Prevalence of Steroid-Induced Hyperglycemia in Patients with Mantle Cell Lymphoma Receiving High Dose Steroids

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PREVALENCE OF STEROID INDUCED HYPERGLYCEMIA IN PATIENTS
WITH LYMPHOMA RECEIVING HIGH DOSE STEROIDS

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Date  

To the Dean for the School of Nursing:  

I am submitting a dissertation written by Veronica Brady and entitled "Prevalence of Steroid Induced Hyperglycemia in Patients with Lymphoma Receiving High Dose Steroids." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.  

Geri L. Wood, PhD, Committee Chair  

We have read this dissertation and recommend its acceptance:  

[Signatures]  

Accepted  
Dean for the School of Nursing
ACKNOWLEDGMENTS

The completion of this stage in my education has not been without sacrifices both personally and professionally, however throughout this process I have been gifted along the way with people who have encouraged, supported and prayed for me.

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Abstract
Prevalence of Steroid-Induced Hyperglycemia in Patients with Mantle Cell Lymphoma Receiving High Dose Steroids
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Background
Hyperglycemia as a result of glucocorticoid administration (steroid-induced hyperglycemia [SIH]) occurs in 32-37% of adult patients with cancer both with and without previous history of diabetes. Patients diagnosed with mantle cell lymphoma (MCL) are often treated with chemotherapy regimens that include high dose steroids as first line therapy. Little is known about the prevalence of steroid-induced hyperglycemia in patients with MCL receiving high dose steroids. Moreover it is not known if how the resulting hyperglycemia is managed impacts time to relapse or death.

Purpose
The primary aim of this study was to determine the prevalence of SIH in MCL patients with and without pre-existing diabetes receiving high dose steroids. The secondary aims were to: (1) determine the persistence of resulting hyperglycemia, (2) determine how hyperglycemia was managed, (3) and to examine the association between hyperglycemia and time to relapse or time to death.

Methods
A retrospective chart review was conducted, of electronic health records of patients over the age of 18, with diagnosis of MCL, receiving treatment at UT MD Anderson Cancer Center between 1/1/2000 through 12/31/2010.

Results
SIH occurred in 127 patients (70% of the cohort), with 57% of SIH being associated with the first cycle of chemotherapy (during or following the 1st course of steroids). Higher mean baseline blood glucose (p=0.0290) and history of diabetes (p=0.0013) were the only factors found to be related to the development of SIH. Hyperglycemia was found to be persistent at 3-6 months in 3 (7%) of the 46 patients with history of diabetes and 4(5%) of the 81 patients with no history. There was no significant difference in SIH management between those with and
without persistent hyperglycemia (p=0.8839) and management of SIH did not show a significant impact on time to relapse or death.

Conclusions

Steroid-Induced hyperglycemia is prevalent in patients receiving high dose steroids with and without history of diabetes with glucose elevations persisting in 5-7% of patients after steroids have been discontinued. However, this retrospective study does not show that SIH has a significant impact on time to relapse or time to death. Prospective studies designed to examine the relationship between the degree of hyperglycemia, the number of hyperglycemic events and time to relapse and death are needed.

Key words: Steroids, hyperglycemia, cancer
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Summary of the Study

The dissertation consists of the dissertation proposal which components include: specific aims, background and significance, preliminary studies, research design and methods, research subject risk and protection, literature cited and appendixes. Also included in the dissertation is the preliminary manuscript entitled "Prevalence of steroid induced hyperglycemia in patients with mantle cell lymphoma receiving high dose steroids, which reports the findings of this research study. The research study was approved by the University of Texas MD Anderson Cancer Center IRB (appendix A) as well as the University of Texas-Health Science Center (appendix B).

The primary aim of this study was to determine the prevalence of steroid induced hyperglycemia (defined as blood glucose >200mg/dL) in patients with and without pre-existing diabetes receiving high dose steroids. Secondary aims included: (1) to examine the association between occurrence hyperglycemia and time to treatment failure in patients with pre-existing diabetes and those with steroid induced hyperglycemia and (2) to determine management of hyperglycemia (use of anti-hyperglycemic medications) in patients with pre-existing diabetes and those with steroid induced hyperglycemia.

In order to explore the aims of the study a retrospective chart review was conducted. Demographic and disease related variables were correlated with blood glucose levels.

Initially the plan was to review records of all adult patients with hematologic malignancies who received fractionated cyclophosphamide,
vincristine, doxorubicin and dexamethasone (hyper-CVAD) as part of their
treatment. This population would include patients with leukemia, lymphoma and
multiple myeloma. However discussions with members of the dissertation
committee resulted in population being limited to patients with lymphoma or
multiple myeloma receiving steroid doses 4x physiologic (dexamethasone 4mg or
methylprednisolone 20mg). After additional meetings with fellow researchers
within the department of Internal Medicine as well as Endocrinology, the
population was further defined as patients with lymphoma being treated between
the years of 2000-2010. Information obtained from tumor registry staff at
MDACC revealed that this would involve approximately 12,700 patient records, of
which only 3,500 received some portion of their treatment at MD Anderson
Cancer Center. Concern about potential differences in patients with B-cell
lymphoma vs T-cell lymphoma vs Mantle cell lymphoma lead to the final
population of interest being those patients newly diagnosed with MCL receiving
treatment at MDACC with potential for follow up for at least one year. Preliminary
discussions with tumor registry staff indicated that there were 438 potential
subjects. The final number of patients with a histologic diagnosis of MCL was
318. This population of patients was chosen due to the fact that it allows for the
examination of homogenous group of patients who have the characteristics
required for this study. This population of patients receives similar doses of
steroid with repeated exposures and is hospitalized for a portion of their
treatment (making obtaining of information regarding blood glucose
measurements and medications administered feasible). The time frame of 2000-
2010 was chosen in that it allowed adequate time for information to be abstracted from hospital records and downloaded into the tumor registry database. As well as to allow adequate time for patients to reach the endpoints of interest, (cancer outcomes—time to relapse and time to death). The final results were that the EHRs of 318 adult patients (>18 years), diagnosed with MCL being treated at The University of Texas MD Anderson Cancer Center between 1/1/2000 – 12/31/2010 were reviewed.

Data from the EHR was initially abstracted using the Data Abstraction Tool (DAT) (appendix D) with variables being defined as outlined in the code book (appendix E). After determining that the data could indeed be abstracted from the EHR, in order to expedite the process, data on variables indicated in the study protocol (Appendix I) were requested from laboratory, pharmacy and clinical operations informatics using the appropriate request forms (Appendices F and G, the clinical operations form is not available). The data was then “dumped” into the appropriate excel spread sheets and cleaned.

During the course of the study it was determined that adequate information on the outcomes defined in the proposal (diabetic ketoacidosis, hyperosmolar non-ketotic state, infections, sepsis, failure to thrive, etc.) were not documented in the EHR, therefore the cancer outcomes were changed to time to relapse and time to death.

The principle findings of this study are reported in the manuscript entitled “Prevalence of steroid induced hyperglycemia in patients with mantle cell lymphoma receiving high dose steroids. Seventy percent of the patients
developed hyperglycemia. Also, higher mean baseline glucose and history of diabetes were the only factors found to be related to the development of steroid induced hyperglycemia. The rate of persistence was low at 5% for those with no history of diabetes and 7% for those with history of diabetes. There was no significant difference in how the resulting hyperglycemia was managed between those with and without persistent hyperglycemia and management did not show a significant impact on time to relapse or time to death.

Appendices A-N include the following materials: UT M.D. Anderson Cancer Center IRB Approval, UT Centralized IRB Review, CPHS IRB UTHSC Confirmation Letter, Data Abstraction Tool, Code Book, Laboratory Data Request, Pharmacy Informatics Data Request Form, Certificate of human subjects protection training, UT M.D. Anderson Cancer Center Protocol PA13-0900, Publications by author related to steroid induced hyperglycemia, and curriculum vitae.
Proposal

Specific Aims

Hyperglycemia as a result of glucocorticoid administration (steroid induced hyperglycemia) in adult patients with cancer is a common occurrence, reported to occur in up to 32-37% of patients (Weiser, et al 2004; Yeung, et al) both with and without previous history of diabetes. Untreated hyperglycemia in patients with cancer may result in impaired wound healing, endothelial dysfunction, decreased immune function, disruption of homeostasis, increased inflammatory cytokines, and increased oxidative stress (Curtis, 2006; Freeland & Funnell, 2012; Patel et al., 2009). Steroids lead to an increase in insulin resistance in all patients and hyperglycemia in many (Clore & Thurby-Hay, 2009). Cumulative dose (higher doses) and duration of exposure increases the risk for steroid induced diabetes (Hwang & Weiss, 2013; Kwon & Hermayer, 2013).

Steroid induced hyperglycemia can often go undetected. Baldwin & Apel (2013) reported that 24 % of patients without history of diabetes treated with glucocorticoids were not monitored while hospitalized. Lack of treatment or under treatment may lead to steroid induced diabetes, which has the same overall health sequela as Type 2 diabetes (T2DM) (Kwon & Hermayer, 2013).

Patients diagnosed with mantle cell lymphoma (MCL) are often treated with chemotherapy regimens that include high dose steroids as first line therapy. Treatment usually consists of 6-8 cycles of chemotherapy given over several months. A study by Weiser et al. (2004) indicated that 37% of patients experienced hyperglycemia (BG > 200mg/dL) during induction therapy with hyper-
CVAD. Studies done in the adult patients with hematologic malignancies, examining the impact of hyperglycemia on clinical outcomes indicate that patients who were over the age of 60 and experienced blood glucose levels greater than 180mg/dL had poorer overall survival and were more likely to develop complicated infections (Vu et al., 2012; Weiser et al., 2004). The study by Vu et al. (2012) also indicated that patients who were on Metformin or Thiazolidinediones (TZDs) had longer progression free survival (PFS).

The primary aim of this study is to determine the prevalence steroid induced hyperglycemia in patients with MCL, following treatment with high dose steroids (dexamethasone 20-40mg daily). The secondary aims are to: (1) determine the persistence of resulting hyperglycemia, (2) determine association between hyperglycemia and selected cancer outcomes and (3) determine how hyperglycemia was managed.

**Hypothesis 1:** Patients with prolonged exposure (≥ 2 exposures, lasting ≥ 2 days) to high dose steroids will develop steroid induced hyperglycemia (Hwang & Weiss, 2013).

**Hypothesis 2:** Patients who received treatment for hyperglycemia with Metformin or TZDs have longer PFS (Vu et al. 2012). The specific aims are to:

**Aim 1.** Determine the prevalence of hyperglycemia, defined as blood glucose >200mg/dL, in patients with and without pre-existing diabetes receiving high dose steroids:

- 1a. Before first cycle of chemotherapy
- 1b. During chemotherapy
1c. Post treatment with steroids

**Aim 2.** Examine association between occurrence of hyperglycemia and time to treatment failure in patients with pre-existing diabetes and those with steroid induced hyperglycemia.

**Aim 3.** Determine management of hyperglycemia (use of anti-hyperglycemia medications) in patients with pre-existing diabetes and those with steroid induced hyperglycemia.

- 2a. Prior to chemotherapy
- 2b. During chemotherapy
- 2c. Following completion of chemotherapy

**Background and Significance**

**Non-Hodgkin's Lymphoma**

The term Lymphoma identifies hematologic malignancies arising from the lymphatic system. Lymphoma develops as the result of white blood cells (lymphocytes) undergoing malignant changes and replicating out of control (Leukemia and Lymphoma Society, 2013). Healthy cells are eventually displaced and malignant lymphocytes accumulate in the liver, spleen, gastrointestinal tract and lymph nodes (Vose, 2012). Lymphoma is classified as either Hodgkin's lymphoma (HL) or non-Hodgkin lymphoma (NHL). HL affects fewer numbers than NHL. Approximately 9,000 persons are expected to be diagnosed with HL in the United States in 2013 compared to approximately 70,000 with NHL. NHL is a diverse group of diseases distinguished by the cancer cells associated with the disease type. The distinction of either indolent or
aggressive is applied to NHL types, with each being associated with factors that affects prognosis. NHL is the seventh most common cancer in women and the sixth most common in men. The incidence increases with age. From age 60-64 the rate increases 17 times (44.6 case/100,000) and from age 80-84 the rate increases more than 47 times (119.7 cases/100,000 population). The five year survival rate for persons with NHL is approximately 71% (Leukemia & Lymphoma Society 2013).

**Mantle Cell Lymphoma.**

Mantle cell lymphoma (MCL) is a B-cell lymphoma. MCL represents a classification of non-Hodgkin’s lymphoma which has several subtypes: (a) classical- indolent clinical course, (b) small cell –mimics lymphocytic lymphoma or B-cell Chronic Lymphocytic Leukemia (B-CLL), (c) pleomorphic –mimics large B cell lymphoma or (d) blastic –which mimics lymphoblastic lymphoma or Acute Lymphoblastic Leukemia (ALL) (Frizzera, 1997; Cortelazzo, Ponzoni, Ferreri and Dreyling, 2011; Smith, 1996). Although MCL is rare, the incidence has increased in the United States- primarily among the elderly, and accounts for 3-10% of all NHL (Cortelazzo et al.; 2011; Doorduijn & Kluin-Nelemans, 2013). The possible etiology of MCL, much like that of NHL, includes exposure to particles, dust, smoking, hair dyes as well as chemical substances such as insecticides, pesticides, solvents and fertilizers. MCL may also have a genetic predisposition. MCL occurs primarily in adults between ages of 60 and 65 years with a higher incidence in males, with males accounting for 60-70% (Doorduijn, & Kluin-Nelemans, 2013). Failure free survival (FFS) times of 10-14
months and complete remission rates of 20-50%, with median overall survival (OS) rates of 2-4 years have been reported (Romaguera et al., 2005). Currently the overall median survival for patients with the pleomorphic or blastic subtypes of MCL is approximately 5 years with 8% surviving more than 10 years.

**Comorbidities and Hematologic Malignancies**

The most common co-morbidities found among patients with hematologic diseases included: hypertension, coronary disease, heart failure, diabetes, chronic obstructive pulmonary disease, arrhythmias and renal failure (Najam, Andre, and Gorin, 2009). Patients reported diabetes, hypertension, myocardial infarction, stroke, and arterial disease as medical late effects of treatment (Baker et al., 2006). Goldberg, et al. (2010) noted an increase in the prevalence of diabetes, dyspnea, hepatic disease and infections among Medicare beneficiaries with myelodysplastic syndromes (a hematologic malignancy) in the United States. Mitri, Castillo, et al. (2008) reported that when compared with persons without diabetes, patients with a history of diabetes had a risk ratio of 1.19-1.41 of developing NHL.

Although NHL in adults is not considered to be one of the most prevalent cancers, the incidence and the decreased survival rate requires further attention. Evaluation of the impact of steroid induced diabetes is particularly relevant due to the fact that patients are diagnosed with NHL at a younger age, receive high dose steroids as part of the treatment regimen, and usually survive long enough to develop side-effects of uncontrolled diabetes. It has yet to be determined if co-
morbid diseases in these persons are treated optimally, whether the disease free survival interval for adults with NHL may be increased.

**Treatment of Mantle Cell Lymphoma**

First line treatment of mantle cell lymphoma (MCL) is chemotherapy. As knowledge of the disease has increased, the combinations of chemotherapeutic agents have varied slightly over the last 10 years. Chemotherapy combinations have consisted of fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD), or Rituximab(R) plus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or R-CHOP, or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) or dexamethasone, high dose cytarabine and cisplatin (DHAP) all with or without stem cell transplant (SCT). The two most common chemotherapy regimens are R-CHOP and hyper-CVAD, +/- Rituximab alternating with Rituximab plus Methotrexate and Cytarabine. In the R-CHOP protocol Prednisone (60mg/m²/day) is given on days 1-5 in each cycle and treatment with hyper-CVAD requires dexamethasone 20-40mg to be given on days 1-4 or 2-5 and 11-14 or 12-15 of each cycle. The chemotherapeutic agents are administered every 21 days for a total of 6-8 cycles either on inpatient or outpatient basis (Caballero et al. 2013, Vose, 2012, Romaguera, 2005). Hyperglycemia as a result of patients receiving these high doses of steroids is a common occurrence among patients with and without a previous history of diabetes.
Glucocorticoids Used in Treatment of MCL

The treatment regimens for MCL generally involve one of two glucocorticoids, dexamethasone 20-40 mg/day times 4 days on days 1-4, 11-14 and or prednisone 100mg/day on days 1-5. Glucocorticoids are known to have strong immunosuppressive and anti-inflammatory properties. Glucocorticoids are utilized for their anti-leukemic properties, and dexamethasone has been shown to be 5-16 times more cytotoxic than Prednisone (Belgaumi et al., 2003). In lymphoid disease glucocorticoids inhibit glucose transport/phosphorylation thus decreasing available intracellular energy. Glucocorticoids also impede cell mitotic division and inhibit protein synthesis resulting in apoptotic cell death (Coleman, 1992; Laane1 et al., 2009). Therefore, the use of these drugs is critical in the chemotherapy regimen when obtaining remission is essential. Although Prednisone is used in some cases, Dexamethasone is usually the glucocorticoid of choice. The primary goal of the drug is to effect leukemic blast cell kill.

Steroid Induced Hyperglycemia/Diabetes

One of the most common problems that impact the adult patient with hematologic malignancies receiving high dose steroid treatment is hyperglycemia. Hyperglycemia is defined as fasting blood glucose readings ≥ 126mg/dL and random blood glucose readings ≥ 200mg/dL (American Diabetes Association, (ADA) 2013). Hyperglycemia is usually a side effect that occurs as the result of treatment, but often times may be due to poorly controlled pre-
existing diabetes. Glucocorticoids are known to have a deleterious effect on
glycemic control. Prolonged exposure to dexamethasone and prednisone leads
to hyperinsulinemia, inhibitory effects on β cell function and is associated with
development of diabetes (van Raalte, Ouwens, & Diamant, 2009). This negative
effect is believed to be due to a variety of factors including: increased insulin
resistance, increased glucose intolerance, decreased peripheral insulin
sensitivity, reduced β cell mass due to β cell dysfunction, and increased hepatic
insulin resistance leading to impaired suppression of hepatic glucose production
(Vigneri et al. 2009; Trence, 2003; Oyer, Shah, & Bettenhausen, 2006; Simmons,
Molyneaux, Yue, & Chua, 2012). Although the belief is that steroid induced
hyperglycemia resolves once steroids are tapered or discontinued, this may not
be true in every case. Trence (2003) suggests that all patients receiving high
dose steroids should be monitored throughout their treatment for development
and persistence of hyperglycemia.

Diabetes is defined as a group of diseases marked by high levels of
blood glucose as a result of defects in insulin production, insulin action or
both. The diagnosis of diabetes is made when fasting glucose on two
separate occasions is ≥126mg/dL, non-fasting glucose ≥200mg/dL with
symptoms or hemoglobin A1c ≥6.5% (ADA, 2013). Steroid induced
diabetes (SIDM) is defined as an abnormal elevation in blood glucose in
persons with and without diabetes as a result of use of glucocorticoids
(Hwang and Weiss, 2013).
Risks associated with steroid-induced hyperglycemia or diabetes is obesity, lack of physical exercise, impaired glucose tolerance, family history, ethnicity and older age (Trence, 2003; Hwang & Weiss, 2013; Fong & Cheung, 2013; Clore & Thurby-Hay, 2009). Conversely according to a study conducted by Simmons et al. (2012) patients who developed new onset steroid induced diabetes (NOSID) weighed less and had less family history of diabetes.

Hyperglycemia related to treatment of hematologic malignancies with dexamethasone occurs at varying rates. Most studies, which have been conducted in the pediatric population suggest rates of hyperglycemia between 10-56% (Roberson, Raju, Shelso, Pui and Howard, 2008; Baillargeon, et al. 2005; Belgaumi, et al. 2003; Sonabend, et al. 2008). However, a study by Weiser et al. (2004), of 278 adults with previously untreated ALL who received dexamethasone as part of their treatment regimen identified hyperglycemia in 37% of these patients.

Several other studies also support these results. A retrospective study by Yeung et al. (2013) of myeloma patients who received steroids as part of their chemotherapy regimen found that 31.7% developed steroid induced diabetes. Pilkey, Streeter, Beel, Hiebert and Li (2012) reported an odds ratio for development of steroid induced diabetes among non-cancer patients of 1.5-2.5. While Gulliford, Charlton, and Latainovic (2006) noted an odds ratio of 1.36 to 2.31 and that 2% of incident cases of diabetes were associated with oral glucocorticoids in a primary care
population. There was 12% incidence of steroid induced hyperglycemia in elderly patients who received glucocorticoids (Kwon & Hermayer, 2013). Among patients with a previous history of diabetes the prevalence of steroid induced hyperglycemia has been documented as 20-50% (Umpierrez et al., 2012). Donihi, Raval, Saul, Korytkowski, and DeVita (2006) and Iwamoto, Kagawa, Naito, Kuzuhara, and Kojima (2004) reported that ≥50% of patients without known diabetes who received high dose steroids (≥ 30mg Prednisone or the equivalent) for ≥ 2 days experienced at least one episode of hyperglycemia and if exposure was >2 weeks patients developed steroid induced diabetes. Fong and Chueng (2013) reported that in the 94% of patients with no previous history of diabetes, who developed hyperglycemia associated with steroids the glucose elevation occurred within 48 hours of the steroid dose being administered. Also a recent study by Gonzalez-Gonzalez, Mireles-Zavala et al. (2013) reported that NHL and ALL patients who received at least 1mg/kg/day of prednisone for 2-3 months had an incidence of 40.6% of secondary diabetes with hyperglycemia occurring between the second and fourth week of treatment. There is little information available regarding the prevalence of steroid induced hyperglycemia in patients who are being treated or those who have completed treatment with high dose steroids following diagnosis of MCL.
Management of Hyperglycemia/Diabetes

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologist (AACE) identify four classes of diabetes: (1) type 1, (2) type 2, (3) drug or chemical induced and (4) gestational. Life style modification consisting of diet and exercise are suggested modes of management of hyperglycemia/diabetes followed by oral agents (sulfonylureas, metformin, TZDs) (Clore and Thurby, 2009, Kwon & Hermayer, 2013, Umphierrez et al., 2012, ADA, 2013, AACE, 2013). Oyer et al. (2006) recommend treating steroid-induced hyperglycemia, drug induced hyperglycemia and steroid induced diabetes similarly. Proposed first line medication therapy for all patients with diabetes is Metformin, if not contraindicated and if it can be tolerated (AACE, 2013; ADA, 2013). However patients with cancer receiving chemotherapy may often experience decreased appetite, nausea, vomiting, and diarrhea all of which make management of hyperglycemia with oral agents somewhat of a challenge (Oyer, 2006). Insulin therapy (either as sliding scale insulin [SSI] or basal bolus insulin [BBI] is recommended for severe hyperglycemia. For years SSI has been used to treat hyperglycemia. SSI insulin is prescribed at the discretion of the provider (Patel et al. 2009). According to the ADA (2013) SSI is ineffective in the majority of patients and often results in hypoglycemia as well as continued hyperglycemia. The use of BBI with short acting insulin analogs before meals is recommended for the most effective management of
diabetes when insulin is required (ADA, 2013; Baldwin & Apel, 2013; Gosmanov, Goorha, Stelts, Pen, & Umpierrez, 2013, Trence, 2003). However there has been no consensus on the units/kg/day or the percent of basal to bolus insulin with which to begin treatment.

**Effects of Hyperglycemia on Cancer Outcomes**

Weiser et al. (2004) indicated that the 37% of patients who experienced hyperglycemia (BG> 200mg/dL) during induction therapy with hyper-CVAD had shorter median survival, shorter complete response duration, and were more likely to develop complicated infections than those who did not develop hyperglycemia. Vu et al. (2012) examined the impact of hyperglycemia in patients with acute lymphoblastic leukemia on clinical outcomes. Data suggests that patients who were ≥ 60 years of age and experienced blood glucose levels greater than ≥180mg/dL had poorer overall survival as well as poorer progression free survival (PFS). This study also indicated that patients receiving Metformin or thiazolidinedione’s (TZDs) had longer PFS. Studies on the prevalence of steroid induced hyperglycemia in adults treated for hematologic malignancies and management of resulting hyperglycemia are lacking. Similarly little is known about the late effects of high dose steroids on glucose metabolism, glycemic control or overall cancer survival.
Research Strategy

Significance

This study addresses the limited information that is currently available regarding the prevalence of steroid induced hyperglycemia, as well as steroid induced diabetes among patients with MCL lymphoma who are treated with high dose steroids. Currently steroid induced hyperglycemia is being regarded as a transient side effect of treatment with high dose steroids without long term sequela. Results of this study may lead to more rigorous monitoring of blood glucose while patients are receiving steroids.

Innovation

This study is innovative in that it addresses the need for information regarding the impact of steroids on the progression of hyperglycemia or development of steroid induced diabetes among patients with MCL who have experienced repeated steroid exposure. Steroid-induced β-cell dysfunction causes insulin resistance which leads to hyperglycemia. The use of steroids may unmask or lead to new onset diabetes. However, there is a lack of information regarding the prevalence of steroid induced hyperglycemia among this cohort of patients. Information gained from this study may lead to a change in the management of steroid induced hyperglycemia. In particular it may heighten awareness that steroid induced hyperglycemia may lead to diabetes, which is a chronic illness,
requiring long term management and thus long term implications for MCL survivors.

Approach

Preliminary Studies

In 2008 the Principal Investigator (PI) conducted a retrospective chart review of 34 patients with ALL or lymphoma who received hyper-CVAD containing dexamethasone 40-80mg for 4 days. This cohort of patients experienced hyperglycemia prior to consultation, and all of them required insulin therapy for management of blood glucose. Despite receiving, on average, 1.2 units/kg/day of insulin the average blood glucose reading was 235 mg/dl (46-483 mg/dl) (Brady, 2008). During subsequent cycles these patients required somewhat higher doses of insulin than during the previous cycle. Review of this data revealed that patients with and without previous history of diabetes experienced significant hyperglycemia.

Research Design

This study will use a retrospective chart review to explore the study aims. Demographic and disease related variables will be correlated with blood glucose levels.

Sample and Setting

Data from the charts of adult patients (>18 years) diagnosed with mantle cell lymphoma, receiving treatment at the University of Texas M. D. Anderson Cancer Center between 1/1/2000-12/31/2010 will be obtained.
Patients previously receiving treatment for lymphoma, those with relapsed disease and those who do not complete treatment at MD Anderson Cancer Center will be excluded. A list of patients meeting the inclusion criteria will be obtained from the MD Anderson Cancer Center Tumor Registry. The charts of all subjects diagnosed with mantle cell lymphoma between 1/1/2000 and 12/31/2010 will be reviewed. It is estimated that a total of 438 charts will be reviewed.

**Data Collection**

After obtaining IRB approval data will be abstracted from charts into the data abstraction tool (see Appendix A).

**Demographics and Disease Related Variables—See Appendix A.**

**Demographic Information—** Demographic information will be obtained from tumor registry or extracted from the electronic health record (EHR) including: gender, race, date of birth, height, weight (at diagnosis and at last documented clinical visit), body mass index (BMI), diagnosis, date of diagnosis, stage of disease, marital status, occupation, surrogate income (based on pay codes), zip code, treatment start and end dates, date last seen at MD Anderson and vital statistics.

**Comorbidities—** Information on comorbid diseases such as, hypertension, kidney disease, heart disease, and hyperlipidemia as well as information on pre-existing diabetes or family history of diabetes will be obtained from Clinical Operations Informatics or EHR.
High Dose Steroids- High dose steroid is defined as a minimum of
dexamethasone 20-40mg, methylprednisolone 240mg or the equivalent
given daily for 2-4 days per chemotherapy cycle. Steroid induced
hyperglycemia, is defined as the blood glucose values >200mg/dL
observed within a cycle following the administration of high dose steroids.
Data on steroids prescribed and dispensed (product name, number of
doses and amount per dose) will be obtained from Pharmacy Informatics
for each cycle.

Laboratory Data- Each patient is expected to receive 2-6 blood
glucose readings daily. (6-36 measurements within 6 cycles of
chemotherapy), 2-4 measurements after each cycle and 4 follow up
glucose measurements at 3, 6, 12 and 24 months after completion of
therapy. (The blood glucose measurements will be considered random-
due to the fact that in patients can receive food on demand and patients
are not consistently fasting when they come in for outpatient lab work.)
Blood urea nitrogen (BUN) and creatinine are expected to be measured
during each cycle, between cycles and at 3, 6, 12 and 24 months after
completion of therapy. This information will be obtained from Laboratory
Informatics Systems

Antidiabetic Medications- Anti-diabetic medications that patient is
currently taking or those that are prescribed and dispensed (product
name, number of doses and amount per dose) during treatment, and
those that patient is on at the time of last documented clinic visit will be obtained from pharmacy informatics or extracted from the EHR.

**Outcomes** - Information on the sequela of hyperglycemia such as, diabetic ketoacidosis (DKA) or hyperosmolar non-ketotic (HHN) and its treatment (insulin drip, transfer to ICU), as well as outcomes: infections (pneumonia), sepsis (septic shock), prolonged hospital length of stay (hospital stay beyond the 4-5 days required for chemotherapy), failure to thrive, multi-organ failure and mortality will be abstracted from the chart.

This information will be downloaded into the Data Abstraction Tool (Appendix C).

**Data Confidentiality Procedures**

Confidentiality of data will be maintained in a variety of ways. HIPAA information will be collected, but will be replaced by a study number in the analytical file. Patients will be identified only via their study number, which will be independently assigned for purposes of the study. These identifiers will be maintained in a locked cabinet on iron key hard drive with access attainable only by the principle investigator. Data will be stored in a database on a computer that is password and firewall protected. Data will be accessed only by the PI and collaborators. Complete confidentiality will be maintained during this retrospective evaluation, manuscript preparation and submission. Study data will be destroyed 2-3 years after data analysis is complete and no additional information is needed from source files.
There will be a link between the patients MRN and the unique identifier; however this information will be locked in the PIs office wand kept in a locked file. Any electronic information will be kept on a password protected institutional computer.

Request for Waiver of Consent/Authorization

A waiver of Informed Consent is requested because this is a retrospective chart review that involves no diagnostic or therapeutic intervention, as well as no direct patient contact and less than minimal risk to patients. The waiver of consent will enable the researchers to retrospectively analyze subject data and will not adversely affect the rights and welfare of the subjects. Due to the fact that this is a retrospective chart review the PI does not anticipate violating the rights or welfare of the patients or their information. Nor will we be intervening in their medical care.

Study staff is unable to obtain consent from study subjects due to the fact that many of the patients being studied are either deceased or no longer being treated at MD Anderson Cancer Center. It is not practical to conduct this research without this waiver since the status of the patient is unknown, i.e. whether they are alive or deceased and it is difficult to trace the whereabouts of the patient.

Procedure to Obtain Informed Consent

A Waiver of Informed Consent was approved and therefore no attempts will be made to contact the patients directly.
Instruments

Data Abstraction Tool (DAT)

The data abstraction tool was developed by the PI in collaboration with Jeffrey Cui (data base developer) and designed to capture information related to the diagnosis and treatment of lymphoma, management of any resulting hyperglycemia, medications taken by patients, comorbidities, etc.

Methods for Data Analysis

This is a retrospective study on the prevalence, persistence and management of steroid induced hyperglycemia, and impact on survival among MCL patients at MD Anderson. The primary aim of this study is to determine the prevalence of steroid induced hyperglycemia in patients with mantle cell lymphoma, following treatment with high dose steroids. With secondary aims being to: (1) determine the persistence of resulting hyperglycemia (2) determine if hyperglycemia impacted selected cancer outcomes and (3) determine how hyperglycemia was managed.

Descriptive analyses including summary statistics and graphic methods will be used to describe the demographic and clinical characteristics of approximately 438 MCL patients.

All cases for which there is at least one blood glucose result per chemotherapy cycle and patient has received high dose steroids for a minimum of two days will be included in the analysis. All cases for which the variable of interest is present will be analyzed. For evaluation of blood glucose readings, the average of all available readings for that cycle will be used for analysis.
**Hypothesis 1.** Patients with prolonged exposure (≥ 2 exposures lasting ≥ 2 days) to high dose steroids will develop steroid induced hyperglycemia

- **Aim 1.** Determine the prevalence of hyperglycemia, defined as blood glucose > 200 mg/dL in patients with and without pre-existing diabetes receiving high dose steroids:
  
  1a. Before first cycle of chemotherapy
  
  1b. During chemotherapy
  
  1c. Post treatment with steroids

For Aim 1: Among the patients who don’t have a diabetes history before treatment, we will report the prevalence of steroid induced hyperglycemia (occurrence of at least one blood glucose measurement ≥ 200 mg/dL) within the treatment period (per cycle and overall total during treatment). Among the steroid induced hyperglycemia patients, the 3-month, 6-month, 1 and 2-year persistence of hyperglycemia will be assessed using random glucose measurements obtained at the time of follow up clinic visits.

**Hypothesis 2.** Patients who received treatment for hyperglycemia with Metformin or TZDs have longer PFS.

- **Aim 2.** Examine association between occurrence of hyperglycemia and time to death in patients with pre-existing diabetes and those with steroid induced hyperglycemia.

For Aim 2: To measure the degree of hyperglycemia, we will use (1) maximum of blood glucose values, (2) overall percentage of blood glucose values > 200 mg/dL, (3) the cycle number of first observing steroid induced
hyperglycemia, and (4) the number/percentage of cycles observing steroid induced hyperglycemia. To measure how well the hyperglycemia was managed, we will use (1) the percentage of blood glucose values >200mg/dL after the cycle first observing steroid induced hyperglycemia, and (2) the percentage of cycles observing steroid induced hyperglycemia after first observing steroid induced hyperglycemia. The initial time point to measure time to relapse and time to death is the date of diagnosis. We will use standard survival analyses, including Kaplan-Meier survival curves, log-rank test, parametric regression models and/or Cox proportional hazard model to examine whether hyperglycemia impacted the survival outcomes time-to-relapse and time-to-death.

- **Aim 3.** Determine management of hyperglycemia (use of anti-hyperglycemia medications) in patients with pre-existing diabetes and those with steroid induced hyperglycemia.

  2a. Prior to chemotherapy
  2b. During chemotherapy
  2c. Following completion of chemotherapy

  For Aim 3: The hyperglycemia management includes 3 kinds of treatments: (1) Metformin or TZDs, (2) all other anti-diabetic medications and (3) no intervention. Among the steroid induced hyperglycemia patients, we will use frequency table to summarize the types of hyperglycemia management.

**Ethical Considerations**

The PI has completed the required human subject's research training and obtained the appropriate documents/certificates.
Risks and Benefits

Risks: There is a risk of confidentiality breach associated with chart review. Care will be taken for following HIPPA regulations, however, there is the possibility that although the patients' information has been de-identified the master documents may be accidentally exposed.

Benefits: The patient's whose charts are reviewed are not likely to receive any benefit from the proposed research; however, society and investigators will benefit from the knowledge gained.

Limitations

Information obtained in this study is dependent on what is recorded in the chart and how this information is abstracted. In the past blood glucose readings were not viewed as an important factor in the treatment of cancer, therefore there may be large amounts of missing data in this area. This study focuses on one type of lymphoma as opposed to reviewing the data from all patients with lymphoma treated at MD Anderson Cancer Center. An additional limitation is the fact that the results will be based on the experience of one institution.

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References


Prevalence of Steroid-Induced Hyperglycemia in Patients with Mantle Cell Lymphoma

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Grants: None

Conflicts of Interest: No disclosures
Prevalence of Steroid-Induced Hyperglycemia in Patients with Mantle Cell Lymphoma

Abstract

Purpose: To determine the prevalence of steroid-induced hyperglycemia (SIH), defined as blood glucose ≥200mg/dL, in patients with and without pre-existing diabetes receiving high dose steroids, as well as the persistence of hyperglycemia, how hyperglycemia was managed, and to examine the association between hyperglycemia and time to relapse or time to death.

Design: Retrospective chart review

Setting: University based cancer center

Sample: 182 patients with diagnosis of mantle cell lymphoma who received ≥2 consecutive doses of high dose steroids for ≥2 cycles.

Methods: Electronic health records of all patients with diagnosis of mantle cell lymphoma receiving treatment between January 2000 and December 2010 were reviewed for two years of follow-up or until death. The Cox proportional hazards regression model was used for univariate analysis and the Kaplan-Meier method was used for comparison of survival curves.

Main Research Variables: Age, body mass index, International Prognostic Index (IPI) score, Eastern Cooperative Oncology Group (ECOG) score, β2 microglobulin, blood glucose and history of diabetes.
**Findings:** SIH occurred in 127 patients (70% of the cohort), with 57% experiencing glucose elevations associated with the first cycle of steroids (during or following the 1st course of steroids). Higher mean baseline blood glucose \((p=0.0290)\) and history of diabetes \((p=0.0013)\) were the only factors found to be related to the development of hyperglycemia. Hyperglycemia was found to be persistent at 3-6 months in 3 (7%) of the 46 patients with history of diabetes and 4 (5%) of the 81 patients with no history. There was no significant difference in hyperglycemia management between those with and without persistent hyperglycemia \((p=0.8839)\) and management of hyperglycemia did not show a significant impact on time to relapse or death. The factors shown to influence time to relapse and time to death include \(\beta_2\) microglobulin, ECOG and IPI scores.

**Conclusions:** Hyperglycemia is prevalent in patients receiving high dose steroids with and without history of diabetes and glucose elevations persistent in 5-7% even after steroids have been discontinued. The study also showed that performance status (ECOG) is an independent predictor of survival outside of the IPI score. It further demonstrates that baseline glucose is related to the development of hyperglycemia. However, this retrospective study does not show that hyperglycemia has a significant impact on time to relapse or time to death. Prospective studies designed to examine this relationship are needed.

**Implications for Nursing:** The majority of patients diagnosed with mantle lymphoma are of the younger age and lower BMI category than we would expect for patients at risk for type 2 diabetes. However, based on the results of this
study we would suggest screening/monitoring for hyperglycemia. Thus patients with mantle cell lymphoma receiving high dose steroids should have hemoglobin A1c performed, fasting blood glucose or random glucose prior to initiation of treatment and be monitored for glucose elevations during treatment and at scheduled intervals for several years after therapy is complete.
Prevalence of Steroid-Induced Hyperglycemia in Patients with Mantle Cell Lymphoma

Steroid-induced hyperglycemia as a result of high dose glucocorticoid treatment has been reported to occur at a rate of 32-60% in patients with cancer both with and without a prior history of diabetes (Harris et al., 2013; Lee et al., 2014; Weiser et al., 2004; Wu et al., 2014). Glucocorticoids are most commonly used in the chemotherapy regimen used to treat mantle cell lymphoma (MCL). They are utilized in treatment for their anti-leukemic properties and dexamethasone has been shown to be 5-16 times more cytotoxic than prednisone (Belgaumi et al., 2003). Glucocorticoids inhibit glucose transport/phosphorylation thereby decreasing available intracellular energy, and the impede cell mitotic division and inhibit protein synthesis resulting in apoptotic cell death (Coleman, 1992; Laane et al., 2009). Fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) +/- Rituximab alternating with Rituximab plus Methotrexate and cytarabine is one of the most common regimens used to treat of MCL in the young, fit patient. This treatment regimen is administered every 21 days for a total of 6-8 cycles, and requires that dexamethasone 20-40mg be given on days 1-4 or 2-5 and 11-14 or 12-15 of each cycle (Caballero et al., 2013; Romaguera et al., 2005; Vose, 2012).

Although the antitumor properties of glucocorticoids are known to be beneficial in the treatment of hematologic malignancies, their use often results in hyperglycemia (Lee et al., 2014). Hyperglycemia is defined as fasting blood
glucose readings of 100-126 mg/dL, post-prandial glucose ≥150mg/dL (American Diabetes, 2014). Glucocorticoids are known to have a deleterious effect on glycemic control by increasing insulin resistance. Prolonged exposure to glucocorticoids leads to hyperinsulinemia, inhibitory effect on βcell function and is associated with development of diabetes (van Raalte, Ouwens, & Diamant, 2009). Glucocorticoids are also believed to increase glucose intolerance, decrease peripheral insulin sensitivity, reduce βcell mass due to βcell dysfunction and increase hepatic insulin resistance leading to impaired suppression of hepatic glucose production (Oyer, Shah, & Bettenhausen, 2006; Simmons, Molyneaux, Yue, & Chua, 2012; Trence, 2003; Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009). It has been suggested that the resulting hyperglycemia is transient and with withdrawal of steroids glucose levels are hypothesized to return to normal (Lowas, Malempati, & Marks, 2009). However, Trence (2003) suggest that patients receiving high dose steroids be monitored throughout treatment for development and persistence of hyperglycemia.

Steroid induced diabetes (SIDM) is defined as an abnormal elevation in blood glucose in persons with and without diabetes as a result of use of glucocorticoids (Hwang & Weiss, 2014). Steroid induced hyperglycemia can often go undetected, and lack of or under treatment may lead to steroid induced diabetes, which has overall health sequelae equivalent to that of type 2 diabetes (T2DM)(Kwon & Hermayer, 2013). Risk associated with the development of steroid-induced hyperglycemia or diabetes are obesity, lack of physical exercise, impaired fasting glucose (fasting glucose of 100-125mg/dL), family history,
ethnicity and older age (Clore & Thurby-Hay, 2009; Fong & Cheung, 2013; Hwang & Weiss, 2014; Trence, 2003). Conversely according to study conducted by Simmons et al. (2012) patients who developed new onset steroid induced diabetes (SIDM) weighed less and had less family history of diabetes than their counterparts who developed T2DM. Untreated hyperglycemia in patients with cancer may result in impaired wound healing, decreased immune function, disruption of homeostasis, endothelial dysfunction, increased inflammatory cytokines and increased oxidative stress (Freeland & Funnell, 2012; Patel et al., 2009).

Although NHL can occur at any age, the average age at diagnosis is mid-60s and the risk of developing the disease increases with age. NHL is also thought to be associated with obesity. This cancer is more common among Whites than African Americans or Asians with a higher incidence among males (60-70%) (Doorduijn & Kluin-Nelemans, 2013). Aschebrook-Kilfoy, Caces, Ollberding, Smith, and Chiu (2013) reported a 130.9% increase in the incidence of MCL from 1992-1994 to 2005-2009, with the most significant increase being in older, white males. With the aging of the American population and increases in obesity rates it can be expected that the incidence of this cancer will increase.

Mantle Cell Lymphoma (MCL) is a B-cell lymphoma and represents 2-10% of all NHL. It is the 7th most common cancer representing approximately 4% of all cancers. The median overall survival (OS) rates for MCL is 2-4 years with failure free survival (FFS) times of 10-14 months (Romaguera et al., 2005). For patients with pleomorphic or blastic subtypes of MCL the current overall median survival
is approximately 5 years with 8% surviving more than 10 years. According to Chandran, Gardiner, Simon, and Spurgeon (2012) being female is an independent predictor of 19.2% improved survival and older patients are likely to have more comorbidities thus limiting their treatment options and increasing risk of complications.

Most patients with MCL present with stage III/IV disease at the time of diagnosis (Dreyling, Hiddemann, & European, 2009). Dreyling et al. (2009) also stated that the clinical features associated with poor prognosis included: advanced stage III/IV, presence of B symptoms and poor performance status, with better outcomes being associated with age less than 65 years and normal $\beta_2$ microglobulin. According to Romaguera et al. (2010) the primary predictors of overall survival and time to failure among patients with MCL were IPI scores which include: age, performance status, stage 3-4, elevated LDH (elevation correlates with tumor burden), extranodal sites (each positive one equals 1 point with the associated risk as follows: 0-1=low, 2=low intermediate, 3-high intermediate, 4-high), pre-treatment $\beta_2$ microglobulin serum levels and mantle cell IPI (MIPI).

First line treatment of MCL is usually chemotherapy. The regimen of choice is hyper-CVAD which has shown a higher complete response rate and longer duration response than other regimens (Foran et al., 2000). Hyper-CVAD treatment involves 2 courses. Course A: Cyclophosphamide, doxorubicin, vincristine and dexamethasone and Course B: methotrexate, leucovorin, sodium bicarbonate, and cytarabine. A cycle includes Course A alternating with Course
B and patients usually receive 6-8 cycles, thus they receive 3-4 cycles of high
dose steroids (dexamethasone) (Abbasi, 2014).

In a study examining the effects of hyperglycemia on clinical outcomes in
patients with hematologic malignancies, it was found that patients over the age of
60 years who experience hyperglycemia (blood glucose >180mg/dL) had a
greater incidence of infections and poorer overall outcomes (Weiser et al., 2004).
Vu et al. (2012) noted that in hyperglycemic patients with acute lymphocytic
leukemia receiving high dose steroids, those who developed SIH and were
managed with TZD or metformin had improved overall survival rates compared to
those who received an intensive insulin regimen. The study by Wu et al. (2014)
reported, that in patients with multiple myeloma, steroid-induced diabetes, along
with age, stage of disease, comorbidity and cytogenetic abnormalities were
significant predictors of decreased overall survival. It was also suggested in this
study that patients with history of diabetes maybe in worse health and thus
receive less intensive therapy than those patients without diabetes.

Studies have been conducted to determine the prevalence of steroid
induced hyperglycemia in patients with cancer undergoing therapy and the
impact of hyperglycemia on clinical outcomes as noted above. However, none of
these studies have focused exclusively on patients with MCL, nor has the
persistence of the resulting hyperglycemia been evaluated. The aim of this study
was to determine the prevalence and persistence of hyperglycemia, defined as
blood glucose >200mg/dL, in patients with mantle cell lymphoma receiving high
dose steroids, how hyperglycemia was managed and to examine the association
between the occurrence of hyperglycemia and the time to relapse or death. We hypothesized that patients with prolonged exposure (≥ 2 exposures lasting ≥ 2 days) to high dose steroids will develop SIH and that patients who received treatment for hyperglycemia with Metformin or TZDs have longer progression free survival.

Methods

Design and Sample

This retrospective study involved the use of tumor registry data to identify patients with diagnosis of lymphoma between 2000 and 2010. This search yielded 12,700 patients (3,500 of which received some portion of treatment at the cancer institution). In an effort to ensure a homogeneous population likely to receive equivalent treatment the population was further defined as patients with a history of mantle cell lymphoma (MCL) treated at the cancer institution. Inclusion criteria for record review were patients over the age of 18 years who received treatment for MCL at MDACC between 1/1/2000 and 12/31/2010 with follow up for two years or until death. After initial identification of 318 patients who met these criteria, the population was further defined to include only those patients who had received dexamethasone 20-40 mg for ≥ 2 cycles (with a cycle being defined as ≥2 doses of dexamethasone separated by ≥ 4 days). The final study cohort consisted of data from 182 patients. Permission was granted from the UTMDACC Institutional Review Board (IRB), to conduct the study.
Measures

Demographic information such as gender, race, date of birth, stage of disease, marital status, occupation, treatment start and end dates, date last seen at the cancer center and vital status were obtained from tumor registry.

Diabetes was defined as patients with a documented history of diabetes, those on anti-diabetic medications at the time of their first visit or those with early am glucose >135mg/dL. Diagnosis of other comorbidities including, hypertension, hyperlipidemia and kidney disease was determined based on documentation in patients past medical history at the time of initial visit. This information was correlated with the data obtained from the Department of Clinical Operations Informatics. Anti-diabetic medications and steroids prescribed and dispensed at the cancer institution were obtained from Pharmacy Informatics. The database was searched for all antidiabetic medications and medications were classified as: Insulin only (to include NPH, regular, glargine, detemir, lispro and aspart) or Medication (which included all oral agents—sulfonylureas, meglitinides, DPP-4 inhibitors, thiazolidinedione’s, and biguanides). The database was also searched for steroids and only those patients who received dexamethasone 20-40mg for ≥ 2 consecutive doses for ≥2 cycles were included.

Laboratory data for blood glucose prior to treatment (from time initial visit to cancer center until start of chemotherapy treatment), during treatment (while receiving chemotherapy) and up to 24 months following completion of chemotherapy, along with blood urea nitrogen (BUN), creatinine and β2 microglobulin (elevated levels indicate poor prognosis) were obtained from
Laboratory Informatics Systems. The laboratory data base was searched for all glucose values for each patient. Glucose values included both those obtained in the lab as well as bedside blood glucose readings obtained via finger stick during admission to the hospital for chemotherapy. Baseline glucose was defined as the blood glucose value at the time of the patients' initial visit to MDACC. Maximum glucose was defined as the highest recorded glucose value (either laboratory or bedside). \(\beta_2\) microglobulin value utilized was that obtained at the initial visit prior to therapy.

Information from the EHR was used to calculate body mass index (BMI) using height and weight (formula: \(\text{lb/in}^2 \times 703 = \text{kg/m}^2\)) obtained at the first visit and categorized as: obese (BMI \(\geq 30\text{kg/m}^2\)) and non-obese (BMI < 30kg/m²). The International Prognostic Index (IPI) scores which include: age, performance status, stage 3-4, elevated LDH (elevation correlates with tumor burden), extranodal sites (each positive one equals 1 point with the associated risk as follows: 0-1=low, 2- low intermediate, 3- high intermediate, 4- high ), were abstracted from the EHR at baseline. Eastern Cooperative Oncology Group (ECOG) scores (scale of 0-5: 0-Fully functional, 1=light work, no strenuous activity, 2=Capable of self-care but cannot carry out work activities, up more than 50% of the day, 3=Limited self-care, in bed or chair >50% of the day, 4= Completely disabled, 5=Dead) were also obtained from the EHR at baseline. Both the IPI and ECOG scores utilized were those recorded prior to the initiation of therapy.
The primary clinic endpoints were time to relapse and time to death. Time to relapse and time to death were calculated based on the date of diagnosis and date of relapse or death, with these dates being censored based on date of last follow-up. Relapse was documented by the lymphoma team as either biopsy proven disease or radiologic findings on PET, MRI or CT. Information regarding survival was obtained from Tumor registry. The major sources of death information utilized by Tumor registry include: (1) Texas Bureau of Vital Statistics, (2) letters and phone calls to patients, with phone calls being made to patients who do not respond to letters and (3) emails or institutional forms sent from MD Anderson employees when they have been notified of a patient’s death.

**Statistical Analysis**

Baseline patient demographics and clinical characteristics were compared between groups (induced and non-induced hyperglycemia) using two sample t-test and Fisher’s exact test. These methods were also used to determine differences in the groups by persistence of hyperglycemia. Fishers’ exact tests were used to determine if management of hyperglycemia differed based on whether there was a persistence of hyperglycemia. Management of hyperglycemia was divided into categories: insulin only, insulin and orals and no intervention. Univariate analysis of time to relapse and time to death were assessed using the Kaplan-Meier method. Logistic regression model was used to predict occurrence of event (hyperglycemia) in the presence of other variables. Cox proportional hazard models were used to determine the relationship between age at diagnosis, \( \beta_2 \) microglobulin, maximum glucose and time to event
(death or relapse). SAS V9.2 (SAS Inc., Cary, NC, USA) and Stata 13 (StataCorp LP, College Station, TX, USA) were used in the analysis. P values of <0.05 were considered statistically significant.

**Results**

**Baseline Patient Characteristics**

Of the 182 patients that met criteria for inclusion in the study, as to be expected, based on information from the literature, the majority of the patients included in the study were males (84%) and 16% were females. Non-Hispanics whites represented the highest number of patients- 170 (93%) with the other 7% being comprised of Blacks, those with Spanish surnames and other. The median age at the time of diagnosis was 62 years (33-82) for those without SIH and 63 years (40-81) for those who experienced SIH. Of these patients 53 (29%) had pre-existing diabetes and 129 (71%) did not. Most (154=84%) had stage IV disease at the time of diagnosis.

**Prevalence of Steroid Induced Hyperglycemia**

Among the 53 patients with documented history of diabetes, 46 (87%) experienced hyperglycemia (BG>200mg/dL) and 81 of the 129 patients without known history of diabetes (63%) experienced hyperglycemia. When examining patient demographic and clinical characteristics of the cohort by group (those who developed steroid induced hyperglycemia and those who did not), there were not significant differences in age, BMI, or history of comorbidities (kidney disease, hyperlipidemia, hypertension) between the two groups. Baseline glucose values were significantly higher among the group that experienced
hyperglycemia (P=0.0290), and more patients with reported history of diabetes experienced hyperglycemia (p=0.0013) (see table 2). Among patients without a prior reported history of diabetes, there were no significant differences in age, BMI, baseline glucose or comorbidities between those who developed hyperglycemia and those who did not.

**Persistence of Hyperglycemia**

A total of 127 patients (70% of the cohort) developed steroid induced hyperglycemia. In the 81 patients with no history of diabetes 4 (5%) had persistent hyperglycemia lasting 3-6 months after treatment. Of the 46 patients with a history of diabetes prior to treatment who developed steroid-induced hyperglycemia 3(7%) remained persistently hyperglycemic 3-6 months following the completion of treatment. Among the patients that developed SIH significant differences were not detected between persistence of hyperglycemia and BMI, comorbidities, history of diabetes, or age. However, baseline glucose was significant (p=0.0543)(see table 3). Comparison of the maximum glucose of those who did not persistent hyperglycemia (298mg/dL ± 117) versus those who did (319mg/dL ±115) was not statistically significant (p=0.3692) (see table 3a).

**Hyperglycemia Management**

Fifty-three patients were documented as having pre-existing diabetes at the time of their initial visit. Of these 26 (49%) had no information on how the diabetes was being treated. Five patients (9%) were on insulin, 18(34%) were on oral agents, 1(2%) was on insulin and orals and 3 (6%) were being managed with diet alone. Of these 53 patients one patient had documented history of type 1
diabetes. During the course of treatment the anti-diabetic medication regimen was intensified for 26 (49%) of the 46 patients with history of diabetes who experienced SIH. Hyperglycemia was managed with a wide range of anti-diabetic medications in the cohort of patients who developed hyperglycemia. Examination of medications used in those with and without persistent hyperglycemia revealed no significant difference in treatment. Of note is the fact that the number of patients treated with insulin only and those receiving no intervention were equal (39.73%) (see table 4).

Predictors of Hyperglycemia

The logistic regression model was used to predict which factors were associated with steroid induced hyperglycemia. The results revealed that only history of diabetes was associated with the development of hyperglycemia (OR 3.03; 95% CI 1.15-7.96; p=0.0246). However it was noted that history of diabetes and baseline glucose were highly associated, therefore when history of diabetes was removed from the model, baseline glucose was found to be statistically significant (OR 1.16 for each 10mg/dL increase; 95% CI. 1.00-1.33; p=0.0479). Comorbidities: hypertension, obesity, kidney disease and hyperlipidemia were not significant predictors of hyperglycemia (see table 5). Due to the limited number of patients (7) with persistent hyperglycemia logistic regression models were not created to examine these effects.

Association between Hyperglycemia and Time to Relapse/Death

Age, β2 microglobulin and maximum glucose were included in the proportional hazards regression model. (Due to the percentage of missing data
ECOG (36%) and IPI (52%) scores were excluded were excluded from this model.) Both age and serum $\beta_2$ microglobulin were found to be significant predictive factors of relapse and death, indicating that as age and $\beta_2$ microglobulin increased so did the rates of relapse and death (see table 7). The occurrence of hyperglycemia did not appear to influence these rates.

Patients with $\beta_2$ microglobulin $>3$ had a median survival of 5.8 years compared to those with serum levels $\leq 3$ (median survival yet to be reached ($p \leq 0.0001$) and shorter median relapse time, 3.9 years compared to those with levels $\leq 3$ (median time to relapse yet to be reached) ($p=0.0020$). ECOG scores were also found to impact time to relapse and death. As ECOG scores improved, so did median time to death. Patients with an ECOG score of 2 had median survival of 3.4 years, those with score of 1 had median survival of 8.39 years and score of 0 was associated with median survival of 11.46 years ($p=0.0442$). Lower ECOG scores were also associated with improved median time to relapse ($p=0.0016$). Survival time also increased with lower IPI score. IPI score of 1 or 2 was associated with median survival of 12.65 years, compared to score of 3-7.63 years and score of 4 -3.64 years ($p\leq 0.0001$) and median time to relapse decreased with increasing IPI scores ($p=0.0075$) (see table 7). Although occurrence of hyperglycemia does not have a statistically significant impact on time to relapse($p=0.0763$) those who experience SIH had a median time to relapse of 4.58 years and those without hyperglycemia have yet to reach median time to relapse (see Figure 1). History of diabetes also is not a statistically significant predictor of relapse however, those with history of diabetes had a
median survival of 4.58 years compared to 6.08 years for those without history of diabetes (p=0.4179). Furthermore, medications used in patients who developed hyperglycemia did not have a statistically significant impact on time to relapse (p=0.2354), those patients who received insulin only had a median time to relapse of 8.19 years compared to that of 3.26 and 3.47 years in patients receiving insulin and oral agents of no therapy respectively) (see figure 2).

Discussion

Steroid induced diabetes (SIDM) was defined by Hwang and Weiss (2014) as an abnormal elevation in blood glucose in persons with and without diabetes as a result of use of glucocorticoids. While Simmons et al. (2012) used the term new onset steroid induced diabetes (NOSID) to define diabetes diagnosed for the first time during steroid therapy. Furthermore in their study (Wu et al., 2014) defined steroid induced diabetes (SID) as ≥ 2 random plasma glucose values ≥200mg/dL in patients with no prior history of diabetes, or the requirement for anti-diabetic medications following glucocorticoid therapy. The lack of consensus surrounding the definition of SID led us to use of the term “steroid induced hyperglycemia” (SIH). Steroid-induced hyperglycemia can be defined as ≥1 glucose value ≥200mg/dL at any time during treatment with glucocorticoids. In this study the resulting hyperglycemia was defined as persistent if patients continued to have glucose values ≥200mg/dL ≥ 3 months following the last dose of steroids within the treatment cycle. We chose the time period of 3 month intervals based on the general practice of having patients with diabetes return to clinic at 3 month intervals for follow up.
The use of high dose steroids is known to cause hyperglycemia. The aims of this study were to determine the prevalence of steroid induced hyperglycemia in patients with and without history of diabetes receiving high dose steroids for the treatment of MCL, as well as to determine if hyperglycemia persisted and how it was managed. We also wanted to examine the association between hyperglycemia and time to relapse or death.

In alignment with information in the literature the majority of our patients were white males, with a median age of 62 years. Although we did not calculate Charlson Comorbidity Index scores (CCI), we did evaluate the presence of comorbid diseases among the cohort. The patients with reported history of diabetes had higher rates of hypertension, hyperlipidemia and had a higher BMI than those with no reported history of diabetes (see table 1). When evaluating the cohort grouped by whether they experienced SIH, although not found to be statistically significant, it was noted that a higher percentage of patients that experienced SIH had kidney disease (10%), hyperlipidemia (56%) and hypertension (36%) (see table 2). The patients in our study received between 2-10 cycles of treatment with Course A (including dexamethasone), with the majority receiving 2 (24%) or 3 (40%) cycles. The prevalence rate of hyperglycemia among the total cohort in this study was 70%, with 57% experiencing glucose elevations associated with the first cycle of steroids (during or following the 1st course of steroids). Of the patients with reported history of diabetes 87% developed hyperglycemia and 63% of those without history of diabetes also experienced hyperglycemia. This was similar to the findings of the
study by Brady et al. (2014) which showed 81% of glucose values accounting for hyperglycemia in the first cycle of treatment among patients with leukemia receiving high dose steroids. However our rate of hyperglycemia was higher than the findings of other studies conducted in patients with lymphoma, multiple myeloma and prostate cancer. These studies showed rates of hyperglycemia of 58.9%, 12.9%, 60%, 31.7% (Harris et al., 2013; Jung et al., 2014; Storey & Von Ah, 2015; Wu et al., 2014) respectively. The finding of higher prevalence in this study may be due to the inclusion of patients who had ≥ 1 blood glucose ≥ 200mg/dL. We chose to define hyperglycemia in this manner because according to the definition by the ADA(American Diabetes, 2014) hyperglycemia is defined as blood glucose 100-126 mg/dL fasting or ≥150 mg/dL post prandial, thus any glucose >200mg/dL is considered to be elevated. Jung et al. (2014) who used the same definition for overt hyperglycemia in patients with multiple myeloma, described a prevalence of only 12.9% during the first 60 days of chemotherapy. The lower prevalence in the Jung study is likely due to the fact that they excluded patients with a prior history of diabetes.

Patients who developed steroid induced hyperglycemia had higher mean baseline glucose values (109mg/dL) than those who did not. As noted in the study by Bowen, Xuan, Lingvay, and Halm (2015) this random baseline glucose of >100mg/dL may be indicative of underlying diabetes. This study showed that patients with a reported history of diabetes were 3x more likely to develop SIH. In this study the additional risk factors for the development of hyperglycemia, described by Clore and Thurby-Hay (2009), Fong and Cheung (2013), Hwang
and Weiss (2014), and (Trence, 2003) were either not significant (obesity and age) or were not evaluated due to the lack of documentation in the EHR (family history) or in the case of ethnicity not evaluated due to the lack of diversity among the cohort of patients (93%-non-Hispanic whites). In the case of obesity 73% of those who did not experience SIH and 71% of those who experienced SIH were not obese (BMI<30) and the mean age of those without SIH was 61.84 (33-82) and those with SIH was 63.20 (40-81). In the general population those who experience hyperglycemia are reported to be obese (BMI>30) and older (over age 65). The presence of comorbidities (kidney disease, hypertension and hyperlipidemia) was not a significant predictor for the development of SIH.

Although it is difficult to determine if there was a permanent deterioration in glycemic status it was noted that during the course of treatment, 26 (49%) of the patients with reported history of diabetes required intensification of their anti-diabetic medication regimen. At some time point during treatment 17(32%) were seen by endocrinology and 2(4%) seen by general internal medicine with changes made to their anti-diabetic medications. For those not seen by endocrinology or general internal medicine it was difficult to determine whether or not anti-diabetic medication regimens were intensified (insulin doses increased or oral agents added) due to the lack of documentation in the EHR.

Steroid induced hyperglycemia persisted in a small number of patients both with (7%) and without (5%) reported history of diabetes. Although it was not found to be statistically significant the patients that had persistent hyperglycemia had a mean maximum blood glucose that was >10mg/dL higher than those
without persistent SIH. This is similar to the findings we had that showed that each 10mg/dL increase in baseline glucose values increased risk of SIH by 16%. Among those with persistent SIH 43% (3) were managed with insulin only.

When examining the time to relapse or time to death, the degree of hyperglycemia (maximum blood glucose) did not have a significant impact. Secondary analysis of only those patients receiving active treatment for reported diabetes revealed that 42% (22) were documented as being prescribed metformin or a TZD. Of those that remained alive at the time of data analysis 11 (55%) were documented as having metformin prescribed. When examining the time to death it needs to be noted that 9 patients (5%) had secondary cancers which could have contributed to their death. There were also 28 patients with documentation of other events that may have contributed to their death. These events included: septic shock/sepsis (5); failure to thrive (1); myelodysplastic disease (6); cardiovascular events (2); pneumonia/respiratory failure (6); AML (2); motor vehicle accident (1); suicide (1) and unknown (4).

It was found that an equal number of patients who developed SIH were managed with insulin only or no intervention (39.37%). This finding is similar to the data from the Centers for Disease Control and Prevention (CDC, 2014) which reports that among patients with diabetes equal numbers (14%) are treated with insulin or no insulin or oral agents. According to Gerards MC1 (2015) although physicians screen for SIH at a rate or 85% only 56% initiate treatment and the majority of them (62%) utilize sliding scale.
Although this study confirmed findings by Romaguera et al. (2010) that age at diagnosis, β₂ microglobulin and IPI scores are significant predictors of time to relapse or time to death, we did not find that degree of hyperglycemia, number of cycles of steroids, self-reported history of diabetes or how hyperglycemia was managed had an impact to time to relapse or time to death.

Limitations

The primary limitations are retrospective and limited sample size for analysis. Other factors of interest such as; family history of diabetes and hemoglobin A1c would have been useful elements in this study however, they were not routinely found in the EHR. The fact that the timing of blood glucose values was not standardized may have affected the outcomes of this study. Also ECOG status and IPI could not be included in the Cox regression model due to large amounts of missing data. Another limitation is that the study included patients from one tertiary referral institution, thus the generalizability is limited to this population.

In review of the information from the EHR secondary cancers were present in 5% of the population at the time of their initial visit. Cancer diagnosis included: papillary thyroid cancer (1), renal cell carcinoma (1), prostate cancer (4), bladder cancer (1), melanoma (1) and testicular (1). The presence of any of these cancers at the time of diagnosis with MCL may have had an impact on the patients overall survival.
Conclusions

The current study confirmed that steroid induced hyperglycemia occurs in patients with MCL receiving high dose steroids. It also showed that there is a high prevalence of hyperglycemia (70%) among patients with MCL receiving ≥2 doses of dexamethasone 20-40mg for ≥2 cycles. Additionally this study examined the persistence of hyperglycemia and found rates of 5-7% among patients with and without a prior history of diabetes. The fact that IPI scores and β2 microglobulin levels impact overall survival and time to relapse was also confirmed. It further showed that baseline glucose at the time of initiation of therapy impacts the development of hyperglycemia suggesting that attention should be paid to blood glucose prior to the initiation of treatment.

Results of this study, much like the findings of Harris et al. (2013) suggest that traditional risk factors associated with the development of T2DM do not apply to patients who develop SIH or SIDM. Although this retrospective study did not show that the degree of hyperglycemia or the management of SIH impact overall survival the survival curves do suggest that there may be a relationship between the development of SIH in patients with no reported history of diabetes and time to death (see figure 3), as well as management of SIH and time to relapse (see Figure 2). The results of these studies suggest that patients receiving high dose glucocorticoids have baseline blood glucose values evaluated and particular attention be given to those patients with values >100mg/dL as they are increased risk for the development of SIH. Large prospective studies designed to evaluate whether achievement of normal blood
glucose values prior to the initiation of therapy will prevent SIH and whether the use of metformin as first line therapy for resulting hyperglycemia impacts time to relapse and time to death.

**Implication for Nursing Practice**

The majority of patients diagnosed with mantle lymphoma are of the younger age and lower BMI category than we would expect for patients at risk for type 2 diabetes. However, based on the results of this study we would suggest screening/monitoring for hyperglycemia as a random glucose >100mg/dL has been found to be strongly associated with undiagnosed diabetes (Bowen et al., 2015). Thus patients with mantle cell lymphoma receiving high dose steroids should have hemoglobin A1c performed, fasting blood glucose or random glucose prior to initiation of treatment and be monitored for glucose elevations during treatment and at scheduled intervals for several years after therapy is complete. Blood glucose readings are commonly found in patient’s charts and identification of those patients with elevated glucose levels prior to and during treatment could lead to more consistent management of hyperglycemia and potentially prevent SIH and improved patient outcomes.
References


Table 1  
**Demographics and clinical characteristics of MCL patients (N=182)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-existing Diabetes</th>
<th>No History of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=53 (29%)</td>
<td>n=129 (71%)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>63 (40-81)</td>
<td>63 (33-82)</td>
</tr>
<tr>
<td>Age of diagnosis &gt;65</td>
<td>29 (55%)</td>
<td>61 (47%)</td>
</tr>
<tr>
<td>Age of diagnosis ≤ 65</td>
<td>24 (45%)</td>
<td>68 (53%)</td>
</tr>
<tr>
<td>Male</td>
<td>49 (92%)</td>
<td>103 (80%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (8%)</td>
<td>26 (20%)</td>
</tr>
<tr>
<td>White</td>
<td>47</td>
<td>123</td>
</tr>
<tr>
<td>Non-White</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Median plasma glucose (baseline)</td>
<td>103 (74-326)</td>
<td>93 (55-179)</td>
</tr>
<tr>
<td>Maximum Plasma glucose</td>
<td>250</td>
<td>237</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>29.74 (21.43-48.8)</td>
<td>27.18 (17.42-42.58)</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>45 (85%)</td>
<td>82 (64%)</td>
</tr>
<tr>
<td>Hyperlipidemia (HLD)</td>
<td>40 (75%)</td>
<td>30 (23%)</td>
</tr>
<tr>
<td>HLD &amp; HTN</td>
<td>37 (70%)</td>
<td>45 (35%)</td>
</tr>
</tbody>
</table>

Table 2  
**Summary Statistics by Steroid-Induced Hyperglycemia (SIH): All Patients**

<table>
<thead>
<tr>
<th></th>
<th>No-SIH</th>
<th>SIH</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (N = 55)</td>
<td>(N = 127)</td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>N</td>
<td>55</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>61.84 (10.45)</td>
<td>63.20 (8.36)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Min - Max</td>
<td>33 – 82</td>
<td>40 – 81</td>
</tr>
<tr>
<td>Baseline Glucose</td>
<td>N</td>
<td>55</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>99.35 (21.74)</td>
<td>109.20 (38.14)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Min - Max</td>
<td>70 – 179</td>
<td>55 – 326</td>
</tr>
<tr>
<td>BMI</td>
<td>Not Obese (BMI &lt; 30)</td>
<td>37 (72.55%)</td>
<td>89 (70.63%)</td>
</tr>
<tr>
<td></td>
<td>Obese (BMI &gt;= 30)</td>
<td>14 (27.45%)</td>
<td>37 (29.37%)</td>
</tr>
<tr>
<td></td>
<td>Unknown/Missing</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>No</td>
<td>54 (98.18%)</td>
<td>114 (89.76%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1 (1.82%)</td>
<td>13 (10.24%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>No</td>
<td>28 (50.91%)</td>
<td>56 (44.09%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>27 (49.09%)</td>
<td>71 (55.91%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>19 (34.55%)</td>
<td>36 (28.35%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>36 (65.45%)</td>
<td>91 (71.65%)</td>
</tr>
<tr>
<td>Self-Reported History of Diabetes</td>
<td>No</td>
<td>48 (87.27%)</td>
<td>81 (63.78%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>7 (12.73%)</td>
<td>46 (36.22%)</td>
</tr>
</tbody>
</table>
Table 3
Summary Statistics by Persistent SIH: Patients with SIH only (N=127)

<table>
<thead>
<tr>
<th></th>
<th>Non-Persistent (N = 120)</th>
<th>Persistent (N = 7)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>120</td>
<td>7</td>
<td>0.6984</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.27 (8.42)</td>
<td>62.00 (7.85)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Min - Max</td>
<td>40 – 81</td>
<td>47 – 73</td>
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<tr>
<td>Baseline Glucose</td>
<td>N</td>
<td>120</td>
<td>7</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>110.08 (38.88)</td>
<td>94.29 (16.79)</td>
<td>0.0543</td>
</tr>
<tr>
<td>Median</td>
<td>97</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Min - Max</td>
<td>55 – 326</td>
<td>69 – 120</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Not Obese (BMI &lt; 30)</td>
<td>82 (68.91%)</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI &gt;= 30)</td>
<td>37 (31.09%)</td>
<td>7 (100.00%)</td>
<td>0.1044</td>
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<tr>
<td>Unknown/Missing</td>
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<td>0</td>
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<tr>
<td>Kidney Disease</td>
<td>No</td>
<td>109 (90.83%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11 (9.17%)</td>
<td>0.1515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (71.43%)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>2 (28.57%)</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>No</td>
<td>52 (43.33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>68 (56.67%)</td>
<td>0.6986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (57.14%)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3 (42.86%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>36 (30.00%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>84 (70.00%)</td>
<td>0.1900</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (100.00%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (0.00%)</td>
<td></td>
</tr>
<tr>
<td>Self-Reported</td>
<td>No</td>
<td>77 (64.17%)</td>
<td></td>
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<tr>
<td>History of Diabetes</td>
<td>Yes</td>
<td>43 (35.83%)</td>
<td>0.7032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (42.86%)</td>
<td></td>
</tr>
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</table>

Table 4
Summary Statistics for Treatment Regimen by 3 & 6-Month Persistence: Patients with Steroid-Induced Hyperglycemia Only

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Total (N = 127)</th>
<th>Non-Persistent (N = 120)</th>
<th>Persistent (N = 7)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Insulin Only</td>
<td>50 (39.37%)</td>
<td>47 (39.17%)</td>
<td>3 (42.86%)</td>
<td>0.8839</td>
</tr>
<tr>
<td>Insulin and Medication</td>
<td>27 (21.26%)</td>
<td>25 (20.83%)</td>
<td>2 (28.57%)</td>
<td></td>
</tr>
<tr>
<td>No Intervention</td>
<td>50 (39.37%)</td>
<td>48 (40.00%)</td>
<td>2 (28.57%)</td>
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</table>

Table 5
Logistic Regression Model to Predict Steroid-Induced Hyperglycemia: All Patients

<table>
<thead>
<tr>
<th>Effect</th>
<th>Full Model</th>
<th>P-Value</th>
<th>Model without Self-Reported History</th>
<th>P-Value</th>
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<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>95% CI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Blood Glucose</td>
<td>1.10</td>
<td>0.94 – 1.28</td>
<td>0.2233</td>
<td>1.16</td>
</tr>
<tr>
<td>Obesity (BMI &gt;= 30)</td>
<td>1.03</td>
<td>0.48 – 2.22</td>
<td>0.9453</td>
<td>1.09</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>5.22</td>
<td>0.63 – 42.98</td>
<td>0.1247</td>
<td>5.44</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.88</td>
<td>0.42 – 1.85</td>
<td>0.7453</td>
<td>1.12</td>
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<tr>
<td>Hypertension</td>
<td>0.89</td>
<td>0.41 – 1.93</td>
<td>0.7686</td>
<td>1.01</td>
</tr>
<tr>
<td>Self-Reported History of Diabetes</td>
<td>3.03</td>
<td>1.15 – 7.96</td>
<td><strong>0.0246</strong></td>
<td></td>
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</table>

* Blood Glucose OR and CI for unit increases of 10 mg/dL
Table 6
Proportional Hazards Model Results for Time to Death and Time to Relapse

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
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<tbody>
<tr>
<td><strong>Time to Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>1.70</td>
<td>1.30 – 2.23</td>
</tr>
<tr>
<td>β₂-Microglobulin &gt; 3</td>
<td>2.41</td>
<td>1.44 – 4.03</td>
</tr>
<tr>
<td>Maximum Glucose</td>
<td>1.01</td>
<td>1.00 – 1.03</td>
</tr>
<tr>
<td><strong>Time to Relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>1.35</td>
<td>1.05 – 1.72</td>
</tr>
<tr>
<td>β₂-Microglobulin</td>
<td>1.93</td>
<td>1.21 – 3.07</td>
</tr>
<tr>
<td>Maximum Glucose</td>
<td>1.01</td>
<td>1.00 – 1.03</td>
</tr>
</tbody>
</table>

Table 7
Summary Statistics for Time to Death and Time to Relapse

<table>
<thead>
<tr>
<th>Time to Death</th>
<th>Total</th>
<th># of Events</th>
<th>Median</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-Induced</td>
<td>No Hyperglycemia</td>
<td>55</td>
<td>23</td>
<td>7.50</td>
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<tr>
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<td>49</td>
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<td>3.47</td>
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</table>
Figure 1. Time to Relapse: Kaplan-Meier Survival Curves by Steroid-Induced Hyperglycemia

Figure 2. Time to Relapse: Kaplan-Meier Survival Curves by Medication Regimen
Figure 3. Time to Death: Kaplan-Meier Survival Curves by Self-Reported History of Diabetes and Induced Diabetes
Appendix A

UT M.D. Anderson Cancer Center IRB Approval
To: Veronica Brady 12/12/2013
From: Veronica Roberts
CC: Geri Wood, Terri S. Armstrong, Victor R. Lavis, Terri M. De Hoyos, OPR Protocol Activations, IRB Help
MDACC Protocol ID #: PA13-0900
Protocol Title: Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids
Version: 01

Subject: Protocol PA13-0900 - Approved, Not Yet Activated, Expedited Review

IRB Approval Date: 12/05/2013

On 12/05/2013 the Institutional Review Board 4, chair or designee administratively approved the above named and numbered protocol.

It was noted that the protocol documents are satisfactory and in compliance with federal and institutional guidelines. It was also noted that risks to human subjects are minimal and that confidentiality of specimens or records/date will be maintained.

Please Note: This study is NOT YET ACTIVATED. No research related activites can begin on this protocol until it has been officially activated by OPR. You will receive a separate activation memo once all of the requirements have been met.

The Waivers of Informed Consent and Authorization have been granted.

The IRB approval expiration date is 12/05/2014

In keeping with the requirements outlined in 45CFR46.109(e) and 21 CFR56.109(f), the IRB shall conduct continuing review of all protocols at intervals appropriate to the degree of risk, but not less than once per year.

To activate this study, please compose a "Request for Activation" memo in PDOL and send it to OPR Protocol Activations.
The existing Informed Consent and/or Waivers of Informed Consent and Authorization cannot be used until the protocol is Activated.

If a Material Transfer Agreement (MTA) is required, it must be obtained prior to Activation.

In the event of any questions or concerns, please contact the sender of this message at (713) 792-2933.

Veronica Roberts 12/12/2013 06:29:44 PM

This is a representation of an electronic record that was signed and dated electronically and this page is the manifestation of the electronic signature and date:

Veronica Roberts
12/12/2013 06:28:48 PM
IRB 4 Chair Designee
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015
To: OPR Protocol Activations  
From: Veronica Brady 
CC: Victor R. Lavis, Terri S. Armstrong, Geri Wood 

MDACC Protocol ID #: PA13-0900  
Protocol Title: Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids  
Version 02  
Subject: Request for Activation - PA13-0900  

Please activate this study.

- Would you like eligibility set up in steps?  
  No  
- If the protocol contains multiple treatment regimens, would you like this information entered in CORe?  
  No  
- If the protocol contains strata, would you like this information entered in CORe?  
  No

Please contact OPR at 713/792-2933 or send an email to 'IRB_Help@mdanderson.org' to discuss protocol set-up preferences in CORe.
Appendix B

UT Centralized IRB Review
**Information for the Overall Principal Investigator** – In addition to submitting an application to your organization’s IRB (designated the “Reviewing IRB”), an “Intent to Submit for Centralized Review” form must be submitted to the IRB office at each participating organization.

**Information for the Site Principal Investigator** - The purpose of this form is to request centralized review at your organization (designated the “Relying Organization”). This request will be considered by your organization and a decision made on a case-by-case basis. The IRB office from your organization will forward the final decision to the Reviewing IRB.

If your organization agrees to Centralized IRB Review, you will be required to submit additional materials in accordance with local policy. The review of local issues by your organization is a separate process from the IRB approval being sought by the Overall PI. Reminder: you are not authorized to initiate research at your organization until both processes are completed: 1) the study is approved by the Reviewing IRB and an approval letter is issued, and 2) the local policy issues have been resolved and an activation letter has been issued by your Organization.

<table>
<thead>
<tr>
<th>Study Title:</th>
<th>Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name and Address of Site Principal Investigator (PI):</strong></td>
<td></td>
</tr>
<tr>
<td>Site PI's Name (Last Name, First Name, MI):</td>
<td>Brady, Veronica J</td>
</tr>
<tr>
<td>Department:</td>
<td>Endocrine Neoplasia and Hormonal Disorders</td>
</tr>
<tr>
<td>PI’s Telephone#:</td>
<td>713-792-1981</td>
</tr>
<tr>
<td>PI’s e-mail</td>
<td><a href="mailto:Veronica.j.brady@uth.tmc.edu">Veronica.j.brady@uth.tmc.edu</a></td>
</tr>
<tr>
<td><strong>Name of the Overall Principal Investigator (PI):</strong></td>
<td></td>
</tr>
<tr>
<td>Overall PI's Name (Last Name, First Name, MI):</td>
<td>Veronica Brady</td>
</tr>
<tr>
<td>Organization:</td>
<td>UT MD Anderson Cancer Center</td>
</tr>
</tbody>
</table>

**3. Which University of Texas Participating Organization will serve as the Reviewing IRB?**

Select only one

| UT at Arlington (UTA) | UT Pan American | UT Medical Branch (UTMB) |
| UT Austin (UT Austin) | UT Permian Basin | UT HSC at Houston (UTHealth) |
| UT Brownsville | UT San Antonio (UTSA) | UT HSC at San Antonio (UTHSCSA) |
| UT at Dallas (UTD) | UT Tyler | UT Health Science Center Tyler |
| UT at El Paso (UTEP) | UT Southwestern | UT MD Anderson |

**4. Which University of Texas Participating Organizations will be engaged in this research?**

Column A – Participating Organizations

Select the Participating Organization(s) that will be engaged in the research

<table>
<thead>
<tr>
<th>Column B – Institutions affiliated with the participating organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insert the institutions affiliated with the participating organization that will also be</td>
</tr>
</tbody>
</table>

- UT at Arlington (UTA)
- UT Austin (UT Austin)
- UT Brownsville
| UT at Dallas (UTD)                  |
| UT at El Paso (UTEP)               |
| UT Pan American                    |
| UT Permian Basin                   |
| UT San Antonio (UTSA)              |
| UT Tyler                           |
| UT Southwestern                    |
| UT Medical Branch (UTMB)           |
| UT Health Science Center at Houston (UTHHealth) |
| UT Health Science Center at San Antonio (UTHSCSA) |
| UT Health Science Center Tyler     |
| UT MD Anderson                     |

**FOR IRB OFFICE USE ONLY**

1. Select the appropriate Organization

<table>
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<tr>
<th>Arlington</th>
<th>Dallas</th>
<th>Permian Basin</th>
<th>Southwestern</th>
<th>HSC San Antonio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin</td>
<td>El Paso</td>
<td>UTSA</td>
<td>UTMB</td>
<td>HSC Tyler</td>
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<tr>
<td>Brownsville</td>
<td>Pan American</td>
<td>Tyler</td>
<td>HSC Houston</td>
<td>MD Anderson</td>
</tr>
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</table>

2. The Investigator’s intention to include this organization as part of the Centralized IRB Review by the IRB designated in item 3 is:

- [ ] Acceptable
- [ ] Not Acceptable

3. Notification Preference – the Reviewing IRB must notify this institution of approvals and study closure using the follow method(s):

- [ ] send a copy of the IRB letter
- [ ] send a monthly statement of listing the protocols approved in the previous month
- [ ] send a weekly statement of listing the protocols approved in the previous week
- [ ] send an copy of the IRB letter to the Site PI at this organization who is then responsible to provide this

4. Federalwide Assurance Information – select the applicable statement(s)

- [ ] The box that applies Subpart A to all research is checked
- [ ] The box that applies Subparts B, C, and D to all research is checked

5. Verification that Reviewing IRB is listed on FWA

- [ ] The IRB designated in Item 3 above is listed on this institution’s Federalwide Assurance
- [ ] The IRB designated in Item 3 above is also listed on the Federalwide Assurance for each affiliated institution listed in Item 4, Column B

6. Signature of the Official Authorized by Organization:

   [Type Name and Title here] Date
Appendix C

CPHS IRB UTHSC Confirmation Letter
TO: Dr. Veronica Brady  
UT-H - GEN - Default Department Code

FROM: Paula Alexander  
CPHS Office

DATE: January 13, 2014

RE: HSC-GEN-14-0022  
"Prevalence of Steroid induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids."

Reference number: 103845

Dear Dr. Brady,

We received an Initial Review Submission Form submission for the above referenced protocol; however, the following information is required by the CPHS office before we can continue processing your request:

Stipulations:
1. We do not have the required Human Subjects Education certificate on file for Veronica Brady. Our education policy and the link to the CITI online training course can be found on our website at http://www.uthouston.edu/cphs/for-researchers/training.htm Once you take the course, CITI administration will forward a copy of the completed certificate directly to CPHS. If we are not in receipt of your certificate during upcoming reviews of studies that you are associated with, you will receive a notice to please fax a copy of the completed certificate to 713-500-7951 so that we may update the iRIS database. Certificates are to be renewed every three years. Please note: HIPAA privacy training is not sufficient.

2. Please provide a copy of the MDACC approval letter for this study.

Please resubmit this request via the iRIS system as soon as you have addressed the issues identified above. If you have any questions, please send them via the correspondence tool within the iRIS system or call the iRIS assistance line at 713-500-7960.

Thank you.
Veronica Brady  
The University of Texas MD Anderson Cancer Center

January 30, 2014  
NOTICE OF PERMISSION TO RELY ON THE UNIVERSITY OF TEXAS (insert name here)  
IRB  
HSC-GEN-14-0022 - Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids.

CHAIRPERSON:  
John C. Ribble, MD  

PROVISIONS:  This permission relates to the research to be conducted under the above referenced title.  
CPHS has reviewed the above submission and determined that it meets the criteria for being reviewed by the University of Texas MD Anderson Cancer Center IRB. Please submit an application to the University of Texas MD Anderson IRB via their electronic system and await written approval.

Research participants must sign authorization for release of medical records unless such authorization is waived by the University of Texas MD Anderson Cancer Center IRB or UT Houston CPHS.

The research should not be initiated until all necessary institutional approvals and signatures have been obtained including but not limited to a fully executed clinical trial agreement and Memorial Hermann Hospital approval (if the research is being conducted at a MHH facility).
Appendix D

Data Abstraction Tool
Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids
PI: Veronica Brady
Clinical Data Collection Form

1. Patient Unique Identifier

2. Patient Medical Record Number

3. Patient name (last, first)

4. Patient date of birth (mm/dd/yyyy) _____/_____/___________

DEMOGRAPHIC DATA

5. Gender:
   - Male
   - Female

6. Race:
   - Other
   - Black, Hispanic
   - Asian or Pac. Islander
   - White, non-Hispanic
   - Native American
   - White, Hispanic

7. Employment:
   - Unknown
   - No
   - Yes

8. Marital Status
   - Unknown
   - Single
   - Married
   - Divorced
   - Widowed

9. Zip Code
DOCUMENTATION OF LYMPHOMA

10. Date of initial lymphoma diagnosis (mm/dd/yyyy)   ___/___/___________

11. Type of MCL

☐ Undefined
☐ Classical-indolent
☐ Small cell – lymphocytic lymphoma, Bcell-Chronic Lymphocytic Leukemia
☐ Pleomorphic- large B cell lymphoma
☐ Blastic- lymphoblastic lymphoma, acute lymphoblastic leukemia

12. Stage of Disease (I-IV):   ________________

13. Presence of Disease in Bone Marrow

☐ Unknown
☐ No
☐ Yes

14. Date of last follow up visit (mm/dd/yyyy)   ___/___/___________

15. Vital statistic (Deceased)   ________________

☐ Unknown
☐ No
☐ Yes

16. Date of death (mm/dd/yyyy)   ___/___/___________

COMORBID DISEASE AT THE TIME OF DIAGNOSIS

17. Hypertension

☐ No
☐ Yes

18. Kidney Disease

☐ No
☐ Yes

19. Hyperlipidemia (high cholesterol, dyslipidemia)

☐ No
☐ Yes

20. Heart Disease (coronary artery disease [CAD], stents, bypass surgery)

☐ No
21. Family history of diabetes
   □ Unknown
   □ No
   □ Yes

22. Patient history of diabetes
   □ Unknown
   □ No
   □ Yes

23. Number of years with diabetes
   □ Unknown
   □ < 1 year
   □ 1-5 years
   □ 6-10 years
   □ 11-15 years
   □ 16-20 years
   □ >20 years

24. Currently taking diabetes medications
   □ Unknown
   □ No
   □ Yes

25. Diabetes Medications (select all numbers that apply)
   □ 1= sulfonylureas (glipizide, amaryl)
   □ 2= biguanides (metformin)
   □ 3= TZDs (actos, Avandia)
   □ 4= DDP4 inhibitors (januvia)
   □ 5= GLP-1RA (byetta)
   □ 6= regular insulin
   □ 7= NPH insulin
   □ 8= Lantus or Levemir
   □ 9= Rapid acting analogs (Aspart, Lispro)
   □ 10= Mixed insulin (70/30, 50/50, 75/25)

26. On diabetes medications at time of last documented clinic visit
   □ Unknown
   □ No
   □ Yes

**CLINICAL DATA**

27. Height (cm) ______________
28. Weight at diagnosis (kg) __________

29. Weight at last documented clinic visit (kg) __________

30. Blood glucose at initial visit (mg/dL) __________

**ON TREATMENT CLINICAL DATA**

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<th>Yes (1) Unknown (2)</th>
<th>Diabetes Medications sulfonyleureas- (1) Meformin (2) TZDs- actos, Avandia (3) Regular insulin (4) NPH insulin (5) Lantus or Levemir (6) Lispro [Humalog] or Aspart [Novolog] (7) Mixed insulin [70/30, 75/25, 50/50] (8)</th>
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Appendix E

Code Book
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</tr>
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<td>Hospital medical record number</td>
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<tr>
<td>Patient name</td>
<td>Last and first name under which patient received treatment</td>
<td>Clinic Station first screen along header “patient summary”</td>
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<td>Patient date of birth</td>
<td></td>
<td>Clinic Station first screen along header “patient summary”</td>
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**DEMOGRAPHIC DATA**

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<th>Gender</th>
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<td>Race/Ethnicity</td>
<td>Race and ethnicity as reported by patient</td>
<td>0= not indicated, unclear, 1= White, non-Hispanic, 2= White, Hispanic, 3= Black, non-Hispanic, 4= Hispanic, 5= Asian or Pac. Islander, 6= Native American</td>
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<td>Employment</td>
<td>Profession/Occupation or being employed as stated by patient</td>
<td>Clinic station transcribed documents—consult notes under social history</td>
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<td>Marital Status</td>
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<tr>
<td>Zip Code</td>
<td>As stated by patient</td>
<td>Clinic Station first screen under header &quot;general&quot;</td>
</tr>
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<td><strong>Mantle Cell Lymphoma (MCL)</strong></td>
<td>Hematologic malignancy treated within the department of Lymphoma/Myeloma</td>
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</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Type of MCL</strong></td>
<td>The classification of MCL as defined by WHO</td>
<td>Clinic Station first screen near bottom under header “cancer diagnosis” or review in pathology reports under favorite modules header on left side of screen</td>
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<tr>
<td><strong>Date of initial diagnosis</strong></td>
<td>The date at which patient was first diagnosed with MCL</td>
<td>Clinic Station under pathology for date of 1\textsuperscript{st} path report or transcribed documents for date of initial Lymphoma/Myeloma visit</td>
</tr>
<tr>
<td><strong>Date of last follow up</strong></td>
<td>The last documented date of patient being seen at MD Anderson Cancer Center</td>
<td>Clinic station Transcribed documents—this will be date of last note documenting actual encounter</td>
</tr>
<tr>
<td><strong>Vital statistic</strong></td>
<td>Patient status: dead or alive</td>
<td>Clinic Station first screen along header “patient summary”</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>High blood pressure: defined as blood pressure $&gt;120/80$</td>
<td>Clinic Station transcribed documents—review consultation notes Based on diagnostic codes (xx) from OPI</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>Elevated BUN, Cr</td>
<td>Clinic Station transcribed documents—review consultation notes Based on diagnostic codes (xx) from OPI</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>High cholesterol, elevated lipids, abnormal lipid profile, dyslipidemia, high triglycerides at the time of diagnosis</td>
<td>Clinic Station transcribed documents—review consultation notes Based on diagnostic codes (xx) from OPI</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>Any family member, primarily 1st degree relative with diabetes (mother, father, sister, brothers, children) at time of diagnosis</td>
<td>Clinic Station transcribed documents—review consultation notes. If any notes from Endocrinology information will likely be there</td>
</tr>
<tr>
<td>Patient previous history of diabetes</td>
<td>T1DM, T2DM, &quot;borderline&quot;, gestational, pre-diabetes, abnormal glucose, steroid induced hyperglycemia, at time of diagnosis</td>
<td>Clinic Station transcribed documents—review consultation notes</td>
</tr>
<tr>
<td>Number of years with diabetes</td>
<td>Use whole numbers only to include number of years since diagnosis of diabetes at time of MCL diagnosis</td>
<td>Clinic Station transcribed documents—review consultation notes</td>
</tr>
<tr>
<td>Taking diabetes medications at time of initial visit</td>
<td>Yes or no as reported by patient at time of MCL diagnosis (Please indicate if medications were prescribed, but patient not taking)</td>
<td>Clinic Station—transcribed notes or Medications—expand and review “Current Medications”</td>
</tr>
</tbody>
</table>
| Diabetes medications | Any medications that are prescribed for diabetes management, oral or injectable being taken at time of MCL diagnosis | Clinic Station—Medications—expand and review “Current Medications” | 1 = sulfonylureas (glipizide, amaryl)  
2 = biguanides (metformin)  
3 = TZDs (actos, Avandia)  
4 = DDP4 inhibitors (janiuvia)  
5 = GLP-1RA (byetta)  
6 = regular insulin  
7 = NPH insulin  
8 = Lantus or Leveimir  
9 = Rapid acting analogs (Aspart, Lispro)  
10 = Mixed insulin (70/30, 50/50, etc) |
|----------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------|
| On Diabetes Medications at time of last meaningful visit | Medications for diabetes listed in medication record | Clinic Station—Medications—expand and review “Current Medications” | 0 = unclear  
1 = no  
2 = yes |

**CLINICAL DATA**

<table>
<thead>
<tr>
<th>Height</th>
<th>Patients height</th>
<th>Clinic station under vital signs tab</th>
<th>Recorded in cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at diagnosis</td>
<td>Patients body weight in kg at time of MCL diagnosis</td>
<td>Clinic station transcribed documents Lymphoma/Myeloma consultation note or under “vital signs” click bulls eye on far right then table on far left next scroll down to date of initial visit and record height and weight</td>
<td>Recorded in kg</td>
</tr>
<tr>
<td>Weight at last meaningful visit</td>
<td>Patients body weight</td>
<td>Clinic station under vital signs tab</td>
<td>Recorded in kg</td>
</tr>
<tr>
<td>BMI at diagnosis</td>
<td>Body Mass Index (calculated)</td>
<td>Calculate based on weight at diagnosis and patient height</td>
<td>Recorded as kg/m²</td>
</tr>
<tr>
<td><strong>Blood glucose at diagnosis</strong></td>
<td>Level of glucose in the blood — this will be the first glucose value following date patient was initially seen for MCL diagnosis (be sure patient has not received steroids prior to this result)</td>
<td>Clinic station— under &quot;Laboratory&quot;— expand time frame to &quot;all data&quot; Look for blood glucose from date of initial consultation with Lymphoma/Myeloma</td>
<td>Recorded as mg/dL</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>ON TREATMENT CLINICAL DATA</strong></td>
<td><strong>Date of 1st treatment</strong></td>
<td>Day/date 1st chemotherapy treatment given</td>
<td>Clinic station transcribed documents — may also correlate with ordersets to verify chemotherapy dates, also nursing documents can be used to verify treatment dates</td>
</tr>
<tr>
<td><strong>Inpatient or Outpatient</strong></td>
<td>Patient status at the time of chemotherapy administered</td>
<td>Clinic station transcribed documents, order sets</td>
<td>0 = unclear 1 = Inpatient 2 = Outpatient</td>
</tr>
<tr>
<td><strong>Steroids type and dose</strong></td>
<td>Dose and type of steroid given with chemotherapy</td>
<td>Clinic station &quot;pharmacy&quot;— completed medications, nursing documentation— MAR, transcribed documents MD, APN/PA note discharge summary if inpatient</td>
<td>0 = other, unclear 1 = dexamethasone 40 mg 2 = dexamethasone 20 mg 3 = dexamethasone 10 mg</td>
</tr>
<tr>
<td><strong>Steroid number of days</strong></td>
<td>Number of consecutive days steroid</td>
<td>Clinic station &quot;pharmacy&quot;— completed</td>
<td>0 = unclear 1 = 4 days 2 = 3 days</td>
</tr>
<tr>
<td><strong>Diabetes Medications Given while receiving steroids</strong></td>
<td>Diabetes medications (ie insulin, metformin, glyburide) given on days of chemotherapy</td>
<td>Clinic station &quot;pharmacy&quot;—completed medications, MAR</td>
<td>1= sulfonlureas (glipizide, amaryl) 2= biguanides (metformin) 3= TZDs (actos, Avandia) 4= DDP4 inhibitiors (januvia) 5= GLP-1RA (byetta) 6= regular insulin 7= NPH insulin 8= Lantus or Levemir 9= Rapid acting analogs (Aspart, Lispro) 10= Mixed insulin (70/30, 50/50, etc)</td>
</tr>
<tr>
<td><strong>Maximum Blood glucose reading during chemotherapy cycle</strong></td>
<td>Blood glucose levels recorded on the dates that chemotherapy was given</td>
<td>Clinic station “laboratory”</td>
<td>Recorded at mg/dL</td>
</tr>
<tr>
<td><strong>BUN and Creatinine</strong></td>
<td>BUN &amp; Cr on the 1st day of treatment</td>
<td>Clinic station “laboratory”</td>
<td>Recorded as mg/dL</td>
</tr>
<tr>
<td><strong>Date of 2nd -6th treatment</strong></td>
<td>Same as above for treatments 2,3,4,5 &amp; 6</td>
<td>Same as above for treatments 2, 3,4,5 &amp; 6</td>
<td>Same as above for treatments 2, 3,4,5 &amp; 6</td>
</tr>
<tr>
<td><strong>Inpatient or Outpatient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Steroids (type, dose &amp; number of consecutive days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood glucose readings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BUN &amp; Creatinine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix F

Laboratory Data Request
Policy: Extraction of Data from the Laboratory Information Systems Databases

Consistent with UT MDACC policy, investigators who have access to LIS data through their medical care and/or QA duties are expected to follow the requirements of the Office of Protocol Research and the Institutional Review Board, as appropriate.

In order to receive data from the LIS, a researcher or clinician must have:

1. Approval by the Director of Clinical Laboratory Informatics or the Chair of the Department, or a designee, and,

When a project is approved, the researcher will meet with designated members of the LIS team to define the scope of the request and mechanisms for retrieving the data. Researchers will not be granted the ability to query the database themselves. The timeline for the data request will also be discussed. Please keep in mind that research and QA queries are prioritized behind clinical operations, and plan in advance accordingly.

Request for Laboratory Information System Data

Date: 1/13/14
Contact person name Veronica Brady
Contact person number 713-792-1981
Contact person e-mail vbrady@mdanerson.org

Purpose of information requested (research, review preparatory to research, QA, other):

Research

Brief outline of data requested:

Blood glucose, BUN and creatinine measurements during treatment and up to 12 months after treatment completed on patients with mantle cell lymphoma treated at MDACC between 1-1-2000 and 1-31-2010 (approximately 438 patients).

I affirm that this information is being requested in compliance with institutional and statutory obligations, including 45 CFR 46 (IRB), HIPAA, and the Office of Protocol Research (signature of PI required)

Veronica J Brady ___________________________ 1-13-2014
Name of PI (print) Signature Date

Return to Mark Routbort, MD, PhD, Director of Clinical Informatics (Box 84, Fax 2-1964)
Appendix G

Pharmacy Informatics Data Request Form
Please complete. Once this request is received it will be reviewed and you will be contacted. Please return the form via email (save & return as email attachment) to ‘Pharmacy Data Request’ using Outlook.

Use the tab key to traverse the document.

<table>
<thead>
<tr>
<th>Contact Name</th>
<th>Department</th>
<th>Date of Request</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veronica Brady</td>
<td>Endocrine Neoplasia and Hormonal Disorders</td>
<td>1/13/2014</td>
</tr>
<tr>
<td>Jeffrey Cui</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone 713-792-1981</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[ ] New Request  [ ] Continuing Request  Date Needed By 1/21/2014

<table>
<thead>
<tr>
<th>Data Used For?</th>
<th>If the data is for research, do you have an Institutional Review Board (IRB) approved protocol?</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Operational purposes – planning, benchmarking, marketing, quality assurance, internal process improvement, or related activities</td>
<td>☑ Yes. The protocol number is PA13-0900.</td>
</tr>
<tr>
<td>☑ Research purposes – hypothesis driven investigations leading to conclusions that will be shared or published</td>
<td>☑ No. We will provide deidentified data using pseudoMRNs or summaries instead.</td>
</tr>
</tbody>
</table>

**Request Details**

Provide background regarding questions you are trying to answer.

Although it has been documented in the literature that steroid induced hyperglycemia occurs as a result of repeated and prolonged exposure to steroids, oftentimes, hyperglycemia is undetected, untreated or under treated using sliding scale insulin in low doses. This lack of treatment or under treatment may lead to the development of steroid induced diabetes, which has the same overall health consequences as type 2 diabetes (T2DM). A study by Weiser, et al. (2004) indicated that 37% of patients experienced hyperglycemia (BG > 200mg/dL) during induction therapy with hyper-CVAD. Two studies done in the adult population examining the impact of hyperglycemia on clinical outcomes indicate that patients who were over the age of 60 and experienced blood glucose levels greater than 180mg/dL had poorer overall survival (Vu, et al. 2012, Weiser, et al 2004). They study by Vu et al. (2012) also indicated that patients who were on Metformin or thiazolidinediones (TZDs) had longer progression free survival (PFS). Rates of hyperglycemia between 10-56% have been reported in studies done in the pediatric population. Studies on the prevalence of hyperglycemia in adults treated for hematologic malignancies and how the resulting hyperglycemia was managed are lacking. Similarly little is known about the late effects of high dose steroids on glucose metabolism, glycemic control or overall survival.

The purposes of this study are to: (1) determine the prevalence and persistence of steroid induced diabetes in patients with mantle cell lymphoma, following treatment with high dose steroids (2) examine how hyperglycemia was managed among this patient population and (3) determine if the degree of hyperglycemia, and how the hyperglycemia was managed impacted cancer outcomes.
Specifically what would you like us to do in regard to this data request? Please be specific in describing your criteria.

Data on steroids prescribed and dispensed (product name, number of doses, amount per dose and dates dispensed), along with anti-diabetic medications prescribed and dispensed (Product name, number of doses, amount per dose and date dispensed) for each patient (MRN's attached).

Indicate for each drug or set of drugs the pharmacy dispensing location:

- IP (Inpatient)
- ATC (Ambulatory)
- Retail (pulls prescriptions filled at MDACC)

Dates/period of interest for the drug(s):
1-1-2000 thru 1-31-2010 OR Included in patient list sent with request.

Specific Data Needed:

- Patient ID
- Name
- Age when dispensed
- Dispense date
- Product name

Relating to amount for administration:

- Number of doses, amount per dose

Relating to amount charged/billed (may or may not be the same as the amount for administration):

- Quantity dispensed
- Drug strength

- Doctor name
- Frequency
- Route/Directions

- Include investigational drugs

Additional data needed:

**Additional Comment**

**Instructions**
Appendix H

Certificate of human subjects protection training
CERTIFICATE OF COMPLETION

is hereby granted to

Veronica J. Brady

Name

to certify satisfactory completion of the

Human Subjects Protection Training Day 1

on

April 15, 2008

Signature
Certificate of Completion

is hereby granted to

Veronica J. Brady

Name

to certify satisfactory completion of the

Human Subjects Protection Training Day 2

on

April 17, 2008

Signature
CERTIFICATE OF COMPLETION

is hereby granted to

Veronica J. Brady

Name

to certify satisfactory completion of the

Human Subjects Protection Training Day 3

on

April 22, 2008

Signature

Susan Twelve-Hume
Appendix I

UT M.D. Anderson Cancer Center Protocol PA13-0900
1.0 Objectives

The purpose of this study is to: (1) determine the prevalence of steroid induced diabetes in patients with mantle cell lymphoma, following treatment with high dose steroids (2) examine how hyperglycemia was managed among this patient population and (3) determine if the degree of hyperglycemia, and how the hyperglycemia was managed impacted cancer outcomes.

2.0 Rationale

Steroid induced hyperglycemia as a results of high dose steroids (dexamethasone 40mg or the equivalent) is a well documented occurrence. Hyperglycemia is defined as blood glucose values > 200mg/dL. According to multiple studies, hyperglycemia related to treatment of hematologic malignancies with dexamethasone occurs at varying rates. Roberson, Raju, Shelso, Pui and Howard, (2008) reported incidences of hyperglycemia among pediatric patients to be 10-15%. In 2005 in a cohort study of 155 newly diagnosed Hispanic patients with B-precursor ALL, Baillargeon, Langevin, Mullins, Ferry, DeAngulo, Thomas, Estrada, Pitney and Pollock noted that 11% of males and 17.5% of females developed transient hyperglycemia during induction treatment. In an earlier study, Belgaumi, et al. (2003) reported hyperglycemia incidence with use of dexamethasone as high as 20%. Also, one of the most recent studies by Sonabend, McKay, Okcu, Yan, Haymond and Margolin (2008) showed rates of hyperglycemia among their study population to be 56%. All of the previously cited studies were done in the pediatric population. One study by Weiser, Cabanillas, Konopleva, Thomas, Pierce, Escalante, Kantarjian & O’Brien (2004), included two hundred seventy-eight adult patients with previously untreated ALL who received dexamethasone as part of their treatment regimen. Documented results showed that hyperglycemia occurred in 37% of these patients.

There is little information available in the literature regarding the prevalence of steroid induced diabetes in patients who are being treated or those who have completed treatment with high dose steroids following diagnosis of lymphoma. Retrospective study by Yeung, et al. (2013) of cohort of myeloma patients who received steroids as part of chemotherapy regimen revealed that 31.7% developed steroid induced diabetes. Pilkey, Streeter, Beel, Hiebert and Li (2012) reported an odds ratio for development of steroid induced diabetes among non-cancer patients of 1.5-2.5. While Gulliford, Charlton, and Latainovic (2006) noted that 2% of incident cases of diabetes were associated with oral glucocorticoids in a primary care population. Among patients with a previous history of diabetes the prevalence of steroid induced hyperglycemia has been documented as 20-50% (Umpierrez et al., 2012). Donih, Raval, Saul, Korytkowski, and DeVita(2006) and Iwamoto, Kagawa, Naito, Kuzuhara, and Kojima (2004) reported that 50% of patients without known diabetes who received high dose steroids (~30mg Prednisone or the equivalent) for ~2 days experienced at least one episodes of hyperglycemia and if exposure was >2 weeks patients developed steroid induced diabetes.
3.0 Eligibility of Subjects

Adult patients (>18 years) with newly diagnosed mantle cell lymphoma, receiving treatment at the University of Texas M. D. Anderson Cancer Center between 1/1/2000 - 12/31/2010, with follow up for at least 6 months to one year following completion of treatment. Patients previously receiving treatment for lymphoma, those with relapsed disease and those who do not complete treatment at MD Anderson Cancer Center will be excluded. A list of patients meeting the inclusion criteria will be obtained from the MD Anderson Cancer Center Tumor Registry.

4.0 Research Plan and Methods

Research Design
This will be a retrospective chart review to study the doses and types of steroids and glucoregulatory medications, including insulin, used in treatment of patients with mantle cell lymphoma. This information will be correlated with blood glucose levels, demographic data, consisting of age, ethnicity, and sex; type and stage of cancer, other medications prescribed, and clinical outcomes, such as relapse, and survival.

Data Collection
After obtaining IRB approval data will be abstracted from charts into the data abstraction tool. The charts of all subjects diagnosed with mantle cell lymphoma between 1/1/2000 and 12/31/2010 will be reviewed. It is estimated that a total of 438 charts will be reviewed. The variables that will be examined include: patient demographics, primary disease treated, comorbid conditions, medications administered, laboratory data, treatment of hyperglycemia, sequelae of hyperglycemia and its treatment, and outcomes (including mortality). Information obtained from tumor registry will include the following: gender, ethnicity, date of birth, diagnosis, date of diagnosis, marital status, occupation, surrogate income (based on pay codes), treatment start and end dates, date last seen at MD Anderson and vital statistics. Blood glucose measurements (at most 6 measurements within 6 cycles of chemotherapy, 2-4 measurements after each cycle and 3 follow up glucose measurements at 3, 6 and 12 months after completion of therapy), BUN and creatinine (one measurement during each cycle, between cycles and at 3, 6, and 12 months after completion of therapy) will be obtained from laboratory information systems. Data on steroids prescribed and dispensed (product name, number of doses and amount per dose), along with anti-diabetic medications prescribed and dispensed (product name, number of doses and amount per dose) will be obtained from pharmacy informatics. This information will be downloaded into the Data Abstraction Tool.

5.0 Statistics and Justification of Sample Size

Descriptive analyses including summary statistics and graphic methods will be used to describe the demographic and clinical characteristics of 438 MCL patients.
For objective 1: Among the patients who don’t have a diabetes history before treatment, we will report the prevalence of steroid induced diabetes within the treatment period. Among the steroid induced diabetes patients, the 3-month, 6-month and 1-year persistence of hyperglycemia will be assessed using the data collected in the follow-up period.
For objective 2: The hyperglycemia management includes 4 kinds of treatments: (1) insulin only, (2) medication only, (3) insulin + medication and (4) no intervention. Among the steroid induced
diabetes patients, we will use frequency table to summarize the types of hyperglycemia management.

For objective 3: To measure the degree of hyperglycemia, we will use (1) maximum of blood glucose values, (2) overall percentage of blood glucose values >200mg/dL, (3) the cycle number of first observing steroid induced diabetes, and (4) the number/percentage of cycles observing steroid induced diabetes. To measure how well the hyperglycemia was managed, we will use (1) the percentage of blood glucose values >200mg/dL after the cycle first observing steroid induced diabetes, and (2) the percentage of cycles observing steroid induced diabetes after first observing steroid induced diabetes. We will use standard survival analyses, including Kaplan-Meier survival curves, log-rank test, parametric regression models and/or Cox proportional hazard model to examine whether they will impact the survival outcomes time-to-relapse and time-to-death.

6.0 Request for Waiver of Informed Consent

A waiver of Informed Consent is requested because this is a retrospective chart review that involves no diagnostic or therapeutic intervention, as well as no direct patient contact and less than minimal risk to patients.

7.0 References


Pharmacotherapy, 24(4), 508-514.


Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids
PA13-0900

Subtitle:

Request for Waiver or Alteration of Informed Consent

Protocol Number: PA13-0900
Principal Investigator: Veronica Brady
Protocol Title: Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids

1. The research involves no more than minimal risk to the subjects.
   This study is a retrospective evaluation of the patients' stored information and will not involve more than minimal risk to the subjects. Subjects are at no more than minimal risk because this is a retrospective chart review. The P.I. will take steps to ensure patient confidentiality. Patients will not be contacted and all collected data will be safely stored and there will be no public access to the data collected. Only research staff and the P.I. will have access to the deidentified material and plans to secure this information are in place. Unique identifiers will be stored as paper documents, linking the patient identifiers with an anonymized sequential identification number. These paper documents will be stored in a locked cabinet in the research offices of the department, with key access limited to the investigators. The electronic database will only contain the identification numbers referencing back to the paper documents. Paper documents containing the unique identifiers will be destroyed (deleted) upon collection and analysis of this data.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
   The waiver will enable the researchers to retrospectively analyze subjects data and will not adversely affect the rights and welfare of the subjects. Due to the fact that this a retrospective chart review, the P.I. does not anticipate violating the rights or welfare of the patients or their information. Furthermore, it will not be possible to influence the rights and welfare of the subjects because we will not be intervening in their medical care.

3. The research could not practicably be carried out without the waiver or alteration.
   This protocol is a retrospective study. Study staff are unable to obtain consent from study subjects because many of the patients being studied in this retrospective study are either deceased or no longer being treated at MD Anderson Cancer Center. It is not practical to conduct this research without this waiver since the status of the patient is unknown, i.e. whether they are alive or deceased and it is difficult to trace the whereabouts of the patient.

4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   We will disseminate our findings by informing appropriate groups of physicians at MDACC, and by posters, publications, etc. for the general medical public.

<table>
<thead>
<tr>
<th>Waiver of Informed Consent Date:</th>
<th>12/12/2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>For IRB Use Only:</td>
<td></td>
</tr>
<tr>
<td>Waiver Approved:</td>
<td>Yes</td>
</tr>
<tr>
<td>Reviewer:</td>
<td>Sanjay Shete</td>
</tr>
</tbody>
</table>
The IRB responsible for review and approval of this waiver was The University of Texas M. D.
IRB 4 IRB00005015

Waiver IC/A Policy
Rev 10.24.02
Waiver of Authorization to Use and Disclose Protected Health Information (PHI)

Protocol Number: PA13-0900
Principal Investigator: Veronica Brady
Protocol Title: Prevalence of Steroid Induced Hyperglycemia in Lymphoma Patients Receiving High Dose Steroids

1. The use or disclosure of the PHI involves no more than minimal risk to the individual's privacy.
   This is based on the following 3 criteria:

   (a) The research protocol includes adequate plans to protect identifiers from improper use.
   HIPAA Identifiers (name, medical record number) will be collected but will be replaced by study numbers in the analytical file; Complete confidentiality will be maintained during this retrospective evaluation, manuscript preparation, and submission.

   (b) The research protocol includes an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research.
   Identifiers (name, medical record number) will be collected but will be replaced by study numbers in the analytical file; Complete confidentiality will be maintained during this retrospective evaluation, manuscript preparation, and submission. All identifiers will be destroyed (deleted from the electronic database) at the completion of data analysis, consistent with conduct of the research.

   (c) The research protocol includes adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, or for other research.
   Complete confidentiality will be kept during this retrospective evaluation, manuscript preparation, and submission. This data will not be used for any other purpose and will not be reused or disclosed to any other person or entity, or for other research. Anonymized information will be retained by the investigator in locked files or password protected databases.

2. The research could not practically be conducted without this waiver or alteration.
   Study staff are unable to obtain authorization from study subjects because many of the patients being studied in this retrospective study are either deceased or no longer being treated at MD Anderson Cancer Center. It is not practical to conduct this research without this waiver since the status of the patient is unknown, i.e., whether they are alive or deceased and it is difficult to trace the whereabouts of the patients.

3. The research could not practically be conducted without access to and use of the PHI.
   This study could only be conducted without access to and use of the PHI. In any attempt to validate the influence or lack thereof the patients' personal health information must be reviewed. This information will not be identified relative to a single patient, results will be generalized.

| Waiver of Authorization Date: | 12/12/2013 |
| Sanjay Shete |  |
| Print Name of IRB Authorized Individual | Signature |
| This waiver was reviewed and approved by the following method: |  |
| Full Committee | Expedited Review |

The IRB responsible for review and approval of this waiver was The University of Texas M. D. IRB 4 IRB00005015
Waiver IC/A Policy
Rev 10.24.02
Appendix J

The impact of hyperglycemia on hematopoietic cell transplantation outcomes
The Impact of Hyperglycemia on Hematopoietic Cell Transplantation Outcomes: An Integrative Review

Jill M. Olausson, RN, MSN, CDE, Marilyn J. Hammer, PhD, DC, RN, and Veronica Brady, MSN, FNP-BC, BC-ADM, CDE

Since Van den Berghe et al. (2001) published the results of their groundbreaking study showing that tight glycemic control in the critical care setting significantly improved patient outcomes, researchers have attempted to understand the relationship between hyperglycemia and patient outcomes in a variety of clinical settings. Hyperglycemia, defined by the American Diabetes Association (ADA, 2013) as a fasting blood glucose (BG) level of 126 mg/dl or greater or a random glucose of 200 mg/dl or greater, is experienced by a large majority of patients during the acute treatment phase of hematopoietic cell transplantation (HCT) (Hammer et al., 2009; Rentschler, 2010), and has, therefore, been studied in this patient population. This review synthesizes the results of these studies.

Hematopoietic Cell Transplantation and Hyperglycemia

HCT is a potentially curative treatment for a variety of malignant and nonmalignant hematologic disorders not resolved through first-line therapies. Although HCT has a high rate of success, it also is associated with a high rate of morbidity and mortality during the acute post-transplantation phase related to infection, organ toxicity, and other complications such as acute and chronic graft-versus-host disease (GVHD) (Appelbaum, Forman, Negrin, & Blume, 2009). Many of the contributors to these adverse outcomes are nonmodifiable. Research is showing, however, that one modifiable factor may be hyperglycemia. Therefore, understanding the scope of the influence of hyperglycemia is essential for optimizing outcomes.

Research completed in a variety of patient populations has shown that hyperglycemia is associated with adverse outcomes in the hospitalized patient and is described in a consensus report by the American Association of Clinical Endocrinologists and the ADA (Moghissi et al., 2009). Hyperglycemia can increase oxidative stress, leading to impaired immune function, decreased healing time, prolonged blood coagulation time, and cause endothelial dysfunction (Hammer &
Hypoglycemia (Vanhorebeek, Langouche, & Van den Bergh, 2007) and glycemic variability (Egi, Bellomo, Stachowski, French, & Hart, 2006) also have been shown to negatively impact outcomes of acute illness. Hyperglycemia is a frequent occurrence in HCT and, therefore, the focus of this review.

The prevalence of hyperglycemia in recipients of HCT is reported to range from 71% (Rentschler, 2010) to 93% (Hammer et al., 2009). That can be related to the stress of acute illness common in hospitalized patients (Butler, Btaiche, & Alaniz, 2005; Godbout & Glaser, 2006; Inzucchi, 2006) or as a side effect of adjunct HCT treatments such as corticosteroids (Butler et al., 2005; Donih, Raval, Saul, Korytkowski, & DeVita, 2006; Fernandez-Miranda et al., 1998), calcineurin inhibitors (Butler et al., 2005; Fernandez-Miranda et al., 1998; Ramos-Cebrian, Torregrosa, Gutierrez-Dalmu, Oppenheimer, & Campistol, 2007), and peripheral nutrition (Klein, Stanek, & Wiles, 1998). Hyperglycemia manifests as a worsening of control of preexisting diabetes or as a new symptom in patients without a known history of glucose intolerance. In many patients, hyperglycemia is transient and resolves when treatment concludes, but in about 17%–30% of HCT recipients, frank diabetes develops (Griffith, Jagaia, & Jagaia, 2010; Karnchanasorn, Malamug, Jin, Karanes, & Chiu, 2012). The purpose of the current review is to evaluate existing evidence and discuss implications for nursing practice in the area of hyperglycemia in the context of HCT.

Methods

Following the guidelines for integrative reviews set forth by Whittemore and Knaf (2005) articles were searched for, reviewed, and eliminated until final selection for analyses. Three electronic databases were searched (PubMed, CINAHL®, and MEDLINE®) using key words hyperglycemia OR blood glucose AND hematopoietic cell transplantation OR bone marrow transplantation. The inclusion criteria were empirical studies, in English, that examined the impact of hyperglycemia on adult HCT patient outcomes from 2000–2013. Twenty-nine articles were initially found. Three additional articles were added from articles referenced in the initial 29 journals. The abstracts from these 32 articles were reviewed for eligibility by the three authors. Twenty of these articles were eliminated because they did not meet the full inclusion criteria, leaving 12 full-text articles for the review.

Content analysis was performed on the 12 articles to address research questions, synthesize data, and summarize findings. Results were based on the major findings, including associations found between hyperglycemia and patient outcomes and risk factors for hyperglycemia. Table 1 provides a summary of these results.

Results

Hyperglycemia and Infection

Infection is a primary cause of death among HCT recipients due to immunosuppression from both the malignancy and the conditioning regimens (Ninin et al., 2001). Hyperglycemia compounds the risk for infection through further compromising immune function by impairing immune cell signaling (Butler et al., 2005). Infections themselves can cause elevations in BG levels (Turina, Christ-Crain, & Polk, 2006) and further promote proliferation of microorganisms, leading to a vicious cycle of hyperglycemia increasing the risk for infections and infections increasing the risk for hyperglycemia. In the studies reviewed, positive associations were seen between hyperglycemia and infection in four (Derr, Hsiao, & Saudek, 2008; Fuji et al., 2009; Rentchler, 2010; Sheean, Freels, Helton, & Braunshweig, 2006) of the five studies with infection as a primary outcome. An earlier study by Fuji et al. (2007) did not find an association between infection and hyperglycemia.

Hyperglycemia and Time to Engraftment

Until the infused hematopoietic cells migrate to the host’s bone marrow, or engraft, the patient remains at high risk for infections. Patients become pancytopenic and, in particular, neutropenic. Neutrophil recovery (absolute neutrophil count greater than 1,000/mm3) is the hallmark of engraftment and can take as long as 3–4 weeks depending on the type of transplantation and stem cell source (Cutler & Antin, 2005). Full recovery of hematopoiesis and the immune system can take several months after an autologous transplantation and as long as two years following an allogeneic transplantation (Antin, 2002), leaving the patient susceptible to infections for a prolonged period. The longer the period of pancytopenia, the greater the associated morbidity and mortality; therefore, understanding any impediments to engraftment is critical. Studies related to time-to-engraftment were mixed. Sheean et al. (2006) found hyperglycemia to increase time-to-engraftment, whereas Karnchanasorn, Malamug, Jin, Karanes, and Chiu (2012) did not find this association in the autologous HCT participant sample studied.

Hyperglycemia and Acute Graft-Versus-Host Disease

Acute GVHD is an immunologic-mediated disease that contributes to transplantation-related morbidity and mortality, with a mortality rate as high as 30% for those with the greatest severity (Barton-Burke et al., 2008). Because of histocompatibility antigen differences, T cells from the donor graft attack the host’s mucous membranes of the skin, gastrointestinal tract, and liver (Barton-Burke et al., 2008). This occurs in 30%–50% of


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| Derr et al., 2008      | Retrospective, cohort study   | 382 adult patients who received allogeneic or autologous BMT at the Johns Hopkins   | **Outcome:** Neutropenic infections with statistical adjustments for age, gender, race, type of cancer, BMT type, and cumulative GCs dose;  | Neutropenic infections: 22% developed one or more infections, with 13% incurring bloodstream infections. During neutropenia, each 10 mg/dl increase in BG preneutropenia was associated with an OR of 1.08 for any infection (p = 0.14); an OR of 1.15 for bloodstream infection (p = 0.001); without GCs, an OR of 1.21 for any infection (p < 0.0001); and an OR of 1.24 for bloodstream infection (p < 0.0001).<br><br>**Other outcomes:** No association was found between mean glycemia and LOS, critical status, or mortality.**
|                        |                               | Sidney Kimmel Cancer Center from November 2002 to November 2006                   | mean glycemia and LOS, critical status, and mortality.                                                                                     |                                                                                                                                                              | BMT populations are at risk for antecedent hyperglycemia and later infection, particularly those who receive GCs during neutropenia. Tight glycemic control may reduce infections.                                                                                                                                                       |
|                        |                               |                                                                                    | BG: Measured during hospital stay (central laboratory and POC testing); BG was measured between admission and 8 am on date of neutropenia. |                                                                                                                                                              |                                                                                                                                                              |
| Fuji et al., 2007      | Retrospective, cohort study   | 112 adult patients who received myeloablative allogeneic HSCT from January 2002 to | **Outcome:** Occurrence of FN, documented infection during neutropenia, organ dysfunction during neutropenia, acute GVHD, OS, and NRM; OS and NRM were assessed with the clinical factors of age, gender, conditioning regimen, donor match, GVHD prophylaxis, and disease risk. |                                                                                                                                                              | An association was noted between degree of hyperglycemia during neutropenia and increased risk of post-transplantation complications and NRM.                                                                                                                                                       |
|                        |                               | June 2006 at the National Cancer Center Hospital in Tokyo, Japan                   | BG: Patients were categorized based on mean fasting BG during neutropenic period after conditioning.<br>• Normoglycemia (< 110 mg/dl)<br>• Mild hyperglycemia (110–150 mg/dl)<br>• Moderate to severe (> 150 mg/dl) |                                                                                                                                                              |                                                                                                                                                              |
| Case-control study.    |                               |                                                                                    |                                                                                                                                                             |                                                                                                                                                              |                                                                                                                                                              |
|                       |                               | 64 patients who received allogeneic HSCT from June 2006 to May 2007 at the National Cancer Center Hospital in Tokyo, Japan | **Outcome:** Documented infectious complications and organ dysfunction were based on glycemic status comparing patients who received IGC and PN management with those who did not. |                                                                                                                                                              |                                                                                                                                                              |
|                        |                               |                                                                                    | BG: Tested every morning. Target BG was 80–110 mg/dl; if morning BG was above target, testing was increased to 2–4 times per day. Categories of BG were 80–110, 111–140, 141–179, and 180 mg/dl or greater. |                                                                                                                                                              |                                                                                                                                                              |
|                        |                               |                                                                                    |                                                                                                                                                             |                                                                                                                                                              |                                                                                                                                                              |

**Table 1. Literature Review**

| ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; BG—blood glucose; BMI—body mass index; BMT—bone marrow transplantation; CI—confidence interval; CRP—C-reactive protein; FN—febrile neutropenia; GCs—glucocorticoids; GVHD—graft-versus-host disease; HSCT—hematopoietic stem cell transplantation; HCT—hematopoietic cell transplantation; HR—hazard ratio; IGC—intensive glucose control; LOS—length of hospital stay; NRM—nonrelapse mortality; OR—odds ratio; OS—overall survival; PN—parenteral nutrition; POC—point of contact; PTDM—post-transplant diabetes mellitus; TBI—total body irradiation; TPN—total parenteral nutrition; WBC—white blood count |

Note. Level of evidence was rated from I (highest) to VII (lowest) and based on Melnyk (2004).
### Table 1. Literature Review (Continued)

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<td>Garg et al., 2007</td>
<td>Retrospective, cohort study</td>
<td>118 inpatients in the BMT unit at Brigham and Women's Hospital from January to June 2006</td>
<td><strong>Outcome:</strong> Mean LOS of normoglycemic versus hyperglycemic groups considering age, gender, presence of infection, diabetes status, renal status, and GC use.</td>
<td>Mean LOS was significant when comparing the normoglycemic group (X = 15.9, SD = 5.7 days) with the hyperglycemic groups (X = 19.8, SD = 9 days, p &lt; 0.01). Significant correlations also were shown between highest BG value and LOS (r = 0.44, p &lt; 0.001) even when excluding patients with infections (r = 0.32, p = 0.03). Patients treated with GCs had higher BGs (X = 111.2, SD = 14.8 mg/dl) and longer LOS (X = 32.1, SD = 11.54 days) than those who did not receive GCs (X = 102, SD = 2.9 mg/dl; X = 17, SD = 6.4 days). Effects persisted when patients receiving GCs were excluded, mean BG and LOS (r = 0.29, p &lt; 0.005) and highest BG value and LOS (r = 0.29, p &lt; 0.005). Gender had no effect on LOS. When patients with preexisting diabetes (X LOS = 17.5, SD = 7.9 days) were added to analysis, study results did not change.</td>
<td>Inpatient BG levels are associated with increased LOS in patients receiving BMT. GC use is associated with hyperglycemia in the BMT setting.</td>
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<td>Gebremedhin et al., 2012</td>
<td>Retrospective, cohort study</td>
<td>328 adults who underwent allogeneic HSCT for AML, ALL, and myelodysplastic syndrome at City of Hope National Medical Center from October 2003 to April 2009</td>
<td><strong>Outcome:</strong> Hyperglycemia (morning serum glucose) and the development of acute GVHD adjusted for donor/recipient characteristics, prophylactic regimen, and mucositis</td>
<td>Among normal to overweight patients, severe hyperglycemia doubled the risk of acute GVHD (HR = 2.71, 95% CI [1.58, 4.65]). In obese patients, severe hyperglycemia did not significantly affect risk of GVHD. Hyperglycemia was associated with male gender, the combination of Hispanic ethnicity with unrelated donor, greater BMI, tacrolimus, GCs, myeloablative conditioning with TBI, and TPN.</td>
<td>Severe hyperglycemia in the first 10 days after allogeneic HSCT in nonobese patients was predictive of acute GVHD.</td>
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All—acute lymphoblastic leukemia; AML—acute myeloid leukemia; BG—blood glucose; BMI—body mass index; BMT—bone marrow transplantation; CI—confidence interval; CRP—C-reactive protein; FN—febrile neutropenia; GCs—glucocorticoids; GVHD—graft-versus-host disease; HSCT—hematopoietic stem cell transplantation; HCT—hematopoietic cell transplantation; HR—hazard ratio; IGC—intensive glucose control; LOS—length of hospital stay; NRM—nonrelapse mortality; OR—odds ratio; OS—overall survival; PN—parenteral nutrition; POC—point of contact; PTDM—post-transplant diabetes mellitus; TBI—total body irradiation; TPN—total parenteral nutrition; WBC—white blood count

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<td>Griffith et al., 2011</td>
<td>Prospective study.</td>
<td>84 adult patients receiving allogeneic HCT without preexisting diabetes at Vanderbilt-Ingram Cancer Center</td>
<td><strong>Outcome:</strong> Factors associated with PTDM at day +100 and association between PTDM and OS were examined, including c-peptide, insulin level, indinavir for HCT, weight, peak steroid dose, duration of steroids, and other immunosuppressant therapy.</td>
<td><strong>Independent predictors of PTDM:</strong> Pretransplantation c-peptide level greater than 3.6 mg/dl (OR = 5.9; 95% CI [1.77, 20.22], p = 0.004); delayed donor allogeneic HCT (OR = 4.3; 95% CI [1.34, 14.2], p = 0.014); and peak steroid dose greater than 1 mg/kg per day (OR = 5.09, 95% CI [1.19, 23.32], p = 0.021)</td>
<td>Higher pretransplantation c-peptide, unrelated donor status, and peak steroid doses in the first 100 days post-transplantation are associated with new-onset PTDM. Patients with PTDM and elevated c-peptide had inferior OS.</td>
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<td>Hammer et al., 2009</td>
<td>Retrospective, cohort study. The purpose was to investigate the associations between glycemic status and infection and mortality rates among allogeneic HCT recipients.</td>
<td>1,275 patients aged 18 years and older with hematologic malignancies who received allogeneic HCT from 2000–2005 at Fred Hutchinson Cancer Research Center</td>
<td><strong>Outcome:</strong> Onset of first infection and NRM with statistical adjustments for age at HCT, severity of disease, type of donor, year of HCT, and presence of grades 2–4 acute GVHD</td>
<td><strong>Infection:</strong> HR of 1.29 for a BG level of 151–200 mg/dl compared to 101–150 mg/dl (p = 0.004); variability HR of 1.41 with a standard deviation of greater than 49 mg/dl compared to a SD of 0–18 mg/dl (p = 0.0001)</td>
<td>Recipients of allogeneic HCT 18 years and older are at risk for infections and NRM with hyperglycemia, hypoglycemia, or increased glycemic variability (collectively termed malglycemia).</td>
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<td>Karnchanasorn et al., 2012</td>
<td>Retrospective, cohort study. The purpose was to examine the impact of BG concentration on the outcomes of autologous HCT.</td>
<td>240 adult patients receiving autologous HSCT who were discharged from City of Hope National Medical Center from January to December 2006</td>
<td><strong>Outcome:</strong> BG average, LOS, time to engraftment, rate of infection; covariates included age, gender, BMI, use of TPN and GCs. Further analysis was conducted to assess the relationship between post-transplantation BG average less than 150 mg/dl and BG average of 150 mg/dl or greater and NRM.</td>
<td><strong>Age, BMI, and TPN had a significant positive effects of pre- and post-transplantation average BG.</strong></td>
<td>Post-transplantation BG was associated with longer LOS but not with platelet or neutrophil engraftment.</td>
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**ALL**—acute lymphoblastic leukemia; **AML**—acute myeloid leukemia; **BG**—blood glucose; **BMI**—body mass index; **BMT**—bone marrow transplantation; **CI**—confidence interval; **CRP**—c-reactive protein; **FN**—febrile neutropenia; **GCs**—glucocorticoids; **GVHD**—graft-versus-host disease; **HSCT**—hematopoietic stem cell transplantation; **HCT**—hematopoietic cell transplantation; **HR**—hazard ratio; **IGC**—intensive glucose control; **LOS**—length of hospital stay; **NRM**—nonrelapse mortality; **OR**—odds ratio; **OS**—overall survival; **PN**—parenteral nutrition; **POC**—point of contact; **PTDM**—post-transplant diabetes mellitus; **TBI**—total body irradiation; **TPN**—total parenteral nutrition; **WBC**—white blood count.

*Note: Level of evidence was rated from I (highest) to VII (lowest) and based on Melnyk (2004).*
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<td>Pidala et al., 2011</td>
<td>Retrospective, cohort study</td>
<td>147 patients with acute GVHD treated with steroids admitted for allogeneic HCT from 2004–2008 at Moffitt Cancer Center in Tampa, FL</td>
<td><strong>Outcome:</strong> The effect of hyperglycemia at 12 weeks post-HCT on OS and NRM, considering the following variables: pre-existing diabetes, age, underlying condition, risk category, remission status at time of HCT, donor characteristics, conditioning regimen, and BMI, GVHD characteristics, GC, and antihyperglycemic therapy.</td>
<td>Baseline diabetes predicted greater maximum, mean, and standard deviation of BG levels. Maximum, average, or standard deviation of glucose values predicted OS, and maximum of average glucose values predicted NRM. Minimum glucose values (0–60 mg/dl) were associated with worsened OS and increased NRM. Patients treated with oral antihyperglycemic agents or insulin had worse OS and increased NRM compared to patients who did not need therapy.</td>
<td>The data suggest an independent adverse effect of dysglycemia in patients treated with Cs for acute GVHD, and argue for stringent glycemic control in this setting.</td>
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<td>Rent-schler et al., 2010</td>
<td>Retrospective, cohort study</td>
<td>160 patients receiving HSCT without pre-existing diabetes in 2004 at the Nebraska Medical Center</td>
<td><strong>Outcome:</strong> Differences existed between participants with hyperglycemia and those without in regards to treatments (TPN and GCS) and renal, cardiac, and infectious complications, GVHD, LOS, and OS outcomes. LOS was adjusted for gender, age, diagnosis, chemotherapy regimen, cardiac and renal complications, infection, GVHD, immunosuppressive medications, insulin therapy, GC use, and TPN.</td>
<td><strong>Hyperglycemia:</strong> Seventy-one percent of patients had hospital-related hyperglycemia. Hospital-related hyperglycemia was associated with increased complications (56% versus 39%, p = 0.05), with infection being the most common (38%). Thirteen percent developed a cardiac complication and 6% developed a renal complication. The majority (93%) was treated with steroids and 39% received TPN.</td>
<td>TPN and increasing age are both risk factors for the development of hospital-related hyperglycemia in HCT recipients. Hyperglycemia was associated with increased risk of complications but was not associated with longer LOS.</td>
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ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; BG—blood glucose; BMI—body mass index; BMT—bone marrow transplantation; CI—confidence interval; CRP—C-reactive protein; FN—fibrinogenemia; GCS—glucocorticoids; GVHD—graft-versus-host disease; HSCT—hematopoietic stem cell transplantation; HCT—hematopoietic cell transplantation; HR—hazard ratio; ICG—intensive glucose control; LOS—length of (hospital) stay; NRM—nonrelapse mortality; OR—odds ratio; OS—overall survival; PN—parenteral nutrition; POC—point of contact; PTDM—post-transplant diabetes mellitus; TBI—total body irradiation; TPN—total parenteral nutrition; WBC—white blood count.

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<td>Sheean et al., 2004</td>
<td>Retrospective, cohort study. The purpose was to determine whether TPN-induced hyperglycemia is associated with adverse outcomes.</td>
<td>48 adult patients admitted to Rush-Presbyterian St. Luke's Medical Center or the University of Illinois Medical Center from July to December 2001 for initial autologous or allogeneic HCT</td>
<td><strong>Outcome:</strong> Hyperglycemia, number and duration of infections, and in-hospital mortality. BG: Recorded once a day from morning blood draw. Hyperglycemia was defined as BG greater than 6.1 mmol/L (110 mg/dL).</td>
<td><strong>Hyperglycemia:</strong> Recipients of TPN experience more hyperglycemia (p &lt; 0.05) after TPN initiation. <strong>Infections:</strong> Recipients of TPN experienced 69% of all infections and 100% of all repeat positive blood cultures (not a significant difference between the TPN and non-TPN groups). <strong>Support:</strong> Recipients of TPN had more platelet transfusions than those not receiving TPN (X = 2.2, SD = 3 versus X = 0.8, SD = 0.9, p = 0.08). <strong>LOS:</strong> Recipients of TPN had greater length of stay and daily charges than those not receiving TPN. <strong>Mortality:</strong> In-hospital differences in mortality were not detected between the TPN groups.</td>
<td>Inpatients receiving HCT and TPN had greater incidence of hyperglycemia when compared to those who did not. The small sample size limited the power of this study.</td>
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<td>Sheean et al., 2006</td>
<td>Retrospective, cohort study. The purpose was to assess the incidence of hyperglycemia and its effects on post-HCT outcomes in patients receiving TPN versus those not receiving TPN.</td>
<td>357 adult patients undergoing autologous and allogeneic HSCT from September 1999 to December 2003 at two urban university hospitals</td>
<td><strong>Outcome:</strong> A comparison was done of hyperglycemia levels in TPN versus those not receiving TPN with consideration given to GC use and donor type. Number of infections, red cell and platelet transfusions, WBC count, platelet engraftment, and hyperlipidemia were examined in relation to TPN use. BG: Recorded once a day from morning blood draw; hyperglycemia was defined as BG of 110 mg/dL or greater. Levels of hyperglycemia were based on percentage of hospital days with BG of 110 mg/dL and greater and 200 mg/dL and greater.</td>
<td><strong>Hyperglycemia:</strong> All patients developed increases in BG levels the first few days of hospitalization with a return to lower levels on subsequent days. Patients who began TPN had more hyperglycemic days than those without TPN, even when stratified by steroid and donor type (88% versus 8%, p &lt; 0.001). <strong>Morbidity:</strong> TPN recipients were two times or more likely to become infected than those not receiving TPN (OR = 2.2; 95% CI [1.4, 3.5]). The association was only slightly attenuated when patients with infections, receiving steroids, and donor type were removed. The association increased in normal and underweight patients with TPN (OR = 4.3; 95% CI [1.7, 10.6]) compared to overweight and obese patients. Allogeneic patients receiving TPN had higher rates of infection (p = 0.001), red blood cell (p = 0.001), and platelet (p ≥ 0.001) transfusions. Patients who received TPN compared to those who did not had significant differences in time to WBC engraftment for autologous (X = 11.9, SD = 2.4 versus X = 11.2, SD = 1.9 days, p = 0.01) and allogeneic (X = 14.8, SD = 4.8 versus X = 12.3, SD = 2.5 days, p = 0.001).</td>
<td>The broad use of TPN in patients undergoing HSCT was associated with profound hyperglycemia, resultant morbidity (increases in infection rates, greater requirements for transfusions, and time to engraftment), and questionable efficacy in the adult, well-nourished cohort.</td>
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all allogeneic transplantation recipients (Goerner et al., 2002), with increased incidence in mismatched and unrelated transplantations, use of peripheral stem cells, and increased age (Dean & Bishop, 2003). Additional risk factors for GVHD include higher doses of radiation, advanced disease, and viral infections in either the recipient or the donor (Anagnostopoulos & Giralt, 2002).

Fuji et al. (2007) showed a positive correlation between degree of hyperglycemia during neutropenia and the risk for the development of grade II–IV acute GVHD. A subsequent study (Gebremedhin, Behrendt, Nakamura, Parker, & Salehian, 2012) found hyperglycemia during the first 10 days after allogeneic HCT to be positively associated with the development of graft-versus-leukemia (the targeted effect that prevents future malignant cells from forming and proliferating) and acute GVHD (the deleterious point past the graft-versus-leukemia effect that can lead to severe adverse outcomes, including death) to be dependent on the underlying diagnosis and patient characteristics. Patients who were normal or overweight had severe hyperglycemia and double the risk of GVHD, whereas patients who were obese had no increased risk (Gebremedhin et al., 2012).

**Hyperglycemia and Length of Stay**

HCT requires extensive inpatient time related to a prolonged depleted immune system. One investigation showed the median length of stay (LOS) post-HCT was 20 days for autologous and 28 days for allogeneic patients (Center for Medicare and Medicaid Services, 2010). Increases in LOS can adversely affect patient quality of life (Prieto et al., 2002) and a transplantation center’s patient flow and costs (Jones et al., 2008). Four studies addressed length of stay in the HCT patient population. Two studies (Garg, Bhutani, Alyea, & Pendergrass, 2007; Karnchanasorn et al., 2012) found increased overall LOS with patients who experienced elevated mean BG levels throughout the transplantation period. Two studies did not find statistical significance when investigating the association between hyperglycemia and LOS (Derr et al., 2008; Rentschler, 2010). Derr et al. (2008) looked specifically at hyperglycemia in the pre-neutropenic phase (9.3 days on average from admission), whereas Rentschler (2010) reviewed hyperglycemia during the entire inpatient phase. Neither of these studies evaluated BG pre-HCT through post-HCT, which may have yielded different LOS findings.

**Hyperglycemia, Overall Survival, and Nonrelapse Mortality**

Studies primarily in the allogeneic HCT patient population have explored the relationship between elevated glucose levels and the primary endpoints of overall survival (OS) and nonrelapsed mortality (NRM). Fuji et al. (2007) found associations between hyperglycemia and decreased OS, and Pidala et al. (2011) found that an increase in glucose levels adversely impacted both OS and NRM. Hammer et al. (2009) found associations between hyperglycemia and NRM in recipients of allogeneic HCT. The study also found that hypoglycemia and increased glycemic variability were associated with NRM in these patients. In addition, the degree of hyperglycemia was inversely associated with OS in several studies (Derr et al., 2008; Fuji et al., 2007; Hammer et al., 2009; Pidala et al., 2011).

**Hyperglycemia and Toxicities**

Complications of HCT include organ toxicities. Researchers investigated whether hyperglycemia was associated with increased organ dysfunction. In Fuji’s earlier retrospective study (2007), an association between hyperglycemia and organ toxicities was noted during the neutropenic stage. In Fuji’s subsequent study (2009), intensive glucose control post-HCT was found to reduce the incidence of renal dysfunction. Garg et al. (2007) also looked at the relationship between hyperglycemia and renal function, but none of the 126 participants demonstrated any degree of renal dysfunction and, therefore, relationships between the variables could not be established. Rentschler (2010) did find that patients with hyperglycemia experienced more organ toxicities, including cardiac and renal complications.

**Treatment-Related Associations With Hyperglycemia**

Corticosteroids are commonly administered during HCT for GVHD prophylaxis and symptom management, in addition to treating other side effects. Corticosteroids cause impairment in insulin secretion and induce peripheral insulin resistance (Donih et al., 2006). Corticosteroids were highly correlated with hyperglycemic events during the HCT process in numerous studies (Derr et al., 2008; Fuji et al., 2007; Garg et al., 2007; Hammer et al., 2009; Pidala et al., 2011). In addition, the dose and length of treatment with corticosteroids were significantly associated with increased BG levels (Pidala et al., 2011). Because patients undergoing allogeneic HCT receive corticosteroids for immunosuppression, it is not surprising that they were found to experience higher rates of hyperglycemia than their autologous counterparts (Griffith et al., 2011).

Total parenteral nutrition (TPN) often is administered when patients are unable to tolerate oral nutrient intake (often from mucositis). Three studies showed increased rates of hyperglycemia in patients who received TPN (Rentschler, 2010; Sheean, Braunschweig, & Rich, 2004; Sheean et al., 2006).
Knowledge Translation

Management of hyperglycemia during the acute phase of hematopoietic cell transplantation (HCT) is an important role for the transplantation nurse.

An increased awareness of glycemic issues in patients during the acute phase of HCT is vital to nurses when planning care in complex patients receiving HCT.

Early glycemic interventions to mitigate hyperglycemia may decrease adverse events related to poor glycemic control.

Patient-Related Factors Associated With Hyperglycemia

Although all patients undergoing HCT are at increased risk for hyperglycemic events, those with preexisting diabetes are assumed to be at even greater risk for hyperglycemic events during treatment. A few studies confirmed this, showing greater hyperglycemic levels in patients with preexisting diabetes (Derr et al., 2008; Pidala et al., 2011) and insulin resistance (Griffith et al., 2011) compared to those with no known history of diabetes/insulin resistance prior to treatment. An additional finding of interest was two studies that reported that patients with normal body mass and hyperglycemia experienced worse outcomes than those of overweight or obese individuals with hyperglycemia (Gebremedhin et al., 2012; Shean et al., 2006).

Older adults have higher rates of diabetes compared to younger age groups (Centers for Disease Control and Prevention, 2011); however, independent of diabetic history, older age also can be a risk factor for hyperglycemic events. In the HCT population, older age was confirmed as a risk for hyperglycemia in a number of studies in this review (Fuji et al., 2007; Gebremedhin et al., 2012; Rentschler, 2010).

Discussion

Although a causal relationship between hyperglycemia and adverse clinical outcomes has not been established, evidence suggesting the deleterious effects of hyperglycemia is mounting. The results of this integrative review showed associations between hyperglycemia and infection, time to engraftment, development of acute GVHD, LOS, toxicities, and OS. Findings regarding patient-related risk factors for hyperglycemia were noted as older age, insulin resistance, and increased body mass index. Patients of normal weight experiencing hyperglycemia had worse outcomes than those who were overweight or obese. Treatment-related risk factors for hyperglycemia included dose and duration of corticosteroids and use of TPN.

A major limitation in the results of this review is the wide variation in the definition of hyperglycemia and the collection of BG data. Of note is the arbitrary assignment of BG levels into categories. For example, Gebremedhin et al. (2012) categorized hyperglycemia by mild (110–150 mg/dl), moderate (151–179.9 mg/dl), and severe hyperglycemia (180 mg/dl and greater), whereas Garg et al. (2007) dichotomized BG values into normoglycemia (less than 100 mg/dl) and hyperglycemia (100 mg/dl or greater). These two studies also provide examples of variations in BG measurements used in the studies. Gebremedhin et al. (2007) used mean morning serum BG levels from daily laboratory draws, whereas Garg et al. (2007) used mean BG values from all available values (central laboratory and point-of-care testing). These discrepancies were found in all studies, making it difficult to synthesize the findings.

Another limitation includes the retrospective design of the majority (10 of 12) of the studies. Therefore, most of the research reports reviewed in this article recommended that prospective studies be conducted to better evaluate the impact of glycemic control on HCT outcomes. Future research ideas were suggested, including testing alternative treatments and supportive care modalities to ascertain whether these mitigate hyperglycemia and subsequent adverse outcomes.

The authors of the current article also noted the benefits of prospective studies as providing the opportunity to determine whether BG data was obtained during the fasting or fed state. The ADA (2013) recommendation for fasting BG levels of between 70–130 mg/dl is based on eight hours of no caloric intake. This provides the rationale for the assumption that morning BG values above this range are hyperglycemic. Because of the wide use of nutritional (parenteral, enteral, and IV) support in the hospital setting, it is difficult to discern if BG values taken during morning blood draws are indeed fasting. Prospective studies would allow for assessment of this variable so better categorization of hyperglycemia could be determined. In addition, prospective studies would allow for greater depth and breadth of the patient experience of having hyperglycemia during the acute HCT phase.

Implications for Nursing

Despite the limitations of these studies, the results have substantial and timely implications for healthcare providers. Population trends, such as the increasing numbers of older adults (Administration on Aging, 2013) concurrent with the ability to offer transplantation as a treatment option to older adults (Karanes et al., 2008), have made the older adult patient population the fastest growing segment of patients receiving HCT (Pasquini, 2013). Because diabetes and
insulin resistance are age-related diseases, healthcare providers will encounter diabetes as a comorbidity of HCT more frequently in the future. Understanding the potential and actual adverse effects of hyperglycemia as well as the patient- and treatment-related risk factors summarized in this article will guide nurses in making informed and appropriate interventions for glycemic control in this complex patient population.

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Appendix K

Hyperglycemic-inducing neoadjuvant agents used in treatment of solid tumors: A review of the literature.
Hyperglycemic-Inducing Neoadjuvant Agents Used in Treatment of Solid Tumors: A Review of the Literature

Denise Soltow Hershey, PhD, FNP-BC, Ashley Leak Bryant, PhD, RN, OCN®, Jill Olausson, RN, MSN, CDE, Ellen D. Davis, MS, RN, CDE, FAADE, Veronica J. Brady, MSN, FNPBC, BC-ADM, CDE, and Marilyn Hammer, PhD, DC, RN

Patients with a solid tumor cancer are at risk for hyperglycemia (blood glucose > 126 mg/dl) during treatments. Hyperglycemia can contribute to the risk for adverse outcomes such as infections and non-malignancy-related mortality, it also may increase the risk for development of clinical toxicities, grade 4 neutropenia, neutropenic fever, sepsis, and neuropathy. Hyperglycemia during cancer treatment is one of the clinical toxicities that can cause chemotherapy dose delays or reductions. In addition, it may decrease the response to chemotherapeutic agents. Understanding the contributors to hyperglycemia in patients with a solid tumor cancer is essential to create interventions for improved outcomes.

The purpose of this integrative review is to explore the specific chemotherapeutic agents that can increase the risk for hyperglycemia and to discuss the related clinical implications among adults with solid tumor cancers. The specific aims are to identify chemotherapeutic agents that contribute to hyperglycemia in adults with solid tumor cancers and discuss implications for nursing practice and future research to mitigate hyperglycemic events in adults with solid tumor cancers receiving hyperglycemic-inducing chemotherapeutic agents.

**Purpose/Objectives:** To review the literature regarding the development of hyperglycemia associated with neoadjuvant agents used in the treatment of solid tumor cancers.

**Data Sources:** Research articles were obtained from PubMed, CINAHL®, and Cochrane Reviews. The following search terms were used alone and in combination: diabetes, glycemic control, chemotherapy, androgen deprivation therapy, interferon-alpha, immunosuppressants, cancer, neoplasms, and hyperglycemia.

**Data Synthesis:** Twenty-two studies were identified reporting the development of hyperglycemic events in patients who received a variety of chemotherapeutic agents.

**Conclusions:** Findings suggest patients are at risk for the development of hyperglycemia from certain chemotherapeutic agents. Docetaxel, everolimus, and temsirolimus alone or in combination with other agents can promote hyperglycemia. Androgen-deprivation therapy commonly used in prostate cancer, increases the risk for the development of hyperglycemia and diabetes.

**Implications for Nursing:** Oncology nurses play an important role in the identification and treatment of hyperglycemia in patients receiving chemotherapy. Future research is needed that focuses on the association between glycemic control and adverse outcomes in patients with a solid tumor cancer who are at risk for treatment-induced hyperglycemia.

**Key Words:** neoplasm; chemotherapy; hyperglycemia

The full text of this article can be accessed at http://ons.metapress.com.

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Appendix L
Safe and effective dosing of basal-bolus insulin in patients receiving high dose steroids for hyper-CVAD chemotherapy. Diabetes Technology and Therapeutics.
Safe and Effective Dosing of Basal–Bolus Insulin in Patients Receiving High-Dose Steroids for Hyper-Cyclophosphamide, Doxorubicin, Vincristine, and Dexamethasone Chemotherapy

Veronica Brady, MSN, FNP-BC, CDE, BC-ADM, Sonali Thosani, MD, Shouhou Zhou, PhD, Roland Bassett, Naifa Lamki Busaidy, MD, and Victor Lavis, MD

Abstract

Background: Hyperglycemia occurs in cancer patients receiving high-dose steroids with cyclophosphamide, doxorubicin, vincristine, and dexamethasone (hyper-CVAD) protocol. The purpose of our study was to determine insulin requirements in patients with hyperglycemia on hyper-CVAD therapy using a systematic algorithm.

Subjects and Methods: We did a retrospective chart review of 23 leukemia inpatients with hyperglycemia (two glucose values >250 mg/dL) on hyper-CVAD chemotherapy managed by the Endocrine Diabetes Inpatient Team algorithm. We reviewed demographic and glycemic data, insulin dosages, and use of oral hypoglycemic agents. Using our algorithm, the dose of insulin for each patient was titrated daily and with each subsequent cycle of hyper-CVAD.

Results: Ninety-one percent of patients had known diabetes. The median body mass index was 32.5 (range, 21.6–40.9) kg/m², and median age was 61 (range, 40–80) years. The overall trend in glucose values across cycles showed a statistically significant decrease with each subsequent cycle of hyper-CVAD. Hyperglycemia accounted for 81% of glucose measurements in the first cycle and 60% of glucose values in the last cycle. Patients received 1–1.3 units/kg of insulin per cycle, and insulin requirements were similar across cycles. The distribution of basal versus bolus insulin for each cycle was 63–77% prandial and 23–37% basal. Nine of the 23 patients had at least one glucose value <70 mg/dL, which accounted for 1.3% of all recorded glucose values. None of the patients had severe hypoglycemia.

Conclusions: Multiple-dose insulin therapy initiated at 1–1.2 units/kg/day, distributed as 25% basal and 75% prandial, reduced hyperglycemia in patients who were receiving high-dose dexamethasone as part of hyper-CVAD.

Introduction

Hyperglycemia, defined as two consecutive glucose values ≥250 mg/dL, often occurs in patients with hematologic malignancies. Although many factors contribute to hyperglycemia in cancer patients, corticosteroids, which are an essential component of various chemotherapeutic regimens, play a significant role. In addition to their inhibitory effect on the immune system and cytotoxicity to cancer cells, steroids play an important role in cancer pain management, prevention and treatment of chemotherapy-induced nausea and vomiting, appetite stimulation, and cancer cachexia.

The prevalence of hyperglycemia and its effect on remission and survival in cancer patients have been reported in many studies previously. At MD Anderson Cancer Center (Houston, TX), in patients with acute lymphocytic leukemia (ALL) treated with induction chemotherapy that included...
high-dose dexamethasone, 37% were noted to have hyperglycemia, but only 7% had a previous diagnosis of diabetes. This study also noted that patients with hyperglycemia had a shorter median survival and were more likely to develop sepsis and infections compared with their euglycemic counterparts. In another study evaluating children with ALL, overt hyperglycemia, defined as a blood glucose value of >200 mg/dL, was seen in up to 56% of children receiving induction chemotherapy. A recent international study has shown an even higher prevalence of hyperglycemia in up to 67% of patients at some time during the induction phase of chemotherapy for ALL. Of note, however, in this study, hyperglycemia was defined as a single fasting glucose value >100 mg/dL. This study also found that hyperglycemia was associated with an increased risk of complicated infections and death.

These patients present a unique therapeutic challenge as they are receiving treatments that contribute to severe hyperglycemia, while their concomitant illness may affect their appetite and activity level. In addition, most of these patients have significant postprandial hyperglycemia, with lesser elevations of fasting glucose levels. Although there have been many studies discussing the use of basal–bolus insulin therapy for management of hyperglycemia in hospitalized patients, there are few studies on management of steroid hyperglycemia. In addition, there is only one study published thus far on how to manage hyperglycemia in cancer patients receiving high-dose corticosteroids. Gosmanov et al. compared the use of basal–bolus insulin with sliding-scale insulin in treatment of patients receiving high-dose dexamethasone as part of their chemotherapeutic regimen, including cyclophosphamide, doxorubicin, and vincristine (hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone [hyper-CVAD]), and found that basal and bolus insulin regimens were an effective and safe approach to management of hyperglycemia in hospitalized patients with hematological malignancies. However, there are no clear recommendations on the starting dose of insulin and the ratio for distribution of the total daily dose as basal and bolus. In this study, we discuss a management algorithm developed by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for treatment of cancer patients receiving high-dose steroid therapy.

Subjects and Methods

As part of a quality improvement project to achieve better glycemic control in this patient population, the inpatient diabetes team reviewed the charts of 100 patients who had received high-dose steroids from our consultation census to determine the distribution of basal and bolus insulin therapy that resulted in the most improvement in glycemic control. After various meetings, we decided on 1.2 units/kg and created an algorithm that was developed and implemented (Fig. 1).

In this study, we reviewed the impact of that algorithm on glycemic control. We conducted a retrospective chart review of inpatients with hematological malignancies who received high-dose dexamethasone (40 mg) by mouth daily for four consecutive days as part of hyper-CVAD chemotherapy. Patients who were included in the study were placed on the algorithm if their blood glucose levels reached >250 mg/dL on two occasions during the same hospitalization while receiving high-dose dexamethasone with glycemic management controlled by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for at least two cycles of treatment. Patients with and without known history of type 2 diabetes mellitus prior to steroids and chemotherapy were included. We excluded patients with type 1 diabetes mellitus or a serum creatinine level of >2.0 mg/dL. In addition to the scheduled insulin dosing, some patients received additional correctional doses of insulin when the blood glucose value was above 250 mg/dL. Dose adjustments were done on a daily basis depending on the dietary status, correctional doses of insulin given, glucose values of the patients, and clinical situation. If patients had received an additional (unplanned) dose of steroids as premedication for blood products or had more than usual carbohydrates for one meal, then we considered those factors in the decision-making process. We created a database of these patients containing individual information on demographics, blood glucose level, insulin therapy, chemotherapy, steroid use, hospital course, and use of oral or injectable antihyperglycemic agents.

At the time of initial consultation, oral and injectable antihyperglycemic medications were continued if there were no contraindications. For patients already on insulin therapy, insulin doses were increased to 1–1.2 units/kg, and basal and bolus redistribution was done as per algorithm. Once patients

FIG. 1. Algorithm developed by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for the management of hyperglycemia in cancer patients receiving high-dose steroids.
were identified as hyperglycemic (two blood glucose values >250 mg/dL), glycemia was categorized as follows: hyperglycemia as a glucose value of ≥180 mg/dL, clinically acceptable glycemia as a glucose value between 71 and 179 mg/dL, and hypoglycemia as a glucose value ≤70 mg/dL. A patient-day was defined by the availability of at least one glucose measurement during the time period that patient received high-dose steroids. Instead of averaging the blood glucose values for each patient, we considered each individual glucose value to account for the variation within 1 day of blood glucose levels. A hyperglycemic patient-day refers to the presence of at least one blood glucose value ≥180 mg/dL with no values ≤70 mg/dL. A hypoglycemic patient-day refers to any glucose value <70 mg/dL.

Subjects were treated according to the High-Dose Steroid Algorithm (Fig. 1), created by the Endocrine Diabetes Inpatient Team. Patients received insulin detemir, insulin glargine, or NPH as basal insulin and insulin lispro, insulin aspart, or regular insulin as prandial insulin. The basal–bolus insulin therapy was titrated to reach previously defined pre-meal blood glucose goals of 100–140 mg/dL and random blood glucose values of below 180 mg/dL, as recommended for noncritically ill patients by the American Association of Clinical Endocrinologists and the American Diabetes Association. If more than 50% of glucose values were above target, then we considered dose adjustment as long as there was not an isolated incidence that could account for the elevations in blood sugar level (i.e., the patient had an unusually large meal and/or received another steroid as pre-medication for blood products).

Capillary blood glucose levels were tested with the SureStep® meter (LifeScan, Milpitas, CA) in all patients before each meal and at bedtime in patients with signs and symptoms of hypoglycemia. Serum blood glucose levels were tested using the glucose oxidase assay. Study approval was obtained from the University of Texas-MD Anderson’s institutional review board.

Statistical analysis

All statistical analyses were done using SAS version 9.2 software (SAS Institute, Cary, NC) and R version 3.0.1 software. Descriptive statistics were used to summarize the data. Means, SDs, and medians were computed for continuous variables for each cohort. For categorical variables, frequencies and percentages were calculated. Two-sample t test was used to evaluate differences between patient subgroups. Longitudinal analysis was performed to evaluate the trend for the success rates of insulin management and blood glucose control, and patient heterogeneity was controlled by random effects. In Figure 2, the solid line was formed based on the statistical regression model. All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

There were 23 hyperglycemic cancer patients who met the criteria above and were managed by the Endocrine Diabetes Inpatient Team. Our sample of hyperglycemic patients comprised 19 men and four women, 57% of whom were white. Ninety-one percent of the patients had a known diagnosis of diabetes prior to chemotherapy. Thirteen patients had a diffuse large B-cell lymphoma, whereas the remaining 10 patients had ALL. The median age of the group was 61 (range, 40–80) years, and the median body mass index was 32.5 (range, 21.6–40.9) kg/m². The baseline characteristics are summarized in Table 1.

All the patients who were on metformin and/or an oral secretagogue (52% and 48%, respectively) were continued

![FIG. 2. Average daily blood glucose values for patients through various cycles of hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy.](image-url)
TABLE 1. SUMMARY OF BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.6 (9.1)</td>
</tr>
<tr>
<td>Median</td>
<td>61.0</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>40.0–80.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.6 (5.4)</td>
</tr>
<tr>
<td>Median</td>
<td>32.5</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>21.6–40.9</td>
</tr>
<tr>
<td>Gender [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (82.6)</td>
</tr>
<tr>
<td>Diagnosis [n (%)]</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13 (56.5)</td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia.

on their oral regimen with the addition of insulin during steroid treatment. For patients not on oral therapy, metformin was added, if there were no specific contraindications, to improve insulin sensitivity. Each patient had blood glucose monitoring before meals and at bedtime, and at least one blood glucose measurement was available for 97% of patient-days.

Of the 278 patient-days, 85% were notable for hyperglycemia, 4% for hypoglycemia, 3% with both hyper- and hypoglycemia, and 8% with clinically acceptable glycaemia. Nine of the 23 patients had at least one glucose value <70 mg/dL, which accounted for 1.3% of all recorded glucose values. No severe hypoglycemia (blood glucose level, <40 mg/dL) was observed. Hyperglycemia occurred in 80% of glucose measurements in Cycle 1 compared with 60% of Cycle 5 measurements, which was statistically significant (Fig. 2 and Table 2). Although there was no clinically meaningful intra-cycle trend in insulin requirements, the average insulin dose received by patients per cycle was 1–1.3 units/kg. Of the insulin administered to patients, the distribution of basal versus bolus insulin for each cycle was 63–77% prandial and 23–37% basal, respectively. Analysis of insulin dosage on demographic and clinical characteristics showed higher doses in patients with higher body mass index.

Patients with history of type 2 diabetes generally required higher doses of basal insulin than those without known diabetes. There was no statistically significant difference in insulin doses among whites and other races or among patients over the age of 65 years (Table 3).

**Discussion**

Hyperglycemia is a known complication of high-dose steroid therapy and occurs commonly in cancer patients. However, to date there are very few published studies on how to manage hyperglycemia in these patients. Although it is known that basal–bolus insulin therapy is more effective than sliding-scale insulin to control blood glucose in this patient population, there are no studies that advise the starting dose for insulin therapy or the distribution of basal or bolus insulin. To our knowledge, this is the only study to propose an algorithm to systematically manage hyperglycemia due to high-dose steroid therapy in cancer patients. This algorithm is currently used in the management of various cancer patients receiving other steroids in doses equivalent to 40 mg of dexamethasone at MD Anderson Cancer Center with similar results.

We recommend documentation of at least two glucose values above 250 mg/dL, before initiating the basal–bolus insulin algorithm. These criteria help identify patients who will require multiple-dose insulin therapy with high-dose steroids, similar to those evaluated in this study. Our study found a small increase in insulin dosage with each subsequent cycle of steroids, although this trend was not statistically significant. This may represent higher doses necessary to achieve better glycemic control or increasing insulin resistance with each cycle, although this was not a primary objective addressed by this study. With the proposed algorithm, the overall trend was a decrease in glucose values without any severe hypoglycemia. Although the numbers of patients who experienced hypoglycemia was slightly higher in the patients on the algorithm in comparison with the published rates of inpatient hypoglycemia, the numbers of patient-days spent in hypoglycemia were in accordance to other studies. And, despite using significantly higher doses of insulin, none of the patients on the algorithm had severe hypoglycemia. However, despite a decrease in glucose trends with subsequent cycles and large and increasing doses of insulin, we were unable to achieve clinically acceptable glycaemia in the majority of our patients. These results reinforce the clinical management challenge that these patients can present.

**Table 2. Comparison of Median Blood Glucose Values Across Various Cycles of Hyper-Cyclophosphamide, Doxorubicin, Vinristine, and Dexamethasone Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>F test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32.8</td>
</tr>
<tr>
<td>n</td>
<td>355</td>
<td>365</td>
<td>233</td>
<td>115</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemic values</td>
<td>288</td>
<td>231</td>
<td>158</td>
<td>67</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia percentage</td>
<td>81.1%</td>
<td>63%</td>
<td>67.8%</td>
<td>58.3%</td>
<td>59.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily average blood glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n</td>
<td>87</td>
<td>91</td>
<td>58</td>
<td>30</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>266</td>
<td>208</td>
<td>217.6</td>
<td>207.8</td>
<td>205.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>264.5 (8.0)</td>
<td>216.7 (6.7)</td>
<td>229.0 (8.7)</td>
<td>204.7 (12.9)</td>
<td>202.6 (16.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are multilevel mixed-effects linear regression for blood glucose levels over time.
Table 3. Comparison of Insulin Dose (in Units) by Patients’ Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Basal dose (units)</th>
<th>Prandial dose (units)</th>
<th>TDD (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;64</td>
<td>16</td>
<td>39.3 (8.2)</td>
<td>0.134</td>
</tr>
<tr>
<td>≥65</td>
<td>7</td>
<td>23.8 (5.8)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.0–25.0</td>
<td>4</td>
<td>31.0 (30.4)</td>
<td>0.0037</td>
</tr>
<tr>
<td>25.1–30.0</td>
<td>4</td>
<td>20.5 (25.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;30.1</td>
<td>15</td>
<td>37.8 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>10</td>
<td>30.7 (29.3)</td>
<td>0.069</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>13</td>
<td>37.9 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Prior diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>2</td>
<td>19.8 (23.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td>21</td>
<td>34.9 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12</td>
<td>43.4 (9.5)</td>
<td>0.124</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>24.9 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>

ALL, acute lymphocytic leukemia; BMI, body mass index; DM, diabetes mellitus; TDD, total daily dose.

For patients without issues of weight loss or malnutrition, we generally place them on 1,800–2,200-calorie carbohydrate-consistent diets with no concentrated sweets so that they get a relatively equal amount of carbohydrates with each meal. We have created insulin order sets where every patient is given a supplemental scale for meals with increases in insulin doses based on patients’ blood glucose level prior to the meal with incorporation of their insulin sensitivity. For patients with variable or poor appetite, the nurses are advised to give the insulin immediately after the meal if the patient consumes >50% of the meal. Every day, we review the blood glucose records from the day prior and adjust the insulin doses according to the glucose trend. For these patients who are on steroids, typically the increase is mostly in the prandial insulin, with a smaller degree of change to the basal insulin dosing. The basal insulin dosing is adjusted if the patient has a rise in blood glucose level overnight and/or hyperglycemia between meals.

Steroids are known to cause mostly postprandial hyperglycemia. Part of the mechanism of hyperglycemia involves peripheral insulin resistance, which leads to an increase in insulin requirements. Better glycemic control is achieved with larger boluses of insulin with meals and relatively smaller doses of basal insulin, to avoid fasting hypoglycemia. This study supports the idea that distributing up to 75% of the total daily dose of insulin over three meals can help control the postprandial surge in blood glucose level that is observed with high-dose steroids. For each subsequent cycle of hyper-CVAD, insulin should be initiated at the total daily dose of insulin given in the previous cycle to achieve euglycemia for quicker glycemic control.

Evaluation of clinical factors that can contribute to insulin requirement showed that patients with prior diabetes and higher body mass index are more likely to require higher doses of basal insulin and total daily doses of insulin, respectively. These results are consistent with what would be expected as these two groups of patients would be more likely to have insulin resistance and further reinforce the need for higher doses of insulin in patients receiving high-dose steroids.

Caring for patients with cancer and hyperglycemia is complex as there are many factors that have to be considered prior to determining the appropriate doses of insulin. The proposed algorithm was evaluated in patients who had a good appetite and were on a regular diet. We do not recommend it for patients with nausea, vomiting, or poor appetite.

This study is limited because of its retrospective nature, and although it is the largest study of its kind, it is still a small sample size. In addition, the reported data may be biased because we only evaluated data on patients who were referred to our diabetes team, which might select for patients who are particularly insulin resistant with uncontrolled hyperglycemia, thus requiring a higher dose of insulin. As most of the patients in the study had diabetes and/or a history of steroid-induced hyperglycemia, it is unclear if the findings would apply to patients without a history of diabetes or steroid hyperglycemia. Furthermore, all of our patients were on a regular diet and allowed to make their own food choices. None of our patients was receiving tube feeds or parenteral nutrition therapy, which could also alter their insulin requirements.

In conclusion, this study suggests that high doses of insulin are needed for patients with a history of type 2 diabetes and steroid-induced hyperglycemia. In addition, it is important to consider the distribution of basal and bolus insulin as this plays a key role in management of hyperglycemia. For patients with documented hyperglycemia on high-dose dexamethasone, multiple-dose insulin therapy initiated up to 1.2 units/kg/day, distributed as 25% basal and 75% prandial, is safe and effective. However, it was difficult to achieve glycemic targets, although the overall trend for each subsequent day in the cycle was in favor of improving control without increasing the risk of hypoglycemia.

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Author Disclosure Statement

No competing financial interests exist.

References


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Appendix M
Management of steroid-induced hyperglycemia in hospitalized patients with cancer: A review.
Management of Steroid-Induced Hyperglycemia in Hospitalized Patients With Cancer: A Review

Veronica J. Brady, RN, MSN, FNP-BC, BC-ADM, CDE, Deanna Grimes, DrPH, RN, FAAN, Terri Armstrong, PhD, APRN, FAAN, FANP, and Geri LoBiondo-Wood, PhD, RN, FAAN

Glucocorticoids are prescribed for hospitalized patients with cancer for a variety of reasons, including cerebral edema, nausea prevention, and as part of a cancer treatment regimen. Glucocorticoids are known to cause hyperglycemia. Hyperglycemia (steroid-induced or otherwise) among noncritically ill hospitalized patients has been shown to lead to increased length of hospital stay, delayed wound healing, increased infections, and higher mortality rates (Llueva & Inzucchi, 2011), which suggests the need for improved management strategies. The purpose of this review was to integrate the published research on the management and the effects of management of steroid-induced hyperglycemia among hospitalized adult patients with cancer with or without preexisting diabetes.

Background

Inpatient hyperglycemia, which occurs in 32%–38% of hospitalized patients, is defined as having blood glucose values greater than 140 mg/dl during hospitalization (Moghissi et al., 2009; Smiley & Umperieze, 2010; Umperieze et al., 2012). This elevated glucose level can occur for various reasons, including omission of antidiabetic agents in patients with known diabetes, stress hyperglycemia as a result of acute illness, and steroid-induced hyperglycemia (American Diabetes Association [ADA], 2013). Regardless of the underlying cause, hyperglycemia in hospitalized patients (with or without diabetes) has been associated with poor outcome (Moghissi et al., 2009). On the basis of the reported incidence of hyperglycemia among hospitalized patients, the ADA’s (2011) Clinical Practice Recommendations suggested that all patients with known diabetes and/or those receiving medications associated with hyperglycemia receive glucose monitoring during hospitalization in conjunction with meals or at meal times or every four to six hours if not eating. In 2013, the ADA further recommended that glucose monitoring be conducted in patients without

Problem Identification: Glucocorticoids are prescribed for hospitalized patients with cancer for a variety of reasons, including cerebral edema, treatment and prevention of nausea, and as part of cancer treatment regimens. Glucocorticoids are known to cause hyperglycemia. The purpose of this study was to integrate the published research on the management and the effects of steroid-induced hyperglycemia in hospitalized adult patients with cancer with or without preexisting diabetes.

Literature Search: MEDLINE®, PubMed, EMBASE, CINAHL®, and Scopus electronic databases were used to identify relevant articles. Bibliographies of included studies were reviewed for any pertinent studies that were not obtained through database search.

Data Evaluation: 1,392 studies were identified. A total of 18 studies that met criteria were fully reviewed, 6 of which met all of the inclusion criteria.

Data Analysis: Data were abstracted from the included studies using a systematic code sheet to document characteristics of the studies and findings on management of hyperglycemia. Characteristics of the studies and findings on management of hyperglycemia were organized into three tables: the patients did not have preexisting diabetes, the patients had preexisting diabetes, and patients with or without preexisting diabetes were both included in the study.

Management and effects of management of hyperglycemia were then compared and synthesized.

Presentation of Findings: Hyperglycemia occurs in hospitalized patients with cancer irrespective of whether patients have a prior history of diabetes. Hyperglycemia resulting from steroids is treated in a variety of ways, but the resulting glycemic control has not been consistently documented. However, this review suggests that scheduled insulin (basal-bolus) is effective in attainment of glucose targets.

Implications for Practice: Nurses should be aware of the effect that steroids have on glycemic control in patients and should be empowered to request or perform blood glucose monitoring when appropriate. Nurses can identify those patients receiving steroids and assess for signs and symptoms of hyperglycemia. They also can review routine laboratory results and assess for hyperglycemia in patients receiving steroids.

Key Words: hospitalized patients; cancer; steroids

Appendix N

Curriculum Vitae
Veronica Brady, RN, MSN, FNP-BC, BC-ADM, CDE
6901 Bertner
Houston, TX 77030

Family Nurse Practitioner

**Doctoral Education**
University of Texas- HSC—Houston, TX
September 2011 through Present—PhD Nursing

**Graduate Education**
University of Detroit-Mercy—Detroit, MI
September 1997 through May 1999-Masters of Science- Nursing
Family Nurse Practitioner

**Graduate Research**
Masters Thesis-University of Detroit-Mercy
African Americans and Healthcare—an Issue of Trust

**Undergraduate Education**
Wayne State University—Detroit, MI
September 1981 through May 1986-Bachelors of Science-Nursing

**Employment History**
UT MD Anderson Cancer Center
February 2007 through present—Endocrine Neoplasia & HD
Focus on care of patients with diabetes and cancer

University of Michigan
May 2006 through January 2007—Pilot project (CHOICES)
Provide acute home care needs at APN level

Henry Ford Health System—Detroit, MI
November 2002 through April 2006—Internal Medicine
Primary focus on care of the diabetic patient

Labor Source 2000—Southfield, MI
June 2002 through 2006—RN
Contingent nursing/Case Manager

University of Detroit-Mercy—Detroit, MI
July 2002 through May 2004—adjunct faculty
Undergraduate education
Vista Maria—Dearborn Heights, MI
July 2000 through May 2002—Director of Health Services
Coordinate health care for adolescent females

St. Johns Health System—Detroit, MI
December 1999 through July 2000—School based health center
Provided care to elementary students

Botsford Hospital—Farmington Hills, MI
1997 through December 1998—Staff nurse
Care of the oncology patient

Sinai Hospital—Detroit, MI
1993 through 1997—Radiation oncology nurse
Care of the patient receiving radiation therapy

Santa Monica Hospital—Santa Monica, CA
1992 through 1993—Manager of the Orthopedic and Oncology units
Responsible for staffing and management of units

Providence Hospital—Southfield, MI
1990-1992—Manager of 36 bed Oncology unit
Responsible for staffing and daily management of unit

Providence Hospital—Southfield, MI
1988-1990—Radiation oncology nurse
Care of the patient receiving radiation therapy

Providence Hospital—Southfield, MI
1986-1988—Staff Nurse
Care of the oncology patient

Clinical Affiliations
American College of Nurse Practitioners
American Diabetes Association
American Association of Diabetes Educators—4/30/2015
Houston Area Nurse Practitioners
Mid-level Providers Council—President (2005)
MDACC Orientation Committee Member—2007 to 2009
American Academy of Nurse Practitioners
STADE member
Sigma Theta Tau—2012 to present
American Nurses Association—2014 to present
Achievements
Recipient—Loretta Ford Nurse Practitioner Award—U of D Mercy—(4/99)
Graduate Student Preceptor—Madonna University, Wayne State University,
University of Michigan, University of Detroit-Mercy, Texas Women’s—(2003 to present)
Winner of Invest in Quality Grant—(8/03)
Pinnacle Award Winner—Excellence in Diabetes Care (2004)
Recipient of Outstanding Patient Educator Award (2007)
Nominee for Clinical Excellence Award (2013)

Presentations and Posters
National Medical Association (NMA) Poster Presentation—Diabetes (5/04)
Michigan Association of Health Plans (MAHP) Poster Presentation—Diabetes (8/04)
Nursing Grand Rounds—Henry Ford Hospital—Care of diabetic inpatient (6/05)
Resident Lecture—Henry Ford Hospital—Diabetes care (8/05)
AMGA Best Practices Award Recipient—Diabetes Care (3/06)
Nursing Lectures-MDACC—Diabetes and Cancer (8-9/07)
P7 Nursing Education Day—Diabetes and Cancer (10/07)
Division of Public Affairs Grand Rounds—MDACC (11/07)
Anderson Network PIKNIK—Diabetes and Cancer (2/08)
3rd Annual Nursing Symposium: Excellence through Innovation (2/08)
Multinational Association for Supportive Care in Cancer (MASCC) Poster
Presentation—Diabetes and Cancer (6/08)
STADE—Diabetes and Cancer (7/08)
American Association of Diabetes Educators (AADE) Poster Presentation—
Diabetes and Cancer (8/08)
Anderson Network’s 20th Annual Patient and Caregiver Conference—Living with
Diabetes and Cancer (9/08)
Fellows Conference—Diabetes and Cancer “Special Cases” (9/08)
ATTD 2009—Athens Greece—High Dose Insulin Requirements in Patients
Receiving High Dose Steroids (Poster) 2/09
American Association of Diabetes Educators—Practice Pearls for the Advance
Practice Nurse (8/09)
American Association of Diabetes Educators—Diabetes and Cancer—
Management of Special Cases (8/09)
Fellows Conference—Pump Therapy: The Basics (11/09)
Methodist Hospitals Quality 2012: Evolving Frontiers in Quality and Patient
Safety—Poster—Symposium—Additional Clinical Benefit to Hyperglycemic
Performance Improvement (09)
5th Annual Oncology Nursing Symposium (Poster Presentation) (2/10)
South Texas Association of Diabetes Educators—Newer Approaches to the Initiation of Insulin Therapy (2010)
American Academy of Nurse Practitioners—Osteopenia, Osteoporosis, Who Needs D?.. (6/10)
American Association of Diabetes Educators—Practice Advice for the Advance Practice Nurse (8/10)
American College of Nurse Practitioners—Diabetes and Cancer (podium presentation) (10/10)
American College of Nurse Practitioners—Vitamin D... Who needs it? (Podium presentation) 10/12
MDACC DoGIM Research Retreat—Attainment of Lipid Targets in MDACC Patients with Diabetes Mellitus (06/2013)
Fellows Conference—Diabetes Management of “Special Cases” (08/2013)
Texas Nurse Practitioners-25th Annual Conference— Vitamin D; Endocrinology Update (podium presentation) 9/28/2013
Myeloma Support Group—Diabetes 101 (podium presentation) 10-12-13
Physicians Assistants Continuing Education (PACE) Lecture—Diabetes Management at MD Anderson Cancer Center (6/9/2014)
MDACC DoGIM Research Retreat—Steroid Induced Hyperglycemia in Patients with Mantle Cell Lymphoma Treated at MDACC (06/2014)
American Diabetes Association 74th Session—Safe and Effective Dosing of Basal-Bolus Insulin in Patients Receiving High Dose Steroids for Hyper-CVAD Chemotherapy—Poster (06/04/2014)
The Saturday Series: Pharmacotherapeutics for the Advanced Practice Nurse—9/20/14
International Hospital Diabetes Meeting—Improving Treatment of Hypoglycemia in Hospitalized Cancer Patients on Insulin Therapy Through Increased Utilization of Hypoglycemia Order Set—Poster (5/2015)

Abstracts


Publications

Brady, V.J., Diabetes and Cancer-Increased Insulin Requirements in Patients with Diabetes Receiving Hyper-CVAD. Endocrine Neoplasia and Hormonal Disorders Newsletter Vol 1, Issue 3, 2008


Certifications
American Nurses Credentialing Center
Board Certification – Family Nurse Practitioner — April 2020
Certified Diabetes Educator—December 31, 2019
Board Certification in Advance Diabetes Management—December 2019
BLS—April 2016

Licensure
State of Michigan Board of Nursing
Nurse Practitioner Specialty Certification

State of Michigan Board of Nursing
Registered Nurse

Board of Nurse Examiners for the State of Texas
Registered Nurse

Board of Nurse Examiners for the State of Texas
Family Nurse Practitioner

DEA Registration Number—MB0939441

Extracurricular Activities/Community Service
Volunteer with TCARE (Lone Star Assoc. of Charitable Clinics)—healthcare for the uninsured
Volunteer with African Cancer Care Inc. (ACCI)—cancer screenings
Volunteer with Camp Lotta Hope—camp for children with diabetes