledge, power, prestige, and social connections in a family's possession that may be used to minimize the risk of disease (Link & Phelan, 1995; Phelan et al., 2010; Phelan et al., 2004). In a study using the Fundamental Cause Theory as a guiding framework, Kim, Dolecek, and Davis (2010) examined the role of available resources in mitigating the risk of ovarian cancer. White women in this analysis were found to have a significantly longer time between initial diagnosis and death compared to Black women, even when prognostic factors such as age and stage of disease at the time of diagnosis were similar (Kim et al., 2010). This finding supports the proposition that there are greater protective

advantages, in the form of available resources, for White women when facing similar heath threats as Black women (Phelan & Link, 2015).

An assumption of the Fundamental Cause Theory is that disparities in health outcomes persist over time despite the emergence of new knowledge and innovative treatment. The reason for this is theorized to be that those in socially advantaged positions are able to employ resources in their possession in ways that are transportable to other threats to their health (Link & Phelan, 1995; Phelan et al., 2010; Phelan & Link, 2015; Phelan et al., 2004). Death from colorectal cancer is more likely if the disease is detected in later stages. Consequently, national guidelines have been implemented, including screening recommendations using colonoscopy to assist in early detection, to improve survivorship. Two studies guided by the Fundamental Cause Theory examined longitudinal mortality data to compare trends in adult survivorship before and after the implementation of these guidelines. The first study showed a widening gap in the rate of morality between African American and White adults between the years 1968 and 2005, the eras before and after the implementation of the screening guidelines (Saldana-Ruiz, Clouston, Rubin, Colen, & Link, 2013). The second study measured the delay in decreasing colon cancer mortality rates across racial groups and found members of the African American race had a 4.1-year delay in experiencing declines in mortality when compared to White adults following the implementation the colonoscopy screening guidelines (Clouston et al., 2017). These two studies provide support to the Fundamental Cause Theory through empirical evidence that available resources are disproportionately available to members of the White race when emerging knowledge and innovation are developed to minimize a health threat, in this case colon cancer.

While no studies of childhood leukemia have used the Fundamental Cause Theory as a conceptual framework to examine the role of race in outcomes, there is evidence that future studies could be guided by the framework. Six studies that met the inclusion criteria lend support to the concept of race as a fundamental cause following the diagnosis of childhood leukemia. All of the studies compared survival between children belonging to different races or ethnicities. Only one study failed to find significant differences in mortality between Black and White children (Bona, Silverman, Wolfe, Blonquist, & Neuberg, 2016). Of the remaining studies, five found that Black children were at significantly increased risk of death from leukemia even when factors such as age at diagnosis, clinical disease features, and era of treatment were controlled (Abraháo et al., 2015; Aplenc et al., 2006; Arcaya et al., 2016; Goggins & Lo, 2012; Hunger et al., 2012). Four studies found that Hispanic children, when compared to non-Hispanic children, were at a significantly higher risk for inferior survival following the diagnosis of leukemia (Abraháo et al., 2015; Aplenc et al., 2006; Bona et al., 2016; Goggins & Lo, 2012). Asian children were found to have poor overall survival compared to non-Hispanic White children in two studies (Abraháo et al., 2015; Goggins & Lo, 2012).

Four studies provide empirical support to the assumption of the Fundamental Cause Theory that inequities persist even when innovation has the ability to minimize a health threat. Over the past two decades, survivorship following the diagnosis of childhood leukemia has increased and is approaching 90% as a result of therapy regimens tailored to improved diagnostic capabilities that allow for precise risk stratification (Pui et al., 2012). In three of the four studies, Black and Hispanic children experienced increased survival over time, but this significantly lagged behind the gains made by

White children during the same observation period (Abraháo et al., 2015; Goggins & Lo, 2012; Hunger et al., 2012). Two of the studies found children of Asian/Pacific Island race to have persistent disparate outcomes over time, and one study found Native American/Alaskan Natives to be at a continued disadvantage (Goggins & Lo, 2012; Hunger et al., 2012). Pui et al. (2012) analyzed SEER data to compare the survival of Black children to that of White children across consecutive treatment eras and reported significantly improved survival in AML, overall, in the more recent timeframe. There were no significant differences in rates of survival between Black and White children diagnosed with AML in the earlier era. But, coinciding with advancements in therapy resulting in improved overall survivorship, this gradient became statistically significant in the recent treatment era with White children experiencing more favorable outcomes than Black children (Pui et al., 2012). It is this persistence of disparate outcomes experienced by children who do not belong to the White racial group, despite the innovation taking place in the science of diagnosing and treating childhood leukemia, that provides support for the Fundamental Cause Theory as a guiding framework for future research.

Infectious complications in the child with leukemia. There is very little evidence in the literature quantifying the impact race has on infectious complications experienced during the treatment of childhood leukemia. The small number of studies that did examine this phenomenon analyzed data from a single institution and thus, were excluded from this review. There were no studies in either the adult or pediatric cancer research literature that specified the Fundamental Cause Theory as the conceptual framework to examine cancer-related infections.

Two studies in this current review of the literature met the inclusion criteria and each reported findings of the association between race and infection in AML patients. Both studies reported their analyses of the same COG trial that enrolled children diagnosed with AML between 1989 and 1995 and did not find significant differences in infection-related mortality between White and non-White children (Aplenc et al., 2006; Sung, Buxton, Alonzo, Gamis, & Woods, 2012). However, in a more recent COG study that took place between 1996 and 2002, Aplenc et al. (2006) reported that there were significant differences in the rate of infection-related deaths for African American and Hispanic children compared to non-White Hispanic children. The findings of these two studies are in Appendix A, Table A2.

Length of stay and cost of hospitalizations for infectious complications. While not specific to leukemia, three studies meeting the inclusion criteria analyzed length of stay for children admitted with chemotherapy-induced neutropenia and fever. In all three studies, it was found that children belonging to non-White racial and ethnic groups were significantly at risk for prolonged length of stay compared to children belonging to the White racial group (Alvarez et al., 2017; Basu et al., 2005; Mueller et al., 2016). Although their study did not directly examine risk factors of increased cost of hospitalization, such as race, Mueller et al. (2016) did determine that the mean charge for a hospitalization lasting longer than three days was $96,023 compared to $65,536 for a hospitalization lasting three or less days. The findings of three these studies are in Appendix A, Table A2.

Covariate Variables. Race, as a fundamental cause influences health outcomes through many of the same pathways as socioeconomic status (Phelan & Link, 2015).

Segregation is one such pathway (Acevedo-Garcia, Lochner, Osypuk, & Subramanian, 2003; Phelan & Link, 2015; Williams & Collins, 2001). Acevedo-Garcia et al. (2003) report that White children living in segregated neighborhoods are less likely to be exposed to concentrated poverty. Specifically, only 1.4% of White children belonging to a poor families live in neighborhoods with concentrated household poverty compared to 16.8% of Black children and 20.5% of Hispanic children belonging to poor families (Acevedo-Garcia et al., 2003). In order to understand and measure race as a fundamental cause it must be determined if racial differences in outcomes persist when other possible pathways that may result in disparities are controlled (Phelan & Link, 2015; Williams & Collins, 2001). In this study, three covariates were included for this purpose: income, insurance status, and access to specialized pediatric care. Six studies meeting the inclusion criteria examined the relationship of race and outcomes in children and young adults with leukemia or infectious complications of cancer therapy while controlling for these covariates. The findings of these six studies are summarized in Appendix A, Table A3.

Four studies determined that Black and Hispanic children have higher mortality than White children following the diagnosis of leukemia, even when the potential influence of income was controlled (Abraháo et al., 2015; Acharya et al., 2016; DeRouen, Parsons, Kent, Pollock, & Keegan, 2017; Kehm et al., 2018). Two of these studies controlled for insurance status in addition to income; and, one study also included whether or not treatment was provided in a pediatric specialized center. In both studies, racial disparities persisted in the adjusted models (Abraháo et al., 2015; DeRouen et al., 2017).

Two studies found that after controlling for income and insurance, children with cancer belonging to non-White racial groups were more likely to have extended stays when hospitalized for the complication of neutropenic fevers (Alvarez et al., 2017; Mueller et al., 2016). Alvarez et al. (2017) found that this inequity persisted when access to specialized care was also accounted for as a covariate.

Current state of knowledge and gaps in the empirical literature. Using the framework as a guide, researchers have shown that social position as a function of racial or ethnic identity is associated with disparate rates of mortality from cancer in adult populations. The findings in the research presented on childhood leukemia mortality echo this influence. However, these studies were not guided by a conceptual framework and thus, report correlations discovered without the benefit of theoretically derived hypotheses. The study of large data sets in the absence of a conceptual framework has the potential to create spurious findings, which may prove to be statistically significant, yet fail to provide a concrete structure for the interpretation of interrelated events, such as race and health outcomes. Additionally, theoretically derived hypotheses, when tested and supported, offer solutions and targets for interventions designed to have a meaningful impact on the health outcomes of persons across diverse populations (Brennan & Bakken, 2015). The current study tested interrelationships between variables and outcomes conceptualized using the Fundamental Cause Theory as a framework. Accordingly, the relationship between the fundamental cause of race and infection in children with leukemia was viewed as a function of the resources available to families that have the potential to mitigate or exacerbate the risks facing these children.

Infectious complications are the second highest cause of mortality in children diagnosed with leukemia (Bailey et al., 2009). Although there are indications in the body of literature presented here that racial disparities exist in the experience of these complications, there is a paucity of research focusing on these inequities (Smits-Seemann et al., 2017). This study, an analysis of existing national administrative data, sought to determine if indeed differences in the severity and consequences of infectious complications in hospitalized children with leukemia exist across racial groups.

Hypotheses

The following hypotheses, guided by the conceptual framework of the Fundamental Cause Theory, were tested in a secondary data analysis of the 2016 Healthcare Cost and Utilization Project Kids Inpatient Database (HCUP KID), a nationally representative database collected at the hospital and state levels and prepared by the Agency for Healthcare Research and Quality (AHRQ).

1. Race is a fundamental cause of health outcomes and influences the likelihood that a hospitalized child will experience infectious complications of leukemia.
    a. Children diagnosed with leukemia belonging to non-White racial groups are more likely have an infection during hospitalization compared to children in the White racial group.
    b. When infection is present during hospitalization children with leukemia belonging to non-White racial groups are more likely to develop severe sepsis compared to children in the White racial group.

2. Race is a fundamental cause of health outcomes and influences the healthcare resources utilized when infectious complications occur during the hospitalization of a child diagnosed with leukemia.
    a. In comparison to White children, children belonging to other racial groups will be more likely to have an extended length of stay when hospitalized with infection.
    b. In comparison to White children, children belonging to other racial groups will incur greater costs during hospitalization when an infection is present.

Theoretical and Operational Definitions

Infectious complications remain the second most common cause of death for children diagnosed with leukemia following resistant or recurrent disease, despite progress in overall survival rates (Basu et al., 2005; Hunger et al., 2012; Smits-Seemann et al., 2017). Race is a fundamental cause of health inequities and may explain the racial disparities in leukemia survivorship that persist over time and may extend to the consequences of infection in this population (Link & Phelan, 1995; Phelan & Link, 2015; Smits-Seemann et al., 2017).

Infection during hospitalization. Infection is the invasion of the body by a pathogen or the clinical syndrome associated with the high probability of the presence of an infectious agent (Conway, 2018). Any case containing the diagnosis of leukemia and at least one concurrent diagnosis indicating the presence of an infection was considered to fit the criteria of an infectious complication while hospitalized (Russell et al., 2014).

Severe sepsis. Severe sepsis is a syndrome of systemic inflammation and organ dysfunction in the presence of infection (Angus et al., 2001). In this study severe sepsis

is defined as the presence of an infection in addition to evidence of one of the following: systemic inflammatory response syndrome (SIRS), severe sepsis, septic shock, mechanical ventilatory support, or vasoactive medications.

Length of stay. In the HCUP KID file, length of stay is measured in days and calculated by AHRQ by subtracting the date of admission from the date of discharge (Agency for Healthcare Research and Quality, 2018).

Cost of hospitalization. The HCUP KID contains a variable measuring the total charges billed to the primary payor. This variable does not accurately reflect the cost of providing care to the child during the hospitalization. The Agency for Healthcare Research and Quality (2018) has provided a cost-to-charge ratio (CCR) calculated for each hospital within the HCUP KID file based upon a number of factors such as hospital size, employee wages, number of medical interns and residents, and geographic location. Multiplying the variable reflecting the total of the charges billed by the CCR results in an amount that provides greater accuracy to the estimated cost of each hospitalization (Agency for Healthcare Research and Quality, 2018).

Race. This study of children diagnosed with leukemia, explored race as a fundamental cause influencing the risk of infectious complications. According to Link and Phelan (1995), "some social conditions may be 'fundamental causes' of disease." Fundamental causes are associated with risk across a spectrum of health threats and work through a variety of mechanisms that are interwoven in one's social position, in the case of this study the racial group to which the child belongs. In the HCUP KID, race is identified during the hospitalization and reported to AHRQ where it is recorded as White, Black, Hispanic, Asian, Native American, other, or missing. If a hospital reports a

child's race and Hispanic/non-Hispanic ethnicity status, the race is recoded as Hispanic (Agency for Healthcare Research and Quality, 2018).

Child. The HCUP KID data file contains discharge information on a nationally representative population of children discharged from hospitals prior to the 21st birthday; therefore, child in the present study is defined as 20 years of age or less (Agency for Healthcare Research and Quality, 2018).

Leukemia. The term leukemia refers to a broad category of cancers of the blood forming organs (National Cancer Institute, 2015). Within the HCUP KID file, ALL is designated by any discharge diagnosis variable containing the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) category code C91. AML is defined as any discharge diagnosis variable containing the ICD-10-CM category code C92. The ICD-10-CM system is a standardized method of coding diagnostic and procedural medical information (Practice Management Information Corporation, 2015). Forms of leukemia that are rarely diagnosed in children were excluded from analysis in this study.

Chapter 3: Research Design and Methods

This chapter describes the research design and methods used for this study. The study is a secondary analysis of the 2016 HCUP KID data file and a description of the process by which the original file was delimited to the sample of interest and the analysis techniques employed in hypothesis testing are provided in detail. The study analyzed the association between race and infection in children with leukemia.

Sample

Sampling Methods. The 2016 HCUP KID contains over three million individual hospital stays collected in 4,200 U.S. hospitals and represents 80% of the hospitalizations of children from infancy to the age of 20 years. In order to provide accurate national estimates, the file must be weighted. This weight is based on hospital characteristics (ownership, bed size, teaching status), geographic characteristics (rural or urban, and U.S. region), and whether or not the institution has received a children's hospital designation. The discharge weight is created with the total number of American Hospital Association admissions serving as the standard (Agency for Healthcare Research and Quality, 2018; Chu, Houchens, Elixhouser, & Ross, 2007). Each case file in the 2016 HCUP KID database represents a pediatric hospitalization. Each case contains as many as 30 discharge diagnosis codes in the ICD-10-CM format and 15 Procedure Coding System codes (ICD-10-PCS) (Agency for Healthcare Research and Quality, 2018).

Sampling was done through a systematic delimitation of the HCUP KID to isolate those children hospitalized with the diagnosis of leukemia. Previous investigations of childhood cancers using the HUCP KID files from 2009 and 2012 served as a guide for sample selection (Mueller et al., 2016; Russell et al., 2014) Cases were included if any of the 30 discharge diagnoses contained the ICD-10-CM codes for ALL (C9100, C9101, or C9102) or for AML (C9200, C9201, or C9102) (Practice Management Information Corporation, 2015). Cases in which the child was diagnosed with an uncommon form of leukemia were not included. Cases with ICD-10-CM codes related to pregnancy or perinatal care were removed from the study sample and these are listed in Table 1 (Practice Management Information Corporation, 2015; Russell et al., 2014). Bone marrow and stem cell transplant are associated with a high risk of morbidity, therefore

any case in which the ICD-10-CM or ICD-10-PCS codes indicated these procedures took place were removed from the final sample; these codes are listed in Table 1 (Practice Management Information Corporation, 2015). To avoid duplicate counting, all records indicating that a transfer to another acute care facility took place were removed (Russell, Street, & Ho, 2016).

Table 1.

Administrative Codes Used to Identify Cases with Evidence of Pregnancy or Transplant

Condition	ICD-10-CM Codes	ICD-10-PCS Codes	Definition
Bone or Stem Cell Transplant	D89.81x		Graft-versus-host disease
	T86.0x		Complications of bone marrow transplant
	T86.5		Complications of stem cell transplant
	Z48.290		Encounter for aftercare following bone marrow transplant
	Z94.x		Transplanted organ and tissue status
		30230G1, 30233G1, 30240G1, 30243G1, 30243G1, 30250G1, 30253G1, 30260G1, 30260G1	Transfusion of non-autologous bone marrow
		30230X0, 30233X0, 30240X0, 30243X0, 30243X0, 30250X0, 30253X0, 30260X0, 30260X0	Transfusion of autologous cord blood stem cells
		30230X1, 30233X1, 30240X1, 30243X1, 30243X1, 30250X1, 30253X1, 30260X1, 30260X1	Transfusion of non-autologous cord blood stem cells
		30230Y1, 30233Y1, 30240Y1, 30243Y1,	Transfusion of non-autologous

Table 1.

Administrative Codes Used to Identify Cases with Evidence of Pregnancy or Transplant

Condition	ICD-10-CM Codes	ICD-10-PCS Codes	Definition
		30243Y1, 30250Y1, 30253Y1, 30260Y1, 30260Y1	hematopoietic stem cells
Pregnancy or Obstetrical Care	O00-O0.9A.xx		Pregnancy childbirth, and the puerperium
	P00-P96.x		Certain conditions originating in the perinatal period

Note. Adapted from Practice Management Information Corporation. (2015). *ICD-10-CM: international classification of diseases, 10th revision, clinical modification, sixth edition, color coded, 2016*. Los Angeles, Calif.: PMIC, Practice Management Information Corp.

The primary independent variable of interest in the present study was the race of the child. The issue of missing data for this variable was addressed on the hospital level and the individual level. Hospitals that did not adequately record race were excluded from the sample using the following data preparation plan. The percentage of cases in which race was coded as "missing" was determined for each hospital. Hospitals were excluded if the percentage of cases coded "missing" was greater than two standard deviations above the mean percentage for the entire sample. In the ALL group, the mean percentage of cases coded as "missing" for all hospitals was 0.0815% with a standard deviation of 0.23%. All discharges from a hospital where greater than 0.55% of cases were coded "missing" race in the ALL group were removed. The mean percentage of cases with race coded as "missing" per hospital was 0.09% for the AML group with a standard deviation of 0.26%, setting the cutoff point for the AML sample at any hospital with greater than 0.62% cases coded as "missing". Following this delimitation of the groups, the individual cases in which race were coded as "missing" were removed and

this accounted for 782 cases, or 2.6%, in the ALL file and 80 cases, 2.0%, in the AML file. Figure 1 depicts the process of delimitation of the HCUP KID to the final groups for ALL and AML cases.

Sample size. Power analysis for multivariate regression was calculated to determine the necessary sample size. Using a moderate effect size (f^2=0.15), power of 0.80 at a 0.05 significance, both the ALL group, containing 26914 cases, and the AML group of 2902 cases exceed the required number of cases (Cohen, 1992).

Instruments and Measures

In this secondary analysis study, variables were limited to the data that were collected originally by each participating hospital and then recoded by AHRQ to conform to the HCUP KID variable format (Agency for Healthcare Research and Quality, 2018). When a variable of interest was not directly available in the HCUP KID file, discharge diagnosis codes and procedures codes were used for its creation. The procedures for each variable's creation are described here.

Dependent variables. Four separate statistical models were used to test the associations between the fundamental cause of race and adverse outcomes in children with leukemia: the risk of infection during hospitalization, the development of severe sepsis when infection is present, the length of hospitalization when infection is present, and the cost of hospitalization when infection occurs. Because ALL and AML are distinctly different forms of leukemia with markedly different approaches to treatment, these four statistical analyses were performed separately within each leukemia group.

Figure 1. *Delimitation of the 2016 HCUP KID File*

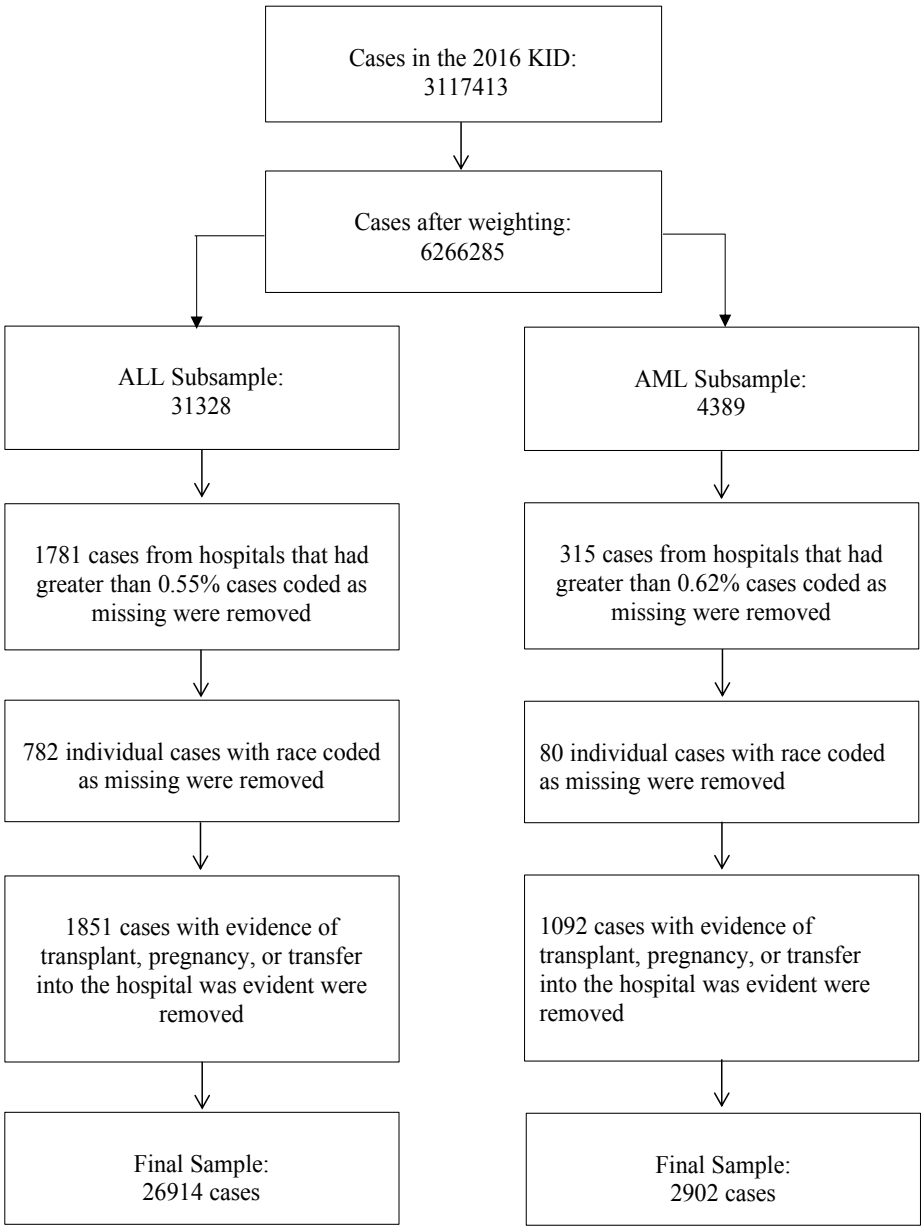

Figure 1. Processing tree for the delimitation of the 2016 HCUP KID file . Rectangles on the left represent the steps of delimitation for the ALL group. Rectangles on the right represent the steps of delimitation for the AML group.

Infection while hospitalized. Each leukemia group was searched for the presence of an infection, as defined in the 2016 ICD-10-CM code list, in any of the 30 discharge

diagnosis variables (Practice Management Information Corporation, 2015). Any case in which there was an ICD-10-CM code for infection identified through this process was coded "1", otherwise the case received the code "0" indicating the absence of infection. In order to validate this method, a randomly generated subsample was created from the ALL group consisting of one percent of the cases in which the infection code was blinded. Every diagnosis in each case within the infection subsample was reviewed manually for the presence of an ICD-10-CM code representing an infection. The infection subset was then unblinded and the manually-derived infection code for each case was compared to the infection code generated through the algorithm created for this purpose. This method of validation found that there was one false positive in the subsample and two false negatives resulting in a sensitivity of 99.1% and specificity of 99.6%. Further examination of the cases within this subsample revealed that an additional ICD-10-CM code, R78.81, bacteremia as a laboratory finding, was unaccounted for in the original variable creation step and was subsequently added to the algorithm (Practice Management Information Corporation, 2015).

Severe sepsis. Since 2003, administrative coding schema has included codes specific to severe sepsis and septic shock (Balamuth et al., 2014). In a multi-hospital study comparing discharge records of children identified as having sepsis, Balamuth et al. (2015) found that the use of these codes had a sensitivity of 73%, specificity of 92%, and a positive predictive value of 79%. Slight improvements in the statistical models in that study resulted when the codes for mechanical ventilation and administration of vasoactive medications were added, and thus these were included in the current study (Balamuth et al., 2015). All diagnoses and procedures codes in each file were searched

for the presence of SIRS, sepsis, septic shock, mechanical ventilation and vasoactive medications. The ICD-10-CM and ICD-10-PCS codes that were used to define the severe sepsis outcome variable are listed in Table 2. Each case that contained evidence of these codes, in addition to evidence of an infection, were coded as severe sepsis. Although there is limited research on the validity for the severe sepsis and septic shock codes in the newer ICD-10-CM administrative coding system, there is evidence that the use of administrative codes to identify cases of pediatric severe sepsis has increased over the time period since their introduction in 2003 (Hartman, Linde-Zwirble, Angus, & Watson, 2013; Ruth et al., 2014; Schuller, Hsu, & Thompson, 2017).

Table 2.

Administrative Codes Used to Create the Severe Sepsis Outcome Variable

Condition	ICD-10-CM Codes	ICD-10-PCS Codes	Definition
SIRS	R65.xx		SIRS, sepsis, septic shock
Mechanical Ventilation	Z99.1x		Dependence on respirator
	J95.85x		Complication of respirator
		0BH1xx	Insertion of device into trachea
Vasoactive medication		3E030X	Administration of vasoactive medication

Note. Adapted from Practice Management Information Corporation. (2015). *ICD-10-CM: international classification of diseases, 10th revision, clinical modification, sixth edition, color coded, 2016*. Los Angeles, Calif.: PMIC, Practice Management Information Corp.

Length of stay. The length of stay (LOS) is a continuous variable, measured in days, provided in in the HCUP KID file (Agency for Healthcare Research and Quality, 2018). Analyses of this variable when the samples were delimited to include only cases in which infection is documented in both the ALL and AML groups revealed a very wide range of values for the LOS. The mean LOS in the ALL population was 8.82 days with a standard deviation of 12.97 days and a range of zero to 241 days. Length of stay for the AML population had similar results with a range between zero and 281 days (M=25.25, SD 24.98). The two percent of cases in each file that fell two standard deviations above the mean were examined for the variables of interest: race, presence of infection, and presence of severe sepsis. These findings indicated that there was a disproportionate percentage of infectious complications in those with very prolonged hospitalizations. Additionally, this small population exhibits a pattern in the racial make-up that justifies keeping these cases. This information can be found in Table 3.

The literature was searched for comparators to the mean length of stay obtained in this population. Evidence exists that children hospitalized with febrile neutropenia as a result of cancer treatment are hospitalized on average 7.5 to 9.9 days, with longer stays in the presence of documented infections (Allareddy, Rampa, & Allareddy, 2012; Alvarez et al., 2017; Mueller et al., 2016; Tai et al., 2017; Wilson, Rafferty, Deeter, Comito, & Hollenbeak, 2014). It is accepted clinical practice to have a child remain hospitalized during the period of extreme myelosuppression following the administration of the intensive chemotherapy required to treat AML. Existing literature reports median lengths of stay following the completion of chemotherapy ranges between 8.5 and 28 days and

these vary depending on complications and institutional policies (Getz et al., 2015; Miller et al., 2016).

Based upon the support of comparative studies with similar mean lengths of stay in these two populations and the evidence that the extreme cases in each group disproportionately contain variables of interest for this study, the LOS variable was dichotomized at the mean LOS for each sample and all cases were retained. A prolonged hospitalization in the ALL group was designated as nine or more days and as 25 or more days for cases of AML.

Table 3

Comparison of Variables of Interest in the Complete Sample and the Subsample of Cases with Extreme LOS

Variable	Complete Sample	Extreme LOS Sample
ALL Group	2914 cases	575 cases
Race (%)		
White	50.0	41.8
Black	7.4	7.7
Hispanic	32.5	40.9
Asian	4.3	4.5
Other	5.9	5.2
Infection Present	53.0%	88.5%
Severe Sepsis Present	3.5%	32.5%
AML Group	2902 cases	58 cases
Race (%)		
White	49.6	43.8
Black	11.6	24.4
Hispanic	19.8	26.5
Asian	7.3	5.4
Other	4.8	7.0
Infection Present	65.9%	97.8%
Severe Sepsis Present	9.7%	39.5%

Note. Extreme LOS is defined as any LOS lasting more than two standard deviations above the mean

Cost of hospitalization. The cost of hospitalization in dollars was calculated by multiplying the variable in the HCUP KID representing the total of the charges by the

CCR (Agency for Healthcare Research and Quality, 2018). Because length of stay and cost of hospitalization are strongly correlated in this population (r^2=.773 in the ALL subsample and r^2=.776 in the AML subsample) cost was also dichotomized at the mean, when infection was present, and a hospitalization with a cost of greater than $34200 for a child with ALL and $93720 for a child with AML was coded as a high cost hospitalization.

Independent Variable.

Race. In the HCUP KID file, race includes the following categories: White, Black, Hispanic, Asian, Native American, and other (Agency for Healthcare Research and Quality, 2018). Race and ethnicity are coded in one variable, race, and this is supplied by the hospital. In cases when race and Hispanic ethnicity were both provided by a hospital, the child's ethnicity was given precedence and race was coded as Hispanic (Agency for Healthcare Research and Quality, 2018). Because children with the designation of Native American in the ALL and AML groups were very small in number, these cases were recoded as "other" race.

Covariate Variables.

Socioeconomic status. In an analysis of SEER data between the years 2000 and 2011, it was found that, although White children had a significant advantage, socioeconomic status mediated the association between race and childhood leukemia survival accounting for 44% of the difference in mortality for Black children and 31% for Hispanic children (Kehm et al., 2018). Therefore, socioeconomic status was included as a covariate in the present study. Socioeconomic status in the HCUP KID is a categorical variable representing a quartile classification of the median income at the level of zip

code but was dichotomized in this present study as low (0-25th and 25-50th percentiles) and high (50-75th and 75-100th percentiles) (Agency for Healthcare Research and Quality, 2018).

Insurance. A review of literature resulted in conflicting evidence of the association between insurance type and childhood cancer outcomes (Kehm et al., 2018; Mueller et al., 2016; Mueller, Walkovich, Mody, Gebremariam, & Davis, 2015). Kehm et al. (2018) did not find that insurance had an effect on childhood cancer survivorship. However, in two analyses of children hospitalized for fever with neutropenia in HCUP KID data from different years, researchers found that insurance type was associated with shorter length of stay. Children having "other" types of insurance had significantly shorter stays in 2009 and those with private insurance had longer lengths of stay in 2012, compared with children having public insurance (Mueller et al., 2016; Mueller et al., 2015). Insurance status has the potential to permit, or limit, treatment options and access to care and was included in the present study, despite these inconsistent findings (Kehm et al., 2018; Mueller et al., 2015). HCUP categorizes the primary source of payment into the following types: Medicare, Medicaid, private insurance, other payment source, self-pay, and "missing" or "invalid" (Agency for Healthcare Research and Quality, 2018). For the purposes of this study, payment source was dichotomized between private and public/other due to the variability at the state level with regard to policies determining how children without private insurance receive healthcare coverage.

Access to care. The HCUP KID has identified children's hospitals as designated by the National Association of Children's Hospitals and Related Institutions (NACHRI) (Agency for Healthcare Research and Quality, 2018). This variable has been tested in

previous research and was used in this study as an indicator of a family's access to experienced pediatric healthcare (Curtin et al., 2014; Leyenaar et al., 2016). In their study of children undergoing cleft palate surgery, Curtin et al. (2014) found that despite higher numbers of children with comorbidities, children undergoing surgery in pediatric hospitals had shorter lengths of stay. This finding indicates that there are potential resources available in designated children's hospitals that could benefit those admitted with complex medical conditions such as leukemia. Chamberlain et al. (2010) found that African American and Native American children with chronic illness hospitalized in California between the years 1999 and 2007 were significantly less likely to be hospitalized in a pediatric-specialized hospital when compared to White children. Additionally, children from lower socioeconomic households and more rural areas were less likely to receive care in specialized hospitals (Chamberlain et al., 2010).

Demographic characteristics. Demographic factors that served as covariate variables include the following variables: gender, region of the U.S. in which care was provided, and urban/rural classification of the child's residence. The child's gender is provided in the HCUP KID (Agency for Healthcare Research and Quality, 2018). The child's residential urban/rural designation is defined by the U.S. Office of Management and Budget (Agency for Healthcare Research and Quality, 2018). The inclusion of this variable has the potential to control for the influence a child's geographic accessibility to the hospital may have on factors such as inpatient versus outpatient treatment of an infection or length of stay. This six-category variable was dichotomized at the midpoint. In order to account for differences that exist due to referral patterns to pediatric-specialized hospitals, environmental and spatial conditions, employment opportunities,

and patterns in racial and immigrant community composition throughout the U.S., geographic region was included as a covariate (Curtin et al., 2014; Kaiser et al., 2015; Mukherjee et al., 2009). These regions are Northeast, South, Midwest, and West (Agency for Healthcare Research and Quality, 2018).

Clinical factors. Based upon previous research that identified factors associated with infection in children with leukemia, the following clinical variables were included as covariates: age, neutropenia, mucositis, weight loss or malnutrition, obesity, disease that is not in remission, and the diagnosis of Down syndrome (Ammann et al., 2015; Delebarre et al., 2015; Hassler et al., 2016; Lange et al., 2005; Loeffen, Brinksma, Miedema, de Bock, & Tissing, 2015; Meenan, Kelly, Wang, Ritchey, & Maurer, 2019; Thurman, Abbott, Jinfang, & Larson, 2017; Withycombe et al., 2009). Corticosteroids and asparaginase are part of ALL therapy and increase the risk of treatment-related insulin insufficiency, which has been associated with infection, therefore, the presence of hyperglycemia was be included in the analyses of the ALL group (Baillargeon et al., 2005; Dare, Moppett, Shield, Hunt, & Stevens, 2013; Pui, Burghen, Bowman, & Aur, 1981; Sonabend et al., 2008). Age, in years, is provided in the HCUP KID file but was converted to a categorical variable to more closely account for age-related risks in leukemia (Baggott et al., 2011). The remaining clinical covariates were developed through an analysis of ICD-10-CM codes in each case. These codes are listed in Table 4. The presence of a central venous access device is a significant contributor to the development of infection and severe sepsis in children with leukemia (Ammann et al., 2015; Baggott et al., 2011; Bailey et al., 2009; Delebarre et al., 2015; Doganis et al., 2013; Hassler et al., 2016; Loeffen et al., 2015; Thurman et al., 2017). The PCS-10-CM

codes in the HCUP KID case file will indicate the insertion of a central venous access device took place during the hospitalization; but, it cannot be determined if a child had a device in place prior to hospitalization resulting in a lower estimate. For this reason, the presence of a central venous access device was not a covariate in this study.

Table 4

Administrative Codes Used to Create the Clinical Covariate Variables

Condition	ICD-10-CM Codes	Definition
Neutropenia	D70.x	Neutropenia
	D61.1	Drug-induced aplastic anemia
	D61.8	Other pancytopenia
Mucositis	B37.0	Candida stomatitis
	K12.1	Other forms of stomatitis
	K92.81	Gastrointestinal mucositis (ulcerative)
Weight loss	E43	Unspecified severe protein-calorie malnutrition
	E44	Protein-calorie malnutrition of moderate and mild-degree
	E46	Unspecified protein-calorie malnutrition
	E640	Sequalae of malnutrition and other nutritional deficiencies
	R63.x	Symptoms and signs concerning food and fluid intake, excluding R63.5 (weight gain)
Obesity	E66.xx	Overweight and obesity
	Z68.3	Body mass index 30-39 adult
	Z68.4	Body mass index greater than 40 (adult)
	Z68.54	Body mass index greater than the 95th percentile (child)
Leukemia, not in remission	C91.00	ALL, not having achieved remission
	C91.02	ALL, in relapse
	C92.00	AML, not having achieved remission
	C92.02	AML, in relapse
Hyperglycemia	E08.xxx	Diabetes mellitus due to underlying condition
	E09.xxx	Drug-induced diabetes

Table 4

Administrative Codes Used to Create the Clinical Covariate Variables

Condition	ICD-10-CM Codes	Definition
	R73.xx	Elevated blood glucose level
	R81	Glycosuria
Down syndrome	Q90.x	Down syndrome

Note. Adapted from Practice Management Information Corporation. (2015). *ICD-10-CM: international classification of diseases, 10th revision, clinical modification, sixth edition, color coded, 2016*. Los Angeles, Calif.: PMIC, Practice Management Information Corp.

Hypotheses and measures for hypothesis testing. Hypotheses proposed in this study and the independent and dependent variables that either were provided in the HCUP KID files or created for the testing of these hypotheses are found in Table 5. Hypothesis testing was performed in the separate groups of ALL and AML cases due to the differences between these two forms of leukemia.

Table 5

Hypotheses and Variables Used for Hypotheses Testing

Hypothesis	Variables for hypothesis testing
Children diagnosed with leukemia belonging to non-White racial groups are more likely to have an infection documented during hospitalization compared to children in the White racial group.	*OV*: Infection while hospitalized *IV:* Race *Covariate variables:* Socioeconomic status Insurance status Access to care (NACHRI designation) Gender Region of the U.S. Urban/Rural residence Age group Evidence of neutropenia Evidence of mucositis Evidence of weight loss Evidence of obesity No evidence of disease remission Evidence of hyperglycemia* Evidence of Down syndrome

Table 5

Hypotheses and Variables Used for Hypotheses Testing

Hypothesis	Variables for hypothesis testing
Children diagnosed with leukemia belonging to non-White racial groups are more likely to have severe sepsis documented when infection is present during hospitalization compared to children in the White racial group.	*OV*: Severe sepsis while hospitalized during hospitalization when infection is present *IV:* Race *Covariate variables:* Socioeconomic status Insurance status Access to care (NACHRI designation) Gender Region of the U.S. Urban/Rural residence Age group Evidence of neutropenia Evidence of mucositis Evidence of weight loss Evidence of obesity No evidence of disease remission Evidence of hyperglycemia* Evidence of Down syndrome
In comparison to non-White children, those belonging to other racial groups are more likely to have an extended length of stay when hospitalized with infection.	*OV:* Extended LOS during hospitalization with infection present *IV:* Race *Covariate variables:* Socioeconomic status Insurance status Access to care (NACHRI designation) Gender Region of the U.S. Urban/Rural residence Age group Evidence of neutropenia Evidence of mucositis Evidence of weight loss Evidence of obesity No evidence of disease remission Evidence of hyperglycemia* Evidence of Down syndrome
In comparison to non-White children, those belonging to other racial groups incur greater costs during hospitalization with infection.	*OV: High-*cost hospitalization when infection is present *IV:* Race *Covariate variables:* Socioeconomic status

Table 5

Hypotheses and Variables Used for Hypotheses Testing

Hypothesis	Variables for hypothesis testing
	Insurance status
	Access to care (NACHRI designation)
	Gender
	Region of the U.S.
	Urban/Rural residence
	Age group
	Evidence of neutropenia
	Evidence of mucositis
	Evidence of weight loss
	Evidence of obesity
	No evidence of disease remission
	Evidence of hyperglycemia*
	Evidence of Down syndrome

Notes. OV is outcome variable, IV is independent variable. *Hyperglycemia was included in the analyses of the ALL group only.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 25 for Mac OSX (SPSS) (IBM SPSS Statistics for Macintosh). A data set containing all variables created for the purpose of the study was maintained as an SPSS data file along with copies of the raw HCUP KID data. SPSS syntax and output files were also maintained. All SPSS files have been stored and protected in accordance with the requirements of the AHRQ HCUP user agreement contract (Agency for Healthcare Research and Quality, 2018).

Characteristics of the sample were determined through descriptive statistical procedures. Frequencies were calculated for all dependent, independent, and covariate variables. Following the analyses of the sample characteristics, determination of the inclusion of each predictor variable was done through bivariate analyses using the chi-square statistic. Conservatively, inclusion of these variables in the final univariate and

multivariate logistic regression models was determined by a test of significance set at .05 level. Unadjusted and adjusted logistic regression models were performed with confidence intervals constructed through bootstrapping to test the hypotheses in both leukemia groups. Final adjusted model fit was assessed with Nagelkerke R^2 and the Hosmer & Lemeshow test (Cohen, 1992; Field, 2013).

Children admitted to the same hospital are likely to have care provided in a systematic way based upon the clinical practice preferences and experience of the health care team members providing the care. Due to this potential effect of the nested or clustered nature of cases within hospitals, a multilevel model has the potential to be the optimal statistical method to use in this setting (Adewale et al., 2007; Heck, Thomas, & Tabata, 2012; Luke, 2004; Raudenbush, 2002). The need for a multilevel model was evaluated, separately for each dependent variable in each leukemia group, through the testing of an intercept-only, or null model, in which there are no predictors and the intercept is allowed to vary. This model provides a measurement that approximates the proportion of variability in the outcome that can be attributed to the clustering of cases within hospitals (Field, 2013; Finch, 2014; Heck et al., 2012; Luke, 2004; Raudenbush, 2002). When the need for multilevel modeling was assessed in both the ALL and AML groups, there was little evidence this type of analysis would benefit the final outcomes in this study. Specifically, the intercept models for all hypotheses in both groups, with the exception that race influences the risk of a high-cost hospitalization, did not show that a multilevel model would have the potential to explain greater than 10% of the variability of the outcome between hospitals When predictors were added to the multilevel model for the cost hypothesis, there was no significant improvement in the model in either the

ALL or AML groups. Therefore, multilevel modeling was not justified for hypothesis testing in either group (Heck et al., 2012; Raudenbush, 2002).

Human Subjects Protection

This study was granted the status of exempt review by the Institutional Review Board (IRB) of Rutgers, The State University of New Jersey. The data contained in the HCUP KID file contains neither personal nor geographic identifiers (Agency for Healthcare Research and Quality, 2018). User-agreement training and certification, as required by the AHRQ, will be maintained throughout the study period.

Chapter 4: Analysis of the Data

The purpose of this study was to investigate relationships between race and the occurrence and impact of infectious complications in children hospitalized with leukemia. This study was a secondary analysis of a nationally representative database of children discharged from U.S. hospitals in the year 2016. The sample of interest was obtained through a process of delimitation of the larger HCUP KID file which was initially weighted to form a nationally representative database of more than six million pediatric hospitalizations (Agency for Healthcare Research and Quality, 2018). The sample was divided into two separate groups, one for each type of leukemia. There were 28614 cases with the diagnosis of ALL between the ages of infancy and 20 years (*M=8.8, SD=5.6*). There were 2902 hospital cases between infancy and age 20 years (*M=9.8, SD=6.7*) diagnosed with AML. Clinical information was provided in the HCUP KID file in the form of diagnosis and procedure codes. These were used to create the variables required for this study. Demographic information including race, the independent variable of interest, was recorded by the hospital and provided in the HCUP KID file.

Analyses of the data for the ALL and AML groups are presented separately in this chapter.

Acute Lymphoblastic Leukemia

Demographics of the Study Sample. A description of the study sample is presented in Table 6. The sample consists of 28614 cases. Each case represents a child's discharge from a hospital. The mean age in the sample was 8.8 years (*SD=5.6*) with the largest number of children between the ages of two and nine years (53%). The majority of children were male (59%). The children's racial group was coded as White, Black, Hispanic, Asian, Native American, and other in the HCUP KID. Due to small numbers, the children belonging to the Native American group were coded in this study as other racial group (Agency for Healthcare Research and Quality, 2018). Most of the children were White (50%), followed by the Hispanic (33%), Black (7%), Asian (4%), and other race (6%). The majority of the children lived in residential areas where the average household income was below the 50th percentile (52%) and less than half had private health insurance (46%). Seventy-nine percent of the children lived in urban areas rather than rural areas (20%) and the largest number of children were hospitalized in the Southern region of the U.S. (39%). Care was more likely to be provided in a general hospital (54%) versus one with a NACHRI designation (46%). Neutropenia was present in just over half of the cases in this sample (51%). Few children had mucositis (10%), obesity (4%), hyperglycemia (5%) and evidence of weight loss or cachexia (11%). ALL with evidence of remission was recorded in 31% of the cases and almost four percent of the cases indicated the child had the condition of Down syndrome.

Greater than half of the cases in the ALL group had an infectious complication present (53%). Fever was the most common infectious complication and was present in 8934 of the cases with ALL. A complete list of infectious complications can be found in Appendix B, Table B1. To test hypotheses 2 through 4 the sample was further delimited to just the 14277 cases with infection documented. Table 6 details the characteristics of this subsample of cases. In the subsample, the largest percentage of children were in the White racial group (51%), followed by the Hispanic (32%), Black (7%), Asian (4%), and other race (6%). A higher percentage of the children with infectious complications lived in residential areas where the average household income was below the 50th percentile (51%) and less than half had private health insurance (46%). Seventy-nine percent of the children lived in urban areas and 20% lived in rural areas. The largest number of children were hospitalized in the Southern region of the U.S. (38%). Care was more likely to be provided in a general hospital (53%) versus one with a NACHRI designation (47%). Neutropenia was present in 71% of the cases. Mucositis (13%), obesity (4%), hyperglycemia (5%), and evidence of weight loss or cachexia (13%) were uncommon complications. The majority of the cases did not have documented evidence that ALL was in remission (69%) and four percent of the cases indicated the child was also diagnosed with Down syndrome.

Table 6

Description of the Study Sample and the Subsample of Cases with Documentation of Infection, ALL

Variable	Frequency (%) ALL Sample (*N*=28614)	Frequency (%) Infection Present (*n*=14277)
Race		
White	13447(50.0)	7323(51.3)
Black	1979(7.4)	951(6.7)

Table 6

Description of the Study Sample and the Subsample of Cases with Documentation of Infection, ALL

Variable	Frequency (%) ALL Sample (*N*=28614)	Frequency (%) Infection Present (*n*=14277)
Hispanic	8736(32.5)	4523(31.7)
Asian	1170(4.3)	632(4.4)
Other	1582(5.9)	849(5.9)
Age Group		
Infant	1318(4.9)	676(4.7)
2-9 Years	14219(52.8)	8404(58.9)
10-14 Years	5760(21.4)	2714(19.0)
15-20 Years	5617(20.9)	2482(17.4)
Sex*		
Female	11003(40.9)	6217(43.6)
Male	15876(59.0)	8033(56.3)
Insurance Type*		
Private	12454(46.3)	6586(46.1)
Public/Other	14430(53.6)	7681(53.8)
Household Income (zip code level) *		
Upper 50th %ile	12493(46.4)	6662(46.7)
Lower 50th %ile	13891(51.6)	7330(51.3)
Place of Residence*		
Rural Area	5357(19.9)	2821(19.8)
Urban Area	21287(79.1)	11311(79.2)
Region of the U.S.		
South	10482(38.9)	5416(37.9)
Northeast	3687(13.7)	1987(13.9)
Midwest	5181(19.3)	2876(20.1)
West	7563(28.1)	3998(28.0)
Type of Hospital		
General Hospital	14468(53.8)	7543(52.8)
Children's Hospital	12446(46.2)	6733(47.2)
Neutropenia		
Present	13608(50.6)	10176(71.3)
Absent	13305(49.4)	4100(28.7)
Mucositis		
Present	2573(9.6)	1863(13.0)
Absent	24341(90.4)	12414(87.0)
Weight Loss/Cachexia		
Present	2817(10.5)	1885(13.2)
Absent	24077(89.5)	12392(86.8)
Obesity		
Present	1132(4.2)	553(3.9)

Table 6

Description of the Study Sample and the Subsample of Cases with Documentation of Infection, ALL

Variable	Frequency (%) ALL Sample (*N*=28614)	Frequency (%) Infection Present (*n*=14277)
Absent	25782(95.8)	13724(95.1)
Disease Status		
Remission	8426(31.1)	4421(31.0)
Remission not Evident/Relapse	18488(68.7)	9855(69.0)
Hyperglycemia		
Present	1384(5.1)	717(5.0)
Absent	25530(94.9)	13560(95.0)
Down Syndrome		
Present	1014(3.8)	592(4.1)
Absent	25900(96.2)	13684(95.9)

Note. *Percentages do not equal 100% due to missing items.

Description of the Study Variables. Descriptive statistics for the study variables are presented in Table 7. In this sample of 28614 cases, the majority had evidence of an infection in the discharge diagnoses (53%). Of those cases in which infection is present, six percent had documentation indicating severe sepsis occurred during the hospitalization. The average length of stay when infection was present was 8.82 days and 30% of the hospitalizations were considered extended stays lasting longer than nine days. The mean cost of hospitalization was $34209 (*SD* = $74634) dollars and 25% of the cases were found to be high cost hospitalizations that were above the mean.

Table 7

Description of the Outcome Variables, ALL

Variable	Mean (SD)	Range	Frequency	%
Infection*				
Present			14277	53.0
Absent			12637	47.0
Severe Sepsis**				
Present			853	6.0
Absent			13423	94.0

Length of Stay**	8.82(12.966)	0-241		
>9 Days			4224	29.6
<=9 Days			10053	70.4
Cost of Hospitalization**	$34209 ($74634)	$263-$2086932		
>$34200			3521	24.7
<=$34200			10756	75.3

Notes. *N=28614. **n = 14277.

Hypothesis Testing. Inclusion of predictor variables in the final models was determined by estimating the chi-square statistic with significance set at .05 level. Unadjusted logistic regression was performed on the variables meeting this threshold for comparison purposes. All hypotheses were tested in adjusted logistic regression models with confidence intervals constructed through bootstrapping (Cohen, 1992; Field, 2013).

Hypothesis 1. The first hypothesis proposed that children belonging to the non-White racial groups would be more likely to have an infectious complication when hospitalized for ALL compared to children in the White racial group. The results of the bivariate analysis found a significant difference between racial groups in the rate of infectious complications, however this finding was in the opposite direction of the proposition of the hypothesis. Fifty-five percent of White children had an infection documented and this was greater than the percentage of children in the other racial groups with infection X^2 (4) =39.901, p<.001. This finding persisted in the unadjusted model with Black children (OR=0.77, p<.001) and Hispanic children (OR=0.95, p<.001) being less likely than White children to have an infectious complication documented during the hospitalization. Children identified as Asian (OR=0.98, p=.768) or other race (OR=.97, p=.535) did not differ from white children in their risk of infection. However, these findings became insignificant when clinical and sociodemographic covariates were added

in the adjusted model. The test of the model coefficients indicated that the final adjusted model was significant X^2 (16) = 6134.3, p<.001. The goodness of fit as measured by the Hosmer-Lemeshow test indicated the model was satisfactory for this data X^2(8) =10.712, p=.219. The Nagelkerke R^2 statistic predicted that 27% of the variance in the occurrence of infectious complications during hospitalization can be explained by this model. These results are summarized in Table 8. There were no significant differences in the risk of infection in hospitalized children with ALL when compared to White children for those belonging to the Black (AOR=0.95, p=.369), Hispanic (AOR=1.00, p=.950), Asian (AOR=1.04, p=.586), or other racial (AOR=1.02, p=.745) groups. Therefore, hypothesis 1 was not supported.

Table 8

Summary of Results of the Test of Hypothesis 1: Odds of Infectious Complication Present During Hospitalization in ALL Cases

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	.773***	.704	.850	.952	.855	1.060
Hispanic	.898***	.851	.948	1.002	.939	1.069
Asian	.982	.871	1.107	1.039	.905	1.193
Other Race	.967	.871	1.074	1.020	.906	1.148
Age Group (ref=2-9 years)						
Infant	.729***	.651	.816	.604***	.531	.686
10-14 years	.617***	.580	.656	.585***	.546	.627
15-20 years	.548***	.515	.583	.575***	.536	.618
Female	1.268***	1.208	1.332	1.185***	1.121	1.253
Neutropenia	6.657***	6.311	7.022	6.404***	6.063	6.764
Mucositis	2.520***	2.303	2.757	1.890***	1.708	2.092
Weight loss	1.910***	1.759	2.075	1.474***	1.341	1.619
Obesity	.839**	.745	.945	1.075	.936	1.235
Downs Syndrome	1.254***	1.104	1.424	1.235**	1.070	1.426
Children's hospital	1.082**	1.1031	1.135	.960	.908	1.017
Region of the U.S. (ref=South)						

Table 8

Summary of Results of the Test of Hypothesis 1: Odds of Infectious Complication Present During Hospitalization in ALL Cases

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Northeast	1.093*	1.014	1.179	1.309***	1.201	1.427
Midwest	1.168***	1.092	1.248	1.373***	1.271	1.482
West	1.049	.989	1.113	1.166***	1.087	1.251

Notes. *p<.05; **p<.01; ***p<.001
Variables not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: ALL remission present, hyperglycemia, income, insurance type, urban or rural residence.
Final model: X^2 (17)=6135.386, p <.001; Nagelkerke R^2 .272; Hosmer & Lemeshow test X^2 10.712 (8)=8.201, p = .414

Hypothesis 2. The second hypothesis proposed that when infection is present during hospitalization, children with leukemia belonging to non-White racial groups are more likely to develop severe sepsis compared to children in the White racial group. This hypothesis was tested in a subsample of cases within the ALL group with infection documented (see Table 7). Of the 14277 children with a documented infection, 853 (6%) developed severe sepsis. Bivariate testing demonstrated that racial differences exist in the development of severe sepsis $X^2(4) = 38.878$, p<.001. A higher percentage of Hispanic children (8%) experienced documented severe sepsis compared to White children (5%). Asian children (7%) and children belonging to the other race category (6%) also had higher percentages of cases with documented severe sepsis compared to White, while the percentage of Black children (5%) was the same as White. This disparate rate of severe sepsis in Hispanic children continued to be evident in the unadjusted model and Hispanic children were more likely to develop severe sepsis than White children (OR 1.59, p<.001). After clinical and sociodemographic variables were controlled in the adjusted model, this finding persisted, and the Hispanic racial group was

associated with a 1.32-fold (p=.002) increased risk of developing severe sepsis compared to White children. There were no significant differences in the likelihood of the development of severe sepsis in Black (AOR=0.88, p=.435), Asian (AOR=1.32, p=.113) or other race (AOR=1.14, p=.429) children when compared to White children. The test of the model coefficients indicated that the final adjusted model was significant X^2 (15) =402.908, p<.001. The goodness of fit as measured by the Hosmer-Lemeshow test was calculated and the model was satisfactory for this data $X^2(8)$ =2.828, p=.945. The Nagelkerke R^2 indicates approximately eight percent of the variance in the development of severe sepsis when infection was present can be explained by the model. These results are found in Table 9. Hispanic children with ALL were found to be at greater risk of developing severe sepsis when an infection was present during hospitalization than White children, a finding that supports the hypothesis. The risk for Black, Asian, and other race children does not differ from that of White children, therefore hypothesis 2 was partially supported.

Table 9

Summary of Results of the Test of Hypothesis 2: Odds of Severe Sepsis When Infection is Present During Hospitalization in ALL

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	1.002	.735	1.367	.880	.638	1.214
Hispanic	1.588***	1.364	1.848	1.323**	1.112	1.573
Asian	1.348	.968	1.878	1.317	.937	1.852
Other Race	1.231	.911	1.663	1.138	.826	1.568
Age Group (ref=2-9 years)						
Infant	1.461**	1.025	2.083	1.378	.964	1.971
10-14 years	2.478***	2.078	2.952	2.346***	1.962	2.805
15-20 years	3.181***	2.684	3.769	3.092***	1.588	3.696
Neutropenia present	2.335***	1.930	2.824	2.356***	1.942	2.857

Table 9

Summary of Results of the Test of Hypothesis 2: Odds of Severe Sepsis When Infection is Present During Hospitalization in ALL

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Weight loss present	2.001***	1.690	2.369	1.665***	1.399	1.983
Obesity	2.116***	1.613	2.776	1.162	.868	1.554
Hyperglycemia	1.964***	1.533	2.517	1.404*	1.082	1.821
Downs Syndrome	1.398*	1.031	1.896	1.404*	1.022	1.918
Private insurance	.798**	.693	.918	.858	.733	1.001
Children's hospital	1.407***	1.224	1.617	1.342***	1.161	1.552
Urban residence	1.217*	1.013	1.463	1.056	.871	1.282

Notes. *p<.05; **p<.01; ***p<.001

Variables not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: sex, mucositis, ALL remission present, income, region of the U.S.

Final model: X^2 (15) =402.908, p<.001; Nagelkerke R^2 .077; Hosmer & Lemeshow test X^2 (8) = 2.828, p=.945

Hypothesis 3. It was hypothesized that children diagnosed with ALL in the non-White racial groups are at greater risk than White children of an extended hospitalization when infection is present. Bivariate analysis supported this hypothesis showing differences between racial groups X^2 (4) =48.885, p<.001. It was found that the percentage of White children having an extended LOS was lower than it was for children of all other racial categories. Black children (OR=1.35, p<.001) and Hispanic children (OR=1.30, p<.001) were more likely to have extended hospitalizations in the unadjusted model. As summarized in Table 10, this association failed to persist when the model was adjusted with the addition of clinical and sociodemographic covariates. There were no significant differences between White children and Black (AOR=1.18, p=.051), Hispanic (AOR 1.08, p=.143) Asian (AOR=1.06, p=.543), or other race children (AOR=0.97, p=.753). The Nagelkerke R^2 estimated that 19% of the variance in the risk of extended

hospitalization was explained by the adjusted model. The test of the model coefficients showed the final adjusted model to be significant X^2 (21) =1989.108, p<.001. The goodness of fit as measured by the Hosmer-Lemeshow test indicated the model was satisfactory for this data X^2(8) =4.669, p=.792. Hypothesis 3 was not supported.

Table 10

Summary of Results of the Test of Hypothesis 3: Odds of an Extended Hospitalization When Infection is Present in ALL

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	1.347***	1.166	1.556	1.177	.999	1.386
Hispanic	1.301***	1.201	1.411	1.079	.975	1.195
Asian	1.108	.927	1.325	1.063	.873	1.295
Other Race	1.069	.913	1.251	.972	.817	1.158
Age Group (ref=2-9 years)						
Infant	2.351***	1.003	2.759	2.067***	1.739	2.458
10-14 years	1.731***	1.577	1.899	1.555***	1.405	1.722
15-20 years	1.852***	1.683	2.037	1.642***	1.475	1.828
Neutropenia present	3.456***	3.136	3.809	3.422***	3.086	3.794
Mucositis present	2.610***	2.364	2.882	1.931***	1.730	2.155
Weight loss present	2.741***	2.484	3.026	2.186***	1.959	2.441
Obesity	2.188***	1.844	2.596	1.479***	1.213	1.803
Hyperglycemia	3.989***	3.418	4.656	3.457***	2.917	4.096
Remission absent	1.774***	1.633	1.927	1.693***	1.549	1.850
Downs Syndrome	1.229**	1.032	1.463	1.267*	1.042	1.540
Income >50th%ile	.874***	.813	.941	.941	.863	1.027
Private insurance	.798***	.742	.858	.847***	.777	.924
Children's hospital	1.109**	1.032	1.192	1.045	.962	1.135
Urban residence	1.115*	1.018	1.223	1.000	.897	1.114
Region of the US (ref=South)						
Northeast	1.196**	1.063	1.337	1.378***	1.217	1.561
Midwest	.772***	.650	.810	.830**	.740	.931
West	1.307***	1.216	1.458	1.273***	1.149	1.410

Notes. *p<.05; **p<.01; p<.001
Not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: sex
Final model: X^2 (21) =1989.108, p<.001. Nagelkerke R^2 .189. Hosmer & Lemeshow Test X^2 (8) =4.669, p=.792

Hypothesis 4. Hypothesis 4 proposed that when infection is present, the risk of a high-cost of hospitalization is greater for a child in the non-White racial group than a child in the White racial group. This hypothesis was supported in the bivariate analysis with all non-White racial groups having a higher percentage of cases in which the hospitalization resulted in a high cost X^2 (4) =66.386, p<.001. In the unadjusted model, compared to White children, those in the Black (OR=1.37, p<.001), Hispanic (OR=1.4, p<.001), and Asian (OR=1.28, p=.008) racial groups had an increased likelihood of incurring high costs when infection was present. When clinical and sociodemographic variables were controlled, this effect persisted for Black children (AOR=1.23, p=.022) and Asian children (AOR=1.25, p=.037), but not for Hispanic children (AOR=1.09, p=.146), or other race children (AOR=1.03, p=.782). These results are found in Table 11. Although the test of the model coefficients indicated that the final adjusted model was significant X^2 (20) =2201.215, p<.001, the data was a poor fit for the model, as measured by the Hosmer-Lemeshow test X^2(8) =19.724, p=.011. The Nagelkerke statistic of .217 determined that 22% of the variance in the risk of a high-cost hospitalization is explained by the adjusted model. In conclusion, Black and Asian children were found to be at greater risk of a high-cost hospitalization compared to White children. Children belonging to the Hispanic and Other racial groups were not found to be at a significantly different risk for a high-cost hospitalization. Hypothesis 4 was partially supported.

Table 11

Summary of Results of the Test of Hypothesis 4: Odds of a High-Cost Hospitalization When Infection is Present in ALL

	Unadjusted		Adjusted	
		95% CI		*95% CI*

Table 11

Summary of Results of the Test of Hypothesis 4: Odds of a High-Cost Hospitalization When Infection is Present in ALL

Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	1.365***	1.172	1.590	1.227*	1.030	1.463
Hispanic	1.399***	1.284	1.523	1.085	.972	1.211
Asian	1.284**	1.067	1.544	1.246*	1.013	1.532
Other Race	1.101	.931	1.302	1.027	.851	1.240
Age Group (ref=2-9 years)						
Infant	2.179***	1.841	2.578	1.920***	1.598	2.308
10-14 years	1.875***	1.700	2.068	1.679***	1.507	1.871
15-20 years	2.266***	2.052	2.501	2.109***	1.884	2.361
Neutropenia present	2.908***	2.627	3.219	2.963***	2.653	3.309
Mucositis present	1.872***	1.688	2.076	1.380***	1.226	1.553
Weight loss present	2.488***	2.249	2.752	1.976***	1.761	2.216
Obesity present	2.735***	2.034	3.248	1.577***	1.291	1.928
Hyperglycemia present	4.478***	3.842	5.220	3.869***	3.263	4.588
Remission absent	2.387***	2.173	2.622	2.412***	2.177	2.671
Income >50th %ile	.904*	.837	.976	.922	.840	1.011
Private Insurance	.885**	.820	.956	.962	.876	1.057
Children's hospital	2.246***	2.077	2.428	2.411***	2.204	2.636
Urban residence	1.320***	1.194	1.459	1.142*	1.014	1.286
Region of U.S. (ref=South)						
Northeast	1.152	.968	1.234	1.354***	1.180	1.554
Midwest	.920	.824	1.028	.918	.811	1.039
West	1.607***	1.465	1.763	1.286***	1.153	1.433

Notes. *p<.05; **p<.01; ***p<.001
Not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: sex, Downs syndrome
Final model: X^2 (20) =2201.215, p<.001. Nagelkerke R^2 .217. Hosmer and Lemeshow Test X^2 (8) =19.724, p<.011

Acute Myeloid Leukemia

Demographics of the Study Sample. A description of the study sample containing the 2902 cases in which AML was documented is presented in Table 12. The mean age in the sample was 9.8 years (*SD=6.7*) with the largest number of children between the ages of two and nine years (34%). There were slightly more males (51%)

than females. Due to small numbers, the children belonging to the Native American group were reassigned for this study to the other racial group (Agency for Healthcare Research and Quality, 2018). Fifty percent of the children were White followed by Hispanic (27%), Black (11%), Asian (5%), and other race (7%). The majority of the children lived in residential areas where the average household income was below the 50th percentile (51%) and less than half had private health insurance (48%). Seventy-nine percent of the children lived in urban areas rather than rural areas (20%) and the largest number of children were hospitalized in the Southern region of the U.S. (40%). Care was more likely to be provided in a general hospital (55%) versus one with a NACHRI designation (45%). Neutropenia was present in the majority of the cases (73%). Sixteen percent of the cases had mucositis documented, 17% had evidence of weight loss or cachexia, and four percent of the cases indicated the child was obese. AML with evidence of remission was recorded in 23% of the cases and 12% of the cases indicated the child was born with Down syndrome.

Two-thirds of the cases in the AML group had an infectious complication present (66%). Fever was the most common infectious complication and was present in 1187 of the cases with AML. A complete list of infectious complications can be found in Appendix B, Table B1. To test hypotheses 2 through 4 the sample was further delimited to just the 1913 cases with infection documented. Table 12 details the characteristics of this subsample of cases with infection. In the subsample, the largest percentage of children were in the White racial group (49%), followed by the Hispanic (27%), Black (12%), Asian (6%), and other race (7%). A higher percentage of the children with infectious complications lived in residential areas where the average household income

was below the 50th percentile (51%) and less than half had private health insurance (46%). Seventy-eight percent of the children lived in urban areas and the 20% lived in rural areas. The largest number of children were hospitalized in the Southern region of the U.S. (38%). Care was more likely to be provided in a general hospital (52%) versus one with a NACHRI designation (48%). Neutropenia was present in 84% of the cases. Mucositis was present in 21% of the cases, obesity was documented in four percent of the cases, and evidence of weight loss or cachexia was present in 20% of the cases. The majority of the cases did not have documented evidence that AML was in remission (80%) and 10% of the cases indicated the child was also diagnosed with Down syndrome.

Table 12

Description of the Study Sample and the Subsample of Cases with Documentation of Infection, AML

Variable	Frequency (%) AML Sample (*N*=2902)	Frequency (%) Infection Present (*n*=1913)
Race		
White	1440(49.6)	938(49.1)
Black	336(11.6)	229(12.0)
Hispanic	768(26.5)	510(26.6)
Asian	156(5.4)	109(5.7)
Other	202(7.0)	127(6.6)
Age Group		
Infant	377(13.0)	233(12.2)
2-9 Years	977(33.7)	659(34.5)
10-14 Years	659(22.7)	457(23.9)
15-20 Years	888(30.6)	564(29.5)
Sex*		
Female	1432(49.3)	945(49.4)
Male	1467(50.6)	966(50.5)
Insurance Type*		
Private	1402(48.3)	882(46.1)
Public/Other	1498(50.6)	1029(53.8)
Household Income (zip code level) *		
Upper 50th %ile	1367(47.1)	902(47.2)
Lower 50th %ile	1468(50.6)	970(50.7)
Place of Residence*		

Table 12

Description of the Study Sample and the Subsample of Cases with Documentation of Infection, AML

Rural Area	579(19.9)	401(21.0)
Urban Area	2276(78.5)	1485(77.6)
Region of the U.S.		
South	1173(40.4)	727(38.0)
Northeast	389(13.4)	253(13.2)
Midwest	609(21.0)	418(21.8)
West	731(25.2%)	515(26.9)
Type of Hospital		
General Hospital	1598(55.1)	997(52.1)
Children's Hospital	1304(44.9)	915(47.9)
Neutropenia		
Present	2115(72.9)	1612(84.3)
Absent	787(27.1)	301(15.7)
Mucositis		
Present	452(15.6)	393(20.5)
Absent	2450(84.4)	1520(79.5)
Weight Loss/Cachexia		
Present	484(16.7)	374(19.5)
Absent	2418(83.3)	1539(80.5)
Obesity		
Present	118(4.1)	80(4.2)
Absent	2784(95.9)	1832(95.8)
Disease Status		
Remission	652(22.5)	397(20.7)
Remission not Evident/Relapse	2250(77.5)	1516(79.3)
Down Syndrome		
Present	346(11.9)	182(9.5)
Absent	2418(83.3)	1730(90.5)

Note. *Percentages do not equal 100% due to missing items.

Description of the Study Variables. Descriptive statistics for the study variables are presented in Table 13. In this sample of 2902 cases, the majority had evidence of an infection in the discharge diagnoses (66%). Of those cases in which infection is present, 14% had documentation indicating severe sepsis occurred during the hospitalization. The average length of stay when infection was present was 25.3 days, and 47% of the hospitalizations were considered extended stays lasting longer than 25 days. The mean

cost of hospitalization was $93720 (SD = $165763) and 32% of the cases were found to be high cost hospitalizations of above the mean.

Table 13

Description of the Outcome Variables AML

Variable	Mean (SD)	Range	Frequency	%
Infection*				
Present			1913	65.9
Absent			989	34.1
Severe Sepsis**				
Present			271	14.1
Absent			1642	85.9
Length of Stay**	25.3(25)	0.281		
>25 Days			894	46.7
<=25Days			10053	70.4
Cost of Hospitalization**	$93720 ($165763)	$137-$2417395		
>$93720			582	31.6
<=$93720			1261	68.4

Notes. *N=2902. **n = 1913.

Hypothesis Testing. Hypothesis testing was previously described and was conducted in the same manner as the ALL cases.

Hypothesis 1. The first hypothesis proposed that children belonging to the non-White racial group would be more likely to have an infectious complication when hospitalized with AML compared to children in the White racial group. The results of the bivariate analysis found that there was no significant difference between racial groups in the rate of infectious complications X^2 (4) =3.095, p<.542. Because a chi square test of the independent variable, race, failed to meet the threshold of a significance test set at .05, univariate and multivariate regression analyses were not conducted. Hypothesis 1 was not supported.

Hypothesis 2. The second hypothesis proposed that when infection is present during hospitalization, children with leukemia belonging to non-White racial groups are more likely to develop severe sepsis compared to children in the White racial group. Bivariate testing demonstrated that racial differences existed in the development of severe sepsis $X^2(4) = 20.396$, $p<.001$. A higher percentage of Hispanic children (20%) experienced documented severe sepsis compared to White children (12%), as did Black children (14%) and children belonging to the other race category (16%) The percentage of Asian children was lower (9%) than White. This increased risk of severe sepsis in Hispanic children continued to be evident in the unadjusted model and Hispanic children were more likely to be affected than White children (OR 1.87, $p<.001$). After clinical and sociodemographic variables were controlled in the adjusted model, this finding persisted and the Hispanic racial group was associated with a 1.55-fold ($p=.006$) increased risk of developing severe sepsis. There were no significant differences in the likelihood of the development of severe sepsis in Black (AOR = 1.22, $p=.366$), Asian (AOR=0.55, $p=.097$), or other race (AOR=1.44, $p=.182$) children when compared to White children in the final adjusted models. The test of the model coefficients indicated that the adjusted model was significant $X^2(9) = 65.938$, $p< .001$. The goodness of fit as measured by the Hosmer-Lemeshow test was calculated and the model was satisfactory for this data $X^2(8) = 15.267$, $p=.054$. The Nagelkerke R^2 indicated approximately six percent of the variance can be explained by the model. These results are found in Table 14. Hispanic children with AML were found to be at greater risk of developing severe sepsis when an infection was present during hospitalization than White children, a finding that supports the hypothesis. The risk for Black, Asian, and other race children

does not differ from that of White children, therefore hypothesis 2 was partially supported.

Table 14

Summary of Results of the Test of Hypothesis 2: Odds of Severe Sepsis When Infection is Present During Hospitalization in AML

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	1.260	.826	1.922	1.219	.793	1.874
Hispanic	1.868***	1.389	2.513	1.554**	1.138	2.123
Asian	.770	.390	1.521	.552	.273	1.113
Other Race	1.408	.837	2.370	1.435	.844	2.439
Age Group (ref=2-9 years)						
Infant	.828	.492	1.396	.849	.502	1.437
10-14 years	2.183***	1.553	3.070	2.098***	1.477	2.980
15-20 years	1.706**	1.218	2.389	1.824**	1.288	2.583
Neutropenia present	1.828**	1.202	2.782	1.779**	1.162	2.723
Obesity	2.056**	1.216	3.476	1.463	.850	2.517
Children's hospital	1.582**	1.220	2.051	1.524**	1.151	2.018

Notes. *p<.05; **p<.01; ***p<.001
Variables not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: sex, mucositis, weight loss, ALL remission status, income, insurance type, urban or rural residence, region of the U.S.
Final model: X^2 (10) =67.726, p<.001; Nagelkerke R^2 .062; Hosmer & Lemeshow test X^2 (8)=15. 267, p=.054

Hypothesis 3. It was hypothesized that children diagnosed with AML in the non-White racial groups are at greater risk than White children of an extended hospitalization when infection was present. Bivariate analyses did not show significant differences between racial groups in the risk of experiencing a prolonged hospitalization X^2 (4) = 8.205, p<.084. The independent variable of race failed to meet the inclusion criterion of significance testing by chi square set at 0.05. Hypothesis 3 was not supported.

Hypothesis 4. Hypothesis 4 proposed that when infection is present, the risk of a high-cost of hospitalization is greater for a child in the non-White racial group than a child in the White racial group. This hypothesis was supported in the bivariate analysis which showed significant differences between the racial groups X^2 (4) =28.974, p<.001. In the unadjusted model, compared to White children, those in the Hispanic (OR=1.50, p<.001) and Asian (OR=2.57, p<.001) racial groups had an increased likelihood of incurring high costs when infection was present. When clinical and sociodemographic variables were controlled, disparities in the risk of incurring high costs between racial groups were not apparent. These results are found in Table 15. The test of the model coefficients indicated that the final adjusted model was significant X^2 (20) =444.259, p<.001, the data was a good fit for the model, as measured by the Hosmer-Lemeshow test X^2(8) =10.483, p=.233. The Nagelkerke statistic estimated that approximately 30% of the variance in the risk of a high-cost hospitalization was explained by the adjusted model. In conclusion, there were not significant differences in the likelihood of a high-cost hospitalization for Black (AOR=1.24, p=.293), Hispanic (AOR=0.94, p=.669), Asian (AOR=1.57, p=.084), and other race (AOR=1.04, p=.879) children compared to White children. Therefore, hypothesis 4 was not supported.

Table 15

Summary of Results of the Test of Hypothesis 4: Odds of a High-Cost Hospitalization When Infection is Present in AML

	Unadjusted			Adjusted		
		95% CI			*95% CI*	
Predictor	*O.R.*	*Lower*	*Upper*	*O.R.*	*Lower*	*Upper*
Race (ref=White)						
Black	1.093	.790	1.512	1.238	.832	1.842
Hispanic	1.504**	1.191	1.899	.935	.689	1.271
Asian	2.566***	1.689	3.897	1.573	.940	2.632
Other Race	.992	.650	1.513	1.040	.625	1.733

Table 15

Summary of Results of the Test of Hypothesis 4: Odds of a High-Cost Hospitalization When Infection is Present in AML

Age Group (ref=2-9 years)						
Infant	1.242	.883	1.749	1.494*	1.003	2.225
10-14 years	2.467***	1.900	3.203	2.021***	1.483	2.755
15-20 years	1.330*	1.029	1.717	1.565**	1.151	2.128
Female	1.425	1.170	1.736	1.604***	1.273	2.020
Neutropenia present	2.424***	1.762	3.334	2.002***	1.385	2.894
Mucositis present	2.282***	1.807	2.880	2.453***	1.862	3.233
Weight loss present	3.168***	2.499	4.016	3.185***	2.428	4.177
Obesity	2.337***	1.492	3.662	1.665	.975	2.846
Remission absent	1.349*	1.051	1.732	1.368*	1.020	1.835
Downs syndrome	.267***	.166	.431	.386**	.223	.666
Income >50th %ile	1.355**	1.111	1.653	1.196	.933	1.533
Children's hospital	3.857***	3.120	4.767	4.666***	3.595	6.055
Urban residence	1.451**	1.131	1.863	1.032	.754	1.413
Region of U.S. (ref=South)						
Northeast	1.256	.915	1.724	1.514*	1.033	2.219
Midwest	1.190	.906	1.562	1.162	.848	1.592
West	2.373***	1.851	3.043	2.080***	1.522	2.844

Notes. *p<.05; **p<.01; ***p<.001
Not included in the model based upon bivariate analysis with chi square test, significance set at p<.05: Insurance
Final model: X^2 (20) =444.259, p<.001. Nagelkerke R^2 .306. Hosmer and Lemeshow Test X^2 (8) =10.483, p<.233

Summary of the Hypothesis Testing

Four hypotheses about the association between a child's race and the infectious consequences of leukemia were tested separately in the two groups, ALL cases and AML cases. There were no significant associations between racial groups and the presence of infection during hospitalization in either the ALL or the AML group. In both the ALL and the AML groups, children belonging to the Hispanic racial group were more likely than White children to have documentation of severe sepsis when infection was present during the hospitalization. There was not a significant association between race and a

prolonged length of stay when infection was present in either group. In the ALL group, Black and Asian children were at greater risk than White children for a high-cost hospitalization in the presence of infection. There were no significant differences in the risk of a high-cost hospitalization in the AML group. This summary of the findings is presented in Table 16.

Table 16

Summary of Hypothesis Testing

Hypothesis	ALL	AML
Hypothesis 1: Children diagnosed with leukemia belonging to non-White racial groups are more likely to have an infection during hospitalization compared to children in the White racial group.	Not supported.	Not supported.
Hypothesis 2: Children diagnosed with leukemia belonging to non-White racial groups are more likely to develop severe sepsis when infection is present during hospitalization compared to children in the White racial group.	Partially supported. Hispanic race was associated with risk of severe sepsis.	Partially supported. Hispanic race was associated with risk of severe sepsis.
Hypothesis 3: In comparison to non-White children, those belonging to other racial groups are more likely to have an extended length of stay when hospitalized with infection.	Not supported.	Not supported.
Hypothesis 4: In comparison to non-White children, those belonging to other racial groups incur greater costs during hospitalization with infection.	Partially supported. Black and Asian races were associated with risk of high cost hospitalization.	Not supported.

Chapter 5: Discussion of the Findings

There have been significant improvements in the overall survival rates for children diagnosed with leukemia in the U.S., yet racial disparities persist (Bhatia, 2011;

Siegel et al., 2017). Successful treatment of leukemia requires immunosuppressive therapy. Subsequently, infectious complications as a cause of death are second only to treatment-resistant disease (Alexander et al., 2015; Bailey et al., 2009; Hunger et al., 2012; Pole et al., 2017). Little has been done to quantify the impact of infectious complications experienced by non-White racial groups despite the fact that this may be an underappreciated contributor to the racial inequities in mortality (Smits-Seemann et al., 2017). This study sought to add to the current body of evidence by examining the associations between race and infectious complications in children hospitalized with leukemia in the U.S. in 2016. This study was a secondary analysis of a national administrative database conducted with the goal of determining if racial disparities exist and to provide empirical justification for future research exploring this phenomenon.

The Fundamental Cause Theory served as the conceptual framework for this study. Rooted within fundamental causes of health outcomes are resources in a family's possession, by virtue of social position, that allow for either the avoidance or minimization of a health threat. Conversely, social position may result in the absence of protective resources. In the framework, these resources are identified as money, knowledge, power, prestige, and social connections. Resources work on two levels. At the individual level families can take advantage of available resources through independent actions (Link & Phelan, 1995). A family can also experience contextual advantage by being situated in a circumstance where the members benefit from available community resources as a result of social position, even in the absence of actions intentionally taken (Link, 2005; Link & Phelan, 1995). These resources can be transferred and utilized as new health threats arise allowing some families, but not all, to

have favorable outcomes resulting in the perpetuation of disparities (Link, 2005; Link & Phelan, 1995; Phelan & Link, 2015). This study examined race as a fundamental cause. The discussion in this chapter regarding the associations between race, as a fundamental cause, and risk of infection, the development of severe sepsis, and prolonged and high-cost hospitalizations will be presented in the context of the theoretical constructs of the Fundamental Cause Theory.

Race and the Risk of Infectious Complications

It was hypothesized that children with leukemia who belonged to non-White racial groups would be at increased risk for infectious complications while hospitalized. Fifty-three percent of the cases in the ALL group and 66% in the AML group had documentation indicating that an infectious complication occurred during hospitalization. Statistical analyses found no significant racial differences in either group; thus, this hypothesis was not supported.

Failure of support for this hypothesis can likely be attributed to two parallel factors: the underestimation of the influence of neutropenia on the risk of infection in children with leukemia, and the lack of consideration given to a critical assumption of the Fundamental Cause Theory. Cancer treatment-related neutropenia is a significant predictor of infection in children (Afzal et al., 2009; Agarwal & Joyce, 2014; Kelly et al., 2013). In the current study, when an infectious complication was documented, neutropenia was found to be present in 71% of cases within the ALL group, and was a highly significant predictor of infection (AOR=6.4, $p<.001$). The therapy required to treat AML is severely myelosuppressive as demonstrated in this study by evidence of neutropenia in 84% of cases with infection. The risk for infection due to neutropenia is

compounded by the requirement of a central venous catheter for the delivery of therapy (Baggott et al., 2011; Bailey et al., 2009). When compared to other childhood cancers, the diagnosis of leukemia is a greater predictor of invasive infection, intensive care utilization, and mortality (Ammann et al., 2015; Delebarre et al., 2015; Hakim et al., 2010; Yacobovich et al., 2015; Zinter, DuBois, Spicer, Matthay, & Sapru, 2014).

The Fundamental Cause Theory posits that when a health risk cannot be avoided, as is the case with the profound neutropenia associated with leukemia therapy, social position does not confer any advantage for members of one race over another. Theoretically, in the presence of neutropenia, an inevitable adverse effect of leukemia therapy, resources available to those families identified as White cannot be deployed to decrease a child's risk of infectious complications. It is possible, that this hypothesis was not supported due to an *a priori* miscalculation of the unavoidable risk of neutropenia that resulted in the inability of families to utilize their available resources. Thus, an incorrect application of the Fundamental Cause Theory's construct of the relationship between available resources and a family's ability to minimize a health threat resulted in a flawed hypothesis.

Race and the Risk of Severe Sepsis

Severe sepsis, a life-threatening complication of treatment-related neutropenia, represents a pediatric oncology nursing emergency (Baggott et al., 2011) A multicenter retrospective analysis of more than 12000 hospitalizations found severe sepsis to be associated with a 9.9-fold increased risk of death in children with cancer treatment-related neutropenia (Basu et al., 2005). In this current study, six percent of the cases with documented infection in the ALL group and 14% in the AML group were identified to

have severe sepsis. The second hypothesis proposed that children in the non-White racial groups would be more likely to have documentation of severe sepsis when infection was present than White children. In both the ALL and the AML samples this hypothesis was partially supported as Hispanic children were at greater risk for severe sepsis, but other racial groups were not found to have significant differences in risk. These risks found in this study were similar to that reported by Smits-Seemann et al. (2017) who determined that, when compared to non-Hispanic White children, Hispanic children with cancer were more likely to require transfer to an intensive care unit for management of infection ($p=.001$). Also, Hispanic children diagnosed with AML and treated between 1996 and 2000 in a clinical trial conducted by COG had a 16% risk of infection-related death, compared to a nine percent risk in White children (Aplenc et al., 2006).

An unexpected finding in the association of race and the development of severe sepsis was that this relationship only applied to Hispanic children and not children belonging to the other non-White racial groups. A study by Basu et al. (2005) examined mortality during hospitalization in which febrile neutropenia was documented and found that not only Hispanic children, but also Black, Asian, and other race children had significantly greater odds of death than White children. The presence of severe sepsis was controlled in that study. It should be noted, though, that this was a study of all childhood cancers and the sample had an over-representation of Black children and under-representation of Hispanic children when compared to the present study sample. One methodological factor that could potentially explain the unexpected finding in this study is the way in which AHRQ coded race in the 2016 HCUP KID file. When a hospital submitted information about a child's Hispanic or non-Hispanic ethnicity, in

addition to race, AHRQ coded that case as Hispanic race, and disregarded the race that was recorded at the hospital-level. This has the potential for the undercounting of Black children resulting in a loss of power for the Black racial group. The findings in the Asian and other race categories may have been the result of small sample sizes in both the ALL and AML groups.

Race and the Risk of Prolonged Hospitalization

The third hypothesis stated that non-White children, compared to White children, would be at greater risk of prolonged hospitalization, in this study longer than 9 days for ALL cases and longer than 25 days for AML cases, when infection is present. When the relationship between race and risk of prolonged LOS was tested in the AML group through bivariate analysis, the results did not meet the threshold of significance set at .05 and no further analyses were conducted to test this hypothesis. These findings were not unexpected and were likely a result of the common practice of retaining children in the hospital until the prolonged myelosuppression caused by the chemotherapy has resolved (Getz et al., 2015; Kavcic et al., 2013; Miller et al., 2016).

In the ALL group there was no association between race and the risk of an extended LOS. This finding contradicted previously reported studies of children hospitalized with febrile neutropenia (Basu et al., 2005; Mueller et al., 2016). While these findings did not support the theorized premise that race may be a fundamental cause of disparities in prolonged lengths of stay for children with ALL, they must be interpreted with caution as several potential confounding factors were not included in the analysis. Whether or not the child was admitted for the sole reason of an infection, or if the child also received chemotherapy while hospitalized, was not accounted for and has the

potential to influence the LOS. Additionally, although the confounding effects of neutropenia, cachexia, obesity, hyperglycemia, and mucositis were controlled, the severity and duration of these complications cannot be determined in the data available in the HCUP KID. Similarly, not all clinical factors could be included in the adjusted model due to the limitations of the available data with the notable example being the presence, or absence, of a central venous access device. Another methodological concern was that the final model was not adjusted for the severity of the infectious complication. This means, for example, that otitis media and pneumonia were both considered infections, but there were no adjustments made to the model to account for the varying degrees of severity. The lack of association between racial differences and the risk of prolonged LOS found in this study differ from the findings of an analysis of national data conducted by Basu et al. (2005). In that study of neutropenia and extended LOS, severe infections including sepsis, pneumonia, bacteremia, and fungal infections were included in the adjusted model and Black, Hispanic, Asian, and other race children were more likely to have prolonged hospitalizations compared to White children.

Race and High-Cost Hospitalizations

The fourth hypothesis tested in this study proposed that children belonging to non-White racial groups would be at increased risk of high-cost hospitalizations when infection was present. A high-cost hospitalization was defined in the AML group as an admission with adjusted costs of more than $93720. The hypothesis was not supported in this subsample. This was most likely attributed to the retention of children in the hospital until the recovery of blood counts following chemotherapy; the cost of necessary interventions such as transfusions of blood products, antimicrobial and antifungal

medications; and the increased likelihood that a more intensive care setting may have been required (Getz et al., 2015; Miller et al., 2016; Winestone et al., 2017).

The findings in the ALL group partially supported this hypothesis in that Black children (AOR=1.23, p=.022) and Asian children (AOR=1.25, p=.037) had higher odds of a high-cost hospitalization compared to White children, defined as greater than $34200. These findings support the theorized premise that race may be a fundamental cause of disparities in high-cost hospitalizations in children with ALL, however, similar methodological concerns to those described in the testing of the third hypothesis existed, as well as the exclusion of potential confounding variables representing high-cost interventions, for example surgery or transfer to an intensive care unit. Finally, due to a very poor model fit, adjustment for length of stay was not made.

Adequacy of the Fundamental Cause Theory in Explaining the Association between Race and Infectious Complications

Few studies have focused on racial differences in the risk of infections faced by children who require treatment of leukemia, yet disparities have been discovered when race was included as a potential confounding variable. None of these studies used a conceptual framework to guide hypothesis development. This study examined race as the independent variable and hypotheses were developed based upon the theorized concept of race as a fundamental cause of infectious complications. The Fundamental Cause Theory postulates that when new circumstances of a health threat emerge, for instance knowledge about prevention or advancements in treatment, those with greater resources will have an advantage in accessing these innovations resulting in the persistence of health inequality. It is this deployment of flexible resources in the face of emerging

health threats that results in an enduring association between social position and risk of mortality (Link & Phelan, 1995; Phelan et al., 2010; Phelan & Link, 2015; Phelan et al., 2004). In contrast, in situations where effective medical interventions are absent or ineffective, available resources are of little assistance, and differences in risk are not dependent upon group membership, in this case a racial group (Link & Phelan, 1995; Phelan & Link, 2015; Phelan et al., 2004; Tehranifar et al., 2009).

The first hypothesis that proposed significantly higher risks for infection among non-White children with ALL and AML was not supported. This provided theoretical support of the Fundamental Cause Theory in that race is not a predictor of the risk of infection because leukemia therapy leaves no racial group with an advantage due to inevitability of treatment-related neutropenia. That is, when there is no mechanism by which to avoid the threat of neutropenia, there will be no difference in the risk of infection, secondary to that neutropenia, based upon membership in a racial group.

Due to the increased risk of infectious complications in immunocompromised children, the American College of Critical Care Medicine has issued guidelines for the early detection of warning signs of impending sepsis in these patients. The guidelines have been used to develop standardized protocols for hospitals and these have resulted in the prevention and minimization of the consequences of severe sepsis in at-risk children (Davis et al., 2017). Implementation of supportive care guidelines and the recognition of the importance of prompt treatment in the event of fever has resulted in declining rates of treatment-related mortality due to infection in childhood leukemia (Baggott et al., 2011; Fletcher et al., 2013; Sung et al., 2008). However, despite this increasing success over time, the framework would propose that a racial gradient would emerge leaving those

with the least resources at greater risk of sepsis. That is, as new knowledge and treatment modalities emerge, some families will benefit from these innovations more than others (Link & Phelan, 1995; Phelan et al., 2004). This construct of the framework is especially evident in the case of AML, where due to the intensity of the therapy required for the treatment, it is common practice that children remain hospitalized until the prolonged neutropenia resolves (Baggott et al., 2011; Getz et al., 2015; Kavcic et al., 2013; Miller et al., 2016; Rubnitz et al., 2010). Even in the context of these precautions, disparate rates of severe sepsis occurred in Hispanic children within the setting of the controlled medical environment. In this study, Hispanic children were found to be at significantly higher risk for severe sepsis than White children providing evidence of the adequacy of the Fundamental Cause Theory as a conceptual framework.

Chapter 6: Summary, Conclusions, Implications, and Recommendations

Summary

This study was conducted to address gaps in the current evidence surrounding the relationship between race and the risk of infectious complications that result from the treatment of childhood leukemia. This study was guided by the framework of the Fundamental Cause Theory and sought to answer the questions: Are there disparate risks of infections dependent upon a child's race and do these disparities impact healthcare resource use? This was a secondary analysis of the 2016 HCUP KID database and the two populations of interest representing cases of ALL and AML were determined through a systematic delimitation of the file. Cases were included if any of the 30 discharge diagnoses contained the ICD-10-CM codes for ALL (C9100, C9101, or C9102) or for AML (C9200, C9201, or C9102) (Practice Management Information Corporation, 2015).

Cases in which the child was diagnosed with a rare form of leukemia, received perinatal care, had evidence of undergoing bone marrow or stem cell transplant, or indication that a transfer to another acute care facility took place were removed (Russell et al., 2016).

The final sample size in the ALL group was 28614 cases. The mean age was 8.8 years (*SD=5.6*), the majority of which were male (59%). Most of the children were White (50%), followed by the Hispanic (33%), Black (7%), Asian (4%), and other race (6%). More than half of the children lived in residential areas where the average household income was below the 50th percentile (52%) and less than half had private health insurance (46%). Seventy-nine percent of the children lived in urban areas rather than rural areas (20%) and the largest number of children were hospitalized in the Southern region of the U.S. (39%). Care was more likely to be provided in a general hospital (54%) versus one with a NACHRI designation (46%). There was documentation of infection in 53% of the cases and of these, six percent had severe sepsis.

The final sample size of the AML group was 2902 cases. The mean age was 9.8 years (*SD=6.7*) and 51% were male. Fifty percent of the children were White followed by the Hispanic (27%), Black (11%), Asian (5%), and other race (7%). Greater than half of the children lived in residential areas where the average household income was below the 50th percentile (51%) and less than half had private health insurance (48%). Twenty percent of the children lived in rural areas, 79% lived in metropolitan areas, and the largest number of children were hospitalized in the Southern region of the U.S. (40%). Care was more likely to be provided in a general hospital (55%) versus one with a NACHRI designation (45%). Sixty-six percent of the cases had infection, and of that 14% developed severe sepsis.

Hypotheses were derived from the Fundamental Cause Theory and analyses performed in this study were done to test the following:

1. Children diagnosed with leukemia belonging to non-White racial groups are more likely have an infection during hospitalization compared to children in the White racial group.
2. When infection is present during hospitalization, children belonging to non-White racial groups are more likely to develop severe sepsis compared to children in the White racial group.
3. In comparison to White children, those belonging to other racial groups will be more likely to have an extended length of stay when hospitalized with infection.
4. In comparison to White children, those belonging to other racial groups will incur greater costs when hospitalized with infection.

Bivariate analyses using the chi square test were conducted to determine if differences existed between the categorical predictors and all four outcomes in each leukemia subtype. Those predictors that met the significance threshold, set conservatively at .05, were included in logistic regression models. Unadjusted and adjusted models were constructed for comparison.

There were no significant associations between race and the risk of a documented infectious complication while hospitalized with either ALL or AML. However, when infection was present, Hispanic race was a significant predictor of increased risk for the development of severe sepsis in children diagnosed with both ALL and AML. There were no significant differences in the risk of severe sepsis in Black, Asian, or other race children when compared to White children in either group. No significant associations

were found between race and the risk of an extended length of stay in the ALL or the AML groups. Asian and Black children were at greater odds of a high-cost hospitalization when infection was present in the ALL group. There were no racial differences in the risk of a high-cost hospitalization in the AML group.

There are notable considerations that must be taken in the interpretation of the results of this study, and each represents an unavoidable limitation of a secondary data analysis. The first limitation was the method used by AHRQ for the coding of race in the HCUP KID file. If a hospital reported race and Hispanic ethnicity in a case file, AHRQ coded these cases as Hispanic. This had the potential to undercount cases in Black, White, Asian and other race groups. The second limitation was the possibility of inaccurate coding of ICD-10-CM diagnoses and ICD-10-PCS procedure codes by the hospitals submitting data to AHRQ. Finally, any study of secondary data is limited by the information that was collected prior to the development of research questions (Brennan & Bakken, 2015). There are clinical factors that have been found to be associated with the development of sepsis that could not be determined with the information available in the HCUP KID. Examples of these factors are the phase of therapy, exposure to corticosteroids, severity and length of neutropenia, and presence of a central venous access device (Afzal et al., 2009; Baggott et al., 2011; Bailey et al., 2009; Delebarre et al., 2015; Hakim et al., 2010; Hakim & Gaur, 2011). In the case of this study, data was collected on inpatient hospitalizations only and does not reflect the entirety of the experience of this population. Variations in care exist between providers that determine if a child with fever is hospitalized or is treated as an outpatient (Delebarre et al., 2015; Hakim et al., 2010; Hakim & Gaur, 2011). Children who are not

hospitalized, yet had an infectious complication, were not captured in the HCUP KID and not accounted for in this study.

Conclusions

Neutropenia is experienced almost universally by children receiving treatment following the diagnosis of leukemia leaving children of all racial groups equally vulnerable to infectious complications, most often in the form of neutropenic fever. A small number of children progress to develop life-threatening severe sepsis. Systematic changes in the care of children vulnerable to the development of severe sepsis have resulted in improvements in its prevention and the recognition of early warning signs, when it does occur. Despite these improvements, a gradient in the risk of severe sepsis in children hospitalized with leukemia exists favoring White over Hispanic children. These findings are consistent with the propositions of the Fundamental Cause Theory and lend credence to its use as a conceptual framework for the exploration of this disparity.

Implications for Nursing

Therapy-resistant or recurrent disease is the primary cause of death in children with leukemia but innovations in the form of precise genetic risk profiling and targeted therapies are improving the rates of survival. Genetic variations have been identified as potential contributors to the development of childhood leukemia and the response to therapy, many of which are common in Asian, Native American, African, and Latin American children (Harvey et al., 2010; Wiemels et al., 2018; H. Xu et al., 2012; Heng Xu et al., 2013; Yang et al., 2015). These discoveries have the potential to explain some of the disparities observed in this current study. However, the Fundamental Cause Theory stresses that concentrating on one intervening factor, as is the premise of targeted

therapies, will not remove the remaining multiple pathways resulting in disparities and they will perpetuate.

New targeted therapies show great promise; however, they also have unique adverse effect profiles. As these therapies improve overall survival for children with difficult to treat leukemia, the Fundamental Cause Theory proposes a gradient will emerge and the inequities will persist. It is possible that, similar to the racial differences in the risk of severe sepsis resulting from conventional therapy found in this study, the adverse effects of newer therapies will also be experienced disproportionately.

This study provides evidence that severe sepsis in children hospitalized with leukemia is not experienced equally across racial groups. Nursing is in the unique position to illuminate the multifaceted nature of supportive pediatric oncology care as medical care moves to a more focused genetic approach. When conducting research, it is important to be cognizant of the multiple pathways in which a fundamental cause can effect a health outcome. Although the current study is unable to explain why Hispanic children experience severe sepsis at increased rates compare to White children, there exists evidence of potential pathways in which this may be occurring in the existing research. Studies have shown differences between Hispanic and White families that may impact a family's health-seeking behaviors, whether severe sepsis develops in the hospital or after a child becomes ill at home. These patterns have the potential to limit the utility of interventions shown to decrease the escalation of the severity of sepsis in children. Previous research of factors that may lessen a family's inclination to seek care immediately in the event of fever include studies of non-adherence to oral chemotherapy at home by Hispanic families or increased levels of depression and anxiety in Hispanic

parents of children following the diagnosis of cancer (Bhatia et al., 2014; Bhatia et al., 2012; Meeske et al., 2013; Wahi, Phelan, Sherman-Bien, Sender, & Fortier, 2016). Evidence exists that there are factors that may impede communication between a parent and the health care team members regarding changes in the hospitalized child's condition. These studies have shown potential communication barriers including assumptions made by healthcare providers about the level of information Hispanic parents desire and barriers for limited-English proficient families (Eneriz-Wiemer, Sanders, Barr, & Mendoza, 2014; Harris et al., 2017; Ilowite, Cronin, Kang, & Mack, 2017; Levas, Cowden, & Dowd, 2011; Wahi et al., 2016).

Recommendations

Future pediatric oncology nursing research must take the initiative to address current disparities and develop an explanatory model that accounts for the multiple pathways that contribute to the sustained inequitable outcomes. The following research should be undertaken:

1. In order to develop an explanatory model, replication of this study must take place through retrospective analyses of the more comprehensive data that has already been collected through pediatric clinical trials and electronic hospital medical records to construct and test controlled models more rigorously. These studies should include:
    a. Additional clinical factors that have the potential to confound the results of this study, but were not available in the HCUP KID, such as prognostic features of the leukemia, recent therapy received, comorbidities, and concurrent complications.

   b. Additional family-level factors such as economic hardship, limited English proficiency, parental education level, environmental influences, and immigration status that may impact risk factors for infection and access to healthcare.
   c. Detailed clinical information about the episodes of severe sepsis including the location and timing to identify areas where access barriers exist and improvements in nursing care can be made.

2. Draw upon research from other areas, such as asthma and perinatal health where racial disparities are being examined within the social-biomedical context. These findings should be incorporated, prospectively, into pediatric leukemia clinical trials. The goal must be to identify measures of environmental risk, allostatic load, stress, biomarkers of inflammation, and other predisposing factors in the development of severe sepsis which can provide empirical support to the proposed explanatory model developed through secondary analyses outlined in item 1.
3. Conduct intervention studies guided by the explanatory model developed through secondary analyses, and verified by clinical trial data, that targets areas where the delivery of care by nurses can be improved.

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Appendix A.

Table A1.

Summary of the Studies Examining Race as a Fundamental Cause of Cancer Health Outcomes

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Kim, et al. (2010)	Retrospective secondary data analysis	351 adult women diagnosed with epithelial ovarian cancer between 6/1/94 and 1/31/98 in Cook County, IL.	OV: Time from diagnosis to death IV: (1) Race (Black, White) (2) Years of education (3) SES at the census tract level (%age of pop living below the FPL. Cox proportional model for hazard ratios	Cumulative survival probability Compared to Black women, White women HR = 2.2 (95% C.I. 1.1-4.1, $p<0.05$)
Saldana-Ruiz, et al. (2013)	Retrospective secondary data analysis	National Center for Health Statistics: Adults diagnosed with colorectal cancer between 1968-2005	OV: Mortality rates per county IV: (1) Race (White, Black) (2) County level SES as a composite index score Negative binomial regression analysis	Mortality Rate Ratio Black race 1.22, (95% C.I. 1.20-1.24, ref=White race)
Clouston et al. (2017)	Retrospective secondary data analysis	National Center for Health Statistics: Adults diagnosed with colorectal cancer between 1968-2010	OV: Timing of decline in CRC mortality rate IV: (1) Race (Black, White) (2) County level SES as a composite index score Layered joint-point regression	Black race was associated 4.1-year delay in colonoscopy-attributable declines vs. White race with an estimated 14,000 preventable deaths
Bona, et al. (2016)	Clinical trial cohort study	575 children diagnosed with ALL treated on consecutive clinical trials at institutions in the Dana Farber Cancer Consortium	OV: Overall survival (OS) IV: (1) Race (White, Black, Asian, Other) (2) Ethnicity (Hispanic/ NH) (3) median household income at the zip code level Kaplan Meier, Cox proportional model for hazard ratios	Overall Survival Hispanic children had OS of 87% vs. non-Hispanic OS of 93% ($p=0.008$) White children had an OS of 91% vs. non-White children OS of 90% ($p=.58$)

Table A1.

Summary of the Studies Examining Race as a Fundamental Cause of Cancer Health Outcomes

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Abrhão, et al. (2015)	Retrospective secondary data analysis	California SEER registry: 9295 children diagnosed with ALL between 1998-2011	OV: Overall survival IV: (1) Race (White, Black, Asian, Hispanic) (2) SES as median income by zip (3) Treatment era as 1988-1995, 1996-2003, 2004-2011 (4) Treatment in a pediatric cancer center (5) Insurance defined as none, private, public, unknown Kaplan Meier, Cox proportional model for hazard ratios	Death Race compared to White Hazard ratio of death Black HR 1.72 (95% C.I. 1.29-2.28). Hispanic HR 1.37 (95% C.I. 1.17-1.62); Asian HR 1.40 (95% C.I. 1.11-1.76) 5-year OS by treatment era: 1988-1995: 93.0% 1996-2003: 94.8% 2004-2011: 95.5%
Aplenc, et al. (2006)	Clinical trial cohort study	1141 children diagnosed AML enrolled in consecutive clinical trials at COG institutions between 1989 and 2002	OV: Overall survival IV: (1) Race (White, Black, Asian, Other) Kaplan Meier, Cox proportional model for hazard ratios	Overall Survival Earlier trial: Black 34% vs White 48% (p=0.007) Hispanic 37% vs. White 48 (p=0.007) Later trial: Black 45% vs. White 60% (p=0.007)
Acharya, et al. (2016)	Retrospective secondary data analysis	Florida and Texas cancer registries 4954 children diagnosed with ALL between 1995 and 2008	OV: Overall survival IV: (1) Race (non-Hispanic White, Hispanic, non-Hispanic Black) (2) Age (3) SES as < 5% poverty level, 5-<20% poverty level, >=20% poverty level (4) Treatment era 1995-2001, 2002-2008 Cox proportional model for hazard ratios	Hazard Ratio of Death Race, compared to non-Hispanic White children: Hispanic HR 1.18 (95% C.I. 1.01-1.39, *p*=.04) Non-Hispanic Black HR 1.31 (95% C.I. 1.03-1.66, *p*=.03)
Goggins & Lo (2012)	Retrospective secondary data analysis	National SEER data: 10796 children diagnosed with ALL between 1988-2008	OV: Overall survival IV: (1) Race (NHW, Black, AIAN, Hispanic, specific	Relative Rate of Death Race, compared to NHW

Table A1.

Summary of the Studies Examining Race as a Fundamental Cause of Cancer Health Outcomes

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
			Hispanic origins, Asian, specific Asian origins (2) Age (3) Sex (4) Immuno-phenotype (5) year of diagnosis Cox proportional model for hazard ratios	Black RR 1.82 (95% C.I. 1.52-2.17, $p<.001$) Hispanic RR 1.89 (95% C.I. 1.67-2.14, $p<.001$) East Asians combined RR 1.48 (95% C.I. 1.17-1.86, $p=.0009$) Survival probabilities by race and treatment era: 1988-1994: All: 0.78 NHW: 0.81 Black: 0.74 Hispanic: 0.72 1995-2001: All: 0.82 NHW: 0.87 Black 0.73 Hispanic: 0.76 2002-2008: All: 0.85 NHW: 0.89 Black 0.82 Hispanic: 0.80

Table A1.

Summary of the Studies Examining Race as a Fundamental Cause of Cancer Health Outcomes

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Hunger, et al. (2012)	Clinical trial cohort study	21626 children diagnosed with ALL enrolled in consecutive COG trials between 1990 and 2005	OV: OS IV: (1) Race (White Black, Other) (2) Ethnicity (Hispanic, non-Hispanic) (3) Sex (4) Immuno-Phenotype (5) Age (6) Risk group defined by NCI guidelines as standard or high Cox proportional model for hazard ratios	Overall Survival Race compared to White by era 1990-1994 Black RR 1.73 (p<0.001) Other 1.58 (p<0.001) Hispanic ethnicity 1.31 (p=0.0024, ref=non-Hispanic) 1995-1999 Black RR 1.60 (p<0.001) Other 1.16 (p=0.0121) Hispanic ethnicity 1.16 (p=0.0645, ref=non-Hispanic) 2000-2005 Black RR 1.37 (p=0.0119) Other 1.27 (p=0.0056) Hispanic ethnicity 1.47 (p<0.001, ref=non-Hispanic)
Pui, et al. (2012)	Retrospective secondary data analysis	National SEER data: children with various cancers diagnosed between 2001-2007	OV: Overall survival IV: Race (Black, White) Kaplan Meier for OS then compared eras with Mantel-Haenszel statistic	Leukemia survival by treatment era 1992-2000 ALL White vs Black race: 85.9% vs 72.8% (p<0.01) AML White vs Black race: 49.9% vs 48.7% (p=.81) 2001-2001 ALL

Table A1.

Summary of the Studies Examining Race as a Fundamental Cause of Cancer Health Outcomes

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
				White vs Black race: 89.0% vs 82.1% (p<0.01) AML White vs Black race: 66.6% vs 46.1% (p=<0.01)

Table A2.

Summary of the Studies Examining Race and Infectious Complications

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Aplenc et al. (2006)	Clinical trial cohort study	1141 children diagnosed with AML enrolled in consecutive COG trials between 1989 and 2002	Sample description IV: (1) Race (White, Black, Other) Chi Square	Rate of infection by race Treatment era: 1989-1995 White 6% Black 11% (*p*=.099) 1996-2002 White 9% Black 13% Hispanic 16% (*p*=.035)
Sung et al. (2012)	Clinical trial cohort study	872 children diagnosed with AML enrolled in a COG trial between 1989 and 1995	OV: Life-threatening or fatal infection IV: (1) Race (White, non-White) Cox proportional hazards model	Odds ratio Odds or infection by type compared to White race: All organisms: Non-White 1.39 (*p*=.127) Bacteria: Non-White 1.19 (*p*=.459) Fungi: Non-White 0.91 (*p*=.790)
Alvarez et al. (2017)	Retrospective secondary data analysis	California Office of Statewide Health Planning and Development	OV: LOS IV: (1) Race (Black, White, Hispanic, Asian, Other)	Adjusted odds ratio for LOS >8 days compared to White

Table A2.

Summary of the Studies Examining Race and Infectious Complications

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
		database: 24,559 hospitalizations of children with cancer related fever/neutropenia between 1983-2011	(2) SES with regard to the FPL Logistic regression	Black OR 1.33 (95% CI 1.18-1.50) Hispanic OR 1.24 (95% CI 1.17-1.31) Asian OR 1.28 (95% CI 1.17-1.41) Other race OR 1.21 (95% CI 1.05-1.39)
Basu et al. (2005)	Retrospective secondary data analysis	University Health Services Consortium database: 12,466 hospitalizations of children with cancer related fever/neutropenia between 1995-2002	OV: (1) LOS (2) Mortality IV: (1) Race (White, Black, Hispanic, Asian, Other), Logistic regression	Odds of LOS > 5 days: Black OR 1.46 (95% CI 1.29-1.67) Hispanic OR 1.75 (95% CI 1.54-1.99) Asian OR 1.53 (95% CI 1.21-1.93) Other race OR 1.51 (95% CI 1.33-1.72) Odds of death: Black OR 1.95 (95% CI 1.37-2.76) Hispanic OR 2.12 (95% CI 1.50-3.05) Asian OR 2.53 (95% CI 1.39-4.60) Other race 1.96 (95% CI 1.37-2.79)
Mueller et al. (2016)	Retrospective secondary data analysis	HCUP KID data file: 13,456 hospitalizations of children with cancer related fever/neutropenia in 2012	OV: LOS IV: (1) Race (White, Black, Hispanic, Asian, Other race) (2) SES as median household income by zip code Logistic regression	Odds of shorter length of stay (<3 days) Race, compared to White: Black: 0.78 (p=.008) Hispanic: 0.85 (p=.037)

Table A3.

Summary of the Studies Examining Variables Addressing Potential Confounding Fundamental Causes for Disparities

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Abraháo et al. (2015)	Retrospective secondary data analysis	California SEER: 9295 children diagnosed with	OV: Overall survival IV: (1) Race (White, Black, Asian, Hispanic)	Hazard Rate for death Race compared to White:

Table A3.

Summary of the Studies Examining Variables Addressing Potential Confounding Fundamental Causes for Disparities

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
		ALL between 1998-2011	(2) SES as median income by zip (3) Treatment in a pediatric cancer center (4) Insurance (none, private, public, unknown) Kaplan Meier, Cox proportional model for hazard ratios	Black 1.72 (95% C.I. 1.29-2.28) Hispanic 1.37 (95% C.I. 1.17-1.62) Asian 1.40 (95% C.I. 1.11-1.76) Lowest SES quintile 1.30 (95% C.I. 1.04-2.27, ref=highest quintile) Treatment in a non-specialized center 1.05 (95% C.I. 0.92-1.19) Insurance type compared to private: Public 1.15 (95% C.I. 1.01-1.32) No insurance 1.22 (95% C.I. 0.83-1.89) Unknown 1.77 (95% C.I. 1.38-2.26)
Acharya, et al. (2016)	Retrospective secondary data analysis	Florida and Texas cancer registries: 4954 children diagnosed with ALL between 1995 and 2008	OV: Death IV: (1) Race (Non-Hispanic White, Hispanic, non-Hispanic Black) (2) SES as percentage of families in poverty at the community level Cox proportional model for hazard ratios	Hazard ratio of death Race compared to NHW: Hispanic children HR 1.18 (95% C.I. 1.01-1.39) Non-Hispanic Black (HR 1.31, 95% C.I. 1.03-1.66) SES compared to 0%-<5% poverty: 5%-<20% 1.29 (95% C.I. 1.03-1.61) >20% 1.80 (95% C.I. 1.41-2.30)
DeRoeun et al. (2017)	Retrospective secondary data analysis	California Cancer Registry: 4247 adolescents and young adults diagnosed with leukemia between 2001 and 2011	OV: Death IV: (1) Race (White, non-White) (2) SES as neighborhood quintile (3) Insurance type Cox proportional hazards model	Hazard Ratio of Death Race, compared to NHW: NHB HR 1.47 (95% C.I. 1.03-2.10) Hispanic HR 1.30 (95% C.I. 1.14-1.47) SES compared to highest quintile: Lowest HR 1.42 (95% C.I. 1.18-1.71)

Table A3.

Summary of the Studies Examining Variables Addressing Potential Confounding Fundamental Causes for Disparities

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
				Lower-middle HR 1.31 (95% C.I. 1.09-1.57) Middle HR 1.30 (95% C.I. 1.08-1.56) Insurance type compared to private/military Public Insurance 1.16 (95% C.I. 1.04-1.29)
Kehm, et al. (2018)	Retrospective secondary data analysis	National SEER: 8492 children diagnosed with ALL and 1832 with AML between 2000 and 2011	OV: Death IV: (1) Race (Black, White, Hispanic) (2) SES using the SEER composite index measured at the neighborhood level Cox proportional hazards model Inverse odd weighting method to test SES as a mediator	Hazard Ratio of Death with SES as mediator Black race 1.17 (95% C.I. 1.07-1.28, ref=White) Hispanic race 1.16 (95% C.I. 1.08-1.26)
Alvarez et al. (2017)	Retrospective secondary data analysis	California Office of Statewide Health Planning and Development database: 24,559 hospitalizations of children with cancer related fever/neutropenia between 1983-2011	OV: LOS IV: (1) Race (Black, White, Hispanic, Asian, Other) (2) SES with regard to the FPL (3) Insurance type (4) Access to a specialized program Logistic regression	Adjusted odds ratio for LOS >8 days compared to White Black 1.33 (95% CI 1.18-1.50) Hispanic 1.24 (95% CI 1.17-1.31) Asian 1.28 (95% CI 1.17-1.41) Other race 1.21 (95% CI 1.05-1.39) Access to a specialized program 1.66 (95% CI 1.54-1.78, ref=non-specialized program) Compared to income <2X FPL: 1-4X FPL 0.89 (0.84-0.95), >4X FPL 0.76 (0.70-0.83) Private insurance 0.74 (0.70-0.78, ref=Public)

Table A3.

Summary of the Studies Examining Variables Addressing Potential Confounding Fundamental Causes for Disparities

Reference	Study Design	Sample	Relevant Variables/ Methodology	Relevant Findings
Mueller et al. (2016)	Retrospective secondary data analysis	HCUP KID data file: 13,456 hospitalizations of children with cancer related fever/neutropenia in 2012	OV: LOS IV: (1) Race (White, Black, Hispanic, Asian, Other race) (2) SES as median household income by zip code (3) Insurance type (private, public, self-pay, other) Logistic regression	Odds of shorter length of stay (<3 days) after adjusting for SES and insurance type Race compared to White: Black: 0.78 (*p*=.008) Hispanic: 0.85 (*p*=.037) Insurance compared to private: Public OR 0.89 (95% C.I. 0.80-1.00) Self-pay OR 1.52 (95% C.I. 0.99-2.33) Other OR 0.74 (95% C.I. 0.59-0.94) SES compared to 1st (lowest) quartile 2nd quartile OR 1.08 (95% C.I. 0.94-1.24) 3rd quartile OR 1.03 (0.90-1.18) 4th quartile OR 1.05 (95% C.I. 0.89-1.23)

Appendix B

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
CHOLERA	A00	0	0
TYPHOID	A01	0	0
SALMONELLA	A02	16	0
SHIGELLOSIS	A03	4	0
GI BACTERIAL INFECTION	A04	1063	190
FOODBORNE BACTERIAL INFECTION	A05	0	0
AMEBIASIS	A06	0	0
PROTOZOAL	A07	31	0
GI VIRAL INFECTION	A08	280	31
GI UNSPECIFIED OR OTHER INFECTION	A09	18	7
TUBERCULOSIS	A15-A19	6	1
PLAGUE	A20	0	0
TULAREMIA	A21	0	0
ANTHRAX	A22	0	0
BRUCELLOSIS	A23	0	0
GLANDERS	A24	0	0
RATBITE	A25	0	0
ERYSIPELOID	A26	1	0
LEPTOSPIROSIS	A27	0	0
OTHER ZOONOTIC INFECTION	A28	3	0
LEPROSY	A30	0	0
MYCOBACTERIA	A31	16	1
LISTERIOSIS	A32	1	0
TETANUS	A35	0	0
DISPTHERIA	A36	0	0
WHOOPING COUGH	A37	4	0
SCARLET FEVER	A38	1	0
MENINGOCOCCAL INFECTION	A39	1	0
STREPTOCOCCAL SEPSIS	A40	94	133
OTHER AND UNSPECIFIED SEPSIS	A41	1140	274
ACTINOMYCOSIS	A42	3	3
NOCARDIOSIS	A43	1	1
BARTONELLOSIS	A44	0	0
ERYSIPELAS	A46	3	0
OTHER BACTERIAL DISEASES	A48	7	1

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
BACTERIAL INFECTIONS, UNSPEC SITES	A49	77	17
SYPHILIS	A50-A53	6	0
GONOCCOCAL INFECTION	A54	1	0
CHLAMYDIAL INFECTION	A55-A56, A70-A74	1	0
CHANCROID	A57	0	0
GRANULOMA INGUINALE	A58	0	0
TRICHOMONIASIS	A59	0	0
ANOGENITAL HERPES	A60	16	0
OTHER STD	A63-A64	2	0
NON-VENEREAL SYPHILIS	A65	0	0
YAWS	A66	0	0
PINTA	A67	0	0
RELAPSING FEVERS	A68	5	0
OTHER SPIROCHETAL INFECTIONS	A69	8	0
TYPHUS FEVER	A75	0	0
SPOTTED FEVER	A77	4	0
Q FEVER	A78	0	0
RICKETTSIOSES	A79	0	0
POLIOMYELITIS	A80	0	0
RABIES	A82	0	0
MOSQUITO-BORNE ENCEPHALITIS	A83	0	0
TICK-BORNE ENCEPHALITIS	A84	0	0
OTHER VIRAL ENCEPHALITIS	A85-A86	4	0
VIRAL MENINGITIS	A87	5	0
OTHER VIRAL CNS INFECTIONS	A88-A89	3	0
ARTHROPOD-BORNE INFECTIONS	A90-A99	1	0
HERPES SIMPLEX	B00	444	63
VARICELLA	B01	38	1
ZOSTER	B02	67	4
SMALLPOX	B03	0	0
MONKEY POX	B04	0	0
MEASLES	B05	0	0
RUBELLA	B06	0	0
VIRAL WARTS	B07	20	8
VIRAL SKIN INFECTION	B08	87	14

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
UNSPECIFIED VIRAL SKIN INFECTION	B09	35	1
OTHER HERPES VIRUSES	B10	11	1
VIRAL HEPATITIS	B15-B19	21	4
HIV	B20	0	0
CYTOMEGALOVIRAL DISEASE	B25	96	20
MUMPS	B26	4	0
INFECTIOUS MONONUCLEOSIS	B27	36	1
VIRAL CONJUNCTIVITIS	B30	24	3
OTHER AND UNSPECIFIED VIRUSES	B33-B34	1290	98
DERMAPHYTOSIS	B35	115	6
OTHER SUPERFICIAL MYCOSES	B36	28	6
CANDIDIASIS	B37	943	126
COCCIDIOMYCOSIS	B38	15	0
HISTOPLASMOSIS	B39	8	0
BLASTOMYCOSIS	B40	0	0
PARACOCCIDIOSOMYCOSIS	B41	0	0
SPOROTRICHOSIS	B42	0	0
CHROMOMYCOSIS & PHEOMYCOTIC ABCESS	B43	0	0
ASPERGILLOSIS	B44	175	43
CRYPTOCOCCOSIS	B45	13	0
ZYGOMYCOSIS	B46	80	8
MYCETOMA	B47	0	1
OTHER MYCOSES	B48-B49	270	63
MALARIA	B50-B54	0	0
LEISHMANIASIS	B55	0	0
TRYPANOSOMIASIS	B56	0	0
CHAGAS	B57	0	0
TOXOPLASMOSIS	B58	3	0
PNEUMOCYSTOSIS	B59	31	1
OTHER PROTOZOAL INFECTIONS	B60-B64	0	0
SCHISTOSOMIASIS	B65	0	0
FLUKE	B66	0	0
EXHINOCOCCOSIS	B67	0	0
TAENIASIS	B68	0	0
CYSTICERCOSIS	B69	0	0
DIPHYLLOBOTHRIASIS	B70	0	0

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
OTHER CESTODE INFECTION	B71	0	0
DRACUNCULIASIS	B72	0	0
ONCHSOCERCIASIS	B73	0	0
FILARIASIS	B74	0	0
TRICHNELLOSIS	B75	0	0
HOOKWORM	B76	0	0
ACARIASIS	B77	0	0
STONGYLOIDIASIS	B78	0	0
TRICHURIASIS	B79	0	0
ENTEROBIASIS	B80	6	0
OTHER & UNSPEC HELMINTHIASES	B81-B83	3	0
STREPTOCOCCUS, STAPHYLOCOCCUS, ENTEROCCOCCUS AS CAUSE OF DISEASE	B95	684	179
BACTERIA AS CAUSE OF DISEASE CLASSIFIED ELSEWHERE	B96	812	148
VIRAL AGENTS AS THE CAUSE OF DISEASE CLASSIFIED ELSEWHERE	B97	1543	142
OTHER INFECTIOUS DISEASE	B99	32	1
INFECTIOUS MENINGITIS	G00-G02	14	0
BACTERIAL CNS INFECTIONS	G042	0	0
NECROTIZING ENCEPHALOPATHY	G043	0	0
CNS ABCESS	G06-G07	32	0
HORDEOLUM	H000	0	0
DACRYOADENITIS	H040	1	1
DACRYOCYSTITIS	H043	4	1
ACUTE INFLAMMATION OF ORBIT	H050	11	1
CONJUNCTIVITIS	H103	13	1
OTITIS EXTERNA	H600-H603	12	4
OTITIS MEDIA	H65-H67	478	38
MASTOIDITIS	H70	25	7
PERICARDITIS	J301	0	1
ENDOCARDITIS	J33	11	3
MYOCARDITIS	J400	1	0

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
GANGRENE	I96	8	1
UPPER RESPIRATORY INFECTION	J00-JO6	1820	182
INFLUENZA	J09-J11	309	11
PNEUMONIA	J12-J18	1124	235
BRONCHITIS	J20	61	5
BRONCHIOLITIS	J21	139	19
UNSPEC LOWER RESPIRATORY INFECTIONS	J22	26	1
PERITONSILLAR ABCESS	J36	4	3
UPPER RESPIRATORY ABCESS	J383, J387, J390	7	1
BRONCHIECTASIS	J470	5	0
LOWER RESPIRATORY ABCESS	J85-J86	35	10
ORAL ABCESS	K046-K047, K122	49	11
APPENDICITIS	K352-K353	43	6
GANGRENOUS HERNIA	K401, K404, K411, K414, K431, K437, K441, K461	0	0
RECTAL ABCESS	K61	87	31
INTESTINAL ABCESS	K630	3	0
PERITONITIS	K65	39	8
RETROPERITONEAL ABCESS	K681	4	0
LIVER ABCESS	K750	14	1
SCALDED SKIN SYNDROME	L00	0	0
IMPETIGO	L01	40	1
CUTANEOUS ABCESS	L02	141	40
CELLULITIS	L03	661	126
LYMPHADENITIS	L04	12	11
PILONIDAL CYST	L050	11	4
OTHER SKING AND SUBCUTANEOUS INFECTIONS	L08	111	6
INFECTIOUS ARTHRITIS	M00-M01	23	1
MYOSITIS	M600	28	11
ABCESS OF TENDON	M650	0	0
SYNOVITIS	M651	0	0
ABCESS OF BURSA	M710	1	0
OTHER BURSITIS	M711	0	0

Table B1

Summary of ICD-10-CM Coding Used to Identify Infectious Complications and Frequencies

Variable	ICD-10-CM Category	Number of ALL Cases	Number of AML Cases
OSTEOMYELITIS	M86	106	14
NEPHRITIS	N10-N12	42	10
CYSTITIS	N390	435	62
SALPINGITIS & OOPHORITIS	N70	0	1
FEVER	R508-R509	8934	1187
SEVER SEPSIS WITH INFECTION	R652	593	199
CENTRAL LINE ACQUIRED BLOOD STREAM INFECTION	T8021	626	165
TRANSFUSION RELATED INFECTION	T8022	1	1
ATYPICAL VIRAL INFECTION	A81	0	0
BACTEREMIA BY LAB	R7881	571	136

Note. Adapted from Practice Management Information Corporation. (2015). *ICD-10-CM: international classification of diseases, 10th revision, clinical modification, sixth edition, color coded, 2016*. Los Angeles, Calif.: PMIC, Practice Management Information Corp.