MALGLYCEMIA AND HEALTH OUTCOMES IN HOSPITALIZED PATIENTS

WITH ACUTE MYELOID LEUKEMIA

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DEDICATION

This dissertation is dedicated to cancer patients, whose demonstration of bravery in the most difficult of situations is my inspiration.

I would also like to recognize the many co-workers and to my Clinical Nurse Specialist colleagues who often, without knowing, provided encouragement through a kind word or action, a smile, or a laugh when needed the most.

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Susan Storey

MALGLYCEMIA AND HEALTH OUTCOMES IN HOSPITALIZED PATIENTS

WITH ACUTE MYELOID LEUKEMIA

Acute Myeloid Leukemia (AML) is the most common hematologic malignancy. Malglycemia is a disorder of glucose metabolism and includes hyperglycemia, hypoglycemia and the combination of hyperglycemia and hypoglycemia. Malglycemia has been shown to occur frequently during hospitalization among critical care patients and has been associated with increased risk of sepsis and mortality. Little is known, however, about the prevalence and role of malglycemia on the health outcomes of AML patients hospitalized for initial induction therapy. Malglycemia may be of particular importance to the patient with AML because, researchers have found that malglycemia may promote cellular changes which facilitate the progression of cancer, alter treatment response, and attenuate immune response.

The purpose of this study was to determine the prevalence of malglycemia (hyperglycemia, hypoglycemia or the combination) and to examine its role on a comprehensive set of health outcomes (neutropenic days, infection, and septicemia, and sepsis, induction hospital length of stay, complete remission and mortality) in AML patients hospitalized for initial induction therapy.

A retrospective cohort study design was used. Records of 103 AML patients, hospitalized for initial induction chemotherapy were reviewed. Results of the study showed that 98% of the AML patients had at least one episode of hyperglycemia, with a prevalence rate of 33% over the entire induction inpatient hospitalization for this population. All patients noted with hyperglycemia also had hypoglycemia and thus, the

prevalence rate of hypoglycemia alone could not be determined. Prevalence of the combination of hyperglycemia and hypoglycemia was 1.4 %. Although not statistically significant, a trend was noted for AML patients with hyperglycemia to experience more days with neutropenia, greater numbers of infection, sepsis, septicemia and death (mortality) than patients without hyperglycemia during induction treatment. Patients with the combination of hyperglycemia and hypoglycemia also experienced an increased risk of developing septicemia (p = .025) and sepsis (p =.057). Future studies with larger sample sizes are needed to confirm these findings.

Findings indicate that malglycemia is common and may have a detrimental impact on outcomes in AML patients. More research is warranted to elucidate clinically significant levels of malglycemia and its impact on health outcomes.

Diane Von Ah, PhD, RN, FAAN, Chair

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LIST OF ABBREVIATIONS

ADA   American Diabetes Association

AML   Acute myeloid leukemia

BMI   Body mass index

BMT   Bone marrow transplant

CBC   Complete blood count

CCI   Charlson Comorbidity Index

CRF   Cytogenetic risk factor

HLOS   Hospital length of stay

ICU   Intensive care unit

NCCI   National Comprehensive Cancer Network

ROS   Reactive oxygen species

WBC   White blood cell

CHAPTER 1. NATURE OF THE STUDY

The following research focuses on malglycemia (hyperglycemia, hypoglycemia, or the combination) and health outcomes in hospitalized patients with Acute myeloid leukemia (AML). The main objective of this study was to examine the prevalence and impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) on the health outcomes of the hospitalized AML patient. Specifically, this study examined the impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) on neutropenic days, infection, septicemia, sepsis, and induction length of stay, overall hospital length of hospital stay, complete remission, and mortality during hospitalization for induction therapy. Findings from this study provide information regarding the prevalence and consequences associated with malglycemia (hyperglycemia, hypoglycemia, or the combination) in the hospitalized patient with AML. Ultimately, this research will be used to support the need for the development of interventions to monitor and control blood glucose, mitigate the untoward consequences associated with malglycemia and improve the quality of life among hospitalized patients with AML.

Significance

It is estimated that the global incidence of new cancer cases will be over 22 million by 2030 (Bray, Jemal, Grey, Ferlay, & Forman, 2012). The current life time risk for developing cancer is 41% (National Cancer Institute, 2012). Cancer is a complex physiologic process that interplays with many body systems. A hematologic cancer, AML, is the most common type of acute leukemia in adults (O'Donnell et al., 2012). It is estimated that approximately 14,000 people are diagnosed and 10,000 die from AML each year in the United States (National Cancer Institute, 2012). The incidence of AML

increases with age (Rodak, Fritsma, & Keohane, 2012) with a median age of diagnosis at 67 years (O'Donnell et al., 2012). A diagnosis of AML is associated with both high acuity and symptom profile and is attributed to the highest number of leukemia-related deaths annually (O'Donnell et al., 2012). The overall survival rate for AML is approximately 30% (Fanning, Sekeres, & Theil, 2009).

An aggressive disease, AML is characterized by the rapid propagation of neoplastic hematopoietic (blood forming) cells and is highly fatal without treatment (Pulte, Gondos, & Brenner, 2010). It presents as an excessive production of blasts (immature blood forming cells) in the myeloid cells such as the white blood cells, red blood cells, or the cells that make platelets, resulting in the crowding of normal blood cells, disruption of normal hematopoiesis, and subsequent failure of the bone marrow (Plass, Oakes, Blum, & Marcucci, 2008). In AML, aberrant cell progression is thought to occur via the inactivation of tumor suppressor cells leading to disproportionately higher rates of cell proliferation than cell death—a process called clonal expansion (Nowak, Michor, & Iwasa, 2006). Clonal expansion occurs in the myeloid blasts located in the peripheral blood, bone marrow, and/or other tissues (O'Donnell et al., 2012).

Treatment for AML is based on age, chromosomal translocation, cytogenetic risk status, and initial response to induction chemotherapy (National Comprehensive Cancer Network [NCCN] Guidelines for AML, 2012). Initial induction chemotherapy may be followed by one to four additional cycles of consolidation chemotherapy and/or stem-cell transplantation (Roboz, 2011). In general, there are three phases of treatment that can be repeated based on response: (a) initial induction chemotherapy, (b) post-remission

consolidation and in some cases stem-cell transplantation (bone marrow transplant [BMT]), and (c) relapse.

The initial induction phase for AML is a crucial time period for the patients. The response to the initial treatment can determine the success or need for subsequent re-induction treatments. Initial induction therapy includes the administration of two cytotoxic chemotherapy agents, cyatarabine (also known as ARA-C) and an anthracycline (either idarubicin or daunorubicin). This standard treatment consists of seven days of continuous intravenous cytarabine infusion during which the anthracylcine is administered over the first 3 days—known as 7+3 (NCCN, 2012; Tefferi & Letendre, 2012). The goal of initial induction chemotherapy in AML is to reduce the leukemic cell population in the body from approximately 10^{12} to below the detectable cytology level of about 10^9 cells and to restore the production of normal blood cells (Lawson, 2013). A bone marrow aspiration after the completion of induction chemotherapy is used to determine if complete remission has occurred. The AML patient continues to receive chemotherapy even if complete remission has been achieved to treat undetected leukemia cells and attempt to thwart relapse (Lawson, 2013).

The severity of side effects associated with the 7+3 depends on the patient's age and comorbidities and the dosage of chemotherapy. Common side effects of treatment include immunosuppression, fatigue, alopecia, and mucositis. Suppression of the bone marrow is the most life-threatening treatment side effect, leaving the patient vulnerable to infection. Bone marrow recovery varies by individual patient characteristics but generally takes 2–3 weeks and is typically required before discharge from the hospital (Texas Oncology, 2014).

During initial induction chemotherapy, medications used in the treatment regimen for AML may also influence malglycemia. Corticosteroids used to potentiate the effects of chemotherapy and to mitigate the emetogenic side effect of chemotherapy can induce hyperglycemia. Additionally, decreases in activity and appetite may influence hypoglycemia and/or the combination (hyperglycemia and hypoglycemia). Therefore, AML patients may be at higher risk for malglycemia (hyperglycemia, hypoglycemia, or combination) as a result of the aggregation of the disease process, treatment, and physical alterations in diet and activity, potentially resulting in detrimental outcomes.

Cancer (AML) and Malglycemia

A complex reciprocal relationship has been observed between cancer, including AML, and malglycemia (hyperglycemia, hypoglycemia, or the combination of hyperglycemia and hypoglycemia). Malglycemia is a disorder of glucose metabolism and includes hyperglycemia (blood glucose $\geq$ 126 mg/dL), hypoglycemia (blood glucose < 70 mg/dL), and/or glycemic variability; defined in this study as the combination of hyperglycemia and hypoglycemia (Hammer et al., 2009; Monnier, Colette, & Owens, 2008; Siegelaar, Holleman, Hoekstra, & DeVries, 2010). Researchers have shown that malglycemia (hyperglycemia, hypoglycemia, or the combination) can detrimentally impact health outcomes in critical care patients (Egi et al., 2008; Egi et al., 2010; Hermanides et al., 2010a; Krinsley, 2003; Krinsley & Glover, 2007). However, few studies have examined the relationship of malglycemia (hyperglycemia, hypoglycemia, or the combination) on outcomes in cancer patients. Therefore, the overarching goal of this study was to focus on three components of malglycemia (hyperglycemia,

hypoglycemia, or the combination) and their impact on health outcomes in hospitalized AML patients.

Overview of Malglycemia and Health Outcomes

Malglycemia (hyperglycemia, hypoglycemia, or combination) may be common among hospitalized patients with or without diabetes. The physiologic and psychological stress of illness, medical treatments, and changes in nutrition and activity can alter the metabolism of glucose resulting in malglycemia. Normoglycemia or acceptable parameters for blood glucose range from 70 mg/dL to125 mg/dL (American Diabetes Association [ADA], 2013). Parameters for hyperglycemia and hypoglycemia also have been established by the ADA. Hyperglycemia is defined as any blood glucose (FBG) $\geq$ 126 mg/dL. Hypoglycemia is defined as blood glucose of $<$ 70 mg/dL (ADA, 2013). Glycemic variability has been measured in various ways including standard deviation mean amplitude of glycemic excursions, mean of daily differences, and average daily risk range. In this study, the combination of hyperglycemic and hypoglycemic fasting blood glucoses served as a proxy measure of glycemic variability.

Hyperglycemia

Hyperglycemia may be prevalent among hospitalized patients. Studies have demonstrated the incidence of hyperglycemia to be approximately 32% of critical and non-critical care hospitalized adult patients (Swanson, Potter, Kongable, & Cook, 2011). Much less is known, however, regarding the prevalence of hyperglycemia in cancer patents. Hammer (2008) reported that 99% of the 1,175 BMT cancer patients had hyperglycemia (blood glucose $\geq$ 126 mg/dL) through day 99 post-transplant. However, BMT cancer patients may not represent all cancer patients because they typically have

aggressive and resistant cancers and undergo more extensive treatment regimens. In AML patients no studies have examined the prevalence of hyperglycemia. Only one study of AML patients, which used different thresholds for hyperglycemia than the ADA definition of ≥ 126 mg/dL, noted 91% of 283 AML patients had at least one blood glucose > 110 mg/dL, and 52% had at least one blood glucose > 150 mg/dL (Ali et al., 2007). This study suggested that hyperglycemia may be a prevalent problem among hospitalized cancer patients including patients with AML, however, more research is needed.

Hyperglycemia also may have a detrimental impact on health outcomes. Clinical research of critically ill patients have demonstrated an association between hyperglycemia and increased incidence of infection and/or sepsis (Benfield, Jensen, & Nordestgaard, 2007), longer hospital length of stay ((HLOS; Krinsley, 2003), and increased morbidity and mortality (Kreutziger, Schlaepfer, Wenzel, & Constantinescu, 2009; Krinsley, 2003; Umpierrez et al., 2002; Van den Berghe et al., 2001). Fewer studies have been conducted in non-critical care patients, but findings suggest that hyperglycemia may be associated with poorer health outcomes. In general medical–surgical patients, hyperglycemia on admission was associated with the deleterious outcomes including increased urinary tract infections, stroke, hemorrhage, infections, ileus, and venous thromboembolism (Carr, 2001; Mraovic et al., 2010), mortality (Kent, Soukup, & Fabian, 2001; Lemkes et al., 2010; Marchant, Viens, Cook, Vail, & Bolognesi, 2009) and longer length of hospital stay (Carr, 2001). In addition, patients with hyperglycemia during hospitalization were found to be more likely to

require a transfer to the intensive care unit (ICU) and less likely to be discharged directly home (Umpierrez et al., 2002).

Among cancer patients, emerging experimental and clinical evidence suggests hyperglycemia may impact health outcomes. Researchers have found that hyperglycemia may impact diagnostic imaging studies, promote cellular changes that facilitate the development and progression of cancers (Barone et al., 2008; Becker, Dossus, & Kaaks, 2009; Duan et al., 2014; Larrson, Mantzoros, & Wolk, 2007; Larsson, Orsini, & Wolk, 2005; Onitilo et al., 2012b; Ryu, Park, & Scherer, 2014), alter response to treatment (Biernacka et al., 2013; Tredan, Galmarini, & Tannock, 2007; Yi-Shing et al., 2013; Zeng, 2010) and/or result in poor health outcomes (infection, mortality, length of hospital stay) in cancer patients (Storey & Von Ah, 2012).

The significance of malglycemia (hyperglycemia, hypoglycemia, or the combination) to outcomes in AML patients is largely unknown and has yet to be fully explored. To date only three studies have been conducted to examine the impact of hyperglycemia on health outcomes in AML patients (Ali et al., 2007; Matias et al., 2014; Storey & Von Ah, 2015). Ali and colleagues (2007) found that hyperglycemia increased the odds of developing infection/sepsis (OR 1.15; $p < .005$), severe sepsis (OR 1.24; $p < .001$), or severe sepsis with respiratory failure (OR 2.04; $p <. 001$) in 283 patients with AML. In Ali and colleagues' study (2007), hyperglycemia also was linked with increases in hospital mortality ($p < .001$). Ali et al. (2007) noted a clear association between even mild levels of hyperglycemia (110 mg/dL–150 mg/dL) and mortality, which remained after adjusting for disease-specific and clinical variables. Matias et al. (2013) noted increased odds for developing a complicated infection (OR 3.97; $p < 0.001$)

and death (*OR* 3.55; *p* < 0.001) when hyperglycemia was present. Storey and Von Ah (2015) found in a pilot study of leukemia patients which included patients with AML, that those patients with hyperglycemia had 1.6 higher odds (*OR* 1.6; *p* < 0.01) of experiencing neutropenia and longer HLOS (2 days versus 15 days; *p* = 0.000) than patients with normoglycemia; however, a relationship between hyperglycemia and documented infection was not noted. Further studies are needed to identify the role of hyperglycemia on health outcomes in this patient population.

Hypoglycemia

Hypoglycemia has been noted to be less common than hyperglycemia in hospitalized patients. The percentage of hospital patients experiencing hypoglycemia is estimated between 5.7% (Swanson et al., 2011) and 10% (Boucai, Southern, & Zonszein, 2011). Among BMT patients, Hammer (2008) noted 16% (189/1175) had at least one episode of hypoglycemia. Few studies among cancer patients, including patients with AML, have examined the prevalence of hypoglycemia.

Although, the occurrence of hypoglycemia is less frequent than hyperglycemia the impact on outcomes also has been shown to be detrimental. Critically ill patients were shown to be 2 (2.1) times (*p* < .001) more likely to die when they experienced hypoglycemia in the ICU (Hermanides et al., 2010b). Bagshaw and colleagues (2009) found hypoglycemia to be associated with death. In fact, patients with hypoglycemia in the ICU (*OR* 1.4; 95% CI [1.31–1.54]) and hospital (*OR* 1.36; CI [1.27–1.46]) were more likely to die than those without hypoglycemia. Gamble, Eurick, Marrie, and Majumdar (2010) noted hospital mortality was higher among patients with admission hypoglycemia when compared to those with normoglycemia ([aHR] 2.96; *p* = .005). In 2,582 diabetic

patients admitted to general medical units, Turchin et al. (2009) found that each additional day with hypoglycemia was associated with an 85.3% increase in the odds ($p = .0003$) of inpatient mortality. These findings suggest that hypoglycemia, though reported less often, also can have a nocuous impact on the health outcomes of hospitalized patients. The impact of hypoglycemia on health outcomes in cancer patients, on the other hand, has not been well studied. Only one study of BMT patients consisting of a variety of cancer diagnoses (chronic myeloid leukemia, AML, acute lymphoblastic leukemia, chronic lymphoblastic leukemia, and non-Hodgins lymphoma) and pre-cancer (myelodysplastic syndrome and aplastic anemia) diagnoses has been conducted to examine the impact of hypoglycemia on health outcomes. Hammer and colleagues (2009) noted an association between hypoglycemia and non-relapse mortality in 1,175 of BMT patients. Specifically, patients with blood glucose of ≤ 89 mg/dL had 2 times higher risk of mortality at 200 days post-BMT (Hammer et al., 2009). Findings from this lone study suggest that hypoglycemia may have a detrimental impact on health outcomes in cancer patients. However, to date no studies have been conducted evaluating the relationship of hypoglycemia on a comprehensive set of health outcomes (neutropenic days, infection, and septicemia, and sepsis, induction HLOS, complete remission, and mortality) in the hospitalized AML patient. Further research is warranted to understand the role of hypoglycemia on health outcomes in AML patients.

Combination of Hyperglycemia and Hypoglycemia

Glycemic variability or fluctuations in high and low blood glucose levels, also can be defined as the combination of hyperglycemia and hypoglycemia. Variations in blood glucose are difficult to measure; a standard statistical measurement has yet to be defined.

In this study, the term *combination*, which includes both episodes of hyperglycemia and hypoglycemia, will be used as proxy for glycemic variability.

The impact of the combination (hyperglycemia and hypoglycemia), a newer phenomenon, has been shown to detrimentally effect the outcomes of critically ill patients. Bagshaw et al. (2009) found critical care patients with glycemic variability had a greater odds of ICU (*OR* 1.5; 95% CI [1.4, 1.6] and hospital (*OR* 1.4; 95% CI [1.3, 1.5]) mortality when compared to patients with hypoglycemia only or those with normoglycemia.

Glycemic variability was studied by two researchers in BMT patients with conflicting results. Fuji et al. (2009) assessed the impact of glycemic variability in BMT patients and infection but no association was noted. However, Hammer et al. (2009) studied glycemic variability in BMT patients and found it to be associated with a 14.5-fold increase in non-relapse mortality. The limited number of studies may be due to the complexity in assessing and collecting measures of glycemic variability.

Overall, malglycemia (hyperglycemia, hypoglycemia, or the combination) may play an important role in impacting health outcomes among hospitalized cancer patients, specifically those with AML. However, there is paucity of research regarding malglycemia (hyperglycemia, hypoglycemia, or the combination) and its impact on health outcomes in the AML patient population. Among AML patients, the impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) has not been well studied. Only two studies have examined the component of hyperglycemia in AML patients. These studies examined the role of hyperglycemia on health outcomes (hospital mortality and sepsis) in AML patients (Ali et al., 2007; Matias et al., 2013). At this time,

no studies among AML patients have included all three components of malglycemia. Because malglycemia (hyperglycemia, hypoglycemia, or the combination) has been associated with poorer outcomes among other patient populations, it is important to determine if malglycemia during hospitalization is associated with poorer health outcomes among this vulnerable population.

Statement of the Problem

Research is needed to determine the prevalence of malglycemia (hyperglycemia, hypoglycemia, or the combination) and its impact on health outcomes of hospitalized AML patients. The frequency with which malglycemia (hyperglycemia, hypoglycemia, or the combination) occurs among patients with hematologic cancers has not been well described. Among cancer patients, studies in BMT patients noted the rate of hyperglycemia to be as high as 93% (Hammer et al., 2009). Despite indications that hyperglycemia is common, there is limited information on the prevalence and impact on health outcomes during induction treatment for patients hospitalized with AML. Researchers have shown a link between malglycemia (hyperglycemia, hypoglycemia, or the combination) and poorer health outcomes in cancer patients (Storey & Von Ah, 2012). However, those studies were limited by focusing solely on hyperglycemia and/or focusing predominately on BMT patients.

Patients with AML may have a high incidence of malglycemia (hyperglycemia, hypoglycemia, or the combination) and as a result may experience poor health outcomes. To date, only three studies have examined the impact of malglycemia on health outcomes in AML patients during hospital admissions. While informative, these studies focused on hyperglycemia and failed identify the important role of all three components of

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malglycemia (hyperglycemia, hypoglycemia, or the combination) on health outcomes in the newly diagnosed AML patient hospitalized for induction treatment—a critical time point in the treatment/survival trajectory for AML patients.

Purpose and Aims of the Study

The purpose of this study was to advance knowledge regarding the prevalence of malglycemia (hyperglycemia, hypoglycemia, or the combination) and evaluate its association with the following health outcomes: neutropenic days, infection, septicemia, and sepsis, HLOS, induction length of stay, complete remission, and mortality in hospitalized AML patients during initial induction chemotherapy. This study will broaden the scope of previous studies and improve understanding of the untoward impact of malglycemia on a comprehensive set of health outcomes in hospitalized AML patients.

Aim 1

Describe the prevalence of malglycemia (hyperglycemia, hypoglycemia, or the combination) among AML patients during hospitalization for induction therapy.

Aim 2

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and neutropenic days controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction therapy.

H2.1.0: There is no association between hyperglycemia and the neutropenic days when controlling for known covariates of age and comorbidities.

H2.2.0: There is no association between hypoglycemia and the neutropenic days when controlling for known covariates of age and comorbidities.

H2.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and the number of neutropenic days controlling for the known covariates of age and comorbidities.

Aim 3

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and infection controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction.

H3.1.0: There is no association between hyperglycemia and infection when controlling for known covariates of age and comorbidities.

H3.2.0: There is no association between hypoglycemia and infection when controlling for known covariates of age and comorbidities.

H3.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and infection when controlling for known covariates of age and comorbidities.

Aim 4

Examine the association(s) between malglycemia (hyperglycemia, hypoglycemia, or the combination) and septicemia controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction.

H4.1.0: There is no association between hyperglycemia and septicemia when controlling for known covariates of age and comorbidities.

H4.2.0: There is no association between hypoglycemia and septicemia when controlling for known covariates of age and comorbidities.

H4.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and septicemia when controlling for known covariates of age and comorbidities.

Aim 5

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and sepsis controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction.

H5.1.0: There is no association between hyperglycemia and sepsis when controlling for known covariates of age and comorbidities.

H5.2.0: There is no association between hypoglycemia and sepsis when controlling for known covariates of age and comorbidities.

H5.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and sepsis when controlling for known covariates of age and comorbidities.

Aim 6

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and HLOS controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction.

H6.1.0: There is no association between hyperglycemia and HLOS when controlling for known covariates of age and comorbidities.

H6.2.0: There is no association between hypoglycemia and HLOS when controlling for known covariates of age and comorbidities.

H6.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and HLOS when controlling for known covariates of age and comorbidities.

Aim 7

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and complete remission controlling for known covariates of age, comorbidities and cytogenetic risk factor (CRF) among AML patients during hospitalization for induction.

H7.1.0: There is no association between hyperglycemia and complete remission when controlling for known covariates of age, comorbidities, and CRF.

H7.2.0: There is no association between hypoglycemia and complete remission when controlling for known covariates of age, comorbidities, and CRF.

H7.3.0: There is no association between the combination of hyperglycemia and hypoglycemia and complete remission when controlling for known covariates of age, comorbidities, and CRF.

Aim 8

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and induction mortality controlling for known covariates of age, comorbidities, and CRF among AML patients during hospitalization for induction.

H8.1.0: There is no association between hyperglycemia and mortality when controlling for known covariates of age, comorbidities, and CRF.

H8.2.0: There is no association between hypoglycemia and mortality when controlling for known covariates of age, comorbidities, and CRF.

H8.2.0: There is no association between the combination of hyperglycemia and hypoglycemia and mortality when controlling for known covariates of age, comorbidities, and CRF.

This is the first study to examine the three components of malglycemia (hyperglycemia, hypoglycemia, or combination) on a comprehensive set of health outcomes in hospitalized patients with AML. Findings from this study provide information regarding the consequences associated with malglycemia (hyperglycemia, hypoglycemia, or the combination) in the hospitalized patient with AML. Ultimately, this research will be used to facilitate the development of interventions to monitor and control blood glucose, mitigate the untoward consequences associated with malglycemia, and improve quality of life among hospitalized patients with AML.

CHAPTER 2. BACKGROUND, REVIEW OF LITERATURE & CONCEPTUAL

FRAMEWORK

The human body has many equally dynamic complex systems embedded within. Malglycemia (hyperglycemia, hypoglycemia, or the combination) and cancer elicit a cascade of reciprocal effects on these systems in the body. See Appendix A for overview of physiologic processes associated with malglycemia, AML and health outcomes. These independent yet reciprocal physiologic processes that occur in malglycemia (hyperglycemia, hypoglycemia, or the combination) and cancer are important to understand, as they may impact toxicities, response to treatment, progression of cancer, survival, and mortality. The purpose of this chapter is to connect the science of malglycemia (hyperglycemia, hypoglycemia, or the combination) research to health outcomes in hospitalized patients with AML. The chapter is divided into four sections including overviews of the following: (a) glucose metabolism and physiologic systems; (b) malglycemia, cancer, and health outcomes; (c) malglycemia, AML, and health outcomes; and (d) conceptual frameworks and the guiding framework for this study. Malglycemia, cancer, and AML are multifarious physiologic processes that involve research from many scientific disciplines; this overview will include information from sources in biology, biochemistry, pathophysiology, endocrinology, immunology, medicine, and nursing.

Part One: Overview of Physiologic Systems

Glucose Metabolism

Maintaining homeostasis in plasma glucose concentrations requires a precise balance between intake, production, and delivery of glucose to cells (Giugliano,

Ceriello, & Esposito, 2008). Glucose is needed for energy and cellular function

(Hammer & Voss, 2012; Martini, Nath, & Bartholomew, 2012) and is transported to the

cell through multiple metabolic pathways (Giugliano et al., 2008). Three primary sources:

intestinal absorption of carbohydrates through digestion, glycogenolysis (conversion of

glycogen stores in the liver to glucose), and gluconeogenesis (formation of new glucose

from glycogen) supply glucose (Gearhart & Parbhoo, 2006; Giugliano et al., 2008;

Martini et al., 2012). Glycogen is the stored form of glucose, an important energy reserve

that is broken down by the liver for mobilization of glucose in times of metabolic need

(Martini et al., 2012; Mizock, 2001). Glyconeogenesis is a complex multi-step process,

whereas glycogenolysis takes place quickly and involves a single enzymatic step (Martini

et al., 2012).

The regulation of glucose is dependent upon hormone release and feedback

mechanisms that include glucagon (hyperglycemic hormone) from the alpha cells, insulin

(hypoglycemic hormone) from beta cells of the pancreas, and hepatic and neural

auto-regulatory mechanisms (Massa, Gagliardino, & Francini, 2011; Mizock, 2001).

Appendix B demonstrates normal glucose metabolism. Glucagon is a hyperglycemic

hormone that accelerates the breakdown of glycogen in the liver and causes the level of

blood glucose to rise within minutes (Giugliano et al., 2008). In addition to glucagon,

catecholamines, cortisol, and growth hormones elevate blood glucose through stimulation

of glycogenolysis, gluconeogenesis, and inhibition of insulin uptake by the cells

(Hammer & Voss, 2012; Martini et al., 2012; Mizock, 2001).

Insulin is a hypoglycemic hormone that enhances cellular uptake of glucose and

synthesis of glycogen by suppressing gluconeogenesis (Hammer & Voss, 2012; Martini

et al., 2012; Mizock, 2001). Insulin increases the permeability of cells to glucose, facilitates the transport of glucose into the cells, and stimulates glycogen formation and causes blood glucose levels to decrease. Insulin binds to insulin receptors on the cell surface and opens the channels for glucose to enter the cells where it is then converted into energy.

Under normal conditions insulin levels fluctuate rapidly to correspond with changes in blood glucose concentrations. Central and peripheral gluco-sensors are important for regulation because they monitor the availability of glucose (Mizock, 2001). In hypoglycemia, counter-regulatory hormones are secreted to elevate blood glucose (Marik & Raghavan, 2004; Mizock, 2001) increasing the rate of impulses among the neurons that stimulate the hypothalamus to increase sympathetic outflow and decrease parasympathetic activity. This elevates blood glucose by promoting glycogenolysis and inhibiting secretion of insulin (Mizock, 2001). In hyperglycemia central receptors in the hypothalamus increase activity that releases the inhibitory sympathetic tone on the pancreas stimulating the release of insulin (Mizock, 2001). Peripheral glucose sensors located in the portal vein, small intestine, and liver decrease the rate of impulses to neurons during times of higher glucose concentrations. These signals are transmitted from the vagus nerve to the medulla, resulting in increased secretion of insulin and hepatic uptake of glucose and inhibition of catecholamines (Mizock, 2001).

Insulin Resistance & Hyperinsulinemia

Insulin is the primary regulator of fat, carbohydrate, and protein metabolism regulating the synthesis of glycogen, inhibiting the synthesis of glucose by the liver, and stimulating the storage and release of fat as well as protein needed for function, repair

and growth of cells (Taubes, 2009). The fundamental role of insulin is to coordinate the use of fuels in the body determining whether they get utilized or stored. Insulin signals information on the availability of fuel from the periphery to the brain and the central nervous system (Taubes, 2009). Under normal conditions when glucose is elevated, insulin stores the excess glucose as fat in tissue or transfers it to muscle. Insulin then conveys a message to the mitochondria of the cell signaling it to use the glucose for energy. As blood glucose drops, insulin mobilizes the fatty acids and signals the mitochondria to utilize those as the energy source instead of glucose (Taubes, 2009; Martini et al., 2012). In addition, insulin has properties that have been shown to reduce inflammation, proinflammatory cytokines, and oxidative stress (Marik & Raghavan, 2004).

When persistent elevations in blood glucose occur, the over-secretion of insulin is no longer able to compensate for combined insulin resistance and high levels of glucose (Kellenberger et al., 2010). Insulin resistance is defined as a decrease in the effective response of tissues to insulin in terms of glucose uptake and inhibition of gluconeogenesis (Becker et al., 2009). Excess body weight and adiposity have been directly linked to this reduction in sensitivity to insulin (Becker et al., 2009). High levels of circulating proinflammatory cytokines Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNFα) sustain insulin resistance and hyperglycemia (Becker et al., 2009). The resistance to insulin causes the pancreas to increase production of insulin resulting in high circulating levels referred to as hyperinsulinemia which, in turn, continues to perpetuate insulin resistance (Shank et al., 2008; Taubes, 2009) and hyperglycemia. Insulin resistance and hyperinsulinemia impair the entry of glucose into cells limiting the

ability of cells to access fuel (Kellenberger et al., 2010) increasing the amount of circulating blood glucose.

Hyperinsulinemia and insulin resistance have been shown to exacerbate inflammation and are considered a major factor contributing to the association between diabetes and cancer (Buysschaert & Sadikot, 2013; Parekh, Lin, Hayes, Albu, & Lu-Yao, 2010; Soop et al., 2002;). Elevated levels of insulin may stimulate cell proliferation and tumorigenesis (production of tumors) by increasing circulating insulin growth factors (Buysschaert & Sadikot, 2013; Onitilo et al., 2012b) that can lead to proliferation of aberrant cells and decreased apoptosis, or controlled cell death (Buysschaert & Sadikot, 2013; Qin, Wang, Tao, & Wang, 2012). Modulation of circulating insulin and glucose levels by anti-diabetic medications appear to play a role in altering cancer risk and is currently being studied (Parekh et al., 2010; Onitilo et al., 2012a).

Hypothalamic-Pituitary-Adrenal Axis

Glucose regulation also occurs via the hypothalamus, which provides high level endocrine control during periods of stress by integrating activities of the nervous and endocrine systems (Martini et al., 2012; Vasa & Molitch, 2001). Through a process of signaling, the hypothalamus synthesizes hormones and transports them to the pituitary gland where they are released into circulation (Kalsbeek et al., 2010; Martini et al., 2012). Corticotropin-releasing hormone is secreted by the hypothalamus, which stimulates the pituitary gland to secrete adrenocorticotropin hormone. As a result, the adrenal glands are stimulated to release the steroid hormones corticosterone and cortisol increasing blood glucose levels (Martini et al., 2012). Glucocorticosteroids are glucose sparing and act by increasing glucose synthesis and glycogen formation in the liver.

Adipose tissue releases fatty acids into circulation and tissues begin to breakdown the fatty acids and proteins for energy utilization rather than glucose (Martini et al., 2012).

Activation of the hypothalamic–pituitary–adrenal axis is an essential component of general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. Physiologic stress such as severe illness challenges the compensatory mechanisms used to maintain homeostasis, resulting in the inability of those systems to continue to adapt. Evidence suggests that patients with and without a diagnosis of hyperglycemia may have poorer outcomes. In fact, Umpierrez et al. (2002) noted in 2,030 hospitalized patients that hyperglycemia was an independent predictor of poor outcomes and that those patients without diabetes who experience malglycemia (hyperglycemia) had significantly higher mortality rates and poorer functional outcomes than patients with the diagnosis of diabetes (Umpierrez et al., 2002).

Oxidative Stress & Cellular Milieu

Mitochondria within the cells are responsible for the production of energy to maintain cell survival and function (Martini et al., 2012). The production of energy is coupled with oxygen consumption then reduced to water with 4% to 5% being converted to reactive oxygen species (ROS) also known as free radicals (Klaunig & Kamendulis, 2004). Byproducts of normal cell metabolism, ROS, and antioxidants modulate ROS and maintain cellular homeostasis (Richards, Wang, & Jelinek, 2007).

Abnormal inflammatory states occur in the presence of malglycemia, causing mitochondrial dysfunction, thus producing more oxygen than required to generate cellular energy. A *superoxide* state occurs in which an over-production of oxidants causes oxidative stress (Giacco & Brownlee, 2010; Wang et al., 2012). Oxidative stress is

defined as an imbalance between production of ROS and the counterbalancing of antioxidants that neutralize and eliminate them (Brinkman et al., 2011; Klaunig & Kamendulis, 2004). Oxidative stress causes interruptions to normal cell metabolism, cell pathway signaling and cell to cell homeostasis (Pitocco et al., 2010; Wang et al., 2012).

Malglycemia (hyperglycemia, hypoglycemia, or the combination) induces oxidative stress in cells (Ceriello et al., 2012; Ceriello & Kilpatrick, 2013; Monnier et al., 2006; Vincent et al., 2005; Wang et al., 2012). When oxidative stress is increased due to malglycemia (hyperglycemia, hypoglycemia, or the combination), cellular responses are initiated that include active cell death, gene activation, and proliferation (Ayra, Pokharia, & Tripathi, 2011; Singh, Jain, & Kaur, 2004), endothelial cell dysfunction, and alteration in important cell signaling cascades (Wang et al., 2012). Additionally, hyperglycemia-induced oxidative stress invokes toxic effects on beta cells by decreasing the level and content of insulin production (Pitocco et al., 2010).

Malglycemia (hyperglycemia, hypoglycemia, or the combination) is a risk factor for the development of cancer and progression of cancer and has been shown to promote a cellular milieu conducive to the promulgation of cancer (Adham et al., 2014; Kellenberger et al., 2010; Li et al., 2012; Onitilo et al., 2012a;). Oxidative stress, which may be precipitated by malglycemia (hyperglycemia, hypoglycemia, or the combination), promotes mechanisms that influence tumor growth such as cell signal transduction, increased DNA damage, and mutations, (Klaunig & Kamendulis, 2004) cellular proliferation (Giacco & Brownlee, 2010; Ziech et al., 2010;) and progression of cells towards cancer development and metastasis (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010; Visconti & Grieco, 2009). Endothelial cell dysfunction caused by oxidative stress

has been associated with increased vascular permeability and subsequent tumor

metastasis (Franses & Edelman, 2011). In addition, persistent oxidative stress can lead to

chronic inflammation activating the immune system which in turn can facilitate cancer

(Calle & Fernandez, 2012; Onitilo et al., 2012b; Reuter et al., 2010).

The Immune System

The immune system is a highly adaptive defense system whose purpose is to

(a) defend against foreign organisms, (b) maintain homeostasis by destroying aged or

damaged cells, and (c) provide surveillance (Goldsby, Kindt, & Osborne, 2000).

Research defined two types of immune response. Innate immunity allows the body to

differentiate between normal self and non-self; it is non-antigen specific with no

immunologic memory. Adaptive immunity is antigen dependent, specific, and has

immunologic memory (Muehlbauer & Schwartzentruber, 2005).

The immune system is impacted by malglycemia (hyperglycemia, hypoglycemia,

or the combination). Animal studies have demonstrated that hyperglycemia for as little as

3 hours can significantly diminish immune function (Kwoun et al., 1997), induce

oxidative stress, and activate the release of cytokines (Ling, Mueller, Smith, & Bistrian,

2003). Malglycemia (hyperglycemia, hypoglycemia, or the combination) has been shown

to attenuate the immune system by triggering prolonged expression of proinflammatory

cytokines impairing immune cell signaling (Dandona, Chaudhuri, & Dhindsa, 2010;

Germenis & Karanikas, 2007). Additionally, hyperglycemia has been noted to impact the

immune system by reducing migration of leukocytes impairing the mechanisms of

phagocytosis and reducing the proliferation of lymphocytes-augmenting vulnerability to

infections (Collier, Dossett, May, & Diaz, 2008; Price & Knight, 2009; Turina, Fry, & Polk, 2005).

Inflammation & Inflammatory Response

The inflammatory process is mediated by a tight network between the immune system, neuroendocrine system, and tumor suppressor network (Fulop et al., 2010). Cytokines regulate the intensity and duration of the immune system response by stimulating or inhibiting activation, proliferation, and/or differentiation of cells, as well as controlling the secretion of antibodies or other cytokines (Goldsby et al., 2000). Cytokines share similar properties with hormones and growth factors, but unlike hormones their action is short-lived (Goldsby et al., 2000). Oxidative stress and the release of proinflammatory cytokines mediate inflammation but also can perpetuate the inflammatory process (Frederico, Morgillo, Tuccillo, Ciardiello, & Loguercio, 2007; Gearhart & Parbhoo, 2006; Leonidou et al., 2007).

The production and release of high levels of proinflammatory cytokines play a significant role in the development and perseveration of malglycemia (hyperglycemia, hypoglycemia, or the combination). Increases in TNFα and IL-6 perpetuate a state of malglycemia (hyperglycemia and hypoglycemia) through the release of the counter-regulatory hormones and modification of insulin signal transduction and reception resulting in insulin resistance (Becker et al., 2009; Dotson, Freeman, Failing, & Adler, 2008; Gearhart & Parbhoo, 2006; Gogitidze et al., 2010; Leonidou et al., 2007). The increased concentration of circulating cytokines disrupts glucose and lipid homeostasis further promoting malglycemia and insulin resistance (Becker et al., 2009) and the continuation of cytokine production (Esposito et al., 2002; Leonidou et al., 2007).

Cells exposed to long durations of inflammation have a greater risk of becoming malignant due to the high secretion of IL-6 and TNFα, which can promote the outgrowth of neoplastic cells (Frederico et al., 2007; Kellenberger et al., 2010). Proinflammatory cytokines, specifically IL-6 and TNFα, have been implicated in the development of cancer (Pothiwala, Jain, &Yaturu, 2009) and also associated with sickness behaviors (depression, fatigue), and lower quality of life in cancer patients (Von Ah, Kang, & Carpenter, 2008). In addition to the development of cancer, inflammation in the tumor milieu modulates responsiveness and resistance to conventional antineoplastic agents (de Visser & Jonkers, 2009; Reuter et al., 2010) and sensitivity to radiation therapy (Reuter et al., 2010).

Malglycemia (hyperglycemia, hypoglycemia, or the combination) and cancer initiate and perpetuate similar pathologic processes and pathways. See Appendix C for shared pathways of malglycemia and AML. Malglycemia (hyperglycemia, hypoglycemia, or the combination), excessive production of insulin, and cancer can lead to decreased immune function, oxidative stress, chronic inflammation, and high levels of circulating proinflammatory cytokines, which are common pathways leading to epigenetic changes, increased tumorigenesis, and cancer promotion. Monitoring for and controlling blood glucose could potentially impede these perpetual nascent pathways and improve response to treatment, symptom profile, and quality of life for cancer patients.

Part Two: Malglycemia, Cancer, and Health Outcomes

Emerging evidence indicates that hyperglycemia in cancer patients may have serious ramifications as it has been shown to affect imaging studies, development of and progression of cancer, increased toxicity, and decreased response to treatment. Rabkin,

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Israel, and Keidar (2010) retrospectively analyzed the ^{18}F-FDG PET/CT results of patients and recorded the presence of diabetes and level of glucose prior to the diagnostic test. Results demonstrated that hyperglycemia at the time of the scan reduced the sensitivity of ^{18}F-FDG PET/CT in detecting malignancy and yielded higher false negative results. In experimental and clinical research, malglycemia (hyperglycemia, hypoglycemia, or the combination) has been associated with increased inflammation (Kellenberger et al., 2010; Wang et al., 2012), proinflammatory cytokine release (Fuji et al., 2007; Mantovani, Allavena, Sica, & Balkwill, 2008), and oxidative stress causing structural changes to the endothelial cells, which increases the likelihood of metastasis (Barone et al., 2008; Becker et al., 2009; Duan et al., 2014). In vitro studies have shown high levels of glucose may aid malignant cells to resist apoptosis (normal programmed cell death) resulting in resistance to chemotherapy (Biernacka et al., 2013; de Visser & Jonkers, 2009; Duan et al., 2014; Tredan et al., 2007; Zeng et al., 2010).

In patients with cancer, malglycemia (hyperglycemia, hypoglycemia, or the combination) has been associated with increased treatment-related complications, poor health outcomes, decreased survival (Derr, Hsiao, & Sauder, 2008; Fuji et al., 2007; Griffith et al., 2011; Matias et al., 2013; Pidala et al., 2011; Villarreal-Garza et al., 2012; Weiser et al., 2004;), and increased mortality (Ali et al., 2007; Fuji et al., 2007, Hammer et al., 2009; Jackson et al., 2012; Matias et al., 2013; Pidala et al., 2011; Soysal et al., 2012).

Storey and Von Ah (2012) conducted the first comprehensive literature review of the impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) on health outcomes in cancer patients. Eleven studies (3,445 cancer patients) were found that

examined at least one indicator of malglycemia (hyperglycemia, hypoglycemia, or glycemic variability) and their impact on at least one of five health outcomes including infection, survival, mortality, toxicity, and length of stay. Since Storey and Von Ahs' (2012) review, the investigator found an additional 10 studies for a total of 21 studies that focus on malglycemia (hyperglycemia, hypoglycemia, or the combination) in cancer (including over 5,000 cancer patients). See Appendix D for literature review and outcome table of findings related to malglycemia and outcomes. The studies ranged over a time span of 9 years from 2004–2014. The majority of those studies (18/21; 86%) focused primarily on one indicator of malglycemia (hyperglycemia) and only two (10%) examined all three indicators of malglycemia—hyperglycemia, hypoglycemia, and glycemic variability (Fuji et al., 2009; Hammer et al., 2009).

The primary outcomes of interest identified from this literature review of malglycemia (hyperglycemia, hypoglycemia, or the combination) and cancer research were infection, survival, mortality, toxicity, and length of stay. Many of the studies looked at multiple outcomes; however, none of the studies included all of the outcomes. While results were mixed, findings suggest that malglycemia (hyperglycemia, hypoglycemia, or the combination) may have a negative impact on outcomes for hospitalized patients with cancer (Storey & Von Ah, 2012). Specifically, increased rates of infection, length of stay, toxicities, and mortality, as well as decreased survival, were reported. The current literature is limited however, in that most 11 of 21 (53%) of the studies in this area focused solely on the BMT population, which patients are considered the most critically ill cancer patients demonstrating a high side-effect profile. Therefore,

results may not generalize to patients with other hematological malignancies such as AML.

Part Three: Malglycemia, AML, and Health Outcomes

Malglycemia, specifically hyperglycemia, may be of particular importance to the patient with AML. Research (Collier et al., 2008; Price & Knight, 2009; Turina et al., 2005) shows that the presence of hyperglycemia exacerbates the blunting of cellular activity decreasing phagocytosis (a function of the neutrophils) and chemotaxsis (cellular movement). Therefore, AML patients with hyperglycemia may be at greater risk for more profound immune-compromise, subsequent infections, longer periods of neutropenia, increased HLOS, and mortality.

Patients with AML are immunocompromised and vulnerable to infections as a result of bone marrow suppression from both the malignancy and the treatment regimens. The bone marrow is suppressed as a result of the rapid clonal expansion of the tumor cells in the bone marrow which contributes to neutrophil dysfunction by crowding out the cells that produce neutrophils. Additionally, chemotherapy agents suppress the bone marrow and damage the stem cells that produce neutrophils. Neutrophils are the first line of defense to the invasion of bacteria. When the bone marrow is suppressed, the number of mature circulating neutrophils are eliminated and are not readily replaced; leading to a condition called neutropenia. Neutropenia is defined as an absolute neutrophil count (ANC) less than 500 cells/mm^2 (Freifeld et al., 2011). Neutropenia may occur in the presence of a normal white blood cell count, which range from 4,000–10,000 cells/mm^2 (Camp-Sorrell, 2005). Therefore, in order to accurately assess the ANC, a complete blood count (CBC) with differential is necessary. Neutropenia leaves the patient vulnerable to

infection/sepsis, which potentially can increase HLOS and mortality. Hyperglycemia in patients with AML may play a contributing role in these adverse outcomes during hospitalization.

These findings suggest that hyperglycemia may impact health outcomes in AML patients. However, research regarding the incidence of malglycemia (hyperglycemia, hypoglycemia, or the combination) and its impact on health outcomes in AML patients is lacking. The limited number of studies on this important topic reveals gaps in knowledge as it relates to the full effects of malglycemia (hyperglycemia, hypoglycemia, or the combination) on the health outcomes of hospitalized AML patients. This study of malglycemia (hyperglycemia, hypoglycemia, or the combination) and outcomes in hospitalized AML patients aligns with the Oncology Nursing Society Research Priorities agenda (LoBiondo-Wood et al., 2014). This study is important because it is the first study to examine the impact of all three indicators of malglycemia (hyperglycemia, hypoglycemia, or the combination) in AML patients on a set of comprehensive health outcomes. Ultimately, this research will facilitate the need for development of interventions to manage blood glucose more effectively and mitigate the adverse consequences of malglycemia (hyperglycemia, hypoglycemia, or the combination), thus improving quality of life for AML patients.

Part Four: Conceptual Frameworks

Theories are constructed to express new ideas or insights or to address unanswered questions about a phenomenon of interest (Walker & Avant, 2005). Smith and Liehr (2008) describe theories as patterns of ideas that represent phenomena in an organized format. Visual depictions of a theory often are used to explain complex

interactions and relationships. Therefore, theory development provides a way to identify and express key ideas that form the foundations for clinical practice.

Analysis of theories includes examining strengths and weaknesses and may determine the need for refinement or additional theory development. Theory analysis is necessary to determine validity and approximation of the concepts to the real world (Walker & Avant, 2005). Walker and Avant (2005) identified six keys steps for theory analysis: (a) identify origins of theory, (b) examine the meaning of the theory, (c) determine logical adequacy, (d) determine usefulness of the theory, (e) provide generalizability and parsimony of the theory, and (f) include testability of the theory. Origins of theory refer to the events that prompted the development of the theory and the evidence to support or refute the theory. The meaning of theory comes by examining the relationships between concepts. Logical adequacy describes the cogent structure of concepts and accuracy with which predictions can be made. Usefulness is determined by how practical and helpful the theory is to the discipline. Generalizability is how widely the theory can be used to explain or predict phenomena. Parsimony explains complex relationships simply and briefly while maintaining its comprehensiveness. Testability implies that hypotheses can be developed from the theory for research and that the theory is supported by strong empirical evidence (Walker & Avant, 2005).

The following section discusses the analysis of three theories related to the phenomena of cancer, malglycemia, and outcomes. The three theories include: the immunologic surveillance theory, the theory of immunoediting, and the malglycemia orbit model. And, finally, the guiding framework for this study, malglycemia and AML outcomes model, will be presented.

The Immunologic Surveillance Theory

In 1909 Paul Ehrlich proposed the concept that the immune system had a protective effect. He posited that aberrant cell production frequently occurred during fetal and post-fetal development, but these cells were recognized as foreign and eliminated or neutralized by the immune system (Baron & Storb, 2006; Dunn, Old, & Schreiber, 2004; Goldsby et al., 2000). In the 1950s McFarlane Burnet and Lewis Thomas introduced and developed the immunologic surveillance theory. Burnett's conceptualization was based on the tolerance of the immune system. He proposed that tumor-specific neo-antigens recognized the early malignant transformation of cells and elicited an adaptive immune reaction to eliminate them (Dunn et al., 2004). Alternatively, Thomas speculated that organisms that had lived for a long time must have had an inherent ability to protect themselves from neoplastic disease. This theory suggested the primary functions of the immune system are to provide continual surveillance, locate and eliminate nascent malignant cells, and regulate the homeostasis of multiple organ systems (Dunn, Bruce, Ikeda, Old, & Schreiber, 2002; Ichim, 2005).

Initial attempts to validate the theory lead to conflicting results, and the theory was abandoned. Several decades later, improved technology in mouse tumor models with determined molecular immunodeficiencies made it possible to validate the existence of the theory and to expand it to include the contributions of both the innate and adaptive immunity (Dunn et al., 2004). It became apparent to scientists that components of the immune system mediated the actions of effector cells and tumor suppressive pathways to confront and destroy spontaneous mutations, thus controlling the development of malignant tumors (Dunn et al., 2002; Germenis & Karanikas, 2007).

The logical hypothesis from this theory is that immunodeficient or immunocompromised individuals have a higher likelihood of developing cancer. Studies conducted in both mice and humans have provided strong evidence to support both the existence and the physiologic relevance of this hypothesis (Dunn et al., 2002). A limitation of this theory, however, is its inability to address the occurrence of cancer in individuals who are immunocompetent.

Theory of Immunoediting

The immunologic surveillance theory was later refined, expanded, and renamed the theory of immunoediting to reflect the belief that the immune system plays a dual role in the complex interplay between tumor development and progression (Dunn et al., 2002; Dunn et al., 2004; Schreiber, 2005). The theory of immunoediting suggests the immune system not only has a protective role against the development of cancer but conversely also can facilitate tumor development by selecting for tumor cell types with reduced immumogenicity (Schreiber, 2005). This explains how malignant tumors have the ability to survive in an immunocompetent host (Dunn et al., 2004).

The immunoediting process of cancer consists of three phases, known as the three E's of cancer immunoediting, which are elimination, equilibrium, and escape (Dunn et al., 2004). This theory addresses the progression towards carcinogenesis via three steps. The first step is elimination, which represents the immune system effectively surveying and destroying rapidly transforming cells. If the developing tumor is eliminated, the process stops and there is no progression to the other two phases (Dunn et al., 2004). The rejection of the tumor requires responses from both the innate and adaptive immune systems.

The equilibrium phase is the longest of the three phases occurring over a period of many years (Dunn et al., 2004). In this phase the tumor cells that survived the elimination phase begin to abound because of their ability to avert attacks from the immune system and in some cases prevent the initiation of an immune response (Dunn et al., 2004; Germenis & Karanikas, 2007). In this phase the equilibrium between immune surveillance and development of cancer is more inclined towards the latter.

The third phase is the escape phase in which the immune system is unable to contain or control the proliferation of the rapidly transforming mutated tumor cells resulting in clinical manifestations of cancer (Dunn et al., 2004; Germenis & Karanikas, 2007). Genetic and epigenetic changes in the tumor cells provide a safe harbor and facilitate immunoevasive strategies promoting growth and resistance to detection and/or elimination by the immune system (Dunn et al., 2004).

According to Schreiber (2005), the most compelling implication of the theory of immunoediting is that most malignant tumors that develop in immunocompetent hosts have undergone immunological sculpting. Immunosculpting consists of the tumor's ability to induce immune tolerance, suppression, and increased pathogenic behavior via cell signaling, rendering control to aberrant and malignant cells by impairing the innate immunoediting process (Reiman, Kmieciak, Manjili, & Knutson, 2008). This theory also is supported by evidence from studies conducted in both mouse and human models (Dunn et al., 2002). The theory is limited because although it specifically addresses the development and progression of cancer, it fails to address the interaction of cancer pathology with other complex physiologic systems.

The Malglycemia Orbit Model

The malglycemia orbit model is a newly introduced model and the first to combine malglycemia, cancer, and outcomes (Hammer & Voss, 2012). This model depicts the non-linear and reciprocal interactions among malglycemia and cancer. The visual structure of the model resembles an atom with a nucleus and three surrounding orbits that are analogous to the electron circulating around the core of an atom (Hammer & Voss, 2012). The core of the model represents the underlying genetic predisposition to cancer and malglycemia. Additional circles around the core include the influencing factors of environment, lifestyle, and comorbidities. The three orbits of the model are paired as: cancer and treatment, impaired immune function and infection, and malglycemia and normal blood glucose. The model represents the constant motion and interaction of the core within the orbits. The model is surrounded by two outcomes: survival and death (Hammer & Voss, 2012).

The malglycemia orbit model describes and depicts the interaction between the predisposition and risk factors and the physiologic processes and outcomes associated with malglycemia. Malglycemia and the resulting cellular changes that influence the formation of and progression of malignancy via cell signaling pathways are discussed. This model is unique in that it includes malglycemia (defined by Hammer & Voss, 2012, as hyperglycemia, hypoglycemia, and glycemic variability), cancer and the associated physiologic processes describing the mechanisms through which they interact with and exacerbate the actions of one another.

A limitation of this model is that it only acknowledges the outcomes of survival and death. Infection is linked to the immune system in the model; however, the impact of

immunosuppression has other untoward effects that were not addressed in the model and include progression of disease, length of bone marrow suppression, and the effect on white and red blood cells. Another limitation is that the model has yet to be empirically tested.

Guiding Framework

The following section provides an overview of the guiding framework of the study. First, the empirical literature that supports the guiding framework will be discussed. Second, an overview of the framework, along with independent and dependent variables and their relationship to one another will be explained. Finally, the framework for this study, malglycemia and AAML outcomes model, will be displayed.

Malglycemia (hyperglycemia, hypoglycemia, or the combination) increases concentrations of circulating proinflammatory cytokines (IL-6, TNFα) that causes insulin resistance and further perpetuates malglycemia (Dotson et al., 2008; Esposito et al., 2002). Malglycemia disrupts the compensatory cellular processes that maintain homeostasis (Kellenberger et al., 2010; Wang et al., 2012). Malglycemia (hyperglycemia, hypoglycemia, or the combination) may be indicative of the patient's overall illness, inflammatory and immune states, or a side effect of treatment, all of which may contribute to adverse outcomes (Dossett et al., 2008).

The etiology of malglycemia (hyperglycemia, hypoglycemia, or the combination) in hospitalized patients is complex and multi-factorial. Pre-existing comorbidities such as diabetes mellitus, pancreatitis, obesity, and age increase the risk for malglycemia (hyperglycemia, hypoglycemia, or the combination) among hospitalized patients (Gearhart & Parbhoo, 2006; Turina et al., 2005). The onset of malglycemia

(hyperglycemia, hypoglycemia, or the combination) in the non-diabetic patient may be a result of increased stress hormone release, peripheral insulin resistance, administration of steroids, TPN (Butler, Btaiche, & Alaniz, 2005; Gearhart & Parbhoo, 2006; Turina et al., 2005), chemotherapy, or immunosuppressive agents. Malglycemia (hyperglycemia, hypoglycemia, or the combination) during hospitalization regardless of the etiology may be a significant predictor of poor outcomes and, conversely, outcomes have been shown to improve when blood glucose is managed (Clement et al., 2004).

Resolution of malglycemia (hyperglycemia, hypoglycemia, or the combination) has been shown to be associated with reduction of oxidative stress, inflammation, and proinflammatory response (Stentz, Umpierrez, Cuervo, & Kitabchi, 2004; Wang et al., 2012). Maintaining normoglycemia during hospitalization of patients with AML may be important to improve response to treatment and decrease the adverse side effect profile that is associated with malglycemia.

Outcomes

The deleterious physiologic processes associated with malglycemia (hyperglycemia, hypoglycemia, or the combination) may contribute to poor health outcomes. Malglycemia (hyperglycemia, hypoglycemia, or the combination) during hospitalization is a significant predictor of poor outcomes (Egi et al., 2006; Egi et al., 2008; Egi et al., 2010; Finfer et al; 2012; Gamble et al., 2010; Hermanides et al., 2010a; Villarreal-Garza et al., 2012). Despite all the available literature among other patient populations, there is limited information on the short- and long-term impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) on outcomes in the

cancer patient (Richardson & Pollack, 2005) specifically as it relates to hospitalized AML patients.

Number of neutropenic days. Neutropenia, defined as an ANC of < 500 cells/mm^2, occurs when there is a significant decrease in neutrophils within the bone marrow (Freifeld et al., 2011). The ANC is indicative of the degree of bone marrow suppression, and the longer the duration of neutropenia, the greater the risk for infection (Freifeld et al., 2011; Schwartzberg, 2006). Patients with AML with profound neutropenia lasting more than 7 days were found to be more susceptible to infection than those with shorter durations (Freifeld et al., 2011; Giamarellou & Antoniadou, 2001; Klastersky et al., 2000). Initial induction chemotherapy for AML causes profound suppression of the bone marrow and recovery can take 2–3 weeks, thus placing the patient at a profound risk for the development of infection.

Malglycemia (hyperglycemia, hypoglycemia, or the combination) increases the level of pro-inflammatory cytokines resulting in an increase in circulating cytokines, thus perpetuating the state of malglycemia (Benfield et al., 2007; Dotson et al., 2008; Fuji et al., 2009). The increase in pro-inflammatory cytokines impairs the immune system by stunting the function of neutrophils and other immune cellular responses (Butler et al., 2005). The intracellular signaling mechanisms of neutrophils are affected by glucose as their phagocytic activity has been shown (in vivo) to be inhibited in the presence of elevated glucose (Saiepour, Sehlin, & Oldenborg, 2003). Similarly, in an in vivo study, researchers noted when metabolic control of blood glucose was obtained, the functions of neutrophils (chemotaxsis, adherence, phagocytosis, and bactericidy) were improved (Walrand, Guillet, Boirie, & Vasson, 2004).

Storey and Von Ah (2015) noted a statistically significant increase in neutropenic days among patients with various types of leukemia (chronic lymphoblastic leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, acute promyelocytic leukemia, AML) who experienced hyperglycemia versus those who were normoglycemic (no episodes of hyperglycemia). Conversely, Karnchanasorn, Malamug, Jin, Karanes, and Chin (2012) failed to demonstrate a relationship between hyperglycemia and the number of neutropenic days among cancer patients undergoing BMT. Overall, the effect of malglycemia (hyperglycemia, hypoglycemia, or the combination) on the neutropenia of patients with AML is largely unknown. This is an important area for further exploration as malglycemia could potentially lengthen the time of bone marrow suppression increasing the likelihood of infection during that patient's most vulnerable time.

Infection. It is estimated that clinically documented infections occur in approximately 20%–30% of neutropenic patients and are usually manifested as a fever (Freifeld et al., 2011). Infection is the most common cause of death in AML patients (Thomas, 2010). The most common sites of infection include the gastrointestinal, urinary, and respiratory tracts, skin (Freifeld et al., 2011), blood stream, and oral cavity (Lech-Miranda et al., 2010). Bacteremia is the most common source of infection occurring in patients with prolonged neutropenia (Freifeld et al., 2011; Yoo et al., 2005). Less common are fungal infections, which are more likely to occur when neutropenia lasts more than 7 days (Freifeld et al., 2011). Infections from molds are rare; however, they are typically life-threatening and occur in cancer patients when neutropenia extends more than 2 weeks (Freifeld et al., 2011).

Malglycemia (hyperglycemia, hypoglycemia, or the combination) may play a role in infectious processes, as it has a direct impact on immunity. In particular hyperglycemia suppresses immune function and normoglycemia enhances immune surveillance (Brunello, Kapoor, & Extermann, 2010). Hypoglycemia has been shown to stimulate the release of proinflammatory cytokines contributing to an inflammatory cellular milieu (Dotson et al., 2008). Cellular inflammation and alterations in immune function can increase susceptibility to infections. An immune-compromised state in conjunction with malglycemia can increase the patient's vulnerability to infection (Germenis & Karanikas, 2007). The majority of studies in cancer patients have focused on the relationship between hyperglycemia and infection. Soysal et al. (2012) found a higher incidence of gram negative and fungal growth among neutropenic non-diabetic cancer patients with hyperglycemia when compared to those with normoglycemia. However, studies have found mixed results. The majority of studies (10/16) in patients with cancer noted a significant increase in infection as blood glucose increased (Ali et al., 2007; Derr et al., 2008; Fuji et al., 2009; Hammer et al., 2009; Jackson et al., 2012; Matias et al., 2013; Rentschler et al., 2010; Sheean et al., 2006; Soysal et al., 2012; Weiser et al., 2004); however, six other studies did not report a relationship (Derr et al., 2009; Fuji et al., 2007; Garg et al., 2007; Griffith et al., 2011; Hardy et al., 2010; Karnchanasorn et al., 2012).

Few studies have studied the relationship of all three indicators of malglycemia in cancer patients. Hammer et al. (2009) found that each component of malglycemia (hyperglycemia, hypoglycemia, or glycemic variability) was positively associated with an

increase in infection among BMT patients. More research, however, is warranted to evaluate the impact of malglycemia on the risk of infection in AML patients.

Septicemia. Septicemia is defined as the systemic disease associated with the presence and persistence of pathogenic organisms or their toxins in the blood (ICD-9 data.com, 2013). Matias et al. (2013) noted a 4-fold increased risk of developing a complicated infection (positive blood cultures) among 280 patients with acute leukemia who experienced hyperglycemia during induction therapy.

Sepsis. Sepsis is defined as acute organ dysfunction, sepsis with multiple organ dysfunction, and severe sepsis (ICD-9 data.com, 2013). Ali et al. (2007) studied the association of hyperglycemia and sepsis in 283 patients with AML and found the odds of developing severe sepsis and severe sepsis with respiratory failure were increased with hyperglycemia.

HLOS. In this study, HLOS included the number of days a patient is hospitalized from admission for initial induction therapy to re-induction therapy or discharge from hospital. Longer HLOS was found to be associated with malglycemia (hyperglycemia, hypoglycemia, or the combination) among non-diabetic BMT patients who experienced malglycemia due to receiving medications (glucocorticosteroids) that affect blood glucose levels (Garg et al., 2007). In non-diabetic BMT patients, longer HLOS also was noted when blood glucose was ≥ 150 mg/dL (Karnchanasorn et al., 2012). Additionally, Storey and Von Ahs' (2015) pilot study demonstrated a statistically significant increase in HLOS among a non-transplant heterogeneous sample of leukemia patients with hyperglycemia when compared to those without hyperglycemia. Conversely, two other studies found no relationship between hyperglycemia and HLOS in BMT patients (Derr

et al., 2008; Rentschler et al., 2010). In a heterogeneous sample of cancer patients admitted for neutropenic fever, hyperglycemia was not shown to increase HLOS (Soysal et al., 2012).

Complete remission. With current treatment regimens, it is estimated the majority (70%–80%) of patients younger than 60 years of age will achieve complete remission (Fernandez et al., 2009; Mandelli et al., 2009); however, the majority of patients will relapse and thus, overall 5-year survival is only 40%–45% (Roboz, 2011; Rowe, 2009). In those patients less than 60 years of age who have a good performance status (general well-being and ability to conduct activities of daily living), 40% to 60% can achieve complete remission (Rowe, 2009); however, the overall cure rate is 10%, with a median survival of less than one year (Buchner et al., 2009; Burnett et al., 2010). Weiser et al. (2004) studied 278 patients with acute lymphocytic leukemia with and without hyperglycemia and found those with hyperglycemia had shorter duration of complete remission than those with normoglycemia. The impact of malglycemia (hyperglycemia, hypoglycemia, or combination) may be an influential factor in the achievement of complete remission. Further research is needed to understand the role malglycemia may play in the achievement of complete remission in AML patients.

Mortality. Seven studies in cancer patients found mortality was higher among those with hyperglycemia (Ali et al., 2007; Fuji et al., 2007; Hammer et al., 2009; Jackson et al., 2012; Matias et al., 2013; Pidala et al., 2011; Soysal et al., 2012). Conversely, two studies did not find a relationship between hyperglycemia and mortality in cancer patients (Derr et al., 2008; Fuji et al., 2009). To date only two studies in patients receiving conventional treatment for AML have examined the role of hyperglycemia on

mortality (Ali et al., 2007; Matias et al., 2013). Both of these studies noted an increase in mortality in patients with hyperglycemia (Ali et al., 2007; Matias et al., 2013). Ali et al. (2007) found mortality to be associated with even mild elevations of blood glucose levels (110–150 mg/dL) in 283 AML patients. Matias et al. (2013) noted among patients with two different types of leukemia those with hyperglycemia had a 3.5-fold increase in likelihood of death than those normoglycemia. Thus, based on this data, researchers suggest that malglycemia may portend a higher risk for mortality in hospitalized AML patients and that attention to it early in the hospitalization may mitigate adverse outcomes.

Covariates

Age. Age is a risk factor for both malglycemia (Hammer et al., 2010) and AML (Rodak et al., 2012). The median age of onset of a diagnosis of AML is 67 years (O'Donnell et al., 2012). Older adults with a cancer diagnosis are at increased risk of malglycemia (Hammer et al., 2010). A lifetime of cellular exposure to assaults from high levels of ROS creates a milieu that facilitates the development of malglycemia, diabetes (Onitilo et al., 2012b), and cancer (Fulop et al., 2010). Additionally, low-grade inflammation that occurs with aging causes cellular alterations in the immune system decreasing its ability to conduct immune surveillance and immunoediting activities (Fulop et al., 2010), thus, increasing susceptibility to infection. In addition, older individuals often do not tolerate aggressive therapies due to poor performance status, comorbid disease processes, decreased clearance of chemotherapy, and poor tolerance to systemic bacterial and fungal infections (Klepin & Balducci, 2009).

Comorbidities. In general cancer patients with comorbidities (other concurrent disease conditions) are at a greater risk for complications, often times necessitating modifications in treatments (Hammer & Voss, 2012). In addition to these challenges, comorbidities may affect outcomes of treatment (Estey, 2010; Etienne et al., 2007; Payandeh, Aeinfar, & Aeinfar, 2012). Etienne et al. (2007) found comorbidities to be an independent predictor of complete remission, and suggest patients, particularly elderly, should be evaluated for comorbidities prior to the initiation of treatment.

CRF. A genetically heterogeneous disorder, AML disrupts the normal functions (self-renewal, proliferation, and differentiation) of the hematopoietic progenitor cells of the bone marrow (Dohner & Gaidzik, 2011). In patients with AML, cytogenetics is used to identify chromosomal aberrations and classify the type. The CRF category is assigned based on the abnormality present. Appendix E is the NCCN guidelines for risk status based on validated cytogenetics and molecular abnormalities. A rating of better-risk, intermediate-risk, or poor- risk informs the treatment regimen and is indicative of response to treatment and overall prognosis (Estey, 2010; NCCN, 2012; Roboz, 2011). Older patients diagnosed with AML frequently present with aggressive disease that includes multiple genetic abnormalities (Etienne et al., 2007; Payandeh et al., 2012; Wilson et al., 2006) that can alter response to treatment (Fernandez et al., 2009; Wilson et al.) and result in poorer outcomes (Etienne et al., 2007; Wilson et al., 2006) including death.

The Malglycemia and AML Outcomes Model

The malglycemia and AML outcomes model was the guiding framework for this study (see Figure 1). The model visually and conceptually postulates relationships

between malglycemia (hyperglycemia, hypoglycemia, or the combination) and health outcomes including: number of neutropenic days, infection, septicemia, sepsis, and induction HLOS, complete remission and mortality in hospitalized patients with AML, and the confounding variables which influence mortality. Malglycemia (hyperglycemia, hypoglycemia, or the combination) and outcomes during the period of initial induction therapy for AML were of prime interest for this research.

An independent variable is defined as the variable that influences the dependent variable (Polit & Beck, 2008). In this model malglycemia is the independent variable. The dependent variable is defined as the variable that is dependent on or caused by the independent variable (Polit & Beck, 2008). The dependent variables for this framework are the health outcomes of interest including: number of neutropenic days, infection, and septicemia, and sepsis, length of hospital stay, complete remission, and mortality. Confounding variables are defined as an extraneous variable(s) that obscure the relationship between the primary variables of the study, requiring statistical control (Polit & Beck, 2008). In this framework the confounding variables were factors known to impact health outcomes and included age, comorbidities, and CRF.

The arrows from the independent variables of malglycemia (hyperglycemia, hypoglycemia, or combination) towards the outcomes (dependent variables) propose that malglycemia has a relationship to health outcomes including: number of neutropenic days, infection, septicemia, sepsis, and induction length of stay, HLOS, complete remission, and mortality. In addition to malglycemia, the confounding variables of age, cytogenetic risk, and comorbidities also may exert influence on the dependent outcome variables. The arrows demonstrate this relationship between the confounding variables

and dependent outcome variables. Age and comorbidities are drawn to show the suggested influence over all eight of the dependent outcome variables (neutropenic days, infection, septicemia, sepsis, induction length of stay, HLOS) whereas CRF is depicted as having potential influence specifically on two dependent outcome variables (complete remission and mortality).

The bi-directional arrows between the independent and dependent variables are indicative of a reciprocal relationship. The dependent outcome variables may stimulate a physiologic response within the body that would in turn cause malglycemia. For instance, infection, septicemia, and/or sepsis have been shown to increase the pro-inflammatory cytokine and oxidative stress response that could facilitate the onset of malglycemia. These relationships have yet to be fully investigated. See Appendix F for full size malglycemia and AML outcomes.

Independent Variable Malglycemia

Dependent Variables

Hyperglycemia
or
Hypoglycemia
or
Combination

Neutropenic days
Infection
Septicemia
Sepsis
Induction/Hospital
length of stay

Complete remission
Mortality

Confounding Variables

Age
Comorbidities

Cytogenetic risk factor
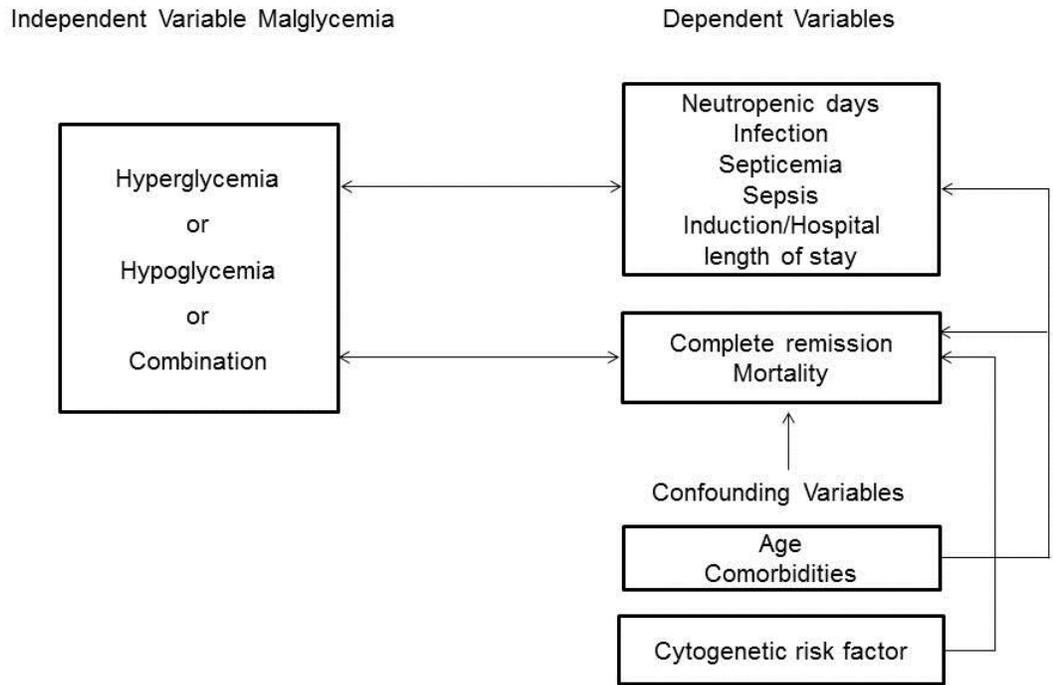
Figure 1. Guiding framework for this study: The malglycemia and AML outcomes model. Copyright 2014 Susan Storey. Used with permission.

CHAPTER 3. METHOD

Study Design

A retrospective cohort study design was used to determine the incidence and prevalence of malglycemia and to examine the relationship between malglycemia (hyperglycemia, hypoglycemia, or the combination) on health outcomes including neutropenic days, infection, septicemia, sepsis, and induction length of stay, HLOS, complete remission, and hospital mortality.

Sample Criteria

The researcher acquired and reviewed hospital pharmacy reports from January 1, 2006—April 30, 2014, to identify subjects receiving the induction 7+3 chemotherapy regimen. The investigator compared selected reports with tumor registry data for patients with the initial diagnosis of AML during the described time period and confirmed through pathology reports and physician documentation in the hospital discharge summary. The investigator reviewed the electronic health records of 150 study subjects to determine if the treatment received was initial induction therapy for AML versus re-induction or consolidation therapy. Of those reviewed, 103 subjects met the inclusion criteria. See Figure 2 for rationale for exclusion from study.
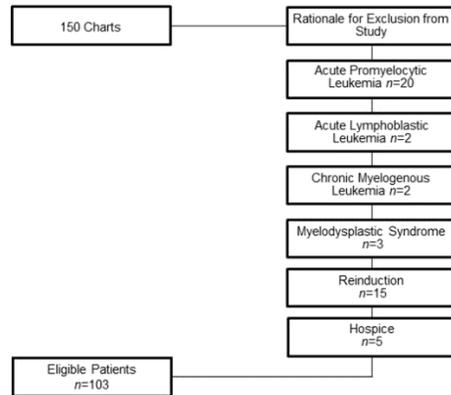
Figure 2. Rationale for exclusion from study.

Inclusion/Exclusion Criteria

Patients admitted to a large multi-site urban hospital system in the Midwest United States who met the following inclusion criteria were considered eligible for the study:

- Diagnosed with AML

- Received 7+3 chemotherapy regimen (cytarabine for 7 days and idarubicin or daunorubicin for 3 days) for initial induction between January 1, 2006, and April 30, 2014

- 18 years of age or older

- Presence of serum fasting blood glucose test results during hospital admission

Patients with diagnosis of other types of leukemia such as acute promyelocytic leukemia, acute lymphoblastic leukemia, and chronic myelogenous leukemia were excluded from the study, as were those with myelodysplastic anemia, a precursor to AML. Patients with AML receiving re-induction therapy or foregoing treatment for hospice also were excluded from the study.

Sample Size

Sample size is an important consideration in study planning and necessary for the reduction in risk of a Type I error. Sample size was based on a minimum number of 10 participants per predictor variable (Field, 2013; VanVoorhis & Morgan, 2007). For this study, the largest number of predictor variables was 6 and thus, the researcher adhered to this guideline by having 103 subjects.

Protection of Human Subjects

The study protocol was approved by the Institutional Review Boards at Indiana University–Purdue University Indianapolis and St. Vincent Hospital, Indianapolis,

Indiana (see Appendix I). The principal investigator and research staff completed the Collaborative Institutional Training Initiative for research ethics in compliance with both Review Boards.

Data Collection

The study investigator collected demographic and medical information to describe the sample. Demographic information extracted from the electronic health record included age, gender, and ethnicity. Medical information to describe the sample included height, weight, CRF, diagnosis of Diabetes Mellitus (no or yes), and comorbidities. Body mass index (BMI) was calculated using the following formula: weight in pounds multiplied by 703/height in inches^2 (Adult BMI Calculator: English, n.d.). The World Health Organization (2013) has five classifications of BMI including: (a) normal (18.5–24.99 kg/m^2); (b) underweight (< 18.5 kg/m^2); (c) overweight (≥ 25 kg/m^2); (d) pre obese (25.00–29.99 kg/m^2); and (e) obese (> 30 kg/m^2).

Independent Variable: Malglycemia

To determine the prevalence of hyperglycemia, hypoglycemia, or the combination, all serum fasting blood glucose values analyzed in the hospital central laboratory were extracted from the medical record from date of induction chemotherapy up to date of re-induction, discharge from the hospital, or death. Hyperglycemia was defined as one or more instances of fasting blood glucose ≥ 126 mg/dL. Hypoglycemia was defined as one or more incidences of fasting blood glucose < 70 mg/dL (ADA, 2013). Combination of hyperglycemia and hypoglycemia were recorded if the study subject had one or more incidence < 70 mg/dL and ≥ 126 mg/dL. Prevalence of hyperglycemia, as noted in previous studies, was determined by identifying the number

of glucose measurements ≥ 126 mg/dL divided by the total number of glucose values (Garg et al., 2007; Hardy et al., 2010). Similarly, prevalence of hypoglycemia was determined by identifying the number of glucose measurements < 70 mg/dL divided by the total of glucose values during the induction period. Prevalence of those with combination was determined by the number of glucose measurements < 70 mg/dL and the number ≥ 126 mg/dL divided by the total number of glucose measurements.

Serum blood glucose testing was conducted in the hospital's central laboratory (by an outside laboratory) on the automated chemistry analyzer, the Beckham Coulter Synchron LX- 20 (Fullerton, California). All laboratory values were analyzed on central laboratory instrumentation that meets the standards required by College of American Pathologists. Daily quality controls were conducted to ensure accuracy of results.

Outcomes

Health outcomes (neutropenic days, infection, septicemia, sepsis, HLOS, complete remission, and mortality) were evaluated from the day of hospital admission for induction therapy to date of re-induction, discharge, or hospital death. The investigator obtained laboratory results from the electronic medical record to assess the outcomes.

Neutropenic Days

Neutorpenic days was recorded as a continuous variable. The number of neutropenic days was defined as the number of days the ANC was < 500 cells/mm^2 from date of initiation of induction chemotherapy to re-induction chemotherapy, discharge from the hospital, or death. An ANC of < 500 cells/mm^2 is clinically considered neutropenia and precautions are set in place to protect the patient from infection. Currently ANC is measured by laboratory serum testing and is automatically reported as ANC on the

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laboratory results page, negating the need for the manual calculation. The following formula determines ANC:

1.   Obtain the CBC with white blood cell (WBC) differential

2.   Add neutrophils segs and bands

3.   Convert sum from (#2) to a percentage

4.   Multiply total by WBC

For example, if WBC = 2000, segs = 10, bands = 5. Segs + bands = 15 or .15. 2000 x .15 = 300 ANC.

In order to determine the ANC, a CBC with differential is required. The CBCs with differential testing were conducted in the hospital's central laboratory (by an outside laboratory) on the automated analyzer, ADVIA 2120i (Siemens Healthcare, USA). All laboratory values were analyzed on central laboratory instrumentation that met the standards required by College of American Pathologists. Quality control is conducted on a daily basis to verify the accuracy of the CBCs. Patients who were neutropenic upon re-induction, discharge from the hospital, or died were censored from the analysis. Patients were value censored if they did not reach the event, which in this case is the return of the ANC to above the threshold of neutropenia, which is indicative of bone marrow recovery.

Infection

The presence of infection was collected as a dichotomous variable (no/yes) and was extracted from the electronic health record from physician documentation via review of the hospital discharge summaries.

Septicemia

The presence of septicemia was collected as a dichotomous variable (no/yes). The presence of septicemia was determined by physician documentation, review of laboratory data, and hospital discharge summaries for the induction time period.

Sepsis

The presence of sepsis was collected as a dichotomous variable (no/yes). The presence of sepsis was determined by physician documentation and review of hospital discharge summaries for the induction time period.

HLOS

The data for HLOS was recorded as a continuous variable and was measured as the number of days from the date of admission for induction therapy to date of re-induction or discharge from the hospital. Patients who died were value censored from the analysis. The rationale for censoring is because these patients did not reach the event that was either date of re-induction or discharge from the hospital.

Complete Remission

The presence of complete remission was collected as a dichotomous variable (no/yes). Data to determine remission status was extracted from physician documentation and/or pathology results of the bone marrow aspirate post-initial induction therapy. Complete remission was defined per the criteria established by the International Working Group (Dohner et al., 2010). These criteria include any of the following:

- Values for ANC (> 1000 /microL) are normal and normal hematopoiesis is restored.

- A bone marrow biopsy reveals no clusters or collections of blast cells; a bone marrow aspiration reveals normal maturation of all cellular components.

- Less than 5% blast cells are present in the bone marrow.

- A previously detected clonal cytogenetic abnormality is absent.

Mortality

Mortality was defined as death during hospitalization for induction chemotherapy and recorded as a dichotomous variable (no/yes).

Covariates

Age

Patient age was extracted from the medical record and entered into the electronic database.

Comorbidities

Comorbidities or co-occurring diagnoses were determined by reviewing admission health and physical forms and discharge summaries. Comorbidities were documented using a comorbidity index called the Charlson Comorbidity Index (CCI; n.d.; Charlson, Pompei, Ales, & Mackenzie, 1987; see Appendix G;). The CCI contains 16 categories of comorbidities assigned weights of 1, 2, 3, or 6; from this weighted score the adjusted risk of one-year mortality is determined. The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality; the higher the score, the more severe the burden of comorbidity (Charlson et al., 1987). The researchers used online CCI calculators to determine the CCI score for all study subjects

and recorded on the data collection tool. The applicability of the CCI has been tested and modified since its development and has continued to demonstrate that it is a reliable measure (Ali et al., 2007; Bernadini, Callen, Fried, & Piraino, 2004; Ghali et al., 1996; Quan et al., 2005; Quan et al., 2011; Schneeweiss & Maclure, 2000).

CRF

Cytogenetics is used to identify chromosomal aberrations and classify the type. The CRF category is assigned based on the abnormality present. The CRF is determined by the identification of specific chromosomal translocations noted. The CRF is based on the NCCN guidelines, which categorize patients based on these translocations into better, intermediate, or poor-risk groups (NCCN, 2012). The study investigator categorized CRF as follows: 0 (*poor-risk*), 1 (*intermediate-risk*), and 2 (*better-risk*).

Data Collection

The study investigator de-identified data collected from the electronic medical record. Patients were given study identification numbers and the data were recorded on data collection forms and entered into an Excel spreadsheet database stored on a secure password-protected computer. The computer and data were stored in a locked office. Data entry was verified by review of data collection form and comparison with electronic database. Discrepancies were resolved by return to the electronic health record. All patient information was de-identified. The researcher transferred data into SPSS and analyzed and described aggregately to ensure no identifying characteristics were reported.

Data Analysis

Analysis for each study aim was performed using IBM SPSS (v 22.0, SPSS, Inc., Chicago, IL). The level of statistical significance for all analyses was set at $p \leq .05$. This level was selected as it decreases the risk of Type 1 error. Type 1 error occurs when the null hypothesis is rejected, when in fact the null hypothesis is correct. Hypotheses were phrased in terms of the null. Two-sided statistical tests were performed because significant differences in either direction were of interest.

Prior to addressing research questions and hypotheses, descriptive statistics were calculated for all variables to evaluate data quality, identify patterns of missing and out-of-range values, and evaluate the tenability for assumptions of statistical tests. Continuous variables (age, neutropenic days, actual BMI, and HLOS) are reported as arithmetic mean (M) with standard deviation (SD) or median (Mdn) and interquartile range (IQR) dependent on the parametric nature of the data. For non-parametric data, IQR was reported along with the median as the best choice of measure of spread and central tendency, when dealing with skewed and/or data with outliers (Munro, 2005). Categorical variables (gender, diabetic status, indicators of hyperglycemia, hypoglycemia, and combined, infection, septicemia, sepsis, comorbidities, CRF, and remission and hospital mortality) were reported as frequency and percentage.

Comparisons of patient demographics between malglycemia groups (with and without hyperglycemia, hypoglycemia, or combination) were conducted to identify significant differences. In addition, outcomes were compared between the malglycemia groups. For continuous variables, the assumption of normality was assessed by use of the Shapiro-Wilk test. A statistically significant difference ($p \leq .05$) indicated data were not

normally distributed. Comparisons of normally distributed data were conducted using an independent t test, while non-parametric data were compared using the Mann-Whitney U test. Nominal data (gender, infection, septicemia, sepsis, complete remission, and mortality) were compared between malglycemia groups using a Fisher's exact test.

Logistic Regression

For Aims 3, 4, 5, 7, and 8, logistic regression analyses were conducted to examine the relationship of malglycemia (hyperglycemia, hypoglycemia, and combination) on the dichotomous outcome variables of infection, septicemia, sepsis, complete remission, and mortality. Direct logistic regression was used for entry of predictors into the model. In this type of logistic regression predictors are entered into the model simultaneously. This is the method of choice when there are no specific hypotheses about the order or importance among the predictor variables (Tabachnick & Fidell, 2012). The logistic regression model included the predictors of age, and CCI (Aims 3, 4, 5). The CRF was added to the model for Aims 7 and 8. The Wald statistic was used to determine the individual contribution of each predictor variable. If the p value was $\leq .05$, the variable was considered to have made a significant contribution to the association of the outcome (Tabachnick & Fidell, 2012).

In logistic regression, statistical assumptions such as normality, linearity, and equal variance within the groups are not required to be addressed prior to analysis (Tabachnick & Fidell, 2012). Logistic regression includes the logarithmic transformation (logit), which serves to resolve the violation of the assumption of linearity (Field, 2013). To determine if the assumptions of logistic regression were met, the investigator evaluated results for (1) multicollinearity, (2) test of overall model, and (3) outliers.

Multicollinearity. Assessment of inter-correlation was conducted using collinearity diagnostics that allows each predictor variable to be examined. Tolerance values were examined for values below .1, which is considered problematic (Field, 2013). Variance inflation factors also were assessed for values greater than 10, which is a cause for concern; the average variance inflation factors was calculated to ensure the score was not substantially greater than 1 (Field, 2013). Lastly, eigenvalues were examined for distribution of variance among the predictors.

Tests of overall model. Goodness-of-fit demonstrates how closely the regression model predicted values and reflect the observed data (Field, 2013). The adequacy of the model at predicting categorical outcomes was assessed using the Hosmer-Lemeshow test goodness-of-fit (Field, 2013). A p value of $\leq .05$ was indicative of a poor fitting model. To determine the amount of variance of the dependent variable explained by the model, the Nagelkerke R^2 was evaluated (Laerd Statistics, 2015).

Outliers. To address the assumption of outliers, standardized residuals were calculated and evaluated. Residuals represent the error present in the model. Small residuals are indicative of a good model fit, whereas large residuals indicate a poor fitting model (Field, 2013). Residuals with values > -3 or < 3 were considered to contain outliers and in violation of this assumption (Field, 2013; Hosmer & Lemeshow, 2000). The presence of outliers introduces bias into the model. The assumptions for these statistical tests were met.

Kaplan-Meier and Cox Regression

For Aims 2 and 6, survival analyses (Kaplan-Meier followed by Cox regression) were used to evaluate the association of malglycemia (hyperglycemia, hypoglycemia, and

the combination) to the number of neutropenic days and induction HLOS. Prior to conducting survival analysis, normality of sampling distribution and linearity for covariates were assessed by statistical methods. The log-rank test statistic was used to determine significance in Kaplan-Meier, and the Wald test statistic was used to determine significance in the Cox regression models. Kaplan-Meier and Cox regression analyses include censored cases, which are cases where the patient did not experience *the event* before the end of the study. For every time point that data are available, the Kaplan-Meier method estimates the probability of surviving (i.e., not experiencing the event) past that particular time point taking into consideration the presence of censored cases. Taken as a whole, therefore, the Kaplan-Meier method estimates the *experience* of survival over a period of time (Laerd Statistics, 2015). Cox regression allows for the addition of predictor variables to the model.

To determine if the assumptions of Kaplan-Meier and Cox regression were met, the investigator evaluated results for (1) mutually exclusive, (2) measureable time to event, (3) minimize left censoring, and (4) independence of censoring and the event. The assumptions for these statistical tests were met.

CHAPTER 4. RESULTS

The purpose of this study was to gain knowledge regarding the prevalence of incidence of malglycemia (hyperglycemia, hypoglycemia, or the combination) and to evaluate its impact on health outcomes in hospitalized AML patients during initial induction chemotherapy. This chapter reports the results from the study.

The population examined consisted of 103 adult patients who received initial induction chemotherapy for AML from January 2006–April 30, 2014. There were a total of 2,429 fasting blood glucose lab values collected within the induction period that on average consisted of a duration of 37 days (2–55 days).

Sample Characteristics

The majority of patients were Caucasian, male, and had a mean age of 59 ($SD = 14.7$) years ranging in age from 18 to 85 years old. The mean BMI for study subjects was 28 kg/m^2 and ranged from 18 to 51 kg/m^2. Twenty-two of the 103 patients included in the study had a documented diagnosis of diabetes mellitus. Table 1 summarizes patient demographic and medical characteristics. The majority of patients did not achieve complete remission; however, most patients survived to discharge (92.2%).

Table 1

Patient Demographic and Medical Characteristics of Sample, N = 103

Characteristics	*Mdn (IQR)*	Minimum	Maximum
Age[a]	59.3 (20.0)	19	85
BMI	27.4 (6.0)	18	51
CCI	5.0 (2.0)	2	10
Fasting blood glucose	119.0 (34.0)	88	178

	N (%)
Gender	
Male	60 (58.3)
Female	43 (41.7)
Race	
Black or African American	7 (6.8)
Caucasian	95 (92.2)
Hispanic	1 (1.0)
Documented Diagnosis of Diabetes Mellitus	22 (21.4)
No of Patients requiring Re-induction	
No	72 (69.9)
Yes	31 (30.1)

Note. IQR = interquartile range. [a]Reported as Mean.

Table 2 presents a summary of the overall patient characteristics by health outcomes.

Table 2

Overall Patient Characteristics by Health Outcome

Characteristics	*n* (%)
Infection	39 (38.0)
Septicemia	28 (27.0)
Sepsis	10 (10.0)

Table continues

Complete remission			
No	62 (60.2)		
Yes	37 (35.9)		
Unknown	4 (3.9)		
Mortality			
No		95 (92.2)	
Yes		8 (7.8)	

	Mdn (IQR)	Minimum	Maximum
Number of neutropenic days	19.0 (10.0)	0	52
HLOS	25.0 (8.0)	2	55

Note. IQR = interquartile range.

The majority of patients experienced at least one episode of malglycemia

(hyperglycemia, hypoglycemia, or combination) with only 5 (< 1%) having no episodes

of malglycemia (hyperglycemia, hypoglycemia, or combination) during hospitalization.

Of those who had malglycemia, 86 (83%) were classified as having hyperglycemia and

12 (11.6%) had combination (hyperglycemia and hypoglycemia). Nine of the 12 (81.8%)

patients with the combination (hyperglycemia and hypoglycemia) had a documented

diagnosis of diabetes. None of the patients had only hypoglycemia as those who had

hypoglycemia also had hyperglycemia. Therefore, patients who experienced both

hypoglycemia and hyperglycemia were discretely classified in the *combination* category.

Prior to addressing the study aims, patient demographics and characteristics were

compared between patients classified as having malglycemia and those who did not have

malglycemia. The only significant differences between those with and without

malglycemia were their BMI and comorbidities (CCI, n.d.). Among those with

hyperglycemia (27.5 versus 22.8), BMI was significantly higher ($p = .029$). For those

with combination (score of 7 versus 5) CCI was significantly higher ($p = .001$). Data on

the CRF was missing on 10 patients; therefore, only 93 were included in the analysis of

complete remission. The NCCN guidelines were used for categorization of CRF. The

majority of patients in both the hyperglycemia and combination groups were classified as

Intermediate-risk group. See Tables 3 and 4 for comparison of patient characteristics by

glycemic status.

Table 3

Comparison of Patient Characteristics by Hyperglycemic Status

Characteristic	Hyperglycemia ($n = 86$)	Non-Hyperglycemia ($n = 5$)	
	Mdn (*IQR*); Min., Max.	*Mdn* (*IQR*); Min., Max	*p*
Age[a]	59.1 (14.8); 19, 85	53.0 (18.2); 40, 84	.381
CCI	5.0 (2.0); 2, 9	4.0 (4.0); 2.0, 6.0	.332
BMI	27.5 (7.0); 19, 51	22.8 (7.0); 18, 29	.029
	N (%)	*N* (%)	*p*
Gender: male	52 (60.5)	1 (20.0)	.157
CRF ($n = 84$)			.399
Poor-risk	32 (40.5)	1 (20.0)	
Intermediate-risk	39 (49.4)	3 (60.0)	
Better-risk	8 (10.1)	1 (20.0)	

Notes. IQR = interquartile range. Min = minimum. Max = maximum. [a]Reported as Mean.

Table 4

Comparison of Patient Characteristics by Combination (Hyperglycemia and

Hypoglycemia) Status

Characteristic	Combination (*n* = 12)	Non-Combination (*n* = 91)	
	Mdn (*IQR*); Min., Max.	*Mdn* (*IQR*); Min., Max.	*p*
Age [a]	64 (17.8); 39, 82	59 (21.); 19, 85	.106
CCI	7 (2.0); 3, 10	5 (2); 2, 9	.001
BMI	27.6 (13); 20, 47	27.4 (6); 18, 51	.978
	N (%)	*N* (%)	*p*
Gender: male	7 (63.6)	53 (57.6)	.758
CRF (*n* = 93)			
Poor-risk	3 (3.2)	33 (35.4)	.673
Intermediate-risk	6 (6.4)	42 (45.1)	
Better-risk	0	9 (9.6)	

Note. IQR = interquartile range. Min = minimum. Max = maximum. [a]Reported as Mean.

Patients with hyperglycemia had more neutropenic days and HLOS than those

without hyperglycemia. The majority of patients with hyperglycemia did not achieve

complete remission. See Table 5 for summary of health outcomes by hyperglycemic

status. Those with combination (hyperglycemia and hypoglycemia) had longer HLOS.

The majority of patients in the combination group did not achieve complete remission.

Table 5

Health Outcomes by Hyperglycemic Status

	Hyperglycemia (*n* = 86)	Non-Hyperglycemia (*n* = 5)
	Mdn (*IQR*); Min., Max.	*Mdn* (*IQR*); Min., Max.
Number of neutropenic days	19.0 (11.0); 0, 52	17.0 (14.0); 3, 26
HLOS	24.0 (8.0); 2, 54	27.0 (7.0); 20, 31
	N (%)	*N* (%)
Infection	27 (34.2)	2 (40.0)
Septicemia	20 (25.3)	0 (0)
Sepsis	6 (7.6)	0 (0)
Complete remission		
No	48 (63.2)	2 (40.0)
Mortality		
Yes	7 (8.9)	0 (0)

Note. IQR = interquartile range. Min = minimum. Max = maximum.

See Table 6 for summary of health outcomes by combination status.

Table 6

Health Outcomes by Combination (Hyperglycemia and Hypoglycemia) Status

	Combination (*n* = 12)	Non-Combination (*n* = 91)
	Mdn (*IQR*); Min., Max.	*Mdn* (*IQR*); Min., Max.
Number of neutropenic days	18 (10); 8, 33	19 (11); 0, 52
HLOS	25 (15); 14, 55	25 (8); 2, 54
	N (%)	*N* (%)
Infection	6 (50)	34 (37.3)
Septicemia	8 (66.6)	20 (21.9)
Sepsis	4 (33.3)	6 (6.5)

Table continues

Complete remission		
No	7 (58.3)	55 (60.4)
Mortality		
Yes	1 (8.3)	7 (7.6)

Note. IQR = interquartile range. Min = minimum. Max = maximum.

The following section reviews the aims and major aims and subsequent results.

Specific Aims and Hypothesis Testing

Aim 1 Prevalence

Describe the incidence and prevalence of malglycemia (hyperglycemia, hypoglycemia, or the combination) among AML patients during hospitalization for induction therapy.

Frequencies were used to determine the percent of AML patients in any of the following categories: hyperglycemia FBG $\geq$ 126 mg/dL or the combination of one or more FBG in the hyperglycemic or hypoglycemic range (FBG $\geq$ 126 mg/dL or $<$ 70 mg/dL). To determine the prevalence of malglycemia for each indicator separately, the mean of the total number of occurrences of hyperglycemia or the combination for all patients was divided by the mean of the total number of FBG tests for all patients taken during the induction period.

Prevalence of hyperglycemia. The mean number of days of hyperglycemia in this sample was 6.25 (minimum 0, maximum 48). The mean number of FBG tests was 23.55 per hospital induction period. This resulted in a prevalence rate of hyperglycemia of 26.5%.

Prevalence of combination. The combination was less prevalent in this sample, with the mean number of days .33 (minimum 0, maximum 7). The mean number of FBG

tests was 23.55 (minimum 3, maximum 55) per hospital induction period. In this sample, the prevalence of combination (hyperglycemia and hypoglycemia) was 1.4%.

The following results must be taking into consideration as they result in small cell sizes and low power:

- The large number of patients with and so few without hyperglycemia

- The small number of patients with combination.

Aim 2 Neutropenic Days

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and neutropenic days controlling for known covariates of age and CCI among AML patients during hospitalization for induction therapy.

Cox regression was used to investigate whether an association exists between malglycemia (hyperglycemia or the combination) and neutropenic days controlling for known covariates of age and comorbidities. Forty-six patients were censored from the analysis because they remained neutropenic at the time of either re-induction, discharge from the hospital, or death.

Hyperglycemia and neutropenic days. Kaplan-Meier analysis was conducted to assess if the number of neutropenic days was associated with hyperglycemia. Estimated medians for the Kaplan-Meier after value censoring were 22 neutropenic days for those with hyperglycemia. This was not statistically significantly $\chi^2(1) = .195$, $p = .163$ longer than those without hyperglycemia, which had an estimated Kaplan-Meier after value censoring median number of 20 neutropenic days.

Due to lack of statistical significance noted in the Kaplan-Meier, further analysis may not be warranted; however, Cox regression was conducted as originally proposed.

Cox regression was used to determine if any of the covariates had an effect. Overall the model was not statistically significant $\chi^2(3) = 6.648$, $p = .084$. Results indicated hyperglycemia was not significantly associated with neutropenic days ($p = .096$); the covariates of age ($p = .045$) was statistically significant; however, comorbidities ($p = .322$) was not statistically significant.

Combination and neutropenic days. Kaplan-Meier analysis was conducted to assess if the number of neutropenic days was associated with combination (hyperglycemia and hypoglycemia). Participants with combination (hyperglycemia and hypoglycemia) had a median number of 19 neutropenic days. This was not statistically significantly $\chi^2(1) = 1.679$, $p = .195$ longer than those without combination (hyperglycemia and hypoglycemia), which had a median number of 22 neutropenic days.

Due to lack of statistical significance noted in the Kaplan-Meier, further analysis may not be warranted; however, Cox regression was conducted as originally proposed. Cox regression was used to determine if any of the covariates had an effect. Overall the model was trending towards statistical significance $\chi^2(3) = 7.043$, $p = .071$. Results indicated combination (hyperglycemia and hypoglycemia) was not significantly associated to neutropenic days ($p = .091$). The covariate CCI was not statistically significant ($p = .227$; 95% CI [1.002, 1.067]); however, age was significantly associated ($p = .040$) $OR = 1.03$; 95% CI [1.002, 1.067] with neutropenic days such that for each increase in age, an increase of one additional day of neutropenia occurred.

Aim 3 Infection

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and infection controlling for known covariates of age and CCI among

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AML patients during hospitalization for induction therapy. Logistic regression was used to investigate whether an association exists between malglycemia (hyperglycemia, hypoglycemia, or the combination) and infection controlling for known covariates of age and comorbidities.

Hyperglycemia and infection. The primary types of infections were urinary tract infection, clostridium difficile, and positive viral and fungal cultures. However, other miscellaneous documented infectious conditions were included such as abscesses, stomatitis, mucositis, colitis, gastritis, cellulitis, tonsillitis, typhlitis, otitis, parotitis, and pneumonia.

Twenty-seven (34.2%) of patients with hyperglycemia developed an infection. Fisher's exact testing was conducted to determine if there was an association between hyperglycemia and infection. In this sample, hyperglycemia was not associated with infection ($p = 1.000$). Given there was not a significant difference in infection rates between the groups and no difference among the covariates (age, comorbidities), additional analysis may not be warranted; however, logistic regression was conducted as originally proposed. Logistic regression models included the covariates of age and comorbidities. To address the assumption of outliers, residuals were examined. Residuals indicated outliers among the variables were not present.

The model was statistically significant, $\chi^2(2) = 1.971$, $p < .366$ (Hosmer-Lemeshow test) indicating the model is not a poor fitting model. The model accounted for 17.0% (Nagelkerke $R^2 = .017$) of the variance in infection and correctly classified 60.2% of cases. Hyperglycemia ($p = .318$) was not a significantly associated to infection in this sample. These results are consistent with the Fisher's exact test results.

Combination and infection. Twelve patients (9.2%) experienced combination. Of those patients, six (50%) developed an infection. Fisher's exact testing was conducted to determine if there was an association between combination (hyperglycemia and hypoglycemia) and infection. In this sample, combination was not associated with infection ($p = .363$). Given there was not a significant difference in infection rates between the groups and no difference among the covariate variables (age, comorbidities) additional analysis may not be warranted; however, logistic regression was conducted as originally proposed.

Logistic regression was conducted to assess if the likelihood of developing an infection was associated with combination (hyperglycemia and hypoglycemia) controlling for age and comorbidities. The model was not statistically significant, $\chi^2(8) = 7.875$, $p = .446$ (Hosmer-Lemeshow test) indicating the model is not a poor fitting model. The model explained 21% (Nagelkerke $R^2 = .021$) of the variance in infection and correctly classified 60.2 % of cases. Hypoglycemia was not significantly associated to infection in this sample, ($p = .245$). These results are consistent with the Fisher's exact results.

Aim 4 Septicemia

Examine the association(s) between malglycemia (hyperglycemia, hypoglycemia, or the combination) and septicemia controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction therapy.

A logistic regression model was used to investigate whether an association exists between malglycemia (hyperglycemia, hypoglycemia, or the combination) and septicemia controlling for known covariates of age and comorbidities.

Hyperglycemia and septicemia. Of the 86 patients who had hyperglycemia, 20 (25.3%) developed septicemia. Fisher's exact testing was conducted to determine if there was an association between hyperglycemia and septicemia. In this sample, hyperglycemia was not associated with septicemia ($p = .332$). Given there was not a significant difference in rates of septicemia between the groups and no difference among the confounding variables (age, comorbidities) further analysis may not be warranted; however, logistic regression was conducted as originally proposed. Models included the covariates of age and comorbidities. To address the assumption of outliers, residuals were examined. Residuals indicated outliers among the variables were not present.

A logistic regression model was conducted to assess if the likelihood of developing septicemia was associated with hyperglycemia controlling for age and comorbidities. The model was not statistically significant, $\chi^2(8) = 3.928$, $p = .864$ (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 13.9% (Nagelkerke $R^2 = .139$) of the variance in infection and correctly classified 74.8% of cases. Hyperglycemia was not significantly associated to infection in this sample, ($p = .163$). These results are consistent with the Fisher's exact results.

Combination and septicemia. Eight of 12 patients (66.6%) with combination (hyperglycemia and hypoglycemia) developed septicemia. Fisher's exact testing was conducted to determine if there was an association between combination and septicemia. In this sample, combination (hyperglycemia and hypoglycemia) was associated with septicemia ($p = .003$). Due to the statistically significant difference in rates of septicemia between the groups additional logistic regression was conducted.

A logistic regression model was conducted to assess if the likelihood of developing septicemia was associated with combination (hyperglycemia and hypoglycemia) controlling for age and comorbidities. The model was not statistically significant, $\chi^2(8) = 4.321$, $p = .827$ (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 18.1% (Nagelkerke $R^2 = .181$) of the variance in septicemia and correctly classified 78.6% of cases. In this sample, patients with combination were 5 times more likely ($p = .025$; OR 4.92; 95% CI [1.27, 19.78]) to develop septicemia. These results are consistent with the Fisher's exact test results.

Aim 5 Sepsis

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or combination) and sepsis controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction therapy. A logistic regression model was used to investigate whether an association exists between malglycemia (hyperglycemia, hypoglycemia, or combination) and sepsis controlling for known covariates of age and comorbidities.

Hyperglycemia and sepsis. Six of 86 (7.6%) patients with hyperglycemia developed sepsis. Fisher's exact testing was conducted to determine if there was an association between hyperglycemia and sepsis. In this sample, hyperglycemia was not associated with sepsis ($p = 1.000$). Given there was not a significant difference in rates of sepsis between the groups and no difference among the confounding variables (age, comorbidities) additional analysis may not be warranted; however, logistic regression was conducted as originally proposed. The model included the covariates of age and comorbidities. To address the assumption of outliers, residuals were examined. Residuals

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indicated outliers among the variables were present; therefore, the assumption was violated.

A logistic regression model was used to assess if the likelihood of developing sepsis was associated with hyperglycemia controlling for age and comorbidities. The model was not statistically significant, $\chi^2(8) = 4.338$, $p = .825$ (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 16.5% (Nagelkerke $R^2 = .165$) of the variance in sepsis and correctly classified 91.3% of cases. Hyperglycemia was not significantly associated to sepsis in this sample, ($p = .136$). These results are consistent with the Fisher's exact test results.

Combination and sepsis. Four of the 12 (33.3%) patients with combination (hyperglycemia and hypoglycemia) developed sepsis. Fishers exact testing was conducted to determine if there was an association between combination and sepsis. In this sample, patients with combination (hyperglycemia and hypoglycemia) were associated with sepsis ($p = .016$). Due to the statistically significant difference in rates of sepsis between the groups additional logistic regression was conducted.

A logistic regression model was conducted to assess if the likelihood of developing sepsis was associated with combination (hyperglycemia and hypoglycemia) controlling for age and comorbidities. The model was not statistically significant, $\chi^2(8) = 4.575$, $p = .802$ (Hosmer-Lemeshow) indicating it is not a poor fitting model. The model explained 19.0% (Nagelkerke $R^2 = .194$) of the variance in sepsis and correctly classified 91.3% of cases. Combination (hyperglycemia and hypoglycemia) was trending towards a significant association to sepsis in this sample. Patients with combination (hyperglycemia and hypoglycemia) were 5 times ($p = .057$; *OR* 4.98; 95% CI [.953,

26.1]) more likely to have sepsis. These results are consistent with the Fisher's exact test results.

Aim 6 Induction HLOS

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or the combination) and induction HLOS controlling for known covariates of age and comorbidities among AML patients during hospitalization for induction therapy. Cox regression was used to investigate whether an association exists between malglycemia (hyperglycemia, hypoglycemia, or the combination) and induction HLOS controlling for known covariates of age and comorbidities. Eight patients who died during induction therapy were censored from the analysis.

Hyperglycemia and induction HLOS. Kaplan-Meier analysis was conducted to assess if patients with hyperglycemia had a longer induction HLOS. Estimated medians for Kaplan-Meier after value censoring were 26 HLOS days for patients with hyperglycemia. Those without hyperglycemia has an estimated median Kaplan-Meier after value censoring of 25 days. This was not a statistically significant $\chi^2(1) = 1.030$, $p = .310$ association.

Due to the lack of statistical significance noted in the Kaplan-Meier, further analysis may not be warranted; however, Cox regression was conducted as originally proposed. Cox regression was used to determine if any of the covariates had an effect. Overall the model was not statistically significant $\chi^2(3) = 5.982$, $p = .112$. Results indicated hyperglycemia was not significantly associated to induction HLOS ($p = .332$).

Combination and induction HLOS. Kaplan-Meier analysis was conducted to assess if patients with combination (hyperglycemia and hypoglycemia) had a longer

induction HLOS. Participants with combination (hyperglycemia and hypoglycemia) had a median HLOS of 26 days, 95% CI [19.52, 32.47]. This was not statistically significantly $\chi^2(1) = 15.44$, $p = .213$ longer than those without combination, which had a median HLOS of 25 days, 95% CI [23.43, 26.56].

Due to the lack of statistical significance noted in the Kaplan-Meier, further analysis may not be warranted; however, Cox regression was conducted as originally proposed. Cox regression was used to determine if any of the covariates had an effect. Overall the model was trending towards statistical significance $\chi^2(3) = 6.534$, $p = .068$. Results indicated combination was not significantly associated to induction HLOS ($p = .223$).

Aim 7 Complete Remission

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or combination) and complete remission controlling for known covariates of age, comorbidities, and CRF among AML patients during hospitalization for induction therapy. Logistic regression was used to investigate whether an association exists between malglycemia (hyperglycemia or the combination) and complete remission controlling for known covariates of age, comorbidities, and CRF. Complete remission status was noted by physician documentation and/or in pathology results. Documentation of remission status was missing for four patients. Additionally, documentation of CRF was missing for 10 patients. Therefore, 14 (10.7%) patients did not have information available on either remission or CRF status and were removed from the analysis. Remission status was present for 99 patients. Only 37 of 99 (36.0%) patients achieved complete remission after the initial induction therapy.

Hyperglycemia and complete remission. Forty-eight out of 86 (63.2%) patients

with hyperglycemia did not achieve complete remission. Fisher's exact testing was

conducted to determine if there was an association between hyperglycemia and complete

remission. In this sample, hyperglycemia was not associated with complete remission

($p = .366$). There was not a significant difference in rates of complete remission between

the groups and no difference among the confounding variables of age and comorbidities;

however, a statistically significant difference was noted between CRF and complete

remission ($p = .001$); therefore, further analysis was conducted. The model included the

covariates of age, comorbidities, and CRF. To address the assumption of outliers,

residuals were examined. Residuals indicated outliers among the variables were not

present.

A logistic regression model was evaluated to assess if the likelihood of achieving

complete remission was associated with hyperglycemia controlling for age,

comorbidities, and CRF. The model was not statistically significant, $\chi^2(8) = 12.522$,

$p = .129$ (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model

explained 19.0% (Nagelkerke $R^2 = .190$) of the variance in complete remission status and

correctly classified 66.7% of cases. Hyperglycemia was not a significant predictor of

complete remission in this sample, ($p = .514$). These results are consistent with the

Fisher's exact test results.

Combination and complete remission. Seven patients (58.3%) with combination

(hyperglycemia and hypoglycemia) did not achieve complete remission; the status for

one patient was unknown. Fisher's exact testing was conducted to determine if there was

an association between combination (hyperglycemia and hypoglycemia) and complete

remission. No association was noted between combination (hyperglycemia and hypoglycemia) and complete remission (p = 1.000). Further analysis may not be warranted; however, logistic regression was conducted as originally proposed. A statistically significant difference was noted (p = .001) in CRF and complete remission; therefore, further analysis was conducted. The logistic regression model included the covariates of age and comorbidities and CRF. To address the assumption of outliers, residuals were examined. Residuals indicated outliers among the variables were not present.

The logistic regression model was used to assess if the likelihood of achieving complete remission was associated with combination (hyperglycemia and hypoglycemia) controlling for age, comorbidities, and CRF. The model was not statistically significant, $\chi^2(8) = 11.36$, p = .182 (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 18.6% (Nagelkerke R^2 =.186) of the variance in complete remission status and correctly classified 64.6% of cases.

The combination was not significantly associated to complete remission in this sample, (p = .755). The covariates of age (p = .670) and comorbidities (p = .892) were not statistically significant. However, as one would expect, CRF category is significantly associated to complete remission status. With each increase in CRF category patients were 3.2 times (p = .001, *OR* 3.17; 95% CI [1.64, 6.14]) more likely to not achieve complete remission. These results are consistent with the Fisher's exact results.

Aim 8 Mortality

Examine the association between malglycemia (hyperglycemia, hypoglycemia, or combination) and induction mortality controlling for known covariates of age,

comorbidities, and CRF among AML patients during hospitalization for induction therapy. Logistic regression was used to investigate whether an association exists between malglycemia (hyperglycemia or the combination) and mortality controlling for known covariates of age, comorbidities, and CRF. Documentation of CRF was missing for 10 patients; therefore, the analysis included 93 patients.

Hyperglycemia and induction mortality. Seven (8.9%) deaths occurred during the induction phase, these seven patients who died experienced hyperglycemia. Mortality was not associated with hyperglycemia ($p = 1.000$). Further analysis may not be warranted; however, logistic regression was conducted as originally proposed. In addition, there was not a significant difference for the confounding variables of age, CRF, and comorbidities ($p = .800$, $p = .757$, $p = .967$, respectively) between those who died and those who did not die. The logistic regression model included the covariates of age, comorbidities, and CRF. To address the assumption of outliers, residuals were examined. Residuals indicated outliers among the variables were present; therefore, this assumption was violated.

A logistic regression was conducted to assess if the likelihood of induction mortality was associated with hyperglycemia controlling for age, comorbidities, and CRF. The model was not statistically significant, $\chi^2(8) = 6.968$, $p = .540$ (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 4% (Nagelkerke $R^2 = .004$) of the variance in induction mortality and correctly classified 92.2% of cases. Hyperglycemia was not significantly associated to induction mortality in this sample ($p = .780$). These results are consistent with the Fisher's exact results.

Combination and induction mortality. Only one of the patients (8.3%) who died during induction had combination (hyperglycemia and hypoglycemia). Fisher's exact testing was conducted to determine if there was an association between combination (hyperglycemia and hypoglycemia) and induction mortality. In this sample, combination (hyperglycemia and hypoglycemia) was not associated with overall induction mortality (p = 1.000). Although there was not a difference among the groups, further analysis may not be warranted; however, logistic regression was conducted as originally proposed.

A logistic regression was conducted to assess if the likelihood of induction mortality was associated with combination (hyperglycemia and hypoglycemia) controlling for age, comorbidities, and CRF. The model was not statistically significant, $\chi^2(8)$ = 7.720, p = .461 (Hosmer-Lemeshow test) indicating it is not a poor fitting model. The model explained 4% (Nagelkerke R^2 =.004) of the variance in induction mortality and correctly classified 92.2% of cases. Combination (hyperglycemia and hypoglycemia) was not significantly associated (p = .882) to induction mortality in this sample.

In summary, this study demonstrates malglycemia, specifically combination (hyperglycemia and hypoglycemia), was associated with septicemia and trending towards an association with sepsis. Although not statistically significant, the impact of hyperglycemia was noted to impact health outcomes such as more neutropenic days and longer HLOS, more infections, septicemia, and sepsis.

CHAPTER 5. DISCUSSION

This was the first study to examine the presence and impact of malglycemia (hyperglycemia, hypoglycemia, or the combination) on a comprehensive set of health outcomes in cancer patients. Specifically, the purpose of this study was to determine the prevalence of malglycemia (hyperglycemia, hypoglycemia, or combination) as well as examine its impact on health outcomes including number of neutropenic days, infection, septicemia, sepsis, induction HLOS, complete remission, and induction mortality in patients with AML. Findings from this study indicate that hyperglycemia is common and both hyperglycemia and the combination (hyperglycemia and hypoglycemia) have significant implications for the hospitalized AML patient.

Prevalence

Hyperglycemia

This is the first study to examine both the incidence and prevalence of malglycemia in AML patients. Similar to other studies, the incidence of hyperglycemia was quite high (83%), with the prevalence rate (total number of occurrences during the induction period) at approximately one-third (26.5%) of the entire sample. The ADA (2013) recommends that hyperglycemia be promptly identified and treated. The study findings for both incidence and prevalence should serve as a wake-up call to clinicians signaling both the need for monitoring and treatment of hyperglycemia in hospitalized AML patients.

Combination (Hyperglycemia and Hypoglycemia)

Less is known regarding the prevalence of hypoglycemia or the combination of hyperglycemia and hypoglycemia. This study found that all those ($n = 12$ or 11%

incidence) with hypoglycemia also had hyperglycemia. This eliminated the ability to calculate the discreet prevalence rate of hypoglycemia in this study.

The prevalence of the combination (hyperglycemia and hypoglycemia) was 1.4%. The prevalence of hypoglycemia or the combination (hyperglycemia and hypoglycemia) has not been well described in the literature. Inconsistencies in the definition and measurement of hypoglycemia and variability have made it difficult to assess its prevalence. However, the prevalence of hyperglycemia or combination noted in this study is similar to those findings among critical care patients where the prevalence was noted as 28% for hyperglycemia and 2.9% had the combination of both during their ICU length of stay (Badawi et al., 2012).

Measurement Issues

The prevalence of malglycemia, specifically hyperglycemia, has been noted as a common problem in the critical care patient. However, there are two challenges noted for interpretation of these results. First, many studies do not divulge how the prevalence rate was calculated and/or use terminology of incidence and prevalence interchangeably. Second, of the few studies that have examined malglycemia, researchers have used varying cut points to define abnormal blood glucose levels. Many of the studies did not use ADA recommended definition of FBG $\geq$ 126 mg/dL as the marker of hyperglycemia. For example Ali et al. (2007), considered hyperglycemia as > 110mg/dL and hypoglycemia as < 60 mg/dL; whereas Matias et al. (2013), used > 100 mg/dL as the marker for hyperglycemia and < 60mg/dL for hypoglycemia. See Appendix H for malglycemia measurement table. The lack of a clear and common definition makes comparisons across studies difficult. Therefore, consistent definitions and terminology

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are crucial to understanding the prevalence of malglycemia (hyperglycemia, hypoglycemia, and combination) in AML patients.

Outcomes

Number of Neutropenic Days

The role of hyperglycemia on neutropenic days has not been well studied. Although not statistically significant, patients in this study with hyperglycemia had two days more of neutropenia than those without hyperglycemia. Similarly, Karnchanasorn et al., (2012) failed to find a relationship between hyperglycemia and neutropenic days in BMT patients. Conversely, two studies including Storey and Von Ahs' pilot study demonstrated a significant association between hyperglycemia and higher number of neutropenic days in BMT and patients with various leukemia diagnoses, respectively (Sheean et al., 2006; Storey & Von Ah, 2015).

Significant findings may have been limited by the high number of patients in the study who had hyperglycemia. Although hyperglycemia was not found to be significantly associated with number of neutropenic days, it is a clinically significant finding as additional days of neutropenia may result in increased risk for infection and longer HLOS.

The combination of hyperglycemia and hypoglycemia was not significantly associated with neutropenic days. Interestingly, those patients with the combination (hyperglycemia and hypoglycemia) had fewer neutropenic days than did those without combination (19 versus 22). One possibility for these findings may be the larger number of patients diagnosed with diabetes (9/12) in this group. Those patients with a known blood glucose disorder such as diabetes may have been more closely monitored with

variations of blood glucose better controlled due to corrective action taken to prevent episodes of hyperglycemia and hypoglycemia. More research is needed to understand the impact of hypoglycemia or the combination (hyperglycemia and hypoglycemia) on neutrophil recovery. These results should be interpreted with caution and may have been impacted by the uneven numbers in the hyperglycemia (large numbers) and combination (small numbers) groups.

The role of malglycemia on the neutropenic days of AML patients is important to continue to study. Researchers (Collier et al., 2008; Price & Knight, 2009; Turina et al., 2005) have shown the presence of malglycemia (hyperglycemia, hypoglycemia, or combination) at the cellular level exacerbates the blunting of cellular activity decreasing phagocytosis (a function of the neutrophils) and chemotaxsis (cellular movement), which could potentially result in increased risk for profound immune compromise, delayed marrow recovery, increased risk for infection, and subsequent longer HLOS.

Infection

Although hyperglycemia was not associated with infection in this study, patients with hyperglycemia had more infections than those who did not have hyperglycemia. These findings are similar to Fuji et al. (2007) who studied 112 BMT patients categorized with normoglycemia, mild, moderate, or severe hyperglycemia, and found no difference in overall infection rates among the groups. In addition, Storey and Von Ah (2015) in their pilot analyses did not find a significant relationship between hyperglycemia and infection in patients with various types of leukemia.

In contrast, Weiser et al. (2004) noted in 287 patients with ALL, those with hyperglycemia were 40% ($p = 0.016$) more likely to develop a complicated infection

(pneumonia or fungal). Matias et al. (2013) similarly noted hyperglycemia increased the risk of complicated infections (sepsis, respiratory, or renal failure; *OR* 3.97; 95% CI [2.08, 7.57]; *p* < 0.001) but did not increase the risk of fungal infections in ALL and AML patients undergoing induction therapy. When comparing BMT patients in a glucose control group to those not in the control group, Fuji and colleagues (2009) noted a significantly higher incidence of documented infection among those with hyperglycemia. Likewise, among 1,175 BMT patients, each parameter of malglycemia (hyperglycemia, hypoglycemia, and glycemic variability) were noted to increase the risk of infection (Hammer et al., 2009).

Combination (hyperglycemia and hypoglycemia) was not associated with infection in this study. The impact of hypoglycemia and the combination (hyperglycemia or hypoglycemia) on infection in patients with cancers or more specifically AML has not been well studied. Hammer et al. (2009) were the first to report detrimental outcomes related to hypoglycemia and glycemic variability among BMT patients. They noted hypoglycemia to be a significant predictor (*p* < .0001) of infection in BMT patients. Additionally they found the risk of infection was highest among those with the most variation in blood glucose. Those with higher variability were 2-fold more likely to have an infection than those with the least variations (Hammer & Voss, 2012). Likewise, Fuji et al. (2009) noted when interventions to control blood glucose were implemented, lower rates of infection ensued.

Limitations of this study may have impacted findings. Results may have been influenced by the smaller sample size or use of prophylactic antibiotic therapy, which was not accounted for in the study.

The majority of studies that examined malglycemia and infection were conducted in BMT patients, who are the most critically ill and therefore, cannot be generalized to other hematologic cancers. More research is needed to assess the impact of malglycemia on infection.

Septicemia

In this study, patients with hyperglycemia were not more likely to experience septicemia than those without hyperglycemia. However, it was noted that more patients with hyperglycemia developed septicemia than those who did not have hyperglycemia. Although this finding was not statistically significant it may be clinically significant in caring for AML patients.

Fuji et al. (2007) who studied BMT patients with normoglycemia, mild, moderate, or severe hyperglycemia, also failed to note a significant difference in septicemia rates among the groups. However, in a follow-up study of BMT patients, these same researchers (Fuji et al., 2009) noted a statistically significant increase in septicemia among those with hyperglycemia receiving standard of care treatment versus those whose blood glucose was kept in the range of 80–110 mg/dL. In addition, Soysal and associates (2012) studied 86 patients of varying cancer diagnoses admitted to the hospital with neutropenic fever and found those with hyperglycemia were more prone to have gram negative bacteria or fungal infections than those neutropenic patients without hyperglycemia. Taken together, these studies indicate more research is needed to fully examine the role of hyperglycemia and sepsis in AML patients.

There is a paucity of information on the role of combination (hyperglycemia and hypoglycemia) and septicemia. In this study, a significant relationship between

combination (hyperglycemia and hypoglycemia) and septicemia was noted. This finding should be interpreted with caution as the number of patients with combination (hyperglycemia and hypoglycemia) was small. However, this finding is plausible as glycemic variation has been shown to stimulate inflammatory cytokine response and oxidative stress (Ceriello et al., 2012; Gogitidze et al., 2010), which could create a milieu conducive to the development of septicemia. Further studies are needed to increase understanding of the pathophysiology of combination (hyperglycemia and hypoglycemia) and its effect on inflammatory and immune response.

Sepsis

Patients with hyperglycemia were not more likely to have sepsis than AML patients without hyperglycemia in this study. Similarly, Fuji et al. (2007) found no difference in sepsis among BMT patients with normoglycemia, mild, moderate, or severe hyperglycemia. However, Weiser et al. (2004) noted in 287 patients with ALL, those with hyperglycemia were 16% ($p = 0.03$) more likely to develop sepsis. Ali and colleagues (2007) also found that hyperglycemia increased the odds of developing infection, severe sepsis, or severe sepsis with respiratory failure in patients with AML. Likewise, Matias et al. (2013) studied 280 patients with ALL and AML and noted almost a 4-fold (OR 3.97; $p < .001$) increase in the odds for developing sepsis when hyperglycemia was present. The failure to find a relationship between malglycemia and sepsis may be due to the large numbers of patients with hyperglycemia and the few without hyperglycemia in this sample .

In this study, patients with combination (hyperglycemia and hypoglycemia) were trending towards a statistically significant association to sepsis. The effects of

malglycemia (hyperglycemia, hypoglycemia, or combination) on increased risk of sepsis has not been fully explored. Research assessing the effects of malglycemia (hyperglycemia, hypoglycemia, or combination) on the development of sepsis is important to study as AML patients who experience sepsis may experience longer HLOS and have a greater risk of mortality.

HLOS

In this study, HLOS was one day longer for those with hyperglycemia than those without. Similar findings were noted by Soysal and colleagues (2012) who also found a non-significant increase of one day longer HLOS among patients with hyperglycemia. Although this finding was not statistically significant, it may be clinically meaningful in caring for patients with AML. Coto and colleagues (2014) noted hyperglycemia was statistically significantly associated ($p = .037$) with longer HLOS (8.2 days versus 7.8 days) and subsequent hospital costs among patients with diabetes mellitus.

The impact of hyperglycemia on induction HLOS in AML patients has not been well studied. In BMT patients (including patients with leukemia), HLOS among those with hyperglycemia ($\geq$ 150 mg/dL) resulted in longer HLOS (14 days +/- 4 days compared to 17 +/- 6 days; $p = .0001$) than for those without hyperglycemia (Karnchanasorn et al., 2012). Garg et al. (2007) noted a significant increase in length of stay (16 days versus 24 days) in 126 BMT patients with hyperglycemia. Similarly, Storey and Von Ah (2015) noted leukemia patients with hyperglycemia had longer HLOS (5.4 days versus 19.6 days; $p = .02$) than those with normoglycemia.

This study did not find an association among those with combination (hyperglycemia and hypoglycemia) on HLOS. There is a deficit in the literature as it

relates to both hypoglycemia and the combination (hyperglycemia and hypoglycemia) on

HLOS. In critical care patients those with hypoglycemia were subject to longer HLOS of

14 days versus 16 days ($p = .05$) than those who did not experience hypoglycemia

(Brunkhorst et al., 2008). Turchin et al. (2009) found among non-critical care patients an

increase of 2.5 days as the number of hypoglycemic events increased ($p < .0001$). No

studies were found that specifically addressed the combination (hyperglycemia and

hypoglycemia) and HLOS. This is important to study as longer HLOS can contribute to

additional costs for patients, poorer outcomes, and loss of revenue for hospitals.

Complete Remission

Neither hyperglycemia nor combination (hyperglycemia and hypoglycemia)

impacted complete remission in this study. Overall, 37 of 99 (37%) patients achieved

complete remission. The majority (34 of 37; 92%) of patients that achieved complete

remission had hyperglycemia. Nine of the 37 (24%) patients had a documented diabetes

diagnosis. These findings are similar to Matias et al. (2013) who examined the complete

remission of 188 leukemia patients (ALL and AML) during induction and did not find a

significant relationship between hyperglycemia and complete remission.

The percent of patients that achieved complete remission (37%) in this study was

notably lower than those of other studies. It is estimated that the majority (70%−80%) of

patients fewer than 60 years of age will achieve complete remission (Fernandez et al.,

2009; Mandelli et al., 2009). Approximately 40%−50% of older patients (> 60 years of

age) who are in generally good health achieve complete remission; however, generally

the cure rate is 10% with median survival less than 1 year (Buchner et al., 2009; Burnett

et al., 2010). This finding may be related to the age and comorbid conditions in this sample.

This study focused on complete remission during the initial induction phase only, achieving complete remission in this time period is critical as this response can be indicative of longer duration of remission. However, complete remission also can be achieved with subsequent re-induction(s) chemotherapy treatments. Future research examining malglycemia longitudinally through the trajectory of AML treatment could yield important information regarding the impact of malglycemia on the duration and timing of complete recovery.

Research has shown CRF to be a principal predictor and the strongest prognostic indicator of complete remission in AML (Orozco & Appelbaum, 2012). The three CRF groups include better-risk, intermediate-risk, and poor-risk (NCCN, 2013). In this study, the majority of patients were in the intermediate-risk category, followed by the better-risk, and poor-risk respectively. In this study the eight patients who died, four were categorized as poor-risk and four as intermediate-risk cytogenetics.

Mortality

In this study, patients with malglycemia (hyperglycemia, hypoglycemia, or combination) did not demonstrate an association with mortality. Eight patients died during the induction period, all of the patients who died during induction had at least malglycemia, seven with hyperglycemia, and one episode of combination. Of those patients who died, only one had the diagnosis of diabetes and experienced the combination (hyperglycemia and hypoglycemia) during the induction period. The low number of deaths is not surprising as generally death during initial induction for AML is

rare. Matias et al. (2013) studied two different types of acute leukemia and noted an

association between hyperglycemia and death. However, those authors did not control for

CRF that could influence mortality. The current study, although with a smaller sample

size, did control for CRF and did not find an association between hyperglycemia and

mortality.

Hammer et al. (2009) were the first to examine all three components of

malglycemia (hyperglycemia, hypoglycemia, and glycemic variability) finding each

component associated with an increase in mortality. They found glucose values >200

mg/dL were associated with an approximately 2 or more fold increased risk of

non-relapse mortality compared to values 101–150 mg/dL ($p < .001$). Moreover, a

minimum blood glucose < 89 mg/dL was associated with a more than 2-fold risk of

non-relapse mortality compared to a minimum blood glucose of 90 mg/dL or more

($p = .0001$). Hammer et al. (2009) reported that among patients with the greatest

variability, risk of death was up to 14-fold higher compared to patients with lower

variability ($p < .0001$).

Variability in glucose has been shown to be more predictive of mortality than

mean glucose alone in critical care patients. Egi and colleagues (2006) found variability

of glucose concentrations were a significant and independent predictor of both ICU and

hospital mortality, noting variability as a stronger predictor of death than mean glucose

concentration. Krinsley (2008) noted a 5-fold increase in mortality among those with the

highest glycemic variability when compared to those with lower variability. Similarly,

the risk of mortality was noted to progressively increase among critical care patients as

the severity and duration of each component of malglycemia occurred (Badawi et al.,

2012). Bagshaw and colleagues (2009) noted critically ill patients who had hypoglycemia (BG < 81 mg/dL) and variability within 24 hours of admission to the ICU were 1.4 (95% CI [1.31–1.54]) times more likely to die during hospitalization. More research is needed to assess the impact of each component of malglycemia on mortality. Since mortality is less likely to occur during initial induction therapy, future research examining malglycemia in initial induction and through the trajectory of AML treatments may yield more information as to its impact.

Summary

Overall, these observations suggest that hyperglycemia is quite common and, although not statistically significant in this study, was clinically meaningful for each of the health outcomes (number of neutropenic days, infection, septicemia, sepsis, HLOS, complete remission, and mortality) in this sample. Specifically those with hyperglycemia had more days of neutropenia and longer HLOS. In addition, more infections, septicemia, and sepsis were noted in the hyperglycemia group than in those without hyperglycemia. The majority of patients who did not achieve complete remission had hyperglycemia. Lastly, the majority of patients who died experienced hyperglycemia.

Additionally, this study highlights that the combination (hyperglycemia and hypoglycemia) although less common, may have a more deleterious effect on patient outcomes than when experienced independently. Assessing patterns and reducing variability may be an important dimension to glucose control in the hospitalized AML patient. More research is needed to explore all the components of malglycemia and its impact on health outcomes.

Limitations

Findings of this study must be reviewed, taking into consideration the limitations noted. The study was limited by the large number of patients who had hyperglycemia, the small number that had the combination of hyperglycemia and hypoglycemia, and no patients with hypoglycemia alone. The small number of patients with the combination (hyperglycemia and hypoglycemia) impacts the power of the study increasing the risk of making a Type II error, which is accepting a null hypothesis that is false (Warner, 2008).

Because this is a retrospective study and based on abstracted chart review some data may be lacking or incomplete. For example, some records did not contain the CRF for analysis. Clinical acuity may have been an important factor that could influence health outcomes but is difficult to measure when abstracting data from chart reviews. The retrospective study design may have limited information as it related to pre-diabetes, undiagnosed diabetes, or glucose-intolerant individuals. Additionally, the ability to tolerate activity, nutritional support, and pharmacologic treatments such as corticosteroids, antibiotics, insulin, or hypoglycemic agents were not collected. These factors are likely to exacerbate blood glucose and/or moderate the impact on glycemic status and subsequent outcomes. Additionally, the use of fasting blood glucose limited the ability to assess glycemic variability throughout each day of hospitalization. These variables or yet unknown factors that were not extrapolated from the data may have confounded the results. Future studies should include, account, and control for these factors.

Strengths of the study included a specific time period within the trajectory of treatment for AML. Standard treatment regimens and similarities in the expected

symptom profiles and HLOS among this patient group during this time period reduced variability. The use of only one abstractor of data facilitated quality control measures and consistency in its collection. An additional strength of this study was the use of the CCI to control for the influence, number, and severity of comorbidities on the health outcomes.

Implications for Practice

This study provides important information regarding the prevalence and impact of malglycemia (hyperglycemia and the combination) on the health outcomes of vulnerable hospitalized AML patients during initial induction therapy. Nurses knowledgeable about the prevalence and ramifications of malglycemia (hyperglycemia, hypoglycemia, or combination) can proactively identify, assess, and intercede on behalf of their patients. The findings from this study, once disseminated, will facilitate nurses in the development of a patient specific plan of care that integrates the knowledge of disease process, cancer therapy, and changes in diet and activity on blood glucose. The oncology nurse plays an important role in the prompt identification of malglycemia and can collaborate with members of the multidisciplinary heathcare team to implement strategies to prevent or mitigate the harmful consequences of malglycemia.

The management of glucose not only improves outcomes for patients but also has ramifications for hospitals. Mandates from the Affordable Care Act require the Centers of Medicare and Medicaid Services to reduce reimbursement to hospitals that are considered lower-performers. The cascading effect of malglycemia, infection, and longer HLOS for the already at-risk AML patient also can result in financial consequences for hospitals.

Future research should include the analysis of actual blood glucose measurements or the aggregation mean blood glucose, or examining various thresholds for malglycemia as it relates to the impact on health outcomes rather than malglycemia as a dichotomous variable. Assessment of the onset of malglycemia, duration, and number of occurrences over the induction period could facilitate the identification of times when patients are most likely to experience malglycemia and to which interventions can be targeted.

Conclusion

This study provides preliminary evidence demonstrating malglycemia, specifically hyperglycemia, is prevalent. In addition, the combination (hyperglycemia and hypoglycemia) during induction for AML has harmful consequences for the hospitalized patient with AML. The limited number of studies on this important topic reveals gaps in knowledge as it relates to the full effects of malglycemia on the health outcomes of hospitalized AML patients. More research is warranted to elucidate clinically significant levels of malglycemia and its impact on health outcomes to inform interventions to mitigate symptoms and improve quality of life for hospitalized AML patients.

Overview of Physiologic Processes Associated with Malglycemia, Acute Myeloid Leukemia and Outcomes

* CRH – Corticotropin – releasing hormone
ACTH – Andrenocorticotropin hormone

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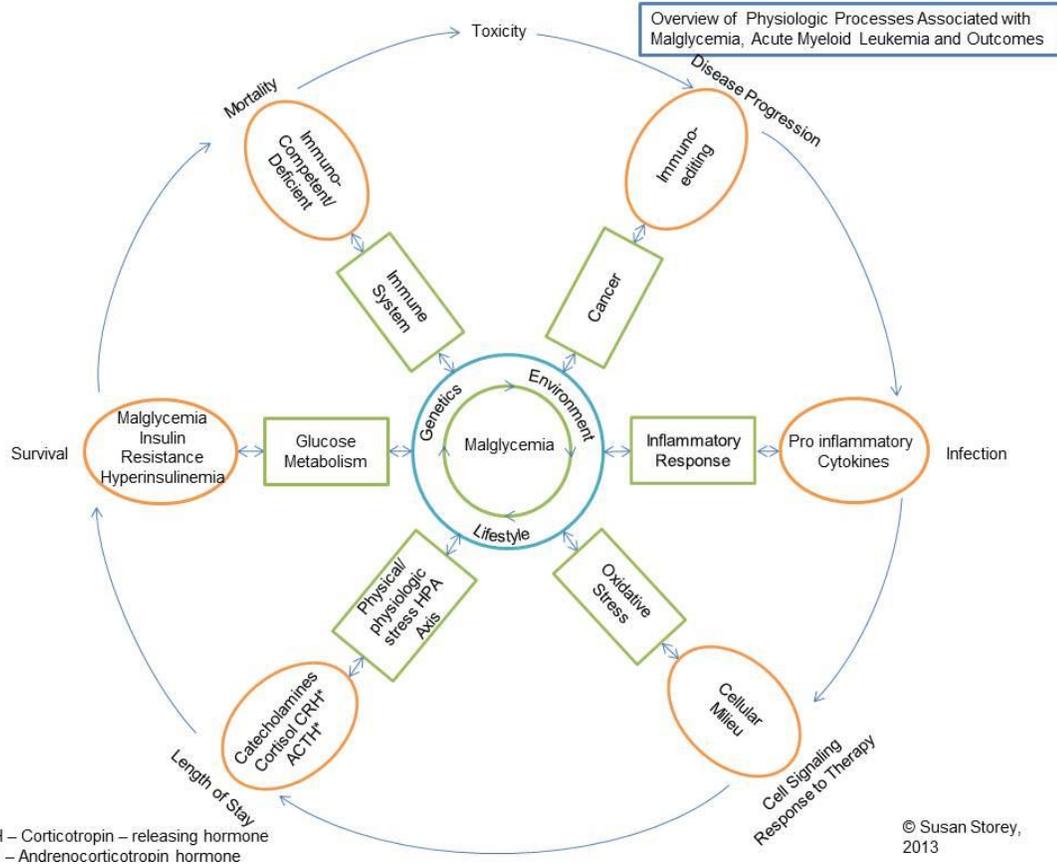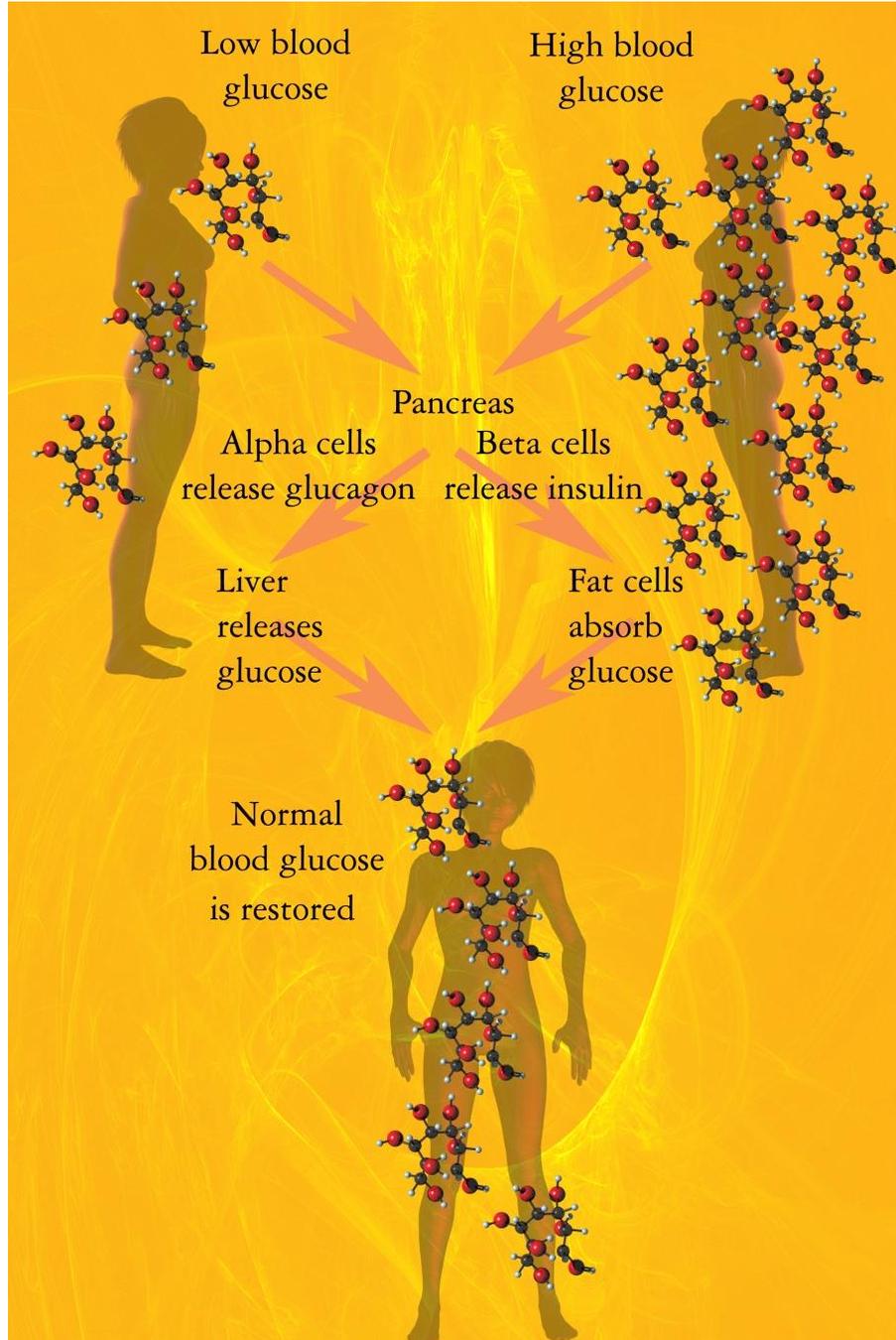
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APPENDIX D. LITERATURE REVIEW AND OUTCOME TABLE

X* Denotes statistical significance				Outcomes			
Author	Sample	Infection	Survival	Mortality	Toxicity	LOS	Findings
Ali et al. (2007)	AML *N* = 283	**X***		**X***			-Rise in mortality even at mild increases of blood glucose -Odds of developing sepsis increased with blood glucose
Brunello et al. (2010)	Non-Hodgkins lymphoma (NHL) & prostate cancer (PC) *N* = 349 162-NHL 187-PC		x		**X***		-NHL patients non-hematologic toxicities (neuropathy, non-neutropenic fever, and fatigue) increased when hyperglycemia present -PC patients with hyperglycemia experienced increase severity in hematologic toxicities (neutropenia, neutropenic fever, thrombocytopenia, and anemia
Derr et al. (2008)	BMT *N* = 382	**X***		x		x	-Hyperglycemia prior to ablative therapy was associated with higher risk for infection after ablative therapy
Derr et al. (2009)	Glioblastoma *N* = 191	x	**X***				-Trend towards infection Higher the mean glucose-shorter the survival time

Study	Population						Findings
Fuji et al. (2007)	BMT (AML, non-Hodgkins lymphoma, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia) *N* = 64	x	**X***	**X***	**X***		-Non-relapse mortality and overall survival and grade of graft-versus-host disease was related to the degree of hyperglycemia -Toxicities of hyperbilirubinemia and proinflammatory markers were significant with elevations in blood glucose
Fuji et al. (2009)	BMT *N* = 126	**X***		x	**X***		-Infection and bacteremia statistically less in the intense glucose control group -Toxicity of c-reactive protein was increased in the intense glucose control group
Garg et al. (2007)	BMT *N* = 126	x				**X***	-Patients treated with glucocorticosteroids had higher blood glucose and LOS -Not significant for infection
Gebremedhin et al. (2012)	BMT *N* = 328				**X***		-Normal to overweight patients when developed hyperglycemia doubled the risk of GVHD -In contrast obese patients had higher incidence of hyperglycemia but it did not significantly increase the incidence of GVHD -Lean patients did not develop hyperglycemia

Study	Population						Findings
Griffith et al. (2011)	BMT	x	**X***				-Identified risk factors for posttransplantation diabetes mellitus (PTDM) as peak steroid dose, pretransplant c-peptide level, unrelated donor. -PTDM is associated with inferior survival -did not find increased infections in patients with PTDM
Hammer et al. (2009)	BMT (AML, non-Hodgkins lymphoma, acute lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia) $N = 1175$	**X***		**X***			-Each glycemic parameter (hypo and hyperglycemia and variability) was associated with infection with greatest risk in the variability group -Each parameter associated with non-relapse mortality
Hardy et al. (2010)	Patients with brain tumors s/p craniotomy $N = 114$	x					-Glucose was not a significant factor in surgical site infections

Study	Population						Findings
Jackson et al. (2012)	Patients peri/ post-operative from colectomy for cancer and 30 days post elective surgery Analyzed 7576 BG on operative day & 5773 on post op day 1	**X***		**X***	x		-Moderate hyperglycemia associated with surgical site infection. -Severe hyperglycemia associated with cardiac arrest and death. -Mild, moderate and severe hypoglycemia and hyperglycemia were associated with myocardial infarction. -Associations similar among diabetic and non-diabetic patients -Trend towards association and need for operative re-intervention
Karnchanasorn et al. (2012)	BMT (autologous) *N* = 240	**x**			x	**X***	-Time to engraftment (platelet and neutrophil) was not statistically significant among those with blood glucose < 150 mg/dL and those with blood glucose >150 mg/dL. -LOS among those with blood glucose < 150mg/dL was statistically less than in those with blood glucose > 150mg/dL (14+/-4 versus 17+/-6; *p* = .0001) -No difference among groups as it relates to infection.
Matias, et al. (2013)	Leukemia patients (ALL & AML) admitted for induction *N* = 280	X*		X*			-High incidence of hyperglycemia during induction therapy -patients with hyperglycemia had 3.9 times risk for developing complicated infection (positive blood culture) -odds of death for patients with hyperglycemia were 3.5 -not difference in the number of fungal infections or complete remission

Study	Sample						Findings
Pidala et al. (2011)	BMT treated with glucocorticosteroids for graft-versus- host disease $N = 173$		X*	X*				-Patients treated with insulin or oral agents suffered significantly worse overall survival than those not requiring them. -Those with sustained blood glucose >200 mg/dL despite treatment suffered worse overall survival and non-relapse mortality
Rentschler et al. (2010)	BMT $N = 160$	X*	-			X*	x	-Hospital related hyperglycemia was associated with increased complications. -LOS increased among those who developed complications but was not associated with hyperglycemia after adjusting
Sheean et al. (2006)	BMT Allogeneic BMT $N = 107$ Autologous BMT $N = 250$ Total $N = 357$	X*				X*	x	-Patients receiving TPN experienced hyperglycemia more frequently and had statistically more infections, use of blood products and delayed white blood cells and platelet engraftment
Sheean et al. (2013)	$N = 112$ SCT	x	x	x		X*	X*	-Patients receiving TPN with hyperglycemia had significantly more neutropenic fevers, need for red blood cells and platelet transfusions, longer length of stay and delays in WBC and platelet engraftment. -No difference was noted in survival and mortality among the groups.

Soysal et al. (2012)	Patients with (Lymphoma, Hodgkins disease lung, prostate and GI cancer) admitted with fever and neutropenia *N* = 86	**X***		**X***				-More of the patients with malglycemia died than in the normoglycemia group. -Higher incidence of gram-negative bacteria and fungal infections among the group with malglycemia.
Storey & Von Ah (2015)	Patients with CML, ALL, CLL, AML *N* = 42	x				**X***	**X***	-Patients with hyperglycemia had a greater incidence of neutropenia and longer HLOS -No difference noted in infection
Villareal-Garza et al. (2012)	Metastatic or recurrent breast cancer *N* = 265		**X***			x		-Patients with a mean glucose of >130 mg/dL during administration of palliative cancer treatments had poorer overall survival than those with normoglycemia.
Weiser et al. (2004)	Acute lymphocytic leukemia *N* = 278	**X***	**X***					-Patients with hyperglycemia more likely to develop infection, sepsis or complicated infection. -Patients with hyperglycemia had significant increase in mortality and recurrence of disease -Delay in neutrophil not statistically significant

APPENDIX E. NCCN CYTOGENETIC RISK

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
Acute Myeloid Leukemia

RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES[1]

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Better-risk	inv(16)[2,3] or t(16;16)[2] t(8;21)[2] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT[5] mutation
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]	Normal cytogenetics: with FLT3-ITD mutation[6]

[1] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[2] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[3] Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013;121:170-177.

[4] For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in CML, with addition of tyrosine kinase inhibitors. See NCCN Guidelines for Chronic Myelogenous Leukemia.

[5] Emerging data indicate that the presence of c-KIT mutations in patients with t(8;21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients should be considered for clinical trials, if available.

[6] FLT3-ITD mutations are considered to confer a significantly poorer outcome in patients with normal karyotype, and these patients should be considered for clinical trials where available. There is controversy as to whether FLT3-TKD mutations carry an equally poor prognosis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

AML-A

Independent Variable Malglycemia   Dependent Variables

Hyperglycemia

or

Hypoglycemia

or

Combination

Neutropenic days
Infection
Septicemia
Sepsis
Induction/Hospital
length of stay

Complete remission
Mortality

Confounding Variables

Age
Comorbidities

Cytogenetic risk factor
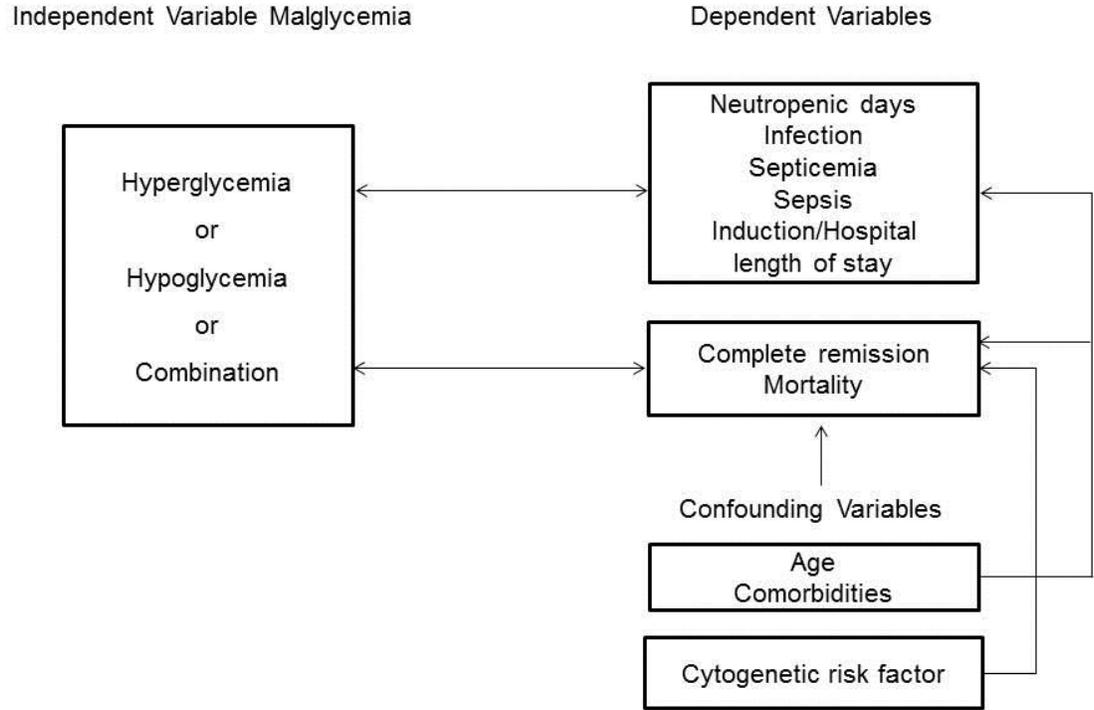
APPENDIX G. CCI

1. Indication
    1. Assess whether a patient will live long enough to benefit from a specific screening measure or medical intervention
2. Scoring: Comorbidity Component (Apply 1 point to each unless otherwise noted)
    1. Myocardial Infarction
    2. Congestive Heart Failure
    3. Peripheral Vascular Disease
    4. Cerebrovascular Disease
    5. Dementia
    6. COPD
    7. Connective Tissue Disease
    8. Peptic Ulcer Disease
    9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)
    10. Moderate to Severe Chronic Kidney Disease (2 points)
    11. Hemiplegia (2 points)
    12. Leukemia (2 points)
    13. Malignant Lymphoma (2 points)
    14. Solid Tumor (2 points, 6 points if metastatic)
    15. Liver Disease (1 point mild, 3 points if moderate to severe)
    16. AIDS (6 points)
3. Scoring: Age
    1. Age <40 years: 0 points
    2. Age 41-50 years: 1 points
    3. Age 51-60 years: 2 points
    4. Age 61-70 years: 3 points
    5. Age 71-80 years: 4 points

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APPENDIX H. MALGLYCEMIA MEASUREMENT TABLE

Author	Study Design	Concept Measured	Source	Statistical tests utilized
Ali et al. (2007)	Retrospective	Hyperglycemia > 110 mg/dL > 150 mg/dL > 200 mg/dL	Serum glucose	<u>Glycemia</u>: Mean, organized by level of mean hospital glucose <u>Outcomes</u>:Student t-test; Wilcoxon rank sum; Chi square; Logistic regression
Brunello et al. (2010)	Retrospective	Hyperglycemia ≥ 100 (fasting) ≥ 140 (post-prandial)	Serum glucose	<u>Glycemia</u>: Mean, standard deviation, median, minimum and maximum <u>Outcomes</u>: Linear regression (complications) Cox regression (overall survival; progression free survival); Logistic regression (toxicity)
Derr et al. (2008)	Retrospective	Hyperglycemia Interquartile range (25th–75th percentile)	All available glucose Serum glucose; point-of-care testing	<u>Glycemia</u>: Mean glycemia from admission to neutropenia <u>Outcomes</u>:Wilcoxan rank-sum, Kruskal-Wallis, Logistic regression (odds for infection)
Derr et al. (2009)	Retrospective	Hyperglycemia Q1 ≤ 94 mg/dL Q2 94–109 mg/dL Q3 110–137 mg/dL Q4 > 137 mg/dL	Serum glucose	<u>Glycemia</u>: Mean glucose divided into quartiles <u>Outcomes</u>:Cox proportional hazards regression(patient characteristics and overall survival)

Fuji et al. (2007)	Retrospective	Hyperglycemia < 110 mg/dL Mild 110–150mg/dL Moderate–severe > 150 mg/dL	Fasting blood glucose	Glycemia: Categorized according to mean glucose Outcomes: Student t-test, Chi square, Wilcoxan rank-sum (patient characteristics), Logistic regression (odds ratios), Kaplan-Meier (Overall survival), Cox regression (hazard ratios for overall survival and non-relapse mortality)
Fuji et al. (2009)	Retrospective/Prospective matched case control	Malglycemia 80–110 mg/dL 111–140 mg/dL 141–179 mg/dL ≥ 180 mg/dL Variability standard deviation of mean glucose	Serum glucose	Glycemia: Mean, standard deviation Outcomes: Student t-test, Chi square, Wilcoxan rank-sum (patient characteristics), Cox regression (Hazard ratios), repeated measures with linear fixed model; Kaplan-Meier (probability of organ dysfunction
Garg et al. (2007)	Retrospective	Hyperglycemia < 91 mg/dL 91–100 mg/dL 101–110 mg/dL 111–120 mg/dL > 120 mg/dL	Serum glucose	Glycemia: Categorized into quintiles according to mean Outcomes: Students unpaired t-test, Chi square, Pearson's correlation coefficient
Gebremedhin et al. (2012)	Prospective	Hyperglycemia Mild (6.11–8.33 mmol/L) Moderate (8.34–9.98 mmol/L) Severe (minimum of 9.99 mmol/L)	Fasting blood glucose Excluded diabetic patients	Glycemia: Morning serum glucose for 10 days post-transplant sufficient to predict GVHD in the subsequent 90 days. General linear model used for fbs days 1–10. Glucose values log-transformed to normalize skewed distribution. Outcomes: Proportions compared using Chi square, means compared using t tests, association between level of hyperglycemia and cumulative incidence of GVHD using univariate analysis w Gray test and multivariate analysis using proportional hazards regression.

Griffith et al. (2011)	Prospective	Hyperglycemia Onset of Post transplantation diabetes mellitus (PTDM) at one fasting blood glucose > 126 or random glucose ≥ 200 mg/dL	Serum fasting blood glucose	Glycemia: Spearman's rank correlation to test relationships of fasting glucose to covariates. Cox proportional hazards model to assess impact of PTDM as time dependent overall survival. Outcomes: Logistic regression to assess for confounding variables. Kaplan-Meier survival curves for overall survival.
Hammer et al. (2009)	Retrospective	Malglycemia < 70 mg/dL ≥ 126 mg/dL Variability a standard deviation of two or more measurements of 29 mg/dL or greater	Serum glucose	Glycemia: Individual, average, minimum and maximum blood glucose. Standard deviation Outcomes: Cox regression, Anderson-Gill model, regression models derived from likelihood-ration test and p value estimates from Wald test
Hardy et al. (2010)	Retrospective matched case control	Hyperglycemia ≥ 130 mg/dL ≥ 150 mg/dL	Serum glucose	Glycemia: Time adjusted glucose-weighting the average of all measurements by the length of time a patient was in a particular glucose measurement. Allows for adjustment of varying number of glucose measurements per patient. To eliminate bias the variable glucose was additionally defined and calculated as the average of the first measurements taken each day. Outcomes: Time weighting glucose measurements, Fisher exact test, Wilcoxan rank-sum, logistic models
Jackson et al. (2012)	Retrospective	Hyperglycemia Hypoglycemia < 80mg/dL Normoglycemia 80–120 mg/dL Moderate hyperglycemia 161–200 mg/dL Severe hyperglycemia > 200 mg/dL	Peri-operative BG (Operative day and post op day 1)	Glycemia:Mean Outcomes: Chi square, two-tailed ANOVA, multivariate log regression

Karnchanasorn et al. (2012)	Retrospective	Hyperglycemia Blood glucose > 150 mg/dL	All available morning blood glucose. Serum glucose; point-of-care testing.	<u>Glycemia</u>: Converted point-of-care values to serum. Blood glucose measured by mean +/- standard deviation. Differences test 1-way analysis of variance or *t*-test.. <u>Outcomes</u>: Least squares regression analysis used to examine relationships between blood glucose and outcomes.
Matias et al. (2013)	Retrospective	One or more fasting blood glucose > 100 mg/dL Looked at early (1 week prior to induction) and late hyperglycemia occurred after neutropenia	Serum fasting blood glucose	MV logistic regression for infection and mortality
Pidala et al. (2011)	Retrospective	Hyperglycemia Proportion of glucose values for each patient and median value calculation > 200 mg/dL	All available glucose Serum glucose; point-of-care testing	<u>Glycemia</u>:Mean, minimum, maximum and standard deviation <u>Outcomes</u>:Mean, median and modes standard deviations (continuous variables), frequency, proportion(categorical), Wilcoxan rank-sum, Fisher exact test, Kaplan-Meier (overall survival), Cox regression
Rentschler et al. (2010)	Retrospective	Hyperglycemia ≥ 2 fasting blood glucose ≥ 126 mg/dL or 1 blood glucose ≥2 00 mg/dL	All available glucose Serum glucose; point-of-care testing	<u>Glycemia</u>: Individual and average blood glucose over LOS were calculated. Median and quartile ranges (<101, 101–108, 109–120, 121–135, and >135 mg.dL), median glucose values compared using Wilcoxan-rank sum test. <u>Outcomes</u>: Categorical variables compared using test and chi square. Associations between time dependent variables using Cox proportional hazards regression.
Sheean et al. (2006)	Retrospective	Hyperglycemia ≥ 110 mg/dL ≥ 200 mg/dL	Fasting blood glucose	<u>Glycemia</u>: Recorded once per day for uniformity Total number of days and percentage of days above the two categories of hyperglycemia. Means, medians, modes and standard deviation <u>Outcomes</u>:Mean, median, standard deviations, Students unpaired t-test, Chi square, Wilcoxan rank-sum, multiple logistic regression (odds ratios)

Sheean, et al. (2013)	Retrospective	Hyperglycemia ≥ 7.0 mmol/L which equals 126 mg/dL	Fasting blood glucose	Glycemia: frequency, means, ranges, standard deviations. Transposed and examined longitudinally to depict average daily BG Outcomes: student t-–test, Wilcoxon rank sum test, Fisher's exact, Chi square Survival and mortality- Kaplan-Meier and Cox proportional hazards.
Soysal et al. (2012)	Retrospective	Hyperglycemia 140 mg/dL or greater	Random blood glucose	Glycemia:Mean, standard deviations, proportions Outcomes:Student t-test, Pearson, Chi square, Logistic regression (odds ratio)
Storey & Von Ah (2015)	Retrospective	Hyperglycemia FBG ≥ 126 mg/dL	Fasting blood glucose	Neutropenia and infection: Fisher's exact HLOS: Kaplan-Meier
Villereal-Garza et al. (2012)	Retrospective	Hyperglycemia >130 mg/dL	Fasting blood glucose	Glycemia: Arithmetic means, standard deviation, medians with ranges Outcomes: Mean, standard deviations (continuous variables), frequency, proportion(categorical), Chi square, Kaplan-Meier (overall survival), log rank tests(comparison among sub groups)
Weiser et al. (2004)	Prospective	Hyperglycemia ≥ 2 glucose determinations of ≥2 00mg/dL during the first 30 days of induction therapy.	Serum glucose	Glycemia: ≥2 glucose determinations of ≥ 200 mg/dL Outcomes: Kaplan-Meier (overall survival, complete remission duration), Chi square, Mann Whitney U test (differences in time to neutrophil recovery), Cox regression (independent predictor)

St.Vincent

Research & Regulatory Affairs
8402 Harcourt Road
Suite 805
Indianapolis, IN 46260
(317) 338-2194
Fax (317) 338-3058

September 13, 2013

Sue Storey, PhDc, RN, AOCNS
2001 W. 86th St.
Indianapolis, IN 46260

R2013-106: Malglycemia in the Hospitalized Acute Myeloid Leukemia Patient

Dear Ms. Storey:

This letter is to confirm that the above mentioned protocol was granted exempt approval by the St. Vincent Institutional Review Board on September 12, 2013.

Please note that research classified as exempt is not subject to continuing review and the other requirements of 45 CFR 46.

Approval by the IRB does not indicate institutional commitment of resources nor does it indicate privileges to perform new procedures. The Institutional Review Boards of St. Vincent Hospital and Health Care Center, Inc., are duly constituted Institutional Review Boards under 21 CFR Part 56 and operate in compliance with Good Clinical Practices and all applicable regulatory requirements.

Please direct all inquires to the Regulatory Affairs Office, 8402 Harcourt Road, Suite 120, Indianapolis, Indiana 46260; the telephone number is 317-338-2194.

Sincerely,

Chair and Co-Medical Director
Institutional Review Board
St. Vincent Hospital and Health Care Center, Inc.
/jlk

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ASCENSION
HEALTH

Core Values

We are called to:

Service of the Poor
Generosity of spirit for
persons most in need.

Reverence
Respect and compassion
for the dignity and diversity
of life.

Integrity
Inspiring trust through
personal leadership.

Wisdom
Integrating excellence
and stewardship.

Creativity
Courageous innovation.

Dedication
Affirming the hope and
joy of our ministry.

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**ST. VINCENT HEALTH
Research & Regulatory Affairs
(317) 338-2194**

fa2013-106

<u>DIRECTIONS</u>: This form is to be neatly typed and submitted to the IRB only when the investigator is contemplating the initiation of a research project which, in the investigator's judgment, is exempt from normal IRB review. The IRB will then determine whether the activity is covered by these regulations.

IRB Study Number::   Research Proposal Title:: Malglycemia in the Hospitalized Acute Myeloid Leukemia Patient

Research activities are exempt from regulations for the protection of human research subjects when the ONLY involvement of human subjects falls within one or more of the categories below. **These exemptions do not apply to research involving prisoners, fetuses, pregnant women, human in vitro fertilization, or when there is additional involvement of human subjects beyond the categories listed below, when deception of subjects may be an element of the research, or when the activity might expose the subject to discomfort or harassment beyond levels encountered in daily life. The exemption of categories 2 or 3 below of exempt research does not apply when individuals under the age of 18 are subjects of the activity, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.**

Effective April 14, 2003, the Health Insurance Portability and Accountability Act (HIPAA) now clarifies policies and procedures relating to de-identification of health information. Considerations for research that is exempt must qualify based on previous regulations (45CFR46) as well as HIPAA regulations when protected health information is used.

Check the appropriate category(ies) that applies to your research project:

☐   1.   Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special educational instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. [45CFR46.101(b)(1)]

☐   2.   This category applies only when the information gathered about the individual does NOT pertain to his/her health. Otherwise, see #3 below.

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless the following two conditions exist: (i) information obtained is recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation. For more details, see the 2nd list of categories below (#3). [45CFR46.101(b)(2)]

☐   3.   This category applies when the information gathered about the individual pertains to his/her health.

Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior as long as the subjects cannot be identified, directly or through identifiers linked to the subjects.   (See the list of identifiers under 7.d. below for details). [45CFR46.101(b)(2)]

☐   4.   All research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey or interview procedures or observation of public behavior that is not exempt under categories 2 or 3 above, (i) if the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. [45CFR46.101(b)(3)]

☐   5.   Research and demonstration projects which are conducted by or subject to the approval of Department of Health and Human Services (DHHS), and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs. [45CFR46.101(b)(5)]. The research or demonstration project must be conducted pursuant to specific federal statutory authority, must have no statutory requirement that an IRB review the project, and must not involve significant physical invasions or intrusions upon the privacy of the subjects.

IRB Study Number:
Research Proposal Title: Malglycemia in the Hospitalized Acute Myeloid Leukemia Patient

☐   6.   Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [45CFR46.101(b)(6)]

☒   7.   Research involving the collection or study of <u>existing</u> data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. [Note: *To qualify for this exemption <u>ALL</u> of the data, documents, records, or specimens must be in existence **before** the project begins*]. In addition, indicate which of the following apply(ies): [45CFR46.101(b)(4)]

☐
☐   a.   The data, documents, or records do NOT include health information.
    b.   The existing data, documents, records, pathological specimens, or diagnostic specimens utilized were obtained by written legal permission prior to April 14, 2003 (e.g. through an informed consent, a waiver of informed consent, or other expressed written legal permission).
        Please define:
☐   c.   The health information pertains only to decedents.
☒   d.   The health information is de-identified. (Note: to qualify for this exemption, either all identifiers must be removed or sufficient number of identifiers removed to be statistically de-identified. See the list of eighteen identifiers below or the Use and Disclosure of Health Information for Research Standard Operating Procedures for details.
        De-identified data must have the following data removed:
- Name
- All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip codes if the geographic unit of combining all the same three initial digits contains more than 20,000 people
- All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated in a single category of age 90 or older.
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URLs)
- Internet protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images; and
- Any other unique identifying number, character, or code.

If, after having completed the Exempt Research Checklist, the investigator still believes the study qualifies as exempt research, complete the rest of this page and submit the original to:

St. Vincent Research & Regulatory Affairs Department
8402 Harcourt Road, Suite 120
Indianapolis, IN 46260

Note that the study cannot be initiated until written acceptance for the IRB is given.

PLEASE ALLOW 5-10 WORKING DAYS FOR EXEMPT REVIEW PROCESSING.

SECTION I: INVESTIGATOR INFORMATION

Principal Investigator: Storey, Sue   **Department:** Clinical Nurse Specialist
(Last, First, Middle Initial)
Address: 2001 W. 86th St., Indianapolis, IN 46260   Phone: 317-338-5668   E-Mail: slstorey@stvincent.org
Contact Person: Sue Storey, PhD (c), RN, AOCNS   Phone: 317-338-5668   E-Mail: slstorey@stvincent.org

If this is a Student Research Proposal, List Name of the Student: Sue Storey   Phone: 317-338-5668

Research Proposal Title: Malglycemia in the Hospitalized Acute Myeloid Leukemia Patient
IRB Study Number:

Sponsor/Funding Agency:_____PI on Grant:_____
Sponsor Proposal #/Grant #:_____Period: From: to
Sponsor Type: ☐ Federal; ☐ State; ☐ Industry   ☐ Not-for-Profit   ☐ Unfunded;   ☐ Internally Funded
Grant Title (if different from research proposal title):

SECTION II: RESEARCH DESCRIPTION

Describe the general purpose, nature, and duration of the study, providing a description of the proposed research objectives and procedures below (in lay terms). Attach a copy of any research instruments (e.g. survey, questionnaire, interview guide).

The purpose of this retrospective descriptive study is to examine the prevalence and impact of malglycemia (hyperglycemia, hypoglycemia, and/or a combination of both hyperglycemia and hypoglycemia) on clinical outcomes (number of neutropenic days, infection, septicemia, sepsis, hospital length of stay, complete remission status and mortality) of patients hospitalized with acute myeloid leukemia. The hypotheses being tested are that there will be an association between hyperglycemia, hypoglycemia and/or a combination of both hyperglycemia and hypoglycemia on number of neutropenic days, infection, septicemia, sepsis, hospital length of stay, complete remission status and hospital mortality.

Signature of Principal Investigator: _x_____) RN, AOCNS **Date:** 9/4/13

SECTION III: EXEMPT REVIEW DETERMINATION

☒ Accepted

☐ Denied

Authorized IRB Printed Name: _____P.T. Hodgin, MD, MPH_____

Authorized IRB Signature: _____ **Date:** 9-12-2013
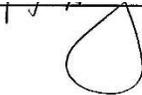
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Ziech, D., Franco, R., Georgakilas, A. G., Georgakila, S., Malmou-Mitsi, V., Schoneveld, O., . . . Panayiotidis, M. I. (2010). The role of reactive oxygen species and oxidative stress in environmental carcinogenesis and biomarker development. *Chemico-Biological Interactions, 188*, 334–339. doi:10.1016/j.cbi.2010.

CURRICULUM VITAE

Susan Storey

EDUCATION

Indiana University, Indianapolis, IN.
PhD in Nursing

Indiana Wesleyan University, Marion, IN.
Master of Science in Nursing

Indiana Wesleyan University, Marion, IN.
Bachelor of Science in Nursing

CERTIFICATIONS

Advanced Oncology Clinical Nurse Specialist (AOCNS)

PUBLICATIONS

Storey, S., & Von Ah, D., (2015). Prevalence and impact of hyperglycemia on hospitalized leukemia patients, *European Journal of Oncology Nursing, 19*(1), 13–17.

Autor, S., Storey, S., & Ziemba-Davis, M. (2013). Knowledge of palliative care: An evaluation of oncology, intensive care and heart failure nurses. *Journal of Hospice and Palliative Care Nurse, 15*(5), 307–315.

Reeves, D., Kam, T. & Storey, S. (2013). Oral antineoplastic handling at health care institutions in the United States: A survey of nurses and pharmacists. *Hospital Pharmacy, 48,* 308–313.

Von Ah, D., & Storey, S., Jansen, C., & Allen, D. (2013). Coping strategies and interventions for cognitive changes associated with cancer and cancer therapy. *Seminars in Oncology Nursing, 29*(4, Special Ed.), 288–299.

Iseminger, K., Burrato, C., & Storey, S. (In press). Ethics consultation and education in oncology: Enhancing the formation of "nurse-as-moral-agent". Book chapter. *Oncology Nursing Society*. Pittsburgh, PA.

Storey, S., & Von Ah, D. (2012). Impact of malglycemia on clinical outcomes in hospitalized cancer patients: A review of the literature. *Oncology Nursing Forum, 39*(5), 458–464.

Storey, S, Linden, E., & Fisher, M. (2008). Showcasing leadership exemplars to propel professional practice model implementation. *The Journal of Nursing Administration, 38*(3), 138–142.

Storey, S., Crist, L., Nelis, D., Murphy, L., & Fisher, M. L. (2007). Creation of a unique career enhancement program for a hospital-based education and development department. *Journal for Nurses in Staff Development, 23*(2), 55–62.

POSTERS

Storey, S., & Von Ah, D**.** *Malglycemia and health outcomes in hospitalized patients with acute myeloid leukemia* (abstract winner). St Vincent Research Symposium, Indianapolis, IN. June 17, 2015.

Storey, S., Brown, J., Foley, A., Newkirk, E., Powers, J., Barger, J., & Paige, K. *Comparative evaluation of antimicrobial coated versus non-antimicrobial coated peripherally inserted central catheters and associated complications: A prospective randomized control trial.* St. Vincent Research Symposium, Indianapolis, IN. June 17, 2015.

Gupta, N., Reeves, D., & Storey, S. *Outcomes of robotic surgeries for colorectal cancer at a community cancer center.* St. Vincent Research Symposium, Indianapolis, IN. June 17, 2015.

Storey, S., & Von Ah, D. *Hyperglycemia in elderly patients hospitalized with leukemia.* 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16–19, 2015.

Tang, C., Guilkey, R., Storey, S., Nielsen, A., & Von Ah, D. *Impact of depressive symptoms and fatigue on quality of life in breast cancer survivors.* 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16–19, 2015.

Guilkey, R., Storey, S., Tang, C., Nielsen, A., & Von Ah, D. *Pain and anxiety and quality of life in breast cancer survivors.* 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16–19, 2015.

Nielsen, A., Guilkey, R., Storey, S., Tang, C., & Von Ah, D. *Physical activity level and symptoms after diagnosis and treatment for breast cancer.* 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16–19, 2015.

Storey, S., & Von Ah, D. *Hyperglycemia among elderly patients with leukemia.* St. Vincent Research Symposium. Indianapolis, IN. June, 2014.

Storey, S., Brown, J., Foley, A., Powers, J., Newkirk, E., Barger, J., & Paige, K. *A comparative evaluation of antimicrobial versus non-antimicrobial peripherally inserted catheters on central line associated blood stream infections: An interim analysis.* St. Vincent Research Symposium. Indianapolis, IN. June, 2014.

Gupta, N., Freeman, R., Storey, S., Reeves, D. Ascioti, A., Davis, C., Dugan, T., Flanders, V., Givens, S., Heikal, M., Jhajria, S., Leagre, C., Liebross, R., Mahidhara, R., Martinez, B., Moallem, M., Shaynak, A., & Toney, B. *The implementation of a risk-directed lung cancer screening program at a community teaching hospital*. St Vincent Research Symposium. Indianapolis, IN. June, 2015.

Gupta, N., Storey, S., Reeves, D., & Shaynak, A. *Outcomes from a community hospital lung cancer screening program*. American Society of Clinical Oncology (ASCO). Chicago, IL. May, 2015

Storey, S., & Von Ah, D. *The impact of hyperglycemia on clinical outcomes of hospitalized patients*. Sigma Theta Tau International 42nd Biennial Convention. Indianapolis, IN. November, 2013.

Storey, S., & Von Ah, D. *Predictors of hyperglycemia in hospitalized patients with leukemia*. Oncology Nursing Society Research Conference. Dallas, TX. October, 2013.

Storey, S., & Von Ah, D. *Outcomes of hyperglycemia in the hospitalized leukemia patient* (abstract winner). St. Vincent Health Research Conference. Indianapolis, IN. June, 2013.

Storey, S., & Von Ah, D. *The impact of hyperglycemia on hospitalized leukemia patients*. Midwest Nursing Research Conference. Chicago, IL. March, 2013.

Storey, S., & Von Ah, D. *Malglycemia and clinical outcomes on the hospitalized leukemia patients*. Oncology Nursing Society Research Conference. Phoenix, AZ. November, 2012.

Storey, S., & Ziemba-Davis, M. *Malglycemia in oncology patients before and after implementation of a hyperglycemia protocol*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2012.

Reeves, D., Kam, T., & Storey, S. *Survey of pharmacists & nurses on oral antineoplastic handling precautions*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2012.

Storey, S., & Ziemba-Davis, M. *Malglycemia in oncology patients before and after implementation of a hyperglycemia protocol*. Purdue University Nursing Research Conference. November, 2012.

Storey, S., Ziemba-Davis, M., & Kussro, M. *Glycemic variations and outcomes in the hospitalized oncology patient*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2011.

Autor, S., Storey, S., & Ziemba-Davis, M. Knowledge of palliative care: Evaluating oncology, intensive care and congestive heart failure nurses and case managers. St. Vincent Health Research Conference. Indianapolis, IN. June, 2011.

Storey, S., Hubner, K., & Ziemba-Davis, M. *Effectiveness and cultural assimilation of an evidence-based practice program for nursing*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2011.

Powers, J., Brown, J., Coddington, A., Fischer, M., & Storey, S. *Evaluation of factors related to the development of central line related bloodstream infections*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2011.

Storey, S. Promoting a safe work environment: *The sampling of the operating room during intraoperative chemotherapy*. St. Vincent Health Research Conference. Indianapolis, IN. June, 2009.

Kussro, M., & Storey, S. Use of probiotics for decreasing the incidence of antibiotic associated diarrhea and clostridium difficile associated diarrhea. St. Vincent Health Research Conference. Indianapolis, IN. June, 2009.

Storey, S. *Evidence-based practice: Measurement of knowledge attitude skills and habits of participants before and after a formal EBP program*. Oncology Nursing Society. Advanced Practice Nursing Conference. Chicago, IL. November, 2007.

PRESENTATIONS

4/17/2015	Storey, S., & Von Ah, D. *Hyperglycemia in elderly patients hospitalized with leukemia*. 39th Annual Midwest Nursing Research Conference, Indianapolis, IN, April 16–19, 2015.
11/2014	Storey, S.**,** & Von Ah, D. *Glucose challenges in older adults: Hyperglycemia in hospitalized elderly patients with leukemia: A pilot analysis*. Gerontologic Society of America. Washington, DC, November 5–9, 2014.
06/2014	Storey, S., & Von Ah, D. *Hyperglycemia among elderly patients with leukemia.* St. Vincent Research Symposium. Indianapolis, IN.
11/2013	Storey, S., & Hubner, K. *Outcomes from a formal evidence-based practice program*. Sigma Theta Tau International, 42nd Biennial Convention. Indianapolis, IN.
10/2013	Storey, S., & Latty, S. *The magical transformation of a culture: Measuring outcomes of a professional practice model*. ANCC National Magnet Conference. Orlando, FL.
06/2013	Storey, S., & Von Ah, D. *Outcomes of hyperglycemia in the hospitalized leukemia patient*. St. Vincent Health Research Symposium. Indianapolis, IN.

03/2011	Fischer, M., & Storey, S. *Tracking CNS time for productivity, focus and research*. National Association of Clinical Nurse Specialists Conference.
10/2009	Hubner, K., & Storey, S. *Outcomes of a formal evidence-based program*. JoAnna Briggs Institute International Convention. Adelaide, AUS.
03/2008	Storey, S., & Jones, D. *The preparation, education implementation of a patient family initiated rapid response program*. National Association of Clinical Nurse Specialists Atlanta, GA.
03/2008	Storey, S., & Hubner, K. *The role of the Clinical Nurse Specialist in the development of a formal evidence-based practice program*. National Association of Clinical Nurse Specialists Atlanta, GA.
10/2008	*Implementing evidence-based practice*. Discussion Panelist. Purdue Calumet-Research Hammond, IN.
11/2008	*The St. Vincent evidence-based practice program*. IUSON Translational Research Luncheon. Indianapolis, IN.
06/2008	Storey, S., & Hubner, K. *Evidence-based practice: Measurement of knowledge, attitude, skills, and habits*. St. Vincent Health Research Conference. Indianapolis, IN.

RESEARCH EXPERIENCE

Hospital

11/2014–05/2015	*Outcomes of robotic surgery for patients with colorectal cancer*. Sub Investigator.
01/2014–present	*The implementation of a risk directed lung cancer screening program at a community teaching hospital*. Sub Investigator.
09/2013–05/2015	*A comparative evaluation of antimicrobial coated vs. non-antimicrobial coated peripherally inserted central catheters on the effect of central line related bloodstream infections*. Principal Investigator.
2007–2013	*Knowledge, attitudes, skills and habits of RN's before and after an evidence-based practice program implementation*. Principal Investigator.
2010–2012	*Glycemic variations and outcomes in the hospitalized oncology patient*. Principal Investigator.
5/2008	*Use of probiotics for decreasing the incidence of antibiotic-associated diarrhea and clostridium difficile associated diarrhea*. Sub Investigator.

1/2008	Product performance evaluation of a drainable fecal collector prototype. Sub Investigator.
4/2007	Environmental sampling of chemotherapy handling, administration and disposal in heated intraperitoneal chemotherapy (HIPEC) surgeries. Principal Investigator.
06/2005	*Development of the St. Vincent professional practice model.* Principal Investigator.

Hospital/Indiana University, Indianapolis, IN

09/2013–05/2015	Malglycemia and health outcomes in hospitalized patients with acute myeloid leukemia

PRECEPTORSHIP EXPERIENCE

08/2006–5/2010	Clinical Nurse Specialist preceptor Indiana University School of Nursing

DISSERTATION RESEARCH STUDY GRANT FUNDING

Sigma Theta Tau, granted February 2014. *Malglycemia in the hospitalized acute myeloid leukemia patient.* Role PI, $5,000.

Foundation, granted February, 2014. *Malglycemia in the hospitalized acute myeloid leukemia patient*. Role PI, $2,250.

PROFESSIONAL AFFILIATIONS & SOCIETIES

2006–present	National Association of Clinical Nurse Specialists
2006–present	Central Indiana Organization of Clinical Nurse Specialist (CIOCNS)
2006–present	Sigma Theta Tau International
2001–present	Oncology Nursing Society
2005–present	Central Indiana Oncology Nursing Society (CIONS)
2012–present	Midwest Nursing Research Society 2012-present
2006–2009	Toastmasters International Local Chapter–Indiana Vice President of Membership 7/07–6/08 Secretary 6/08–7/09
01/2006–08/2009	Institutional Review Board (January 2006–August 2009)

HONORS & AWARDS

Elite 50 Award–Indiana University–Graduate and Professional Student Government (April 2015)

Indiana University–Purdue University–Elite 50 Award (April 2015)

Indiana University Graduate School Travel Scholarship Award (November 2014)

Clinical Nurse Specialist Foundation Jan Bingle Scholarship Award (May 2014)

Indiana University School of Nursing William and Doris Rodie Dissertation Award (February 2014)

Indiana University School of Nursing PhD Leadership Fellowship Award (February 2014)

Sigma Theta Tau International Rising Star Award (November 2013)

Research Abstract Winner (Nursing category). St. Vincent Health Research Symposium (June 2013)

Oncology Nursing Society Susan Baird Excellence in Clinical Writing Award (May 2013)

Oncology Nursing Society Foundation Connections Research Conference Scholarship (November 2012)

Indiana University Graduate School Travel Scholarship Award (November 2012)

Walther Cancer Scholarship–Indiana University School of Nursing (October 2012)

Professional Nurse Recognition Award (May 2012)

Mary Humble St. Vincent Foundation Scholarship Award (April 2009)

COMMITTEE MEMBERSHIP

National

Glucose Control in Patients with Cancer Nursing Taskforce

Regional

Central Indiana Clinical Nurse Specialist Scholarship Committee