EXAMINING THE RELATIONSHIP AND UTILITY OF INSULIN RESISTANCE AND GLYCEMIC VARIABILITY TO PREDICT MORTALITY AND INFECTION IN ADULTS WITH BURN INJURIES

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ABSTRACT

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Severe burn injury results in critical illness accompanied by hypermetabolism and hyperglycemia. Most burn centers balance glycemic control while attempting to avoid adverse hypoglycemic events. The lack of studies explicitly examining the nuances of glycemic control in burns remains a problem. The purpose of this study was to investigate the relationship between glucose control, insulin resistance, glycemic variability, and outcomes in patients with burn injury. Specifically, the researcher examined the ability of glucose control (GC), glycemic variability (GV), and insulin resistance (IR) to predict mortality, infectious complications, length of stay, and discharge disposition. The Newman systems model was used as a theoretical framework to guide this research. A retrospective review of medical records at a verified burn center aimed to assess the correlation of GC, IR, and GV with outcomes in a population of critically ill adults with greater than 20% total body surface area burns over the last 5 years. Using a stepwise approach to control for Baux score, the mean ($p = 0.025$), minimum ($p = 0.004$), maximum ($p = 0.028$), morning ($p = 0.010$), and delta ($p = 0.012$) of glucose levels were significant predictors of mortality. The morning glucose ($p =$

0.043) and percentage of time within the glucose target range ($p = 0.017$) were predictive of discharge disposition. The maximum ($p < 0.001$), minimum ($p < 0.001$), and delta ($p < 0.001$) of glucose values, as well as the total number of insulin doses ($p = 0.017$), were predictive of length of stay. Measures of GC can predict death, length of stay, and discharge disposition. GV and IR were less important in predicting outcomes than GC alone. Patients with diabetes have marked difficulty in achieving GC, and these patients have the most apparent challenges with GV and IR.

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Severe burn injury is one of the most severe forms of illness and results in an unparalleled inflammatory response. Specialized centers treat patients with burn injuries to promote good outcomes because burn patients are different from other critically ill populations. Some critical care management strategies are the same for burn-injured patients, and some are not. For example, the diagnosis of sepsis is very different for patients with burn injury, but the treatment of sepsis with early goal-directed therapy and source control is the same. Nutrition is vital for all critical care patients but more so for those with burn injuries. Pain control is essential for all critical care populations but more complex for burns. For this reason, burn injury is a specialty area in adult and pediatric critical care, and examining treatment methods specific to this specialty population is imperative.

Background

According to the American Burn Association (ABA), burn injury accounts for 486,000 injuries annually in the United States, 40,000 of which are severe enough to require hospitalization (2016). While the survival rate for all burn injuries is 96.8%, mortality is much higher for those with severe burn injury or burns with a total body surface area (TBSA) of over 20% (ABA, 2016). Patients with burn injury have a heightened susceptibility to infection due to skin loss, an essential barrier against

invasion and other factors. About 4,500 people die from their burn injury annually; however, up to 10,000 will die from an infection related to burn injury (Centers for Disease Control and Prevention [CDC], n.d.). This emphasizes how crucial early recognition and aggressive treatment of infection is for burn-injured patients.

The hypermetabolic response is a hallmark of severe burn injury leading to a dramatic loss of lean body mass (Pidcoke et al., 2007). The hypermetabolism expressed by patients with burn injury surpasses trauma and sepsis patients in severity and duration (Porter et al., 2016). The hypermetabolic response causes protein catabolism that exceeds protein synthesis resulting in overall protein and muscle loss. This muscle destruction has severe consequences for the burn-injured patient, including delayed wound healing and increased risk of infections, both of which are especially dangerous for patients with large open wounds. Higher mortality is demonstrated with loss of more than 25% of lean body mass (Pidcoke et al., 2007). Muscle destruction contributes to insulin resistance (IR) because skeletal muscle holds a large portion of insulin-stimulated glucose uptake receptors (GLUT-4) and may be responsible for up to 75% of glucose removed from the blood, making muscle a critical target for insulin when it comes to the regulation of glucose levels (Barnard & Youngren, 1992). Anabolic hormones can be used to combat catabolism by increasing muscle protein synthesis; several have been tried, including insulin (Jeschke, Kulp, et al., 2010), recombinant growth hormone (Branski et al., 2009), insulin-like growth factor-I, oxandrolone (Porro et al., 2012), and testosterone (Ferrando et al., 2001). Insulin is also thought to decrease protein loss in critical-care populations (Bogdanovic & Jeschke, 2012). Insulin is a well-established

medication with a beneficial side effect profile, including reducing BG levels, and thus is doubly helpful for severe burns (Pidcoke et al., 2007).

Hyperglycemia

Hyperglycemia is common in critical illness (Honiden & Inzucchi, 2011) and can be used as a marker of severity of illness and a predictor of hospitalized patients' outcomes (Mowery et al., 2009). Hyperglycemia is associated with complications and worsening outcomes in multiple patient populations, including trauma and burn-injured patients (Hemmila et al., 2008). In patients with severe burn injuries, hyperglycemia was studied as a predictor of infection as far back as 1978 (Kucan et al., 1979). The natural response to trauma causes sympathoadrenal stimulation triggering catecholamines and glucocorticoid release (Eakins, 2009). Some studies suggest hyperglycemia causes endothelial dysfunction, promoting an inflammatory response, platelet degranulation, and coagulopathy, all contributing to organ hypoperfusion (Ballian et al., 2010).

Blood glucose (BG) targets/goals vary by institution and provider clinical practice preferences. However, for the purpose of this study, hyperglycemia is defined as a random BG level above 180 mg/dl following the American Diabetes Association (ADA) recommendations, and severe hyperglycemia is defined as greater than 250 mg/dl (ADA, 2020). Further, glucose control (GC) is measured by maximum and minimum BG (BG) values, in addition to the mean and mean morning BG. The percent of measurements inside the target range is also used to demonstrate overall GC.

Insulin Resistance

IR is a well-known phenomenon after trauma and burn injury (Pidcoke et al., 2007). IR is impaired insulin sensitivity when the body does not respond to insulin typically. Individuals with IR have a built-up tolerance to insulin, making it less effective. Hypermetabolism with hyperglycemia and hyperinsulinemia are attributes of IR in burn-injured patients (Ballian et al., 2010). IR is independently associated with mortality in critical-care patients even when BG is overall well-controlled (Mowery et al., 2009). The origins of IR in burn-injured patients are two-fold; increased hepatic glucose output and limited ability to stimulate glucose disposal into skeletal muscle (Porter et al., 2016).

Measures of IR reported in the literature include median insulin dose and insulin infusion mathematical multiplier. The mathematical multiplier (MM) method for an insulin infusion was first introduced by White et al. in 1982 when assessing dosing calculations for patients with insulin infusions. When regression was performed, the scientists identified the intercept at 60 and a slope of 0.02, thus the dawn of the MM equation for insulin infusion in critical care: [(BG – 60) * 0.02] = insulin infusion rate in units per hour. The MM is currently used by many institutions and computer decision support software algorithms for managing insulin infusions. Adjusting the MM with rising or falling glucose levels further adapts the infusion rate to the individual patient response. The MM has since been validated for use in a hospital setting to adapt insulin infusion titration to patient response (Davidson et al., 2005).

Not all institutions utilize a MM method when titrating insulin infusion for glycemic control. Some use computerized decision support programs with proprietary

algorithms, and others still use traditional manual titration protocols. The best method for adjusting insulin infusions in critical care or the burn population has not yet been established.

The burn center for this study utilizes a MM method embedded into a clinical decision support tool in the electronic health record for the nursing staff. The nursing staff enters the patient's measured BG level and the ordered glucose target for the insulin infusion, and the tool calculates the next insulin drip-rate. The nursing staff then changes the insulin infusion pump to the calculated infusion rate for the next hour.

For this study, the MM is used as a surrogate measure of IR; the higher the MM, the greater the IR. Changes in the MM reflect a change in IR. A calculation of delta, the difference between the highest and lowest values of the MM, was performed to represent this change in IR. Calculations of delta MM were completed daily for 14 days for this study. Additional measures of IR include the total insulin doses, mean insulin dose administered per day, and total insulin dose administered.

Glycemic Variability

There remains significant variability in insulin dosing for individual patients and patient populations (Honiden & Inzucchi, 2011). Both variabilities in GC and insulin dosing may substantially affect overall patient care and outcomes. Some research points towards decreasing variability in glycemic control as the source of improved outcomes rather than avoiding hyperglycemia alone (Honiden & Inzucchi, 2011; Mowery et al., 2009). Even when patients achieve glycemic control within established parameters, the

mortality rate may still suffer when there is increased variability within the glucose range (Honiden & Inzucchi, 2011).

Glycemic variability (GV) has been measured in several diverse ways in both inpatient and ambulatory care literature. The best measure of GV for the critical care setting is not established, and various researchers have used different analysis methods. Expressions of GV include glycemic lability index (Ali et al., 2008), mean amplitude of glycemic excursion (MAGE; Ali et al., 2008; Kovatchev et al., 2006), the delta of BG measurements (Pisarchik et al., 2012), a standard deviation of BG measurements (Ali et al., 2008; Egi et al., 2006), percent excursion from target range (Pidcoke et al., 2009), percent coefficient of variation (Dahagam et al., 2011), and average daily risk range (ADRR; Farhy et al., 2011). Studies using these various measures of GV have seen an association of GV with increased mortality, infection, and adverse outcomes in both burn and non-burn populations. No study can be found comparing the various measures of GV to ascertain which is most accurate.

The percent coefficient of variation is the measure endorsed by the ADA (2020) to measure GV, although not specifically in an acute care setting. Additional measures of GV for this study are the standard deviation, statistical variance, the delta of the daily BG measurements, ADRR, and MAGE. All of these measurements can be performed by analyzing only BG values and do not require any secondary analysis or complex algorithms. Future work to better explore the best measure of GV is planned but outside the scope of this study.

Intensive Insulin Therapy

In 2001, Van den Berghe et al. published the result of a prospective randomized controlled trial (RCT) indicating a direct improvement in morbidity and mortality in surgical intensive care unit (ICU) patients treated with intensive insulin therapy (IIT). The treatment group in this study used a target glucose range of 80–110 mg/dl. The control group received standard therapy for that institution using a 180–200 mg/dl BG target range. In addition to the 46% drop in mortality, the treatment produced fewer bloodstream infections, renal failure, transfusion polyneuropathy, and decreasing ventilator days and ICU days for the treatment group. Later in 2009, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) investigators published their international, multicenter RCT indicating that IIT increased mortality among adults in ICUs owing to the dramatic increase in the incidence of severe hypoglycemia. This study's much larger population included both medical and surgical ICUs. Interestingly, most patients' cause of death was from a cardiovascular source rather than directly from a hypoglycemic event. However, the study personnel could not ascertain the source of this connection based on the study design (NICE-SUGAR, 2009).

Also, in 2009, a prospective RCT compared intermediate GC to IIT in adult critical care patients across 21 locations. The Glucontrol study was stopped prematurely due to disproportionally high rates of hypoglycemia and thus was underpowered to make an outcome determination (Preiser et al., 2009). Similar results occurred with the VISEP

trial in 2008; the rate of hypoglycemia in the IIT group was concerning enough to stop the trial (Brunkhorst et al., 2008).

In summary, in addition to many other trials, these two landmark studies concluded that the hyperglycemic response to critical illness could not go unchecked as an acceptable standard of care; however, the exact goal was unclear. Further, a significant portion of the literature regarding insulin control in patients with burns is over a decade old. Many of the existing burn studies are undersized, and few are prospective in design. As the topic of glucose management went out of vogue, many burn centers adopted their own standard of care without a robust and evidence-based consensus on the guidelines. Whatever type of control an institution selects for glycemic targets, the most crucial measure of success seems to be avoiding hypoglycemia.

Statement of the Problem

Despite some mounting evidence favoring moderate GC, some burn centers still practice and promote tight glycemic control. Additionally, GV has also been examined in general ICU and sepsis patients (Ali et al., 2008) and burn critical care (Farhy et al., 2011; Pisarchik et al., 2012). Some of the research findings have supported GV as being more sensitive in predicting mortality than glucose levels alone. Lastly, some research supports IR as a marker of mortality and outcomes in ICUs (Mowery et al., 2009). There is a gap in knowledge regarding which of these three variables is most predictive of outcomes. Assessing and comparing all three variables, GC, GV, and IR, helps determine which variables are most important for monitoring burn critical care. The lack of studies explicitly examining a population of patients with burn injury remains a

problem for this specialty area. Burn-injured patients are often excluded when examining critically ill patients because of their heightened inflammatory and metabolic responses. Results in various studies demonstrate that glycemic control is not a "one size fits all" approach, and nuances may be critical for specialty populations such as burn patients.

Purpose of the Study

The purpose of this study was to investigate the relationship between glycemic variables, insulin dosing, and outcomes in a critically ill population of adults with burn injury.

Specifically, the study examined the ability of GC, GV, and IR to predict clinical outcomes (mortality, length of stay, and discharge disposition) and infectious complications.

Research Questions

This research sought to examine the following for adults with burn injuries:

1. What is the relationship between glucose control (GC), insulin resistance (IR), glycemic variability (GV), mortality, and infection in critically ill, burn-injured patients?
2. Which variables (GC, IR, GV, or all) are most predictive of mortality and infection in critically ill burn-injured patients?

The researcher hypothesized that poor GC, increased IR, and increased GV would be present in patients who died during their initial hospitalization after burn injury. It was expected that worsening GC and an increase in IR and GV would also contribute to an increase in infections. Overall outcomes, including hospital length of stay and discharge

disposition, were expected to be affected by GC, IR, and GV significantly. This was the first study of its kind to compare the prediction capabilities and the effects of all three of these variables at once. The results may help clinicians narrow down the best method to track performance and guide critical care decisions regarding all aspects of GC.

Significance of the Study

GC has been established to be essential for hospitalized patients and patients in the ICU especially. Studies have shown the importance of GC on the early signaling of sepsis and infection (Hirasawa et al., 2009). In the hospital setting, GC has long been the responsibility of the nursing staff (Lynn, 2011). The policy of the burn center where this data was collected provides nursing staff with authority to check a patient's BG level when deemed necessary by nursing judgment in addition to when ordered by providers, thus promoting autonomy for the bedside critical care nurses.

This study helps fill the gap in the literature regarding the relationship between GC, GV, and IR on outcomes in burn-injured patients. Since little research exists in the burn population on this topic, studies from general critical care populations inform the research. In addition, while multiple studies exist examining the impact of each of GC, GV, and IR on patient outcomes individually, the work is unique by examining all three variables together in a single study. Learning specifically about these relationships aids in future protocol development for glucose targets, glucose monitoring, insulin dosing regimens, and potentially early identification of complications like infection and sepsis.

Findings from this study may be used to identify relationships that are important to managing the burn-injured patient. In addition, results can be used to identify or

mitigate the stress response causing hyperglycemia, create better treatment strategies for IR to prevent complications, and optimize burn management to aid the patient in restoring balance using holistic nursing care.

Theoretical Framework

The Neuman system model (NSM) was introduced in the 1970s by Betty Newman (Neuman & Fawcett, 2010). The model focuses on the human need to be protected from stress. According to the NSM, causes of stress can be remedied through nursing interventions. The human body strives to maintain balance or homeostasis, and stressors from differing sources may disrupt this necessary balance (Neuman & Fawcett, 2010).

Major Concepts of the NSM

The NSM identifies many concepts, definitions, and relationships (Neuman & Fawcett, 2010). Significant definitions related to the model are found in Table 1.1. The NSM is visualized as a concentric set of rings that protect the organism (Neuman & Fawcett, 2010). At the center of the rings is the organism's basic structure. The organism's basic structure comprises the genetic structure, physiologic strengths and weaknesses, organ function, ego, temperature control, and other common factors. The rings create a protective shield around the organism in a successive pattern. Each concentric ring is influenced by physiological, psychological, sociocultural, developmental, and spiritual variables. These five interacting variables are interconnected in patients and systems and must be considered simultaneously in the nursing process. The normal line of defense segregates wellness from illness. Moving closer to the basic

structure, the lines of resistance are activated when stressors (known, unknown, or universal) penetrate the normal line of defense, and the client or system becomes out of balance. The flexible line of defense lies outside the normal line of defense and consists of protective measures that can be taken to strengthen against invasion. A diagram to better elucidate the relationship between the basic structure and the lines of defense and resistance is provided (see Figure 1.1). Nursing's principal focus is on maintaining patient homeostasis through accurately assessing stressors and assisting the patient in adjusting or adapting (Neuman & Fawcett, 2010).

Table 1.1

Definitions from the NSM

Term	Definition
Basic Structure	The source of the five client system variables and represents human processes of living and dying within the context of the fluid intersection of the five interrelated and interacting client system variables. The basic structure represents the basic client system energy resources.
Flexible Line of Defense	A protective, according to like mechanism that surrounds and protects the normal line of defense from invasion by stressors. The greater the expansiveness of this line from the normal line of defense, the greater the degree of protectiveness.
Health	A continuum of wellness to illness, dynamic in nature, that is constantly subject to change.
Lines of Resistance	Protection factors activated when stressors have penetrated the normal line of defense, causing the reaction of symptomatology. The resistance lines ideally protect the basic structure and facilitate reconstitution toward wellness during and following treatment as the stressors reaction is decreased and client resistance is increased.
Negentropy	A process of energy conservation that increases organization and complexity, moving the system toward stability at a higher degree of wellness.

Normal Line of Defense	An adaptational level of health developed over time and considered normal for a particular individual client or system; it becomes a standard for wellness deviance determination.
Nursing	A unique profession concerned with all variables affecting clients in their environment. Nursing is preventive intervention.
Reconstitution	Represents the return and maintenance of system stability, following treatment of a stressor reaction, which may result in a higher or lower level of wellness than previously.
Stability	A desired states of balance or harmony while system energy exchanges take place without disrupting the character of the system. The dynamic nature of stability is seen as the client, as a system, adequately copes with stressors to retain, attain, or maintain optimal health and integrity.
Stressors	Environmental factors that are intra-, inter-, and extra personal in nature and that have the potential for disrupting system stability by penetrating a system's lines of defense and resistance. The effect of stressors that are perceived as negative is referred to as stress, whereas the effect of stressors that are perceived as positive is referred to as eustress.
Wellness/Illness	Wellness is a stable condition in which system subparts are in harmony with the whole system. Wholeness is based on the interrelationships of variables which determine the amount of resistance to stressors. Illness is on the opposite continuous form of wellness and represents instability and energy depletion among the system parts or subparts affecting the whole.

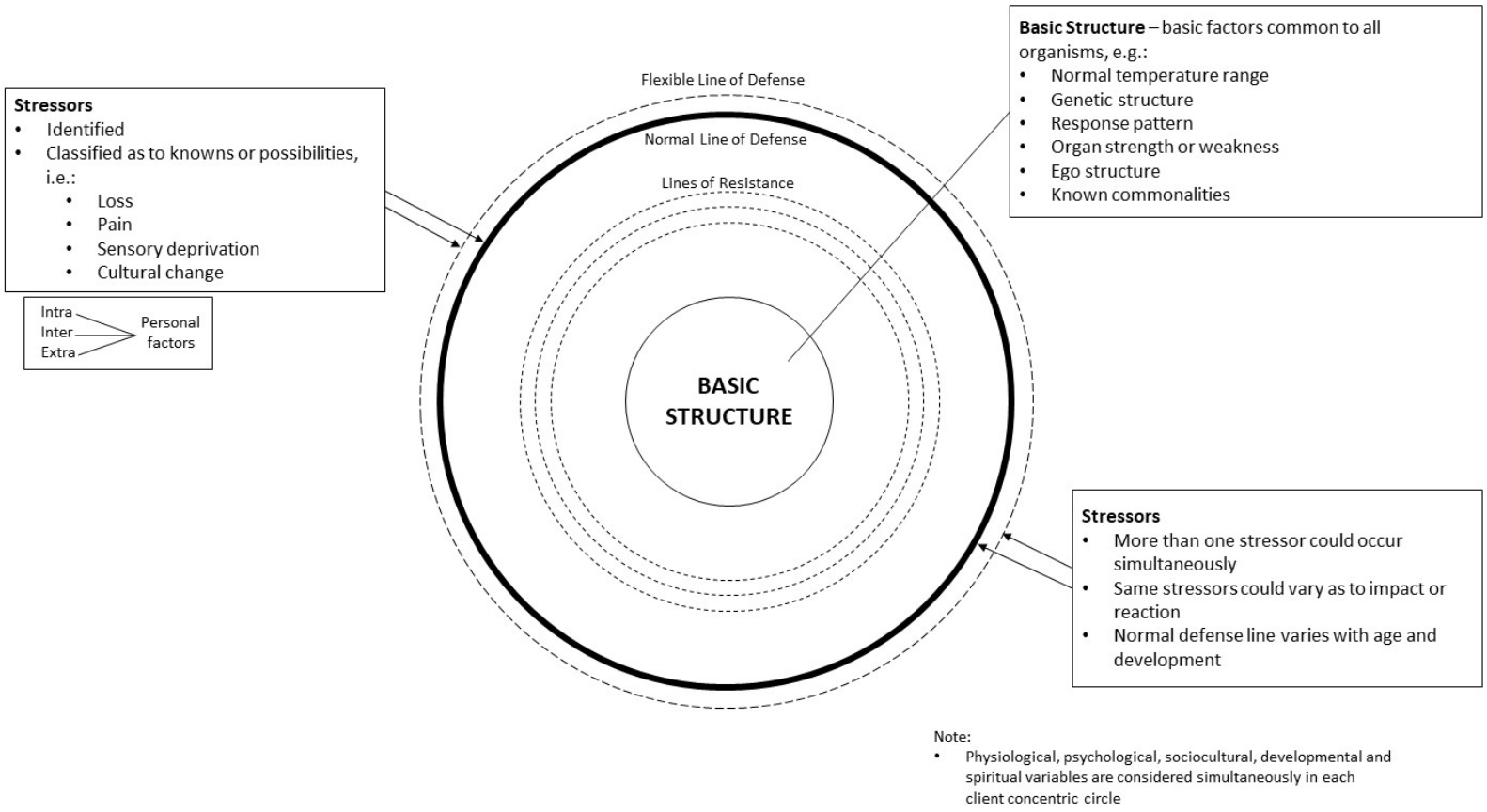
Note. Adapted from *The Neuman Systems Model* (5th ed.) by B. Neuman & J. Fawcett, Copyright 2010 from Pearson.

The NSM is one of the grand nursing theories that has been adapted and developed over time, thus maintaining relevance to nursing. The NSM cannot be tested in its entirety. It has, however, been used extensively in nursing and medical research as a conceptual framework (Fawcett, 2018; Neuman & Fawcett, 2010). Maintaining

homeostasis is central to nursing in the acute care setting, so this theory is easily adapted for this research. For research purposes, the model assumes a standard to measure illness as a deviation from the normal line of defense; thus, it can be adapted to many nursing research endeavors across nursing specialties (Beckman et al., 2012).

Figure 1.1

The NSM



Assumptions of the NSM

The underlying assumptions of the NSM are presented for review (see Table 1.2). The client as a system is dynamic, constantly exchanging energy with the environment (Neuman & Fawcett, 2010). Wellness is on an energy continuum to support a state of balance. When more energy is available than required, the body moves towards a state of health; when less energy is available than necessary, the body moves towards a state of illness or death. The relationships among the concepts and terms are primarily focused on the reaction to stressors of any type.

Table 1.2

Assumptions of the NSM

	Assumptions
1	Each patient system is a unique composite of factors and characteristics within a range of responses contained in a basic structure.
2	Many known, unknown, and universal stressors exist. Each differ in their potential for upsetting a client's usual stability level.
3	Each patient has evolved a normal range of responses to the environment referred to as the normal line of defense. It can be used as a standard by which to measure health deviation.
4	The inter-relationships of patient variables can, at any point in time, affect the degree to which a client is protected by the flexible line of defense against possible reaction to stressors.
5	When the flexible line of defense is incapable of protecting the patient against an environmental stressor, that stressor breaks through the line of defense.
6	The client is a dynamic composite of the inter-relationships of the variables, whether in a state of illness or wellness. Wellness is on a continuum of available energy to support the system in a state of stability.
7	Each patient has implicit internal resistance factors known as LOR, which function to stabilize and realign the patient to the usual state of wellness.

8	Primary prevention is applied in patient assessment and intervention, in identification and reduction of possible or actual risk factors.
9	Secondary prevention relates to symptomatology following a reaction to stressors, appropriate ranking of intervention priorities, and treatment to reduce their noxious effects.
10	Tertiary prevention relates to adjustive processes taking place as reconstitution begins, and maintenance factors move them back in a cycle toward primary prevention.
11	The patient is in dynamic, constant energy exchange with the environment.

Note. Adapted from "Neuman's Systems Model" by A. Petiprin, 2020, retrieved from paragraph 2 (https://nursing-theory.org/theories-and-models/neuman-systems-model.php).

Application of the NSM to Research

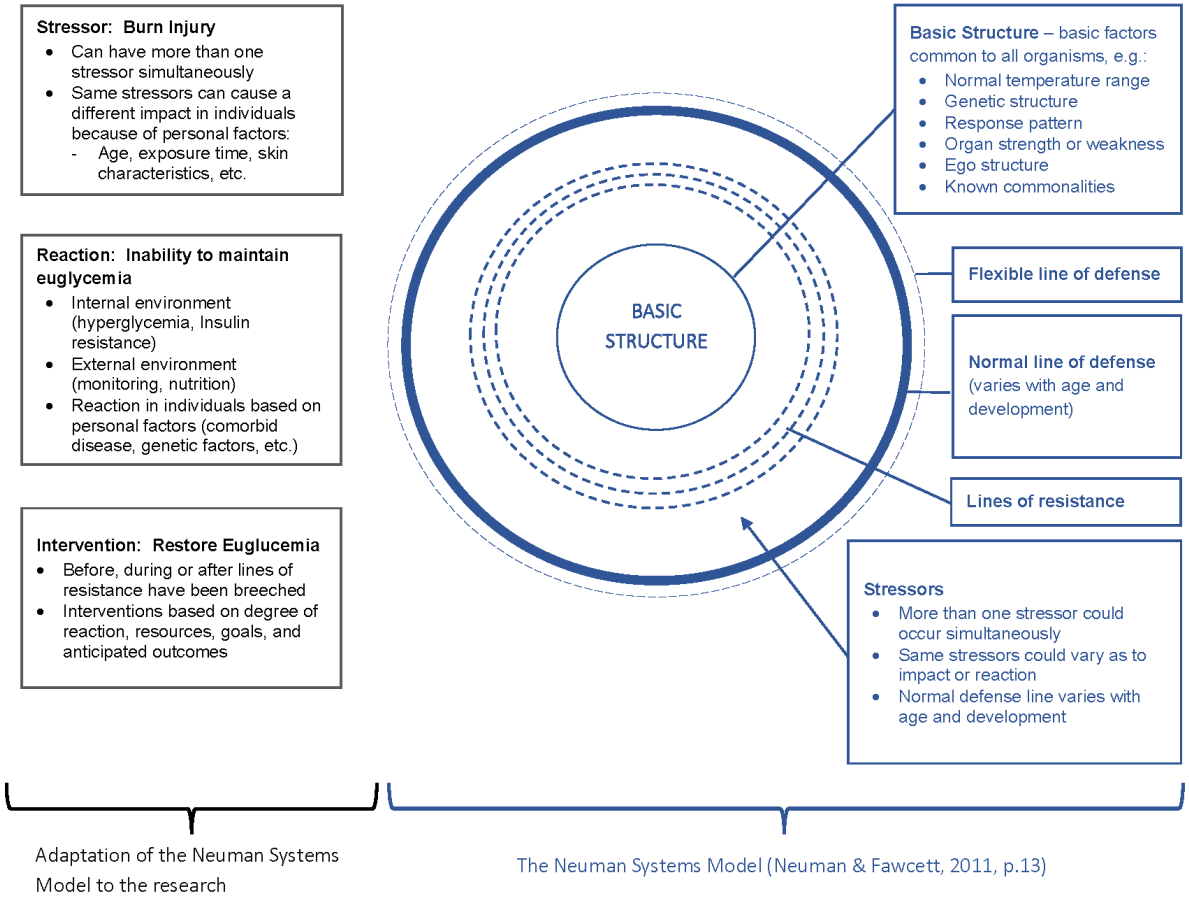
The NSM provides a framework for answering the research questions of the study (see Figure 1.2). The basic structure of the human being with a burn injury influences their response to the stressor. This includes temperature regulation, which is significantly altered in persons with burns, the genetic structure, which affects some restoration factors such as scar tissue formation, response patterns, the baseline functioning of organ systems including underlying diseases or dysfunctions that affects outcomes, the ego structure, which is especially important considering the permanent disfigurement associated with burns, and other known commonalities to human beings.

The physiological, psychological, sociocultural, developmental, and spiritual variables are all altered in patients with burn injury, thus causing stress and imbalance to the system. Recognizing the importance of how all variables interact simultaneously, this

research focuses on the physiological variable alterations in patients who have suffered burn injuries specifically.

Figure 1.2

Adaptation of NSM to the Research



Note. Adapted from *The Neuman Systems Model* (5th ed.), by B. Neuman & J. Fawcett on page 13.

A surrogate for the severity of illness for this population is used to quantify the alteration in the physiologic variable; in this case, the revised Baux score. The revised Baux score uses a combination of age, TBSA, and the diagnosis of inhalation injury to create a score that serves as an empirical indicator to measure or quantify the imbalance caused by the injury. The revised Baux score has been used extensively in the burn population as a standard measure of severity of illness and has been externally validated (Dokter et al., 2014).

The environment also impacts the patient's ability to adapt to stressors. In the study, the internal environment is altered, as evidenced by the necessity for external regulation of BG. GC is usually a part of homeostasis. Depending on baseline functioning, BG usually is in balance. Still, when a stressor is applied, burn injury, the balance is disrupted, and the body requires nursing assistance. When stressors invade the normal line of defense, illness and complications result. For this study, the stressor is burn injury, and an alteration in adaptation occurs, resulting in abnormal GC. This alteration is quantified and measured as the predictor variables for this research, such as BG levels and insulin dosing. For burn-injured patients, infection is the most acute and highest priority complication. Infection can dramatically deplete the energy supply of the organism in this instance and worsen the client's condition. The presence of infection and mortality are the criterion variables used for this study. An infection is measured as positive culture results from the blood, respiratory tract, urinary tract, or burn wounds. Mortality is measured as death during hospitalization.

Study Assumptions

This study assumes that the nursing staff was trained and proficient in assessing the need for, performance, and interpretation of any BG measurement. Secondly, this study assumes that the nursing staff followed the prescribed protocol for administering insulin as ordered. Additionally, the glucometer used by the institution automatically downloaded all BG measurements into the medical record based on the nursing staff following institutional protocol and scanning the patient's identification band prior to checking BG and administering any insulin doses.

Limitations

A retrospective review cannot determine causality due to a lack of control or bias that may have occurred at the time of treatment. This study was limited by external factors that may have affected the manual data collection. For example, the principal investigator could make an error when transcribing data from the electronic health record onto the data collection tool by misreading or mistyping a value. The principal investigator takes care to double-check the correct patient's electronic health record and right study identification number before abstracting data onto the data collection tool. The study was also limited by any errors in data abstraction via the data query created by the study site who provided the data from the electronic health record. The principal investigator outlined the exact requirements of data necessary for the research, but the possibility of error in creating the query was inherent. Additionally, during manual data abstraction, the principal investigator verified the first ten BG values in the electronic health record with the data provided by the study site query as a means of validation.

Chart review carries with it the possibility of missing data. In this instance, this risk was very low because of the automatic download of all BG readings and the institutional policy for scanning the patient identification band before checking BG levels and administration of insulin. However, a possibility exists for system malfunction, glucometer error, or nursing and support staff not following institutional policy and procedure. Other potential opportunities for missing data exist if a test or diagnostic study to identify a medical diagnosis were never ordered. For example, if a hemoglobin A1c was not collected and reported for a study subject, a missing data point results because of the study's retrospective nature.

The statistical analysis using regression was limited by confounding variables that may impact the results. Confounding variables identified in advance of statistical analysis for this research include the revised Baux score, a measure of severity of illness. It stands to reason that those patients with more severe injuries would likely suffer worse dysregulation of their homeostasis and have worse outcomes. Other potential confounding variables may include age, comorbidities, a diagnosis of DKA, or another metabolic derangement that impacts the patient's response to burn injury or burns so severe they were deemed non-survivable. Participants with DKA were excluded from the study. The researcher controls for the revised Baux score during statistical analysis, the most significant confounding variable for burns.

Strengths

A significant strength of the methodology was the inclusion of over 40,000 glucose measurements for the study. Additionally, every insulin dose administered

during the study period on study subjects was included, and every MM for the subjects on an insulin infusion. Insulin dosing was part of the study data, which allows for evaluating insulin dosing changes over time based on glucose measurement. Collecting this data via a query of the electronic health record was a strength as manual data collection would increase the possibility of transcription error when transcribing so many numbers.

Conceptual and Operational Definitions

Many conceptual and operational definitions of research terms are provided in Table 1.3. A few are highlighted as follows.

Burn-injured patients are typically cared for in specialized centers due to a myriad of unique aspects of care that are foreign to non-specialists. Many patients with burn injuries also have accompanying inhalation injury that worsens their severity of illness and outcomes. This is accounted for in the revised Baux score that is used to control for injury severity.

Revised Baux score (RBS) is used to define the severity of injury specifically for burned patients. It was created as a predictor of mortality. The revised Baux score takes into account the patient's age, TBSA of burn injury, and the presence or absence of inhalation injury to determine the severity of the injury (RBS = age in years + TBSA [+ 17 if positive for inhalation injury or + 0 if negative for inhalation injury]). The most recently reported revised Baux score associated with a 50% case fatality is 109.6 (Roberts et al., 2012). The point of futility exists at a Baux score of 160, meaning patients with a calculated revised Baux score of 160 or beyond have injuries deemed non-survivable (Roberts et al., 2012). Because of the efficacy of the RBS in predicting outcomes,

researchers often utilize this measure when reporting on burns to illustrate the severity of the injury and how that may impact findings.

Hyperglycemia is defined by the ADA as BG greater than 180 mg/dl, with severe hyperglycemia defined as greater than 250 mg/dl (ADA, 2020).

Hypoglycemia is defined by the ADA in progressive levels. Level 1 hypoglycemia is glucose 54–69 mg/dl, Level 2 hypoglycemia is BG less than 54 mg/dl, and Level 3 hypoglycemia is a low BG level accompanied by mental status changes or severe physiologic response such that they require assistance for treatment. Level 2 and Level 3 hypoglycemia require immediate life-saving intervention (ADA, 2020).

Glucose Control refers to the overall control of the patient's BG levels in the hospital setting. Overall, GC is assessed using measures of BG levels. In the ambulatory setting, GC may be measured by a hemoglobin A1c. Measures of GC for this research study included:

- maximum BG,
- minimum BG,
- delta of BG
- mean BG and
- mean morning BG, and
- percent of BG measurements within the target range.

Blood Glucose Target Range for hospitalized patients endorsed by the ADA is a glucose range of 140–180 mg/dl for the majority of patients with some specific cohorts

benefiting from a target of 110–140 mg/dl only if the target can be achieved without significant hypoglycemia (ADA, 2020).

Insulin Resistance (IR) is impaired insulin sensitivity when the body does not respond to insulin normally. Individuals with IR have a tolerance to insulin, making it less effective. Patients exhibiting IR require more insulin to achieve GC than what would typically suffice. This research's IR measures included:

- the cumulative total dose of insulin per day,
- mean insulin per day,
- total number of insulin doses, and
- delta of the MM for patients on an insulin infusion.

Glycemic Variability (GV) is measured in the ADA standard for ambulatory patients as the percent coefficient of variation is in the target range. Many other measures of GV have been cited in the literature. However, the ADA does not provide guidance on the measurement or importance of GV in the inpatient setting (ADA, 2020). The measures of GV for this research included:

- standard deviation,
- statistical variance,
- the percent coefficient of variation,
- delta of BG measurements,
- ADRR, and
- MAGE.

Table 1.3
Definitions of Research Terms

Term	Conceptual Definition	Operational Definition
Critically ill, burn-injured patients	The population for the study	Adult patients ages 18 to 89 admitted to a Regional ABA Verified Burn Center with a greater than or equal to 20% TBSA burn injury.
Glucose Control	A measure of how well the patient's BG level is controlled during the hospitalization. This is conceptualized as BG values statistically assessed in various methods, including median, maximum, and minimum values	Measured by the hypoglycemia rate, maximum BG, minimum BG, the delta of BG, mean BG, mean morning BG, and percent of BG measurements inside the target range
Insulin Resistance	When cells in the body fail to respond, usually to insulin either secreted by the pancreas or provided intravenous or subcutaneous administration to decrease BG levels	Measured by the cumulative total dose of insulin per day, mean insulin per day, the total number of insulin doses, and delta of the MM for patient non an insulin infusion.
Glycemic Variability	A measure of the variability of the GC for the patient. Wide swings or variations in GC, as opposed to steady states, may be necessary for outcomes in this population	Measured by standard deviation, statistical variance, percent coefficient of variation, delta BG measurements, average daily risk range, and MAGEs
Glucose Target	The goal BG level desired by the healthcare team. The ordered glucose target is used to guide insulin infusion dose adjustments	The upper and lower limits ordered by the provider when placing an order for the insulin infusion
Infectious complications	Complications associated with infection or actual infections diagnosed during the initial hospitalization for burn injury	Culture-positive infection of the blood, respiratory tract, urinary tract, and wounds

Term	Conceptual Definition	Operational Definition
Culture positive infection of the blood	Bloodstream infection is either associated with central venous access or not associated with central venous access; this is a significant source of morbidity and worsening outcomes for burn-injured patients	Presence of positive blood cultures either with or without the presence of a central venous catheter. The pathogen is identified in blood culture and accompanied by fever, chills, or hypotension.
Culture positive infection of the urinary tract	A urinary tract infection is suspected to be caused by a urinary catheter's presence; this is a significant source of morbidity and worsening outcomes in a burn-injured patient	Presence of positive urine cultures either with or without a urinary catheter. The pathogen is identified in the culture and accompanied by signs and symptoms, including fever, urinary symptoms, or systemic symptoms.
Culture positive infection of the wounds	An infection on the surface of any burn wound impacts wound healing and may contribute to morbidity and worsening outcomes for the burn-injured patient	Presence of positive wound cultures with greater than 10^5 CFU/gram of growth. The pathogen is identified in the culture and accompanied by signs and symptoms, including fever, graft loss, wound changes, or systemic symptoms.
Culture positive infection of the respiratory tract	An infection in the respiratory system acquired before or after hospitalization may contribute to morbidity and worsening outcomes for the burn-injured patient	Presence of positive respiratory cultures. The pathogen is identified in the culture and accompanied by the presence of signs and symptoms, including fever, changes in sputum characteristics, changes in respiratory support, or systemic symptoms.
Mortality	A measure of death during the hospitalization	Death during the initial hospitalization after burn injury.

Note. ABA = American Burn Association; TBSA = total body surface area; BG = blood glucose; MM = mathematical multiplier; CFU = colony forming units

Summary

Severe burn injury is one of the most severe forms of illness and results in an unparalleled inflammatory response. While some critical care management strategies can be translated to patients with severe burn injury, many are unique to this population. Specialized centers are needed to provide best practices for patients with burn injuries.

Severe burn injury results in critical illness accompanied by hypermetabolism resulting in muscle destruction and IR. The resultant hyperglycemia is associated with poor outcomes and complications in trauma and burn patients and has been used as a predictor of infection for some time. Insulin infusions are often used to combat this hyperglycemia as an aggressive measure to control blood sugars. For most insulin infusion protocols, nursing is responsible for titrating the insulin infusion to achieve a prescribed target glucose range using either manual titration tables or calculation protocols. The safest and most efficient way to titrate an insulin infusion protocol has yet to be determined. Additionally, much debate about the best glucose target has occurred across critical care literature. Whatever type of control an institution selects for glycemic targets, the most crucial measure of success is undoubtedly avoiding hypoglycemia.

GV is also thought to play an important role in outcomes, maybe even more so than BG levels alone. Some studies demonstrate that even when average glucose levels are within parameters, mortality may suffer if variability is high (Honiden & Inzucchi, 2011). Most burn centers balance moderate glycemic control while attempting to avoid

adverse hypoglycemic events. The lack of studies explicitly examining the nuances of glycemic control in burns remains a problem. The NSM provides a framework to guide this research to investigate the nuances of how GC, IR, and GV impact outcomes for patients with burn injuries. The retrospective study looks for relationships between GC, GV, IR, mortality, and infection for adults with burn injuries. The study also examines the ability of GC, GV, and IR to predict mortality and infectious complications in this population. Assessing and comparing all three variables, GC, GV, and IR, together versus just individually helps determine which predictors are most important for monitoring burn critical care. No other study has compared all three variables in the literature to determine which is most important to outcomes. Findings from this study may be used to identify relationships that are important to managing the burn-injured patient. Results can be used to identify or mitigate the stress response causing hyperglycemia, create better treatment strategies for IR, prevent complications, and optimize burn management to aid the patient in restoring balance using holistic nursing care.

CHAPTER II

AN INTEGRATIVE LITERATURE REVIEW ON GLUCOSE CONTROL, INSULIN RESISTANCE, AND GLYCEMIC VARIABILITY IN PATIENTS WITH BURN INJURIES

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ABSTRACT

The purpose of this review was to elucidate best practices and literature gaps regarding glycemic control in burn critical care. The strategy included all studies reporting on glucose control, glycemic variability, or insulin resistance, and the care of burn-injured patients. Three major electronic databases were utilized (PubMed, CINAHL, & Nursing and Allied Health ProQuest). A total of 107 records were identified. Of these, 88 records were retrieved with full text. After screening and eligibility, 39 articles were included in the review. The data was organized into nine themes after analysis: impact of diabetes on burn injury, sepsis diagnosis and prediction, the interplay of anemia on point-of-care glucose testing, clinical decision support for insulin therapy, glycemic variability, pediatric glucose control, hyperglycemia, insulin infusions, and novel or adjunctive treatments for glucose control. Glycemic control considers a myriad of factors that play a role, not just the glucose target. Future efforts should focus on optimizing glycemic control, monitoring and benchmarking hypoglycemia, correcting inaccurate

point-of-care glucometer results, the use of clinical decision support mechanisms to track glucose control parameters, identifying the best measure of glycemic variability, and investigating novel strategies to augment glucose control.

KEYWORDS: burns, glycemic variability, insulin resistance, glucose control, hyperglycemia

INTRODUCTION

Hyperglycemia has been associated with complications and worsening outcomes in multiple patient populations, including trauma and burn-injured patients.[1] In patients with severe burn injuries, hyperglycemia has been studied as a predictor of infection as far back as 1978.[2] Patients with burn injury have a heightened susceptibility to infection due to skin loss, an essential barrier against invasion, and other factors. About 4,500 people die from their burn injury annually; however, up to 10,000 die from an infection related to burn injury.[3] Early recognition and aggressive treatment of infections are crucial for burn providers.

A hypermetabolic response, the hallmark of severe burn injury, leads to a dramatic loss of lean body mass.[4] The hypermetabolism expressed by patients with burn injury exceeds that of trauma and sepsis patients in severity and duration.[5] Hypermetabolism results in protein catabolism that exceeds protein synthesis resulting in overall protein and muscle loss. This muscle destruction has severe consequences for the burn-injured patient, including delayed wound healing and increased risk of infections, both of which are especially dangerous for patients with large open wounds. Muscle is a critical target for insulin when regulating glucose levels, so this muscle degradation contributes to insulin resistance.[6] Anabolic hormones can be used to combat catabolism by increasing muscle protein synthesis; several have been tried, including insulin, [7] insulin-like growth factor-I, oxandrolone,[9] testosterone,[10] and recombinant growth hormone.[11] Insulin is also thought to decrease protein loss in critical care populations.[8]

Insulin is a well-established medication with a beneficial side effect profile, including reducing blood glucose levels, and is thus doubly helpful for large size burns.[4]

Insulin resistance (IR) is a well-known phenomenon after trauma and burn injury.[4] IR has been independently associated with mortality in critical care patients even when blood glucose (BG) is overall well-controlled.[12] The origins of IR in burn-injured patients are two-fold; limited suppression of hepatic glucose output and limited ability to stimulate glucose disposal into skeletal muscle.[5]

In 2001, Van den Berghe et al. published the result of a prospective RCT indicating a direct improvement in morbidity and mortality in surgical intensive care unit patients treated with intensive insulin therapy (IIT).[13] The treatment group in this study used a target glucose range of 80–110 mg/dl. The control group was standard therapy for that institution using a BG target range of 180–200 mg/dl. In addition to the 46% drop in mortality, the treatment produced improvements in bloodstream infections, renal failure, transfusion polyneuropathy, and decreasing ventilator days and ICU days for the treatment group. However, later in 2009, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) investigators published their international, multicenter RCT indicating that IIT increased mortality among adults in ICUs owing to the dramatic increase in the incidence of hypoglycemia.[14] This study's much larger population included both medical and surgical ICUs. Similar results occurred with the VISEP trial, where the trial had to be stopped due to the rate of hypoglycemia in the IIT group.[15] In addition, a prospective RCT compared intermediate glucose control (GC) to IIT in adult critical care patients across 21 locations. The

GLUONTROL study was stopped prematurely due to disproportionally high rates of hypoglycemia and thus was underpowered to make an outcome determination.[16]

Rationale

In summary, the evidence presented supports that the hyperglycemic response to critical illness cannot go unchecked as an acceptable standard of care; however, the exact goal is unclear. Results, demonstrated in numerous studies, support that glycemic control is not a "one size fits all" approach, and nuances may be critical for special populations. The lack of studies explicitly examining a population of patients with burn injuries remains a problem. Burn-injured patients are often excluded when looking at critically ill patients because of their heightened metabolic responses. Examination of the literature, including identifying the gaps, is critical in providing the foundation for future research needs.

Objectives

The purpose of this integrative literature review was to elucidate best practices and literature gaps by analyzing the existing knowledge regarding glycemic control, specifically in patients with burn injuries. Target glucose ranges, insulin dosing or IR measures, the impact of glycemic variability (GV), and nuances of insulin infusion protocols were examined.

METHODS

A search strategy was developed to identify all studies reporting on GC, GV, or IR in the care of burn-injured patients, as demonstrated in Table 2.1. Three major electronic databases were utilized (PubMed, CINAHL, & Nursing and Allied Health

ProQuest) with no time limitation to review all available literature. The author performed title and abstract screening first on all studies returned from the search. Next, the full text of the articles was reviewed for relevance. The application of screening and eligibility to the search strategy is illustrated in Figure 2.1. By narrowing using specified inclusion and exclusion criteria, the review is focused on only relevant publications. Citations in all included studies were also screened for inclusion.

Table 2.1. Search Criteria and Identification of References

Criterion	Detail
Search Terms (MeSH terms, title, and Abstract)	*Independent Variables:* glucose control OR blood glucose OR insulin resistance OR glycemic variability OR hyperglycemia AND *Population:* burns OR burn injury OR burn unit OR thermal injury AND *Setting:* critical care OR intensive care unit OR ICU
Databases	PubMed, CINAHL, & Nursing and Allied Health ProQuest
Language	English
Timeframe	No limit
Date search performed	1/20/2021 and 5/18/2021

Eligibility Criteria

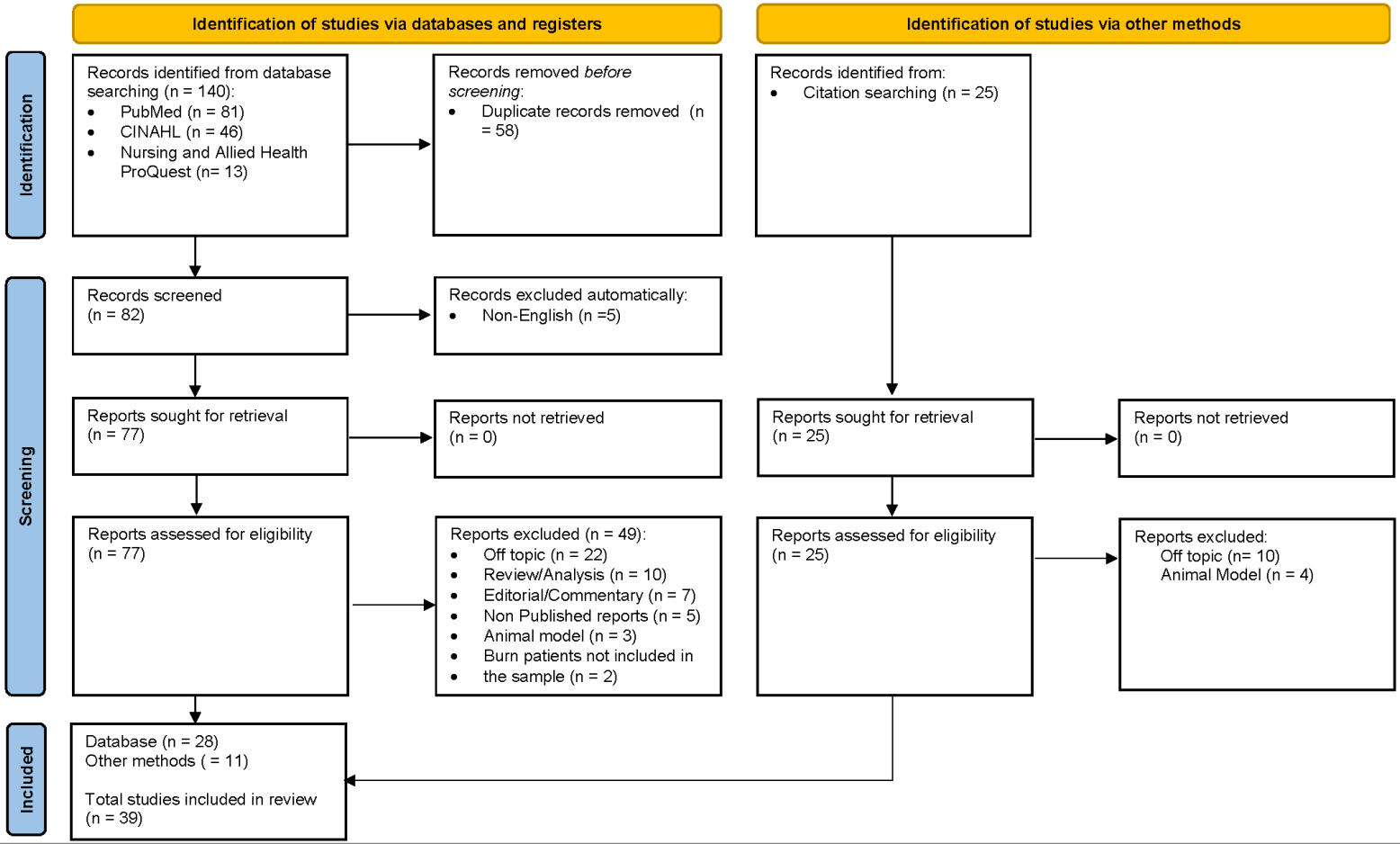
Studies were included if examining GC, GV, or IR in a critical care setting, including patients with burn injuries. Studies were excluded if using animal models, if burn patients were excluded, or if the study does not relate to patient management or GC. Unpublished manuscripts were not included (abstracts or dissertations). Journals without

peer review were also excluded. Additionally, letters to the editor, commentaries, and summary/review articles were excluded. The flowchart of study selection is provided (Figure 2.1) following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines.[17] The comprehensive search strategy was then combined with purposive sampling via citation searching of the reviewed articles to find any other relevant research.

Data Extraction and Reporting

Data extracted from all eligible studies were entered into a data collection form designed by the author. The following information was collected: authors, publication date, study design, age of the study population, number of subjects, glucose target, any measure of IR, any measure of GV, insulin infusion dosing method, and any relevant findings. Data were also grouped into identified themes for the review.

Figure 2.1. Flowchart of Study Selection [17]



Definitions

Burn injured patients are typically cared for in specialized centers due to a myriad of unique aspects of care that would be foreign to non-specialists. Many patients with burn injuries also have accompanying inhalation injury that worsens their severity of illness and outcomes.

Hyperglycemi**a** is defined by the American Diabetes Association (ADA) as BG greater than 180 mg/dl, with severe hyperglycemia defined as greater than 250 mg/dl.[18]

Hypoglycemia is defined by the ADA in progressive levels. Level 1 hypoglycemia is glucose 54–69 mg/dl, Level 2 hypoglycemia is BG less than 54 mg/dl, and Level 3 hypoglycemia is a low BG level accompanied by mental status changes or severe physiologic response such that they require assistance for treatment. Level 2 and level 3 hypoglycemia require immediate lifesaving intervention.[18]

Glycemic Targets for hospitalized patients set by the ADA is a glucose range of 140–180 mg/dl for most patients with some specific cohorts benefiting from a target of 110–140 mg/dl only if the target can be achieved without significant hypoglycemia.[18]

Insulin Resistance (IR) is impaired insulin sensitivity when the body does not respond to insulin typically. Individuals with IR have a built-up tolerance to insulin, making it less effective.

Glycemic Variability (GV) is measured in the ADA standard for ambulatory patients as the percent coefficient of variation of the patients is in the target range. The ADA does not provide guidance on the measurement or importance of GV for the hospital setting.

An integrated literature review synthesizes the literature on a topic of interest even when heterogeneous research methodologies are used. This methodology allows for the analysis of experimental and non-experimental research together. The summary notates differences in results, evaluates the strengths and opportunities for improvement of published literature, and identifies gaps in the knowledge-based that are important to the stated problem. The methodology for this integrative literature review is in congruence with Whittemore & Knaff .[19] This review is limited to management strategies to control BG levels, and as such, research that is not patient care focused was excluded. The author acknowledges the impact of animal models, basic science, nutrition, and metabolism on the response to burn injury; however, outside the scope of this integrative review.

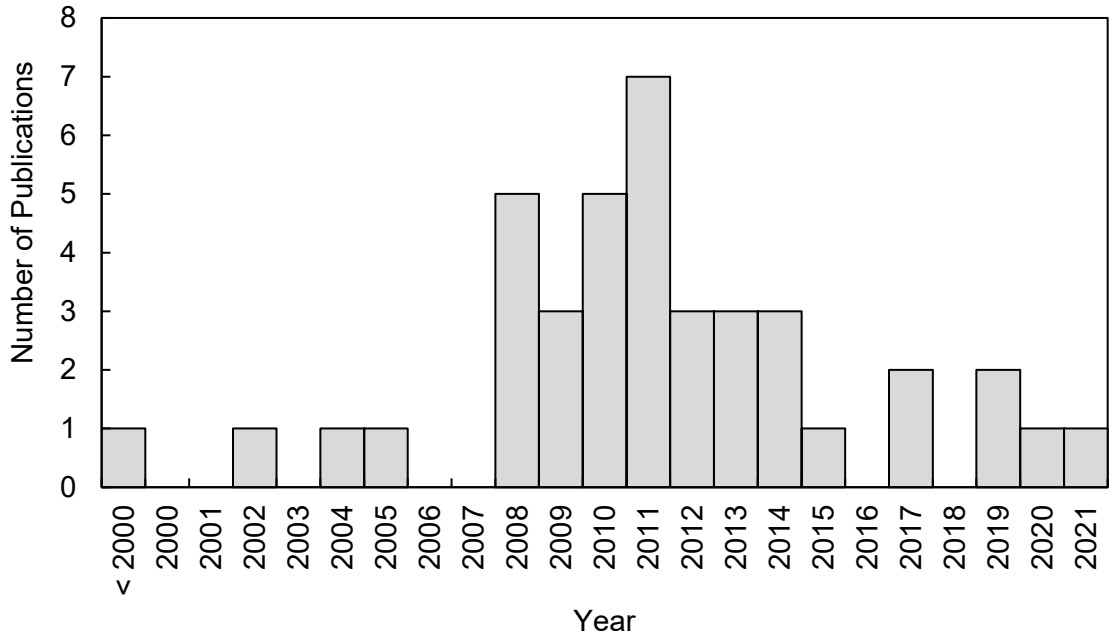
RESULTS

Study Identification

A total of 82 records were identified with the search strategy from all three databases. Of these, five were unable to be found in English and were excluded automatically. Seventy-seven records were retrieved with full text for eligibility screening. Next, two articles were excluded due to the lack of burn patients included in the sample. Three additional articles were excluded with animal models. Five were found to be nonpublished abstracts or dissertations. Seven were commentary or letters to the editor, and an additional ten were summary or review articles. Lastly, 22 were excluded as off-topic, meaning the report did not focus primarily on patient care and management of GC in burn-injured patients. Of those that were off-topic, reasons

include a nutrition focus, metabolism focus, basic science, and when hyperglycemia was used in a prediction algorithm. The remaining 39 articles were included in this review. A summary of the number of publications per year is also provided in Figure 2.2.

Figure 2.2. Number of Publications per Year



Study Analysis

The data was organized into nine themes after analysis: the impact of diabetes on burn injury, sepsis diagnosis and prediction, the interplay of anemia on the point of care glucose testing, utilization of clinical decision support for insulin therapy, GV, pediatric GC, hyperglycemia, insulin infusions, and novel and adjunctive treatments for GC. Only 23 of the included articles were written in the last decade. A summary of the literature review findings is presented in Table 2.2.

The Impact of Diabetes on Burn Injury

Several researchers have explored the impact of prediabetes and diabetes on burn outcomes. Conclusions from four different studies differ slightly but overall point towards a more difficult hospital course for patients with diabetes and prediabetes than those without the diagnosis. Three studies used a history of diabetes in combination with admission hemoglobin A1c levels to determine the diagnosis of diabetes or prediabetes. Dahagam et al.[20] did not find differences in outcomes for patients with diabetes when compared to those without diabetes which is in opposition to the other studies. However, this group used only a pre-existing diagnosis of diabetes abstracted from the medical record and not verified with a hemoglobin A1c, thus potentially missing persons who have not yet been diagnosed with diabetes. This potentially common occurrence may have contributed to this confounding result.[20] Studies with a diagnosis verified with hemoglobin A1c indicate that patients with burn injury and diabetes tend towards a higher length of stay, higher amputation rate,[21] and increased time to wound closure.[22] Patients with prediabetes even suffered difficulty with increased mortality and problems with GC.[23] Burn centers should assess the presence or absence of diabetes verified with a hemoglobin A1c on admission to ascertain future difficulties with glycemic control, wound healing, and risk for complications.

Sepsis Diagnosis and Prediction

It is known that GC plays a vital role in identifying and potentially predicting sepsis; several studies were found to examine the role of BG in sepsis. As far back as 1979,[2] researchers used BG levels at the time of blood culturing to predict the organism

responsible for infection and tailor antibiotics. Kucan, Heggers, and Robson[2] determined that if the patient had a BG greater than 130 at the time of fever, a Gram-positive bacterium was suspected, and the reverse for a BG less than 110. More recently, modern researchers sought to create an algorithm to quickly classify burn-injured patients with sepsis for epidemiological studies using the electronic health record.[24] This algorithm was elegantly simple and included only the ICD -9 codes for sepsis, stress hyperglycemia or hyperglycemia, and the presence of insulin infusion. This was thought to capture those already diagnosed with sepsis and cleverly capture patients who may have had sepsis that went undiagnosed. Simply adding the GC parameters increased their sensitivity and specificity remarkably, and the algorithm performed well in assessing sepsis after discharge.

Real-time aid in identifying and diagnosing sepsis is crucial to early, life-saving intervention. Patients with burn injury have abnormal physiology making sepsis identification more difficult than in general ICU populations. In 2007, leaders in burn care gathered for the American Burn Association Consensus Conference on Burn Sepsis and Infection Group to determine clinical criteria for burn sepsis.[58] This criterion should trigger a clinician response to prompt investigation and rapid goal-directed therapy. These ABA sepsis criteria are presented in Table 2.3.

Table 2.3. ABA Sepsis Criteria [58]

At least 3 of the following must be present:

Physiologic Variable	Parameters
Temperature	> 39° or < 36.5° Celsius

Tachycardia	Adults > 110 BPM Pediatrics > 2 SD above age-specific norms (85% age-adjusted max heart rate)
Thrombocytopenia (beginning 3 days after initial rescuscitation)	Adults < 100,000/mcl Pediatrics < 2 SD below age-specific norms
Hyperglycemia (in the absence of pre-existing DM)	Untreated plasma glucose > 200 mg/dl IR (i.e., insulin infusion at >7 units/hour or >25% increase in insulin requirements over 24 hours)
Inability to continue enteral feedings > 24 hours	Abdominal distention Enteral feeding intolerance Uncontrollable diarrhea
In addition to the above, at least 1 documented infection is identified:	
Culture positive infection	
Pathologic tissue source identified	
Clinical response to antimicrobials	

BPM = beats per minute; SD = standard deviation; mcl = microliters; DM = diabetes mellitus

The ABA sepsis criteria have been tested by several in the burn world and found lacking. Researchers from one institution showed the ABA criteria do not correlate with bacteremia at their center; however, this study was limited by not including any other forms of sepsis.[25] However, the researchers found that the maximum insulin infusion rate was statistically significant on multivariate analysis supporting the importance of IR. Another study from the same institution found their novel prediction algorithms more sensitive than ABA sepsis criteria.[26] This group found a distinct set of six criteria to

predict sepsis, one of which was hyperglycemia with BG greater than 150 mg/dl. The significance of the prediction criteria is that they are readily available in the electronic health record, and the potential for data mining exists for early recognition. Again, other forms of sepsis, not bacteremia, were excluded by the researchers.

Additionally, Singh et al. discovered that insulin dosing increased 48 hours before positive blood cultures were drawn.[27] Ray et al. have used hyperglycemia as early as admission to predict infection in burn patients.[28] Other nuances of glycemic control may contribute further to this field with the noble goal of identifying sepsis early and accurately using clinical decision support.

Researchers additionally found that some bacterial infections may increase the likelihood of IR or glucose intolerance. Acinetobacter species are found to have an insulin-cleaving protease which may inhibit insulin activity in the plasma. Because of insulin inhibition, the bacterial infection would mandate greater insulin doses to achieve control.[29] Chen et al. found that early excision of burned eschar and allografting alone decreased IR using the euglycemic-hyperinsulinemic glucose clamp method.[45] Surgical intervention and excision of burned eschar are recommended within the first seven days of burn injury. This finding adds to the support for the standard of care for burn-injured patients.

Anemia and Point-of-Care Glucose Testing

Laboratory analysis of BG is measured in the sample plasma, whereas point-of-care glucometers utilize whole blood. This difference in the analysis is the reason anemia impacts point-of-care glucose measurements but not laboratory samples. Point-of-care

devices use a calculated volume of plasma based on standard values to determine the plasma glucose concentration. If the concentration of erythrocytes is significantly different from expected values, the resultant calculates are false, and an inappropriate calculated plasma glucose concentration results.[57]

Anemia impacts some single-channel point of care testing machines for BG testing by causing falsely elevated BG measurements. This, in turn, can cause the masking of hypoglycemia in the anemic patient. The clinical significance of this cannot be understated as Mann et al. showed most ABA verified burn centers use restrictive transfusion strategies.[30] This practice would lead one to assume most critically ill burn-injured patients are anemic much of the time. A mathematical correction for the anemia has been produced and validated on up to four different single-channel point of care glucometers.[31,32] Four-channel point-of-care glucometers have a built-in formula for anemia correction and can be trusted even for an anemic patient. For burn centers using restrictive transfusion practices, adopting a mathematical formula for correcting BG results should be considered if procurement of the more accurate four-channel glucometers cannot be acquired.

Clinical Decision Support for Glucose Control

Computerized decision support (CDS) software has modernized the process of insulin infusion therapy. Traditional manual titration algorithms cannot adapt to the patient's response to treatment. CDS software eases the process of insulin infusion titration when using formulas. Three different institutions validated the safety and efficacy of using CDS for titration of insulin infusion protocols for a total of 143

patients.[33,34,35] All three protocols tested used different glycemic targets and did not reveal their proprietary formulas. Hypoglycemia rates were assessed in each of the studies, and all used the proportion of hypoglycemic BG measurements out of the total BG measurements expressed as a percentage. This uniformity makes comparison easy, and each showed adequate safety for using the CDS program when guiding insulin infusion titration. Of note, however, the institutions used differing hypoglycemia levels, and homogeneity in reporting hypoglycemia is necessary for comparison across groups. Assessing if specific mathematical formulas are better suited to burn-injured patients than others would be the next step in determining best practices for burn centers. Further exploration of the potential for in-line continuous glucose monitoring systems, as demonstrated by Elder et al., may lend to even more safety and efficacy in GC in the future and should be explored.[36] Future exploration of continuous feedback systems that include measurement of BG, titration of insulin infusion, and administration of appropriate dosing with safety mechanisms in place would produce ideal glycemic control of the burn-injured patients.

Glycemic Variability

Significant effort has been put forth on glycemic targets for critical care of burn-injured patients and less specialized populations. Reports indicate, however, that glycemic control may need to encompass more than merely glucose targets. GV impacts may overall GC for burn centers though it is less often included when assessing performance or outcomes. Different methods of measuring GV have been used by burn centers, including the average daily risk range, or ADRR,[37] glucose excursions outside of

the target,[38] the delta of the BG measurements, and the percent coefficient of variation.[39] Two of the mentioned studies show that even when mean daily glucose is within target, an increase in GV is associated with mortality and sepsis.[37,39] Measures of hypoglycemia were not included in the analysis. Still, it would be interesting to see if variability towards hypoglycemia versus variability towards hyperglycemia were more impactful on outcomes considering the strong association of hypoglycemia and mortality. Lastly, the studies did not use the same glucose targets for glycemic control, supporting the need for definitive determination of what glucose targets should be used.

Pediatric Glucose Control

The literature regarding the care of pediatric burn-injured patients makes apparent the importance of GC. IR in the pediatric burn population specifically was assessed by Cree et al. and found to correlate with fatty acid oxidation and activation of protein kinase C — both of which have been implicated in various other forms of hyperglycemia and IR, most notably type 2 diabetes.[40] Further, two studies from 2010 indicate that controlling glucose levels decreased resting energy expenditure and attenuated hypermetabolism and inflammatory responses.[41,42] Jeschke et al. showed that in a group of 208 pediatric patients, early morning glucose of 130 mg/dl or lower was beneficial and improved infectious complications, sepsis, and mortality.[41] One strength of this study is the measurement of IR being included; they found IR was worse in those patients with poor GC. Fram et al. also reported improved metabolic parameters with better GC; their center used a target of 80–110 mg/dl.[42] One limitation of this study is that the comparison group had very liberal glucose targets being 80–215 mg/dl — there are

undoubtedly many opportunities for improved GC between these extremes, so perhaps a middle ground would have been beneficial. The Fram et al. group assessed hypoglycemia rates as a measure of performance and listed a 3% hypoglycemia rate; however, no comparison of hypoglycemia rate between control and study groups is mentioned.[42] Additionally, the BG level signifying hypoglycemia is unclear.

Hypoglycemia was found by Jeschke et al. to be a crucial factor in burn-related morbidity and mortality in pediatric patients.[43] Their matched cohort found hypoglycemia rates associated with increased inflammatory response, hypermetabolism, sepsis, multiple organ failure, and mortality than those without an incidence of hypoglycemia even after adjusting for severity of illness. The group defined hypoglycemia as a BG less than 60 mg/dl. This statistical model showed that hypoglycemia leads to poor outcomes rather than only signaling worsened disease severity. In the data presented, the hypoglycemia group and no hypoglycemia group had similar daily average glucose values. However, the hypoglycemia group had higher daily maximum values and lowered daily minimum values, indicating that more significant glucose variability played a role but was not elaborated on by the research team.

When looking specifically at respiratory infections in pediatric patients, Kraft et al. showed that systemic glucose levels greater than 150 mg/dl were associated with a higher incidence of bacterial growth in lung tissue and a longer duration of mechanical ventilation.[44] The group suggests that the direct association of glucose in airway secretions due to systemic hyperglycemia leads to bacterial growth and infection. Unfortunately, the study did not measure airway secretions glucose levels, so this avenue

of association cannot be verified. The results nonetheless indicate GC is vital in the prevention of respiratory infection for burn centers. Most of the burn-specific pediatric GC literature presented is from the same group of researchers at few institutions. More heterogeneous studies are warranted to examine if these findings are specific to the like-minded group or if other burn centers achieve similar results. The likelihood is high that pediatric best practices may differ from adult best practices regarding GC.

Hyperglycemia

Hyperglycemia in the adult population also worsens muscle protein breakdown, as demonstrated by Gore et al.[46] A German group examined early hyperglycemia during the burn hock phase and associated mortality.[47] Chen and colleagues found that early excision and allografting of burn wounds can decrease hyperglycemia and IR.[45] Neither of these groups examined hypoglycemia or GV in their analysis, but the Chen et al. group did examine IR using the insulin sensitivity index.

A survey of a national database looking at burn patients produced an association of hyperglycemia with survival which is in opposition to most clinical findings where hyperglycemia is associated with mortality and infection; however, these results may be in error due to the use of administrative data sets or the inclusion of burns of all sizes, not just severe burns.[48] Small size burn injuries, less than 10% total body surface area (TBSA), are often treated as outpatients and sent home to be cared for by primary care. An elevated BG level in these patients may not be treated before discharge from the emergency center. These minor burn injuries treated in ambulatory settings would skew

the results and demonstrate one limitation in using secondary data or comparing minor and severe burn injuries together.

Insulin Infusion

Five studies were found to examine insulin infusion therapy in burn centers with varying targets for GC, only one of which was a prospective design. All the reported studies included some measure of hypoglycemia but in various statistical measures with no homogeneity for cross-analysis. Four of the studies had manual scales for titration of the insulin infusion protocols without mathematical adjustments for a patient response as far as can be ascertained from the study reports. Cochran et al.'s evaluation of 30 patients resulted in a minimal incidence of hypoglycemia when using IIT with a goal of BG less than 120 mg/dl.[49] The results indicate safety and efficacy in reaching targeted glucose, but no outcome measures were included. The Hemmilia et al. group results suggest that even single maximum glucose of 140 mg/dl may increase the risk of infection; however, their use of IIT did not produce a mortality benefit or length of stay improvement for 152 patients.[1] Wiser et al. showed that insulin therapy with a 131–150 mg/dl target produced higher rates of hypoglycemia and no improvement in mortality for 38 patients.[50] Murphy et al. showed that earlier GC is associated with improved mortality even when adjusted for severity of illness.[51] This group used a target glucose range of 110–150 mg/dl and included a GV measure using standard deviation for 46 total patients. GV was higher in the group that failed to achieve early GC. Gibson's group looked at achieving GC with an average daily BG less than 150 mg/dl before day 3 of the hospitalization.[52] This group had previously implemented an IIT program in their surgical ICU, and this study

compared the implementation in the burn center with the previous program. When the target average daily BG was achieved by day 3, reduced mortality resulted. In this study, IR was referenced and measured with mean daily insulin requirement. Again, in presenting the data for this study, the episodes of hypoglycemia are present in the poorly controlled groups for both types of ICU patients, indicating GV plays a role.

Wahl et al. implemented an ICU bundle in the burn center that included assessing glucose levels to maintain less than 140 mg/dl and found decreased infectious complications.[53] However, that study included various other portions of a sepsis prevention bundle, and like this, the link specifically to GC cannot be affirmed. Lastly, Stoecklin et al. examined a historical cohort as the burn center evolved from no GC to doctor driven GC with a target of 72–108 mg/dl to nurse-driven GC with a target of 72–108 mg/dl, and finally to nurse-driven GC with a target of 108–144 mg/dl.[54] The final evolution, more moderate glycemic control, was safe and had fewer hypoglycemic events. However, infectious complications increased over this period, which may be influenced by high rates of hyperglycemia, GV, or other factors, especially considering the historical control design.

Novel and Adjunctive Therapies

A novel therapy studied in burn-injured patients includes using a glucagon-like peptide-1 (GLP-1) as an adjunct to insulin to achieve GC. One pediatric and one adult study exist. Mecott et al. examined the use of exenatide in pediatric patients administered subcutaneously as a first-line agent.[55] The treatment called for the addition of insulin therapy if glucose levels remained outside the target. The GLP-1 group had lower

administered doses of insulin to control glucose levels. In the adult study of using GLP-1 to augment GC, the medication was administered as an infusion and IIT. This study also showed favorable outcomes with improved stability of GC. The researchers specifically looked at GV and showed improved GV in the GLP-1 groups. However, each study determined GV via a different method, using the percent coefficient of variation and one using MAGE.[55, 56] Hypoglycemia was determined at different levels in the two groups as well. More uniformity in reporting outcomes and variables regarding GC is necessary to determine best practices.

Table 2.4. Summary of Key Recommendations

1	Because of the apparent association of hypoglycemic events with mortality, a standardized measure of hypoglycemia rates should be benchmarked and followed within and across burn centers.
2	For burn centers using restrictive transfusion practices, adopting a mathematical formula for correction of BG result should be considered if procurement of the more accurate four-channel glucometers cannot be arranged.
3	Investigation into nuances of glycemic control that may improve early identification and accuracy of sepsis diagnosis using clinical decision support and the electronic health record is warranted
4	Burn centers should consider assessing a hemoglobin A1c on admission to identify patients at risk for challenges with glucose control and complications.
5	Assessing glycemic variability is important when considering overall glucose control; the best method of assessing GV is unknown.
6	Novel therapies may play an essential role in the improvement of glucose control and should be investigated further.

DISCUSSION

A summary of recommendations based on this literature review is provided in Table 2.4. Euglycemia is essential for all critically ill patients, especially so those with burn injuries. The glucose curve is U-shaped — dangerous at both the upper end and lower end. A causal relationship between hyperglycemia and death cannot be made because of the myriad factors impacting burn patient mortality. However, hyperglycemia, IR, and GV may all be indicators of a physiologic derangement that increases a patient's risk of death. A comparison of the literature review articles and measures of GC is provided in Table 2.5. The table highlights the inconsistency in reporting and measurement of GC variables.

Hyperglycemia is strongly associated with sepsis in critical care populations. For patients with burn injury, sepsis is the top source of mortality beginning 48 hours after injury. Sepsis is more difficult to identify early in patients with burn injuries than other critical care populations because of the systemic inflammatory response and hypermetabolism from burn wounds previously discussed.

Hyperglycemia has been used in many studies to aid in the diagnosis of sepsis for the burn population. In a consensus statement, the ABA identified one out of the six triggers concerning infection as hyperglycemia in the absence of preexisting diabetes. This is further clarified to specify a BG of more than 200 mg/dl or IR exemplified by an insulin infusion greater than seven units per hour or an increase in insulin requirements greater than 25% in one day.[58] This criterion was specified for patients who do not have diabetes, so by what criteria do patients with diabetes qualify? The supporting evidence

for insulin infusion dose of 7 units per hour is explicitly lacking, granted IR is essential. A better measure of IR would consider changes over time or patient response to insulin dosing rather than an absolute number.

Because of the apparent association of hypoglycemic events with mortality, a standardized measure of hypoglycemia rates should be benchmarked and followed across burn centers. A suggestion of using the ADA classification of level I, II, and III hypoglycemia are recommended as these are established criteria from the expert organization.[18]

For burn centers using restrictive transfusion practices, adopting a mathematical formula for correcting BG results should be considered if procurement of the more accurate four-channel glucometers cannot be arranged. For institutions with single-channel glucometers, the calculation with every BG check would be demanding for the nursing staff to perform. A suggestion of employing the information technology team to create a clinical decision support tool to aid in the conversion should be considered. Coupling the mathematical conversion for anemia with a CDS tool to assist insulin infusion dose adjustments seems prudent.

Burn patients are almost always on continuous enteral or parenteral nutrition due to their high metabolic demand. Because enteral or parenteral feeding places the patients in a constant postprandial state, glycemic targets for these patients should never be below 140 mg/dl because of the substantial risk of hypoglycemia if continuous nutrition is abruptly stopped.[18] Further, considering that ileus or tube feeding intolerance is another

aspect of the ABA sepsis criteria, burn patients may be at greater risk of hypoglycemia during periods of sepsis because of nutrition malabsorption or metabolic changes.

Metformin has shown promise in decreasing IR and improving glycemic control.[46] Metformin's mechanism of action is to block hepatic glucose production and improve peripheral insulin sensitivity. This mechanism alone does not cause hypoglycemia in patients, dramatically increasing its attraction as an alternative agent. However, the medication is associated with lactic acidosis because of the blocking of oxidative pyruvate metabolism, resulting in lactic acid production. The clinical relevance of this lactic acidosis is limited in studies thus far, with no clinically significant instances reported in several trials.[46,59] Analogs of the incretin hormone GLP-1 promise to decrease the total insulin dosages required to maintain target glucose levels with a short-acting half-life (~2 minutes), leading to a low risk of severe hypoglycemia. The two studies investigating the use of GLP-1 in patients with burn injuries to augment insulin therapy show promise and should be further investigated.

Future Research

Areas of further study include ascertaining if specific insulin infusion algorithms achieve GC faster, with less variability, and with lower hypoglycemia rates than others when using CDS. The possibility of continuous feedback loops with in-line measurement of blood glucose is a promising option considering how time-consuming managing an insulin infusion is for nursing staff. Determining the best method for assessing the impact of GV is essential for burn centers and possibly all critical care populations. For example, we do not know if variability towards hypoglycemia is more relevant than

variability towards hyperglycemia or if variability is equally impactful on both ends of the spectrum. Lastly, burn centers do not know definitively what glucose targets should be used to manage our complicated population best. Despite multiple calls for more prospective and randomized trials looking into details regarding GC for burn-injured patients as early as 2008, none have been undertaken.

CONCLUSION

Glycemic control strategies to limit iatrogenic hypoglycemia while ameliorating the harmful effects of poor GC are critical to positive outcomes. In short, glycemic control must consider many factors that play an essential role, not just a glucose target. More research is needed to identify the best target for burn-injured patients and how GV and IR play a role in outcomes. Additionally, determining the best measurement of glucose variability and hypoglycemia to track and benchmark is vital for continuous performance improvement of burn centers. Lastly, pooling the data from GC parameters together to create an early and accurate warning system for sepsis may have a tremendous impact on timely, goal-directed therapy.

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TABLES

Table 2.2. Literature Review Summary Table

Source	Purpose	Study Design, Sample/ Setting	Glucose Target (mg/dl)	Significant Findings
Impact of Diabetes on Burn Injury				
Dahagam et al., 2011 [20]	To evaluate glucose control and clinical outcomes in diabetic burn intensive care unit patients.	Retrospective Adult n=462	80–110	A preexisting diagnosis of diabetes did not influence outcomes, including mortality, ventilator days, ICU days, and hospital length of stay.
Murphy et al., 2020 [21]	To compare clinical outcomes after burn injury across the continuum of pre-injury GC.	Retrospective Adult n=1,137		Burn injured patients with diabetes have a higher hospital length of stay and higher amputation rate when compared to a burn-injured patient with prediabetes or those without diabetes.
Schwartz et al., 2011 [22]	To carefully assess wound repair and recovery of a diabetic and nondiabetic burn patient to predict outcomes among diabetic patients.	Prospective Adult n=163		For burn-injured patients, time until wound closure is significantly prolonged for patients with diabetes despite increased grafting, pointing towards more graft complications.
Somerset et al., 2014 [23]	To assess the effects of prediabetes on post-injury GC and clinical outcomes.	Retrospective Adult n=208		Patients with burns and prediabetes (HgA1C 5.7 – 6.4) had a higher mortality rate than burn-injured patients without a diagnosis of diabetes. The prediabetes group

				also had more difficulty with GC during the hospitalization when compared to patients without diabetes.
Sepsis Diagnosis and Prediction				
Kucan et al., 1979 [2]	To determine the type of organism responsible for sepsis before initiation of antibiotic therapy using BG level.	Retrospective Adult n=214		This study found that if a patient is hyperglycemic at the time of fever, the patient is more likely to have a gram-positive bacterial growth on cultures, and if the patient is hypoglycemic at the time of fever, gram-negative bacteria was more likely.
Rech et al., 2017 [24]	To develop an algorithm to identify sepsis and septic shock in burn-injured patients incorporating criteria from the ABA sepsis definition for research purposes.	Retrospective Adult n=407		This novel algorithm is accurate and straightforward to help identify sepsis in the burn cohort with good sensitivity and specificity and equivocal discriminative ability to ICD-9 coding.
Hogan et al., 2012 [25]	To evaluate the ABA sepsis criteria correlation with bacteremia.	Retrospective Adult n=196	< 200	The ABA sepsis criteria do not correlate with bacteremia
Mann-Salinas et al., 2013 [26]	To determine whether systemic inflammatory response syndrome and ABA criteria predict sepsis in the burn patient and	Retrospective Adult n=59	< 150	Six novel predictors of sepsis were identified including HR > 130 b/min, MAP < 60 mmHg, base deficient < -6, temperature < 36*C, use of

	develop a model representing the best combination of novel clinical sepsis predictors.			vasoactive medications, and glucose > 150 mg/dl.
Singh et al., 2021 [27]	To determine the exact thyme point at which the insulin requirement increases among nondiabetic burn patients with sepsis.	Retrospective Adult n=58		The total daily insulin dose increased 48 hours before positive blood culture.
Ray et al., 2017 [28]	To determine if admission hyperglycemia predicts infectious outcomes.	Retrospective Adult n=411	< 150	Hyperglycemia is better at predicting infection regardless of a patient's preexisting diagnosis of diabetes.
Furniss et al., 2005 [29]	To determine if infection with Acinetobacter spp. Is associated with the acquisition of glucose intolerance in burn patients.	Prospective Adult n=473	< 110 mg/dl (fasting)	Acinetobacter infection is associated with elevated fasting glucose after controlling for TBSA in burned patients. This is thought to be caused by an insulin-cleaving protease found in Acinetobacter species which inhibits plasma insulin.
Anemia and Point of Care Glucose Testing				
Mann et al., 2008 [30]	To determine if ABA verified burn centers use POC glucose meters to implement IIT, in combination with restrictive transfusion	Prospective Pediatric/Adult n=44	< 120	The combination of IIT and restrictive transfusion practices may lead to potentially dangerous underreporting of hypoglycemia.

	practices, inadvertently increasing the risk of undetected hypoglycemia because of the hematocrit effect.			
Pidcoke et al., 2009 [31]	To identify the most critical source of glucometer error in hemodynamically stable patients	Retrospective/ Prospective Adult n=60		Anemia hides hypoglycemia readings due to error in point of care glucose monitors - this is the mathematical formula to correct anemia and compute the correct BG level.
Mann, Salinas, et al., 2008 [32]	To analyze error rates of three different POC glucometer brands and determine mathematical correction formulas for each.	Prospective Adult n=196		The authors created and tested a mathematical formula to correct for hidden hypoglycemia due to anemia for 4 distinct types of point of care glucometers.
Clinical Decision Support				
Lee et al., 2012 [33]	To assess if a computerized insulin GC program would be effective and safe when used in the burned patients.	Retrospective n=31	90–150	CDS programs used for calculating insulin infusion dosages are safe and effective for burn centers.
Mann et al., 2011 [34]	To determine the safety and efficacy of computer decision support software to control serum glucose concentration in a burn intensive care unit.	Randomized Adult n=18	80–110	CDS algorithm for IIT was tested on patients and compared to a manual algorithm in a self-control series design. The CDS algorithm showed better time in the target range without

				an increase in hypoglycemic events.
Sood et al., 2012 [35]	To determine that a computer-based GC program is a safe and effusive means of achieving normoglycemia in the burn population without increasing the incidence of hypoglycemia.	Retrospective Adult n=94	100–150	CDS algorithm for IIT is effective at getting to target rapidly, staying in target 63% of the time, and preventing hypoglycemia.
Elder et al., 2019 [36]	To assess the accuracy of continuous glucose, monitor with in-line capability in the burn intensive care setting.	Observational Adult n=10		A continuous bedside glucose monitor developed for use within vascular access can be used in burn centers.
Glycemic Variability				
Farhy et al., 2011 [37]	To relate the BG variable of burn ICU patients to outcomes using a sensitive measure of glucose variability in the average daily risk range.	Retrospective Adult n=980		GV in the low and high end of the BG scale contributes to mortality more than simple averages of glucose levels for burn-injured patients. Mean BG and the SD of BG did not predict mortality the same as ADRR. This study

				links the ADRR as a measure of GV to other outcomes in addition to mortality.
Pidcoke et al., 2010 [38]	To examine if GV alone might identify patients who are at higher risk of death.	Retrospective Adult n=49	80–110	For the burn-injured patients in this study, mortality in the high variability group is twice that of the low variability group showing the impact of GV on outcomes.
Pisarchik, Pochepen, & Pisarchyk, 2012 [39]	To examine the daily glucose excursion as a measure of GV in severely burned patients.	Retrospective Adult n=172	63–144	Even when the mean daily glucose level was within a target range, GV (using Delta) was associated with death and sepsis in burn-injured adults.
Pediatric Burns				
Cree et al., 2008 [40]	To attempt to understand some of the mechanisms involv3d in the development of IR following trauma.	Prospective Pediatric n=30		IR following burn injury is accompanied by decreased insulin signaling and increased protein kinase C-β activation.
Jeschke et al., 2010 [41]	To determine which glucose levels are associated with improved morbidity and mortality in thermally injured patients.	Retrospective Pediatric n=208	< 130	Patients with a daily morning glucose level of 130 mg/dl have attenuated hypermetabolic and inflammatory responses and lower incidence of infections, sepsis, and mortality.

Fram et al., 2010 [42]	To institute IIT protocol in an acute pediatric burn unit and study its benefits mechanisms.	Prospective Pediatric n=29	80–110	Controlling BG levels to less than or equal to 120 mg/dl using IIT protocol improves insulin sensitivity and mitochondrial oxidative capacity while decreasing resting energy expenditure.
Jeschke et al., 2014 [43]	To determine the prevalence of hypoglycemia after burn injury and whether hypoglycemia is associated with increased post-burn morbidity and mortality.	Prospective Pediatric n=760		Hypoglycemic episodes correlate with injury severity and inhalation injury and are associated with higher post-burn morbidity and mortality even when adjusted for injury severity.
Kraft et al., 2014 [44]	To determine whether a BG cutoff value exists for severely burn-injured pediatric patients increases the risk of pulmonary infections.	Prospective Pediatric n=106	<150	Systemic glucose levels higher than 150 mg/dl are associated with a higher incidence of pneumonia.
Hyperglycemia				
Chen et al., 2011 [45]	To examine if early wound excision in patients would also reduce the IR induced by major burn.	Adult n=41		Excision and allografting during burn shock have an immunomodulatory effect on the inflammatory mediators and further reduce IR induced by major burns.

Gore et al., 2002 [46]	To assess if hyperglycemia influences energy expenditure or the extent of muscle protein catabolism in severely burned adults.	Retrospective Adult n=29	< 130	Severe hyperglycemia is associated with higher phenylalanine levels (signifying muscle protein catabolism); thus, hyperglycemia increases the rate of muscle breakdown.
Holm et al., 2004 [47]	To evaluate BG levels in severely burned patients with conventional management and analyze the association between early hyperglycemia and clinical outcome.	Prospective Adult n=37	180–200	In this study group, early hyperglycemia was associated with mortality.
Veeravagu et al., 2015 [48]	To describe national trends, improvement, demographics, hospital length of stay, hospital charges, and mortality for burn patients with and without inhalation injury from a national database and to compare to the National Burn Repository.	Retrospective Adult n=506,628		Based on examining secondary data from a large national database, patients with hyperglycemia demonstrated lower mortality rates. This is in opposition to most current literature. These findings may represent an error in the administrative dataset or represent the sample that includes even minimal burns.
Intensive Insulin Therapy				

Cochran et al., 2008 [49]	To review the experience with an IIT protocol to evaluate the safety and efficacy of aggressive glycemic control in patients with acute burn injury or life-threatening soft tissue infection.	Adult n=30	< 120	Hyperglycemia in ICU patients with burns or soft tissue infection can be effectively managed with intensive insulin protocol aiming at BG of less than 120 mg/dl with minimal incidence of hypoglycemia.
Hemmila et al., 2008 [1]	To evaluate our experience with IIT in burn-injured ICU patients regarding mortality, morbidity, and use of hospital resources.	Observational Adult n=152	100–140	A single maximum glucose level above 140 in this study group signified a risk of infection. The use of IIT did not confer mortality or length of stay benefit but did improve some infection rates.
Wiser et al., 2019 [50]	To compare the effect of standard and tight glycemic control protocols on mortality and hypoglycemic events in critical care burn patients.	Retrospective Adult n=38	131–150	Tight glycemic control in burn patients was associated with higher rates of hypoglycemia with no improvement in survival in the acute care setting of burn trauma care.
Murphy et al., 2011 [51]	To determine the influence of early glycemic control on eh outcomes of critically ill patients with burn injury.	Retrospective Adult n=46	110–150	Earlier BG control is associated with improved mortality even when adjusting for TBSA, age, and inhalation injury.
Gibson et al., 2009 [52]	To determine whether critical ill burn patients benefit from tight glycine control achieved by IIT in a manner analogous to the benefits	Prospective Adult n=37	< 150	Focusing on glycemic control with an average daily BG less than 150 by day 3 was associated with a mortality benefit.

	already documented in SICU patients.			
Wahl et al., 2010 [53]	Evaluating if the deployment of the core ICU measures would reduce both catheter-related BSI and VAP rates in the burn ICU.	Prospective Adult n=179	< 140	Documentation and assessment of morning BG value less than 140 were part of a bundle of ICU core measures implemented to reduce infectious complications and mortality.
Stoecklin et al., 2016 [54]	To evaluate the safety of general ICU GC protocols applied in major burns receiving prolonged ICU treatment.	Retrospective Adult n=229	72–108 or 108–144	The GC protocol improved glycemic control in burns and was safe with regards to hypoglycemia.
Novel and Adjunct Therapies				
Mecott et al., 2010 [55]	To assess if exenatide would decrease plasma glucose levels post-burn to levels like those achieved with IIT and reduce the amount of exogenous insulin administered.	Randomized Pediatric/Adult n=24	80–140	Patients dosed with a GLP-1 had lower total doses of insulin and retained similar rates of hypoglycemia.
Galiatsatos et al., 2014 [56]	To determine if the addition of continuous infusion of glucagon-like peptide-1 to IIT would result in better GC, reduced requirement of	Prospective, Randomized Adult n=18	144–180	An infusion of GLP-1 during IIT is safe and improves GC with less GV.

	exogenous insulin administration, and fewer hypoglycemic events.	

ICU = intensive care unit; GC = glucose control; HgA1C = hemoglobin A1C; ABA = American Burn Association; ICD-9 = International Classification of Diseases, ninth revision; HR = heart rate; MAP = mean arterial pressure; BG = blood glucose; TBSA = total body surface area; POC = point of care; IIT = intensive insulin therapy; CDS = clinical decision support; GV = glycemic variability; SD = standard deviation; ADRR = average daily risk range; GLP = glucagon-like peptide

Table 2.5. Comparison of Articles with Various Glucose Control Measurements

Source	Measure of hypo-glycemia	Measure of IR	Measure of GV
Chen et al., 2011		Insulin sensitivity index	
Cochran et al., 2008	Incidence of hypo- per protocol day (<60 mg/dl)	Yes	
Cree et al., 2008			
Dahagam et al., 2011			COV
Elder et al., 2019			
Farhy et al., 2011			ADRR
Fram et al., 2010		Yes	
Furniss et al., 2005			
Galiatsatos et al., 2014	Patient count with at least 1 hypo- event (<50 mg/dl)	Yes	COV
Gibson et al., 2009	Patient count with at least 1 hypo- event (<60 mg/dl)	Yes	
Gore et al., 2002			
Hemmila et al., 2008	Number of days with at least 1 hypo- event / total days (<70 mg/dl)		
Hogan et al., 2012		Yes	
Holm et al., 2004			
Jeschke et al., 2010		Yes	
Jeschke et al., 2014	Count of hypo- episodes (<60 mg/dl)		
Kraft et al., 2014		Yes	
Kucan et al., 1979			

Lee et al., 2012	Incidence / total BG (<50 mg/dl)		
Mann et al., 2008			
Mann et al., 2011	Incidence / total BG (<60 mg/dl & <40 mg/dl)		
Mann, Salinas, et al., 2008			
Mann-Salinas et al., 2013			
Mecott et al., 2010	Hypo- events / patient-month (<60 mg/dl)	Yes	MAGE
Murphy et al., 2011	Patient count with at least 1 hypo- event (<70 mg/dl & < 40)		SD
Murphy et al., 2020			
Pidcoke et al., 2009			
Pidcoke et al., 2010			Excursion outside target
Pisarchik, Pochepen, & Pisarchyk, 2012			Delta, COV
Ray et al., 2017			
Rech et al., 2017			
Schwartz et al., 2011			
Singh et al., 2021		Insulin dose	
Somerset et al., 2014			SD
Sood et al., 2012	Incidence / total BG (<70 mg/dl)		
Stoecklin et al., 2016	Incidence / total BG (<72 mg/dl & <41 mg/dl)		SD
Veeravagu et al., 2015			
Wahl et al., 2010			
Wiser et al., 2019	Patient count with at least 1 hypo- event		

IR = insulin resistance; GV = glycemic variability; COV = percent coefficient of variation; ADRR = average daily risk range; BG = blood glucose; MAGE = mean amplitude of glucose excursion; SD = standard deviation

CHAPTER III

METHODOLOGY

Research Design

The study was a retrospective analysis of burn patient data from a large burn center in Lubbock, TX. A predictive, correlational design was used to examine relationships between the selected variables in this group of subjects with burn injury. This research was submitted to the institutional review board (IRB) of Texas Woman's University, and the study site IRB at TTUHSC in Lubbock, TX and was approved as an exempt study.

Specifically, the research questions for the study were:

1. What is the relationship between glucose control (GC), insulin resistance (IR), glycemic variability (GV), mortality, and infection in critically ill, burn-injured patients?
2. Which variables (GC, IR, GV, or all) are most predictive of mortality and infection in critically ill burn-injured patients?

Homogeneity of Treatment Study

The researcher engaged in some preliminary work to identify variation in care and the incidence of hyperglycemia despite protocolized interventions at the study site prior to the pilot study. Assumptions are often made that protocols standardize the care provided; however, this may not be the case if variation in how the protocol is ordered or

administered exists. The purpose of this preliminary study was to examine if the use of insulin infusion protocol resulted in homogenous control of BG levels and treatment of patients at the study site for the research.

The principal investigator investigated the irregularities of BG management in a small subset of patients on an insulin infusion located at the same verified burn center as for this research. Provider-dependent factors were examined, such as when insulin infusions were initiated and the parameters used for glucose targets on the order plan. Nursing-dependent factors were explored, such as dosing and frequency of BG checks. This preliminary work is referred to as the Homogeneity of Treatment Analysis.

Homogeneity of Treatment Analysis

The specific components of this preliminary assessment in the order of sequence were:

1. Choose the 15 most recent patients who meet the criteria for inclusion. Adults (18–89 years of age) who are admitted to the Burn Center receiving an insulin infusion while in the Burn Center with TBSA greater than 15% were included. Patients with diabetic ketoacidosis and those who have a length of stay of fewer than 48 hours were excluded.
2. Review the electronic health record of this case series to determine glucose levels and insulin targets on the insulin infusion protocol ordered in the medical record.

3. Assess the data to determine if there were differences in glycemic control, order entry, or BG checking of this small group to assess for homogeneity of treatment.

Because this preliminary research project involved protected health information from the electronic health record, Institutional Review Board (IRB) approval was obtained. Fourteen subjects met inclusion and exclusion criteria and had their electronic medical record reviewed to determine the homogeneity of treatment and application of insulin infusions at the study site. Patient characteristics are listed (see Table 3.1). Thirteen of the 14 patients were male (92.9%), and two died (14.3%).

Table 3.1

Patient Characteristics of Homogeneity of Treatment Study, n = 15

			95% Confidence Interval for Mean			
	Mean	Standard Deviation	Lower Bound	Upper Bound	Minimum	Maximum
Age (years)	52.1	14.2	43.9	60.3	32	78
BMI	29.82	6.43	26.11	33.53	19.13	29.97
Revised Baux Score	95.11	21.03	82.96	107.26	64	135.5
Hospital LOS (days)	45.93	24.72	31.66	60.2	15.2	83.2

Note. BMI = body mass index; LOS = length of stay

Results indicated that the management of GC for the subjects was similar, with no significant differences in provider-dependent or nurse-dependent factors (see Table 3.2). All the patients had similar orders, with most glucose targets being 120–180 mg/dl (n = 9, 64.3%) and the next most frequent being 140–180 mg/dl (n = 3, 21.4%). Since the time of this preliminary work, the study site has changed to a standard glucose target of 140–

180 mg/dl to align with recommendations from the ADA. The average BG level prompting initiation of the insulin infusion was 333.4 mg/dl (*SD* 76.6, *Variance* 5453.10), which was quite high with significant variance. Institutional protocol suggests beginning an insulin infusion if two or more measurements are greater than 180 mg/dl.

Table 3.2

Homogeneity of Treatment Analysis

	Mean	Standard Deviation	95% Confidence Interval for Mean		Minimum	Maximum
			Lower Bound	Upper Bound		
Average BG (mg/dl)	161.45	10.29	155.51	167.39	148.66	184.05
Percent of BG Inside the Target Range (%)	53.50	13.75	45.56	61.44	20.34	78.20
BG Before Initiation of Insulin Infusion	333.43	76.63	289.18	377.68	204.00	465.00
Ordered Insulin Infusion Lower Target	121.43	14.60	113.00	129.86	80	140
Ordered Insulin Infusion Upper Target	177.14	10.69	170.97	183.32	140	180
Mean Number of Glucose Checks per Day on the Insulin Infusion	23.57	8.82	18.24	28.91	11.38	40.80

Nurse-dependent factors include the frequency of glucose checks per day on the insulin infusion, and the results indicate homogeneity with an average of 23.57 measurements per day on the insulin infusion (*SD* 8.82, *Variance* 77.88). There should be approximately 24 BG measurements per day for patients on an insulin infusion. This may have been altered if the patient was not on the insulin infusion the entire 24 hours of

the day. Examples of when this would apply include when insulin was stopped for the operating room or due to cessation of enteral nutrition to prevent hypoglycemia.

Based on this preliminary work, results support that the ordering practices and administration of insulin infusion at the study site resulted in homogeneous care for critically ill, burn-injured patients. This was important for the current research as it mitigates the possibility that differences in treatment regarding GC between providers and nursing staff contribute to differences in outcomes. This homogeneity of treatment analysis adds to the construct validity of the research.

Pilot Study

A group of 20 subjects was chosen at random who met inclusion criteria for a pilot study. After a brief chart review, three subjects were excluded based on age, leaving 17 remaining subjects for the pilot study analysis. The study subjects examined for the pilot study were not included in the sample of this research.

Data were abstracted from the electronic medical record, including demographics (e.g., age, gender, BMI, weight), severity of injury data (e.g., TBSA, type of burn, presence of inhalation injury), outcomes data (e.g., length of stay, in-hospital death, and discharge disposition), lab values (e.g., HgbA1C, BG), medication administration (e.g., insulin, glucose), and infection data (e.g., bacteremia, wound infection). A portion of this data collection tool was used in the homogeneity of treatment analysis previously described. Much of the data collection tool proved helpful in the calculations done for that small preliminary work.

Data elements used in the data collection tool were literature supported. For example, GC has been expressed in publications using several methods. Mean daily BG (Pisarchik et al., 2012), daily morning BG (Cree et al., 2008), the percent of glucose measurements within the target range (Sood et al., 2012), the percent of BG measurements outside of the target range, and daily maximum BG (Hemmila et al., 2008) have all been used as expressions of the overall GC of patients in research. Based on the literature review, hypoglycemia should be closely monitored because of the mortality impact when examining overall GC for ICU patients and is also included. This study examines hypoglycemia in the levels defined by the ADA (2020).

Mowery et al. (2009) first used the insulin infusion multiplier as a surrogate measure of IR in critically ill surgical patients. Because of the literature supporting this methodology, all MMs were collected for study subjects and were included in the data collection tool. Additionally, total or daily insulin dosing may illuminate IR as dosing requirements increase; thus, all insulin dosing was included during data collection tool development.

The ADA endorses using the percent coefficient of variation to measure GV in the outpatient setting. However, there is no recommended strategy for acute or critical care to assess GV, as demonstrated in the literature review. Dahagam et al. (2011) utilized this approach in examining outcomes for patients with diabetes who have burn injuries. The delta of BG may also provide clues as to the onset of infection, according to Pisarchik and colleagues (2012). This research examines GV using the percent coefficient of variation, standard deviation, and delta of BG measurements.

The research strives for rigor by building on previously published works. The data collection tool selected relevant variables from the literature and this researcher's prior work described above. The study fills a significant knowledge gap as no current research exists examining which combination of the predictor variable(s) (GC, IR, GV, or all) best predicts mortality and infection.

The manual data collection process for the pilot took approximately 25–35 minutes per study subject. The study site was contacted to inquire about maximizing the electronic data query information and was able to identify a method for gathering some information in the query that was previously obtained manually. This was estimated to decrease the manual data collection to less than 15 minutes per subject, a significant improvement.

The researcher used daily maximum BG, daily mean BG, 14-day mean BG, 14-day mean morning BG, and hypoglycemia rate for levels I and II hypoglycemia to assess GC. The percent within the target glucose range was used to illustrate compliance with the protocol targets. To assess IR, the researcher used daily insulin total, daily maximum insulin infusion rate, delta insulin infusion rate, 14-day insulin total, 14-day mean insulin per day, daily mean MM, daily delta MM, and 14-day mean MM. To assess GV, the researcher used the percent coefficient of variation of BG, the standard deviation of BG, and the delta of BG for the 14-day study period.

The following data analyses were performed to inform the dissertation method and design. Preliminary data analysis began with categorical distributions. The researcher ran a frequency analysis of all categorical variables to determine if there were

a roughly equal number of subjects in each group. Gender was unequally distributed, as is common in burn injury research, whereas most adult burn patients are male. Next, each continuous variable was checked for missing data, outliers, and normality.

Missing data were easy to identify in this small pilot study by examining the data collection tool and looking for missing values. There were no missing data on this small group of subjects. Any missing data in the research study was addressed individually using one of three methods. The first option was for the researcher to delete the case or variables that involve missing data. The second choice was to estimate and replace the missing values based on prior knowledge or calculation of the means. The third option to address missing data was assessing and replacing the missing data using a regression approach (Mertler & Reinhart, 2017).

Outliers can distort the result of a statistical test and, as such, need to be dealt with (Mertler & Reinhart, 2017). A single outlier can significantly influence the results of a statistical test, even making data significant when it would not have been otherwise. Correlation tests are susceptible to outliers. If the statistical analysis results are to represent most of the data, outliers must be eliminated or transformed. A box-plot graph highlighted cases with values greater than 1.5 box lengths outside the median, as those should be considered outliers (Mertler & Reinhart, 2017). For the pilot study, the researcher removed extreme outliers as identified from box-plots and included hospital length of stay, 14-day mean insulin dose per day, 14-day total insulin, mean morning BG, and 14-day mean BG.

Normality, linearity, and homoscedasticity are critical assumptions for multivariate statistical testing (Mertler & Reinhart, 2017). Violating normality and performing statistical analysis results in bias in the results. A more robust statistical analysis can be achieved with normally distributed data. Histograms and normal Q-Q plots were performed for all continuous variables in this analysis to assess for normalcy. In addition, skewness and kurtosis were included in the analyses to determine symmetry and peak distribution, respectively.

In Table 3.3, normally distributed, continuous variables for demographics were summarized by reporting the mean, standard deviation, and descriptive statistics. There were 16 males in the pilot group, making up 94% of the subjects. Seven of the subjects (41.2%) died during the hospitalization, accounting for an abnormally high mortality rate for the small sample. A P-value less than 0.05 was considered to indicate statistical significance. The researcher used IBM SPSS Statistics for Windows, Version 25.0 (SPSS Corp, Armonk, NY) for analysis.

Table 3.3

Demographics for Pilot Study Subjects, n = 17

			95% Confidence Interval for Mean					
	Mean	Std. Deviation	Lower Bound	Upper Bound	Minimum	Maximum	Skew	Kurtosis
Age	47.33	11.87	40.76	53.91	29	68	0.420	-0.532
Weight (kg)	88.23	24.34	74.72	101.71	55.3	144.0	0.952	0.583
BMI	29.06	6.99	25.19	32.93	19.1	44.4	0.471	0.053
Revised Baux Score	90.43	24.08	77.10	103.77	65	128	0.615	-1.434

Hospital LOS (days)	35.63	25.75	21.90	49.35	7	88	1.084	-0.004

Note. BMI = body mass index; LOS = length of stay

Research Question 1

What is the relationship between GC, IR, GV, mortality risk, and infection in critically ill, burn-injured patients?

Correlation measures which two or more variables have a relationship (Mertler & Reinhart, 2017). Correlation does not describe or imply causation, only the presence of a connection between the variables (Field, 2005). Spearman's correlation is applicable when the data are not normally distributed (Field, 2005).

This pilot study research question was examined using Spearman's rho. As expected, the outcome variables correlated significantly with the revised Baux score including mortality (r = -0.830; $p < 0.000$), discharge disposition (r = 0.848; $p < 0.000$), and specifically respiratory infection (r = 0.586; p = 0.013). This supports the good planning for using stepwise regression to control the revised Baux score when assessing Research Question 2. Many of the independent variables (IV) were also related to one another; measures of GC correlated with both GV and IR.

The Benjamini-Hochberg procedure was utilized to decrease the false positive rate or type I error in the pilot results (Thissen et al., 2002). Benjamini-Hochberg procedure is often preferred over a Bonferroni correction as Bonferroni tends to be overly conservative, increasing the risk of Type-II error (Thissen et al., 2002). The Benjamini-Hochberg procedure calculations are provided, accepting a 20% false discovery rate.

After adjusting for this correction, the significant correlations are highlighted with an asterisk on Table 3.4.

Table 3.4

Significant Correlations between dependent and independent variables

Independent Variable	Dependent Variable	Correlation Coefficient	P-value	Rank	Benjamini Hochberg critical value (i/m)*Q
Mean MM for hospital day 1	Discharge Disposition	-0.793	0.001	1	0.013*
Mean MM for hospital day 1	Mortality	0.718	0.006	2	0.025*
Delta insulin for hospital day 2	Mortality	-0.686	0.007	3	0.038*
Mean insulin for hospital day 14	Discharge Disposition	-0.700	0.008	4	0.050*
Mean insulin for hospital day 2	Mortality	-0.636	0.015	5	0.063
Mean MM for hospital day 1	Hospital length of stay	-0.662	0.019	6	0.075
Mean insulin for hospital day 14	Mortality	0.634	0.020	7	0.088
Mean insulin for hospital day 3	Urinary Tract Infection	0.656	0.021	8	0.100
Delta insulin for hospital day 5	Wound Infection	-0.581	0.023	9	0.112

Mean MM for hospital day 1	Respiratory Infection	-0.619	0.024	10	0.125
Mean MM for hospital day 12	Urinary Tract Infection	0.765	0.027	11	0.137
Mean MM for hospital day 13	Urinary Tract Infection	0.840	0.036	12	0.150
Mean insulin for hospital day 11	Urinary Tract Infection	0.557	0.039	13	0.163
Delta insulin for hospital day 3	Urinary Tract Infection	-0.596	0.041	14	0.175
Mean insulin for hospital day 14	Hospital length of stay	-0.588	0.044	15	0.188
Mean insulin for hospital day 12	Urinary Tract Infection	0.521	0.046	16	0.200

Note. MM = mathematical multiplier on the insulin infusion; I = rank of the *p*-value; m = total number of tests; Q = accepted false discovery rate.

* = significant after Benjamini-Hochberg procedure

Outcome variables, including mortality and discharge disposition, were significantly correlated with the mean MM on the insulin infusion on the first hospital day; however, some were positive, and some were negative associations (see Table 3.4). Mortality was associated with the change in insulin for hospital Day 2 (r = -0.686; p = 0.007). Additionally, discharge disposition was associated with mean insulin dose for hospital Day 14 (r = -0.7; p = 0.008). Other correlations exist between urinary tract infection and various measures of IR and GV, as demonstrated in Table 3.4, but after

correction for type I error, this relationship did not remain significant. This may represent the time necessary before urinary tract infections present in hospitalized patients with burn injuries, as findings supported this relationship beginning on Day 3. Examining this relationship in a more adequately powered sample size may reveal stronger relationships. Similar results were found with wound infection and hospital Day 5, perhaps representing the time necessary for wound colonization to occur. Hospital Day 14 may represent a significant time for IR as well.

The researcher also examined correlation coefficients for possible multicollinearity. In Spearman's correlation, only one variable had a correlation coefficient greater than 0.8, that being the presence of urinary tract infection and mean MM on an insulin infusion for hospital Day 13. Though this correlation was not significant after controlling for type I error, the researcher took note of this high correlation coefficient and more closely evaluated multicollinearity with the regression model using the variance inflation factor (VIF) and tolerance.

Research Question 2

Which variables (GC, IR, GV, or all three), controlling for severity of illness, are most predictive of mortality and infection in critically ill, burn-injured patients?

A regression analysis has the primary purpose of developing a model to predict values on a dependent variable (DV) for members of a population (Mertler & Reinhart, 2017). Logistic regression is used when the DV is categorical, there is a large set of predictor variables, and the researcher wants to determine which one makes a significant impact on the prediction model. In the pilot study, the results of the correlation

performed to answer Research Question 1 supported controlling for the severity of illness (revised Baux score) in answering Research Question 2. There was a significant correlation between the revised Baux score and both the IV and DV variables. This also matched the researcher's knowledge and experience, knowing that the revised Baux score was a significant predictor of outcomes because it measures the severity of the injury. Regression is also very sensitive to outliers. For the pilot data analysis, the outliers were addressed before correlation studies were performed.

For the pilot data analysis, logistic regression was completed in a stepwise approach, first controlling for the revised Baux score to determine which IVs were most predictive of mortality and infection. None of the predictor variables was found significant in this small pilot sample. Lack of significance would most likely be due to the small sample size creating an underpowered study. For logistic regression, the sample size is especially important when a large number of predictor variables are used as it may cause very high standard errors. However, results from this pilot support the importance of using the stepwise approach for analysis and examining the revised Baux score as a confounding variable in the research.

The researcher can predict the time necessary to complete the entire data collection for the dissertation research from this pilot data analysis. The study site expanded the data available for the electronic data query, decreasing the researcher's time required for manual data abstraction. The principal investigator spent approximately 25–35 minutes doing manual data abstraction on each subject for this pilot, but with the inclusion of the expanded electronic data query, the estimated time for manual data

collection was 15 minutes or less per subject. If the researcher achieves an adequately powered sample size of $n = 133$ for the research, that equates to 34 hours of manual data collection.

Missing data were not a significant issue for the pilot and was not anticipated to pose a significant problem for the research study. Several outliers were identified and removed from the pilot as anticipated by the researcher. Additional statistical measures using the available data obtained from the electronic data query may be considered for the research. The author proposes to add a daily measure of the change in BG level rather than a 14-day delta value. This may add to the prediction capabilities of the variable when associated with time and infections. The pilot study showed that some variables were significant on certain days of hospitalization, which may be an important finding. Other data calculations proved less critical and were eliminated, such as the minimum insulin dose on the insulin infusion per day — considering IR was associated with maximum insulin dosing. Tracking the treatment of hypoglycemia, for example, was not essential because institutional policy mandates dextrose administration for hypoglycemia. Instead, the researcher used the ADA-approved hypoglycemia rate to track both Levels I and II hypoglycemia. Other areas where variables were removed for the research study based on pilot findings are outlined in Table 3.5. These changes further cut down on time sorting and analyzing data without sacrificing rigor in this vital research. Overall, this pilot study was helpful to inform the research in execution, data preparation, and data analysis.

Table 3.5

Changes in Variables for Research-Based on Pilot Study

	GC	GV	IR	Other
Variables Eliminated	Percent outside target Total insulin doses Total glucose checks 14-day Minimum BG	14-day Delta BG	14-day Maximum insulin infusion rate 14-day Minimum insulin infusion rate Daily Minimum Insulin dose Daily Mean insulin infusion rate Daily change in insulin infusion rate Daily Maximum MM Daily Minimum MM	Total dose of dextrose for hypoglycemia Treatment of hypoglycemia with dextrose The presence of continuous nutrition
Variables Added		Daily Delta BG		

Note. GC = glucose control; GV = glycemic variability; IR = insulin resistance; BG = blood glucose; MM = mathematical multiplier

Research Study

Setting

This study took place at a Burn Center verified by the American Burn Association. The burn center is verified for both pediatric and adult burn care. The

burn center is in a rural region of west Texas with over a 300-mile radius transfer area. Patient transfers come to the burn center for a higher level of care from a large portion of Texas, New Mexico, southeast Colorado, Oklahoma, and southwest Kansas. In 2020, 504 patients were seen by the burn center, and 360 of those were admitted. One-third of the patients were pediatric. About 10% of burns cared for at the burn center are considered severe with greater than 20% TBSA. The burn center participates in clinical research in collaboration with a clinical research institute and a center of research excellence.

One limiting factor of a retrospective study design is that management strategies and advances in science occur over time. The body of evidence for clinical practice inherently changes with new research and may influence care decisions. Because these changes over time cannot be controlled in retrospective research, it becomes a limitation of the study design. Regardless of the 5-year study period, it has been known that hyperglycemia left unchecked is harmful for more than a decade. This institution has had an insulin infusion protocol for the treatment of severe hyperglycemia since 2005. Since 2007, there have been no changes to the protocol, only changes to nursing documentation in the electronic health record — the computer now performs the calculations for nursing staff to ease their workload. The burn center medical director and assistant medical director have remained the same throughout the study period and were the primary attendings managing burn-injured patients. They are board-certified surgical critical care intensivists who utilize evidence-based guidelines to standardize practice and reduce variability for most aspects of burn critical care.

Additionally, the inpatient Advanced Practice Registered Nurses (APRN) worked consistently over the study period assisting in the day-to-day management of critically injured patients. This combination of evidence-based care and consistency in inpatient management over time may limit the known issue of historical change with retrospective research. Other threats to validity for this design include the single-group and single-center design, allowing for no comparison.

Population and Sample

The study population was critically ill, burn-injured adults. Inclusion criteria included adults, ages 18 to 89 years admitted to the Burn Center of a Regional ABA verified burn center with greater than or equal to 20% TBSA burn injury. Exclusion criteria included patients who transfer or die within 72 hours of the injury and those admitted with a diagnosis of diabetic ketoacidosis (DKA). The study covered the first 14 days of hospital admission after injury.

Rationale

Because pediatric patients often have different treatment protocols than adult patients, they were not part of the study scope or research aims. An age of 90 years or greater could also be an identifying characteristic. The limit of 89 years was a requirement by the study site IRB, where the data collection took place because of the limited number of nonagenarians in the community.

Patients with burn injuries greater than 20% TBSA are typically considered severe burns and have a significant increase in capillary permeability and resultant burn shock (Pham et al., 2008). These patients have disruption from homeostasis significant

enough to have the dramatic metabolic changes known to burn injury. Minor burn injuries may not have a metabolic disturbance significant enough to cause the hyperglycemia of critical illness currently under investigation. Additionally, patients with DKA experience a different metabolic process than typical burn hypermetabolism and were excluded.

Patients who die within 72 hours of burn injury mostly have nonsurvivable injuries beyond the metabolic response that can be ameliorated with good resuscitation efforts and critical care. This study focuses on research in patients with survivable injuries that might contribute to positive outcomes in the future. Lastly, if patients were transferred out to another facility within 72 hours of burn injury, there would be insufficient data to answer the research questions.

According to the literature, sepsis in burn patients occurs starting the first week after injury and remains a threat if the patient has open burn wounds, even months later (Greenhaulgh, 2017). Lengthy hospitalizations for severely burn-injured patients can last 90 days or more. Capturing the data from the entire hospitalization was not feasible for this study. Other studies have used a study period of three days (Singh et al., 2021; Murphy et al., 2011), up to the entire length of stay (Hemmila et al., 2008). With a 14-day study period, the opportunity for capturing the first episode of sepsis or infection in subjects is high. Additionally, more time in the burn center may introduce more confounding variables when operations and complications begin to compound. The 14-day study window was a strength in this study when compared to the 3-day study period of other reports but remains feasible to perform.

Sample Size

The researcher performed a power analysis for sample size estimation. Effect size estimates were determined based on prior research in the literature. Mowery and colleagues (2009) found significant differences in IR in a study of critically ill surgical patients, as measured by insulin infusion multiplier and median insulin rate in survivors and non-survivors ($p < 0.01$). Based on the odds ratio of 1.68, power analysis revealed that for an effect of this size to be detected (80% chance) as significant at an alpha level of 0.05, a sample of 133 subjects would be required. This burn center admits approximately 50–60 patients per year with extensive burn injuries. Looking back five years would provide an estimated 200 patients to examine for inclusion and exclusion criteria. This oversampling was necessary to allow for potentially missing data and the application of inclusion and exclusion criteria.

Protection of Human Subjects

To protect human subjects, approval from the IRB at Texas Woman's University was obtained for both the pilot study and this study (see Appendix A). Additionally, the study site provided a secondary IRB submission and was approved by the IRB at TTUHSC. This TTUHSC IRB is included in Appendix B. Next, the health system that houses the Timothy J. Harnar Burn Center, where patients were admitted and received expert care, provided a research approval letter for the study. This research approval letter is included in Appendix C.

Safety Risks

There were no direct safety risks to subjects as all data collection was retrospective. Breach of confidentiality was a risk for this study. This risk was mitigated by collecting no personal identifiers on the Data Collection Tool.

Destruction of Protected Health Information

After complete data collection, the Master List containing protected health information was permanently destroyed following the study site institutional policy. This was performed at the close of the study time frame listed on the IRB approval letter.

Data Collection Procedures

Data was collected using a retrospective, electronic medical record review approach. Much of the data was abstracted via an electronic data query. This minimizes the risk of transcription or coding error during data collection and complying with minimum necessary data exposure.

After all approvals and documentation, the study site performed a query of the electronic health record following the inclusion and exclusion criteria producing a subject list for the investigator. A subject list containing protected health information (PHI) in the form of medical record numbers, encounter numbers, and the date of admission for participants was obtained as part of the data collection. The principal investigator assigned each participant a Study identification (ID). Saving the file with a link between the PHI and the Study ID was necessary to verify study data to help ensure accuracy and allow the principal investigator to go back to the chart to

collect any missing data, if necessary, during the study time frame. The only copy of this file was kept on a password-protected computer, inside the principal investigator's encrypted folder in the Box storage account. This account was set up and approved for PHI by the study site. The file with PHI was not downloaded onto any computer, workstation, or external disk/drive. The study site institutional policy for the protection of this type of PHI is included in Appendix D.

The subject list from the electronic query was transmitted in an Excel file format to the principal investigator via email. Transmission of PHI via internal email to the principal investigator from the study site team was permitted and approved by the study site IT security team. This is the typical process by which research queries are delivered to internal affiliates conducting research.

Application of Inclusion and Exclusion Criteria

The data query by the study site was performed using inclusion criteria (age, TBSA, and dates for study window) and one exclusion criteria (death/transfer within 72 hours of admission). This query created the subject list for the research.

Electronic Data Abstraction

For the subjects meeting inclusion and exclusion criteria, the study site also obtained the vast majority of data electronically. This electronic data query minimized the amount of time the principal investigator accessed the electronic health record. This meets the HIPAA minimum necessary standard under the rules and regulations at the study site. Additionally, this electronic data query addresses the potential pitfalls of retrospective chart review through bias. Electronic data query eliminates abstractor

conscious or subconscious bias as well as interpretation of the chat entries. Information obtained from the electronic data query included demographics, injury data, outcomes, glucose measurements, insulin dosing, and insulin infusion multipliers. Table 3.6 presents all data points gathered via electronic data abstraction.

Table 3.6

Variables Electronically Queried

Variable Category	Variable Collected
Demographics	Age (years) Gender (0- male, 1 - female, 2 - other) BMI (kg/m2) Weight (kg)
Severity of Injury	TBSA Type of burn (1- thermal; 2- chemical; 3- electrical) Inhalation injury (0- no, 1 - yes) Revised Baux Score
Mortality Risk	In-hospital Death (0 - no, 1 - yes) Discharge disposition (0 - home, 1 - nursing facility, 2 - rehab facility, 3 - hospice, 4 - other) Hospital LOS (days)
Glycemic Control	All BG values for the entire 14-day study period
Insulin Infusion Mathematical Multiplier	All insulin infusion MM for the entire 14-day study period
Insulin Dosing	All insulin doses for the entire 14-day study period

Note. BMI = body mass index; TBSA = total body surface area; LOS = length of stay; BG = blood glucose; MM = mathematical multiplier

The Master List

The query produced an Excel spreadsheet with the subjects and query data and was renamed "Master List TWU IRB#" by the principal investigator.

This query file was transmitted to the principal investigator and saved in a secure file location. This file with PHI was referred to as the Master List. This Master List was the only file with protected health information and was secured according to approved procedures. From the Master List, the following procedures were performed to create the Data Collection Tool. The Data Collection Tool was an Excel file that contains only de-identified data for the study analysis and was stored on a personal, password-protected device.

Assigning Study ID

The first three columns on the Master List have protected health information and include the subject medical record number, encounter number, and admission date. On the Master List, the principal investigator added a column after the third column called "Study ID," and subjects were numbered 1–#n in order of sequence.

The Data Collection Tool

Once the Study ID was assigned, the de-identified queried chart data was transferred to an Excel file named "Data Collection Tool TWU IRB #." This file was referred to as the Data Collection Tool. The Data Collection Tool was set up in the same format as the query results to ensure all information was transmitted in the appropriate sequence. Beginning with the Study ID column, the data was transferred in a simple copy and paste maneuver. The first three columns of the Master List containing protected health information were included in the transfer. The principal investigator then verified that all data was organized in proper columns and rows before proceeding.

Manual Data Abstraction

After all electronic data queries were completed and transmitted to the Data Collection Tool de-identified, the remaining data were manually abstracted. The Data Collection Tool already had Study ID numbers as well as all electronically abstracted data. One exclusion criterion was ascertained at the time of manual data abstraction, the diagnosis of diabetic ketoacidosis. At the time of manual data abstraction, this remaining exclusion criterion was applied. However, none of the subjects was identified to have a diagnosis of DKA.

Table 3.7

Variables Manually Abstracted on the Data Collection Tool

Variable Category	Variable Collected
Diabetes	Does the patient have diabetes? (0 - no, never diagnosed; 1 - diagnosed with injury based on HbA1c; 2 - takes oral antidiabetics at home; 3 - takes insulin injection at home; 4 - uses insulin pump at home) HbA1c (%) first measured since the injury
Infections	Infection with positive cultures during the 14-day study window? (0 - no, 1 - yes) Days from Injury to Infection

Note. HbA1c = hemoglobin A1c.

Next, manually abstracted data were entered into the Data Collection Tool according to the unique Study ID number. Any remaining data not collected from the study site query were gathered manually from the electronic health record by the principal investigator and entered directly into the de-identified Data Collection Tool. This manual data collection included the hemoglobin A1c value, the

administration of dextrose for the treatment of hypoglycemia, the presence of continuous feeding, and data about the presence or absence of culture-positive infection. Table 3.7 presents the information gathered via manual data abstraction. No names, dates, or other identifiers were collected on the data collection spreadsheet.

The principal investigator needed to notate access to the subject's electronic health record that was granted for research purposes. Inside the electronic health record, an option exists to click and assign a relationship. When an electronic health record was accessed for research data collection, a relationship was assigned to the principal investigator inside the electronic health record as "research." This signals why the principal investigator accessed the patient's electronic health record.

Pre-Analysis Data Screening

Pre-analysis data screening was performed to address any data quality issues before performing the statistical tests, which assured the researcher that valid conclusions could be elicited from the data (Mertler & Reinhart, 2017). Preliminary data analysis began with the proportions of all categorical variables. To start, the researcher ran a frequency analysis of all categorical variables to determine if there was an equal number of subjects in each group. Gender was anticipated to be unequal as the vast majority of adult burn patients are male, and this proved correct. Next, each continuous variable was checked for missing data, outliers, and normality (Mertler & Reinhart, 2017). A single outlier can significantly influence the results of a statistical test, even making results

significant when they would not be otherwise. Outliers can easily be identified using a box-plot graphical method. A box plot highlights cases with values greater than 1.5 box lengths outside the box (Mertler & Reinhart, 2017). Once an outlier was identified, the first action was to examine if the outlier resulted from an error.

Normality, linearity, and homoscedasticity are critical assumptions for multivariate statistical testing (Mertler & Reinhart, 2017). Violating normality and performing statistical analysis results in bias in the results. A more robust statistical analysis is achieved with normally distributed data. However, Spearman's correlation was preferred over Pearson's correlation in this study because it remains applicable when the data are not normally distributed (Field, 2005).

Treatment of the Data

Categorical variables are displayed as absolute and relative frequencies. Normally distributed continuous variables are reported with mean and standard deviations. Continuous variables that are not normally distributed are reported with a median and quartiles. Differences in proportions were compared using chi-square or Fisher exact tests. Welch's t-test was chosen to compare the mean of groups where equal variances could not be assumed. Spearman's rho was chosen for correlation analysis because data for one or more variables are expressed in ranks or categories. Spearman's correlation is applicable when the data are not normally distributed (Field, 2005). The Benjamini-Hochberg procedure was utilized to decrease the false positive rate or type I error when performing the correlation analysis. The Benjamini-Hochberg procedure is

often preferred over a Bonferroni correction as Bonferroni tends to be overly conservative, increasing the risk of Type-II error (Thissen et al., 2002).

Logistic regression analysis was performed when assessing dichotomous DVs, and linear regression was performed when assessing continuous DVs. The Wald statistic was used to determine significance for logistic regression and had an associated p-value. The researcher anticipated the revised Baux score (RBS) to have significant multicollinearity and a close association with the DVs, as the literature supports. Because of this influence on outcomes, a stepwise approach was used for regression analysis.

A 95% confidence interval was used when reporting odds ratios. Statistical significance was reported at a P-value of 0.05 or less. IBM SPSS Statistics for Windows, Version 25.0 (SPSS Corp, Armonk, NY) was used for most analyses. Additionally, R studio (R Core Team, 2013) was used to compute ADRR and MAGE using the "iglu" package for interpreting data from continuous glucose monitors (Broll et al., 2021).

Research Question 1

What is the relationship between GC, IR, GV, mortality, and infection in critically ill, burn-injured patients?

The first research question in the study was examined with correlations using Spearman's rho. Correlation analysis measures a linear relationship between two or more variables (Mertler & Reinhart, 2017). Correlation does not describe or imply causation, only the presence of a relationship between the variables (Field, 2005). The degree to which this relationship exists is the correlation coefficient, a quantitative measure of

correlation. Statistical significance can be assessed with correlation coefficients to help determine which relationships are critical. Spearman's rho was chosen because data for one or more variables are expressed in ranks or categories. Spearman's correlation is also applicable when the data are not normally distributed (Field, 2005).

When arranging the categorical variables for the research, the researcher categorizes the data, so the most favorable outcome was the lowest number, and the least favorable outcome was the highest number. For example, mortality was created such that the number 0 represents survival, and the number 1 represents death. A lower length of stay was more favorable than a greater length of stay. Likewise, on discharge disposition, the most favorable outcome would be discharge home, followed by inpatient rehabilitation, then a nursing facility, then hospice care, then death. This was important when interpreting the positive or negative correlation between variables. A positive correlation indicates the variables move in the same direction; as one variable increases, so does the other. A negative correlation indicates the variables are related but moving in opposite directions; as one variable increases, the other variable decreases.

Research Question 2

Which variables (GC, IR, GV, or all three), controlling for severity of illness, are most predictive of mortality and infection in critically ill, burn-injured patients?

For the second research question, the researcher used a logistic regression model to assess the prediction capability of the IV on the DV. Regression is related to correlation in that the stronger the correlation between two variables, the higher degree of prediction is possible between the two variables. Where correlation only establishes a

relationship, regression takes the relationship a step farther and establishes the ability to predict one variable based on existing variables (Field, 2005). A significant correlation relationship may not translate into prediction when regression is performed. Logistic regression was used for research questions in which the DV was categorical (Polit & Beck, 2017). The regression equation was used to predict the probability that the subject falls into one of the DV categories (Mertler & Reinhart, 2017). If mortality was the DV, in this case, regression measures the probability that the individual lives or dies based on the predictor variables. Linear regression was used to assess the DVs that were continuous (hospital length of stay) or categorical (discharge disposition). A stepwise approach was utilized in much the same way as the logistic regression.

Logistic regression was also appropriate because the predictor or IVs do not have to meet any assumptions regarding the distribution of scores. Variables that are not normal, non-linear, or do not have equal variances can still be assessed using logistic regression. Also, predictor variables can be ordinal, nominal, or scale variables. For scale variables, if distribution tests for normalcy, linearity, and equal variance are performed and the conditions met, the analysis will be strengthened. The Wald statistic was used to determine significance for logistic regression and has an associated p. In this research, all of the predictor variables were scale variables; however, some of the DVs were ordinal hence the use of logistic regression.

Additionally, for logistic regression, it was essential to address the ratio of cases to predictor variables. If too few cases or too many predictor variables are being assessed, substantial standard errors may result. This may have been the case in the small

pilot study examining only 17 subjects but many variables. Collapsing or combining several of the IVs may help or increase the number of cases examined. The goodness of fit was also crucial for logistic regression. When analyzed, if any of the models have an expected frequency of less than one or if 20% of the variables have a frequency of less than 5, the analysis should be repeated after the researcher reconsiders the variables. Lastly, logistic regression is susceptible to bias from highly correlated variables.

Assessing for multicollinearity when using logistic regression is essential because if one variable can perfectly or strongly predict the outcome variable, it may cause confusion or overpower other important predictors. The estimate of one predictor variable's influence on the DV may be less precise if more than one predictor variables are highly correlated (Field, 2005). A high likelihood of multicollinearity can be assumed if the correlation coefficient is exceptionally high, as in greater than 0.8 in either direction (Field, 2005). Other measures of multicollinearity include the variance inflation factor or VIF and tolerance. Values of VIF greater than 10 indicate significant multicollinearity. Tolerance is a measure of multicollinearity among IV specifically. Tolerance is reported with regression, and values of 0.1 or lower represent significant multicollinearity (Mertler & Reinhart, 2017). On the regression coefficients output, if any of the variables have a calculated tolerance of equal to or less than 0.1, multicollinearity is a problem. Typically, the offending variable can be eliminated when this is the case because another variable is already measuring much the same thing.

Each IV (GC, IR, GV, or all three) was examined in a separate logistic regression model controlling for Baux score as an indicator of the severity of illness. The

researcher used stepwise regression to control for the Baux Score by entering it first and then each of the predictor variables individually into the model for analysis. This was done for each DV (mortality and infection) and then, again, separated infection into the subcomponents of blood, respiratory, urinary tract, and wound. Other outcomes variables were also assessed using linear regression, including hospital length of stay and discharge disposition.

CHAPTER IV

ACHIEVING GLUCOSE CONTROL WITHIN THE TARGET RANGE IS PARAMOUNT TO GLYCEMIC VARIABILITY OR INSULIN RESISTANCE IN BURN-INJURED ADULTS

A paper submitted for publication in

Burns

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ABSTRACT

PROBLEM Severe burn injury results in critical illness accompanied by hypermetabolism and hyperglycemia. Most burn centers balance glycemic control while attempting to avoid adverse hypoglycemic events. The lack of studies explicitly examining the nuances of glycemic control in burns remains a problem. **PURPOSE** The purpose of this study was to investigate the relationship between glucose control, insulin resistance, glycemic variability, and outcomes in patients with burn injury. Specifically, the researcher examined the ability of glucose control (GC), glycemic variability (GV), and insulin resistance (IR) to predict mortality, infectious complications, length of stay, and discharge disposition. **METHODS** A retrospective review of medical records at a verified burn center aimed to assess the correlation of GC, IR, and GV with outcomes in a population of critically ill adults with greater than 20% TBSA burns over the last five years. **RESULTS** Using a stepwise approach to control for Baux score, the mean (p =

0.025), minimum ($p = 0.004$), maximum ($p = 0.028$), morning ($p = 0.010$), and delta ($p = 0.012$) of glucose levels were significant predictors of mortality. The morning glucose ($p = 0.043$) and percentage of time within the glucose target range ($p = 0.017$) were predictive of discharge disposition. The maximum ($p < 0.001$), minimum ($p < 0.001$), and delta ($p < 0.001$) of glucose values, as well as the total number of insulin doses ($p = 0.017$), were predictive of length of stay. **CONCLUSIONS** Measures of GC can predict death, length of stay, and discharge disposition. GV and IR were less important in predicting outcomes than GC alone. Patients with diabetes have marked difficulty in achieving GC, and these patients have the most apparent challenges with GV and IR.

KEYWORDS: burns, glycemic variability, insulin resistance, glucose control, hyperglycemia

INTRODUCTION

Hyperglycemia has been associated with complications and worsening outcomes in multiple patient populations, including trauma and burn-injured patients [1]. In patients with severe burn injuries, hyperglycemia has been studied as a predictor of infection as far back as 1978 [2]. Patients with burn injury have a heightened susceptibility to infection due to skin loss, an essential barrier against invasion, and other factors. About 4,500 people die from their burn injury annually; however, up to 10,000 die from an infection related to burn injury [3]. Early recognition and aggressive treatment of infections is an essential skill for burn providers.

Hyperglycemia

Hyperglycemia is common in critical illness [4]. It can be used as a marker of severity of illness and a predictor of hospitalized patients' outcomes [5]. Hyperglycemia has been associated with complications and worsening outcomes in multiple patient populations, including trauma and burn-injured patients [1]. The natural response to trauma causes sympathoadrenal stimulation triggering catecholamines and glucocorticoid release resulting in hyperglycemia, among other symptoms [6]. Some studies suggest hyperglycemia causes endothelial dysfunction, promoting an inflammatory response, platelet degranulation, and coagulopathy, all contributing to organ hypoperfusion [7].

Insulin Resistance

Insulin resistance (IR) is impaired insulin sensitivity when the body does not respond to insulin normally and is a well-known phenomenon after trauma and burn injury [8]. Individuals with IR have a tolerance to insulin, making it less effective.

Hypermetabolism with hyperglycemia and hyperinsulinemia are all attributes of IR in burn-injured patients [7]. IR has been independently associated with mortality in critical care patients even when BG (BG) is overall well-controlled [5]. The origins of IR in burn-injured patients are two-fold; increased hepatic glucose output and limited ability to stimulate glucose disposal into skeletal muscle [9].

Measures of IR used in the literature include median insulin dose and insulin infusion mathematical multiplier (MM). The MM method for an insulin infusion was first introduced by White et al. in 1982 when assessing dosing calculations for patients with insulin infusion catheters [10]. When regression was performed, the scientists identified the intercept at 60 and a slope of 0.02, thus the dawn of the MM equation for insulin infusion in critical care: [(BG – 60) * 0.02] = insulin infusion rate in units per hour. The MM is currently used by many institutions and some computer decision support software algorithms. Adjustments of the MM can be made with rising or falling glucose levels further to adapt the infusion rate to the individual patient response. The MM has since been validated for use in a hospital setting to adapt insulin infusion titration to patient response [11].

Not all institutions utilize a MM method when titrating insulin infusion for glycemic control, however. Some use computerized decision support programs with proprietary algorithms, and others still use traditional manual titration protocols. The best method for adjusting insulin infusions in critical care or the burn population has not yet been established.

Glycemic Variability

There remains significant variability in insulin dosing for individual patients and patient populations [4]. Even when patients achieve glycemic control within targeted parameters, the mortality rate may still suffer from increased variability [4]. Some research points towards decreasing variability in glycemic control as the source of improved outcomes rather than the avoidance of hyperglycemia alone [4, 5].

Glycemic variability (GV) has been measured in several diverse ways in both inpatient and ambulatory care literature. The best measure of GV for the critical care setting is not established, and various researchers have used different analysis methods. Expressions of GV include glycemic lability index [12], mean amplitude of glycemic excursion (MAGE) [12, 13], the delta of BG measurements [14], a standard deviation of BG measurements [12, 15], percent excursion from target range [16], percent coefficient of variation [17], and average daily risk range (ADRR) [18]. Studies using these various measures of GV have seen an association of GV with increased mortality, infection, and adverse outcomes in both burn and non-burn populations. No study exists comparing all the various measures of GV to ascertain which is most accurate.

Literature Review

In 2001, Van den Berghe et al. published the result of a prospective RCT indicating a direct improvement in morbidity and mortality in surgical intensive care unit patients treated with intensive insulin therapy (IIT) [19]. The treatment group in this study used a target glucose range of 80–110 mg/dl. The control group was standard therapy for that institution using a 180–200 mg/dl BG target range. In addition to the

46% drop in mortality, the treatment improved bloodstream infections, renal failure, transfusion polyneuropathy, and decreased ventilator days and ICU days for the treatment group. However, later in 2009, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) investigators published their international, multicenter RCT indicating that IIT increased mortality among adults in ICUs owing to the dramatic increase in the incidence of hypoglycemia [20]. This study's much larger population included both medical and surgical ICUs. Similar results occurred with the VISEP trial, where the investigation had to be stopped due to the rate of hypoglycemia in the IIT group [21]. In addition, a prospective RCT compared intermediate glucose control to IIT in adult critical care patients across 21 locations. This study, GLUONTROL, was stopped prematurely due to disproportionally high rates of hypoglycemia and thus was underpowered to make an outcome determination [22].

In a consensus statement, the American Burn Association (ABA) identified one out of the six triggers concerning infection as hyperglycemia in the absence of preexisting diabetes [23]. This is further clarified to specify a BG of more than 200 mg/dl or IR exemplified by an insulin infusion greater than seven units per hour or an increase in insulin requirements greater than 25% in one day [23]. This criterion was specified for patients who do not have diabetes, so what criteria do patients with diabetes qualify? The supporting evidence for insulin infusion dose of 7 units per hour is explicitly lacking, granted IR is essential. A better measure of IR would consider changes over time or patient response to insulin dosing rather than an absolute number.

A significant portion of the literature regarding insulin control in patients with burns is over a decade old. Many of the existing burn studies were undersized, and few were prospective in design. As the topic of glucose management went out of vogue, many burn centers adopted a standard of care without a robust and evidence-based consensus on the particulars. Based on the literature review, areas in need of further study include determining the best method for assessing the impact of GV for burn centers and possibly all critical care populations. Burn care clinicians do not know definitively what glucose targets should be used to manage our complicated population best. Despite multiple calls for more prospective and randomized trials looking into details regarding glucose control (GC) for burn-injured patients since as early as 2008, no large-scale, multicenter studies have been undertaken.

Euglycemia is essential for all critically ill patients, especially those with burn injuries. The glucose curve is U-shaped — dangerous at both the upper end and lower end. A causal relationship between hyperglycemia and death cannot be made because of the myriad factors that impact burn patient mortality. However, hyperglycemia, IR, and GV may all be indicators of a physiologic derangement that increases a patient's risk of death.

PURPOSE

The purpose of this study was to investigate the relationship between glycemic variables, insulin dosing, and outcomes in a critically ill population of adults with burn injury. Specifically, the study examined the ability of GC, GV, and IR to predict clinical

outcomes (mortality, length of stay, and discharge disposition) and infectious complications.

Research Questions

This research sought to examine the following for adults with burn injuries:

1. What is the relationship between glucose control (GC), insulin resistance (IR), glycemic variability (GV), mortality, and infection in critically ill, burn-injured patients?

2. Which variables (GC, IR, GV, or all) are most predictive of mortality and infection in critically ill burn-injured patients?

METHODS

This study was a retrospective analysis of burn patient data from a large burn center in west Texas. A predictive, correlational design was used to examine relationships between the selected variables in this group of subjects with burn injury. This research was submitted to the institutional review board (IRB) of the educational institution of the investigators and the study site IRB. The study was approved as exempt.

Setting

This study took place at a Burn Center verified by the American Burn Association (ABA). The burn center is verified for both pediatric and adult burn care. The burn center is in a rural region of Texas with over a 300-mile radius transfer area.

A limiting factor of a retrospective study design is that management strategies and advances in science occur over time. It has been known for more than a decade that hyperglycemia left unchecked is harmful. This institution has had an insulin infusion

protocol for the treatment of severe hyperglycemia since 2005. Since 2007, there have been no changes to the protocol, only changes to nursing documentation in the electronic health record — the computer now performs the calculations for nursing staff to ease their workload. The burn center medical director and assistant medical director have remained the same throughout the study period and were the primary attendings managing burn-injured patients. They were board-certified surgical critical care intensivists who utilize evidence-based guidelines to standardize practice and reduce variability for most aspects of burn critical care.

Additionally, the inpatient Advanced Practice Registered Nurses worked consistently over the study period assisting in the day-to-day management of critically injured patients. This combination of evidence-based care and consistency in inpatient management over time may limit the known issue of historical change with retrospective research. Other threats to validity for this design include the single-group and single-center design, allowing for no comparison.

Glucose targets/goals vary by institution and provider based on clinical practice. However, for this study, hyperglycemia was defined as a random BG level above 180 mg/dl following the American Diabetes Association (ADA) guidelines, and severe hyperglycemia was defined as greater than 250 mg/dl [24]. The standardized glucose target for burn patients was a range of 140–180 mg/dl. The burn center utilizes a MM method for insulin infusion rate adjustments embedded into the electronic health record's clinical decision support tool.

All burn patients greater than 20% TBSA receive enteral nutrition support or supplementation beginning on the first hospital day. Parenteral nutrition was utilized only for patients who were unable to tolerate enteral nutrition support. Additionally, a registered dietitian follows their course throughout hospitalization for evidence-based nutrition support recommendations. The center also utilizes a continuous feeding approach for operations and procedures. Enteral nutrition was continued up until anesthesia or through the operation if feasible depending on patient circumstances.

Population and Sample

The study population was critically ill, burn-injured adults. Inclusion criteria included adults, ages 18 to 89 years admitted to the Burn Center of a Regional ABA Verified Burn Center with greater than or equal to 20% TBSA burn injury. Exclusion criteria were patients who transfer or die within 72 hours of the injury and those admitted with a diagnosis of diabetic ketoacidosis (DKA). A study period of 5 years from 2016 through the end of 2020 provided the necessary sample size after power analysis.

Data Collection Procedures

Data was collected using a retrospective, electronic medical record review approach. Much of the data was abstracted via an electronic data query. This minimizes the risk of transcription or coding error during data collection and complies with minimum necessary data exposure. The data query was performed using inclusion and exclusion criteria. After completion of the electronic query, the remaining data were manually abstracted. The researcher manually verified 10% of the charts to ensure the validity of the electronic data query.

Outcome Measures

The primary outcome measure for the study was mortality from any source during the initial hospitalization after burn injury. Other outcome measures include the length of stay, discharge disposition, and presence or absence of infection. Infection was further divided into a culture-positive infection from the blood, respiratory tract, urinary tract, or wounds during the first 14 days of hospitalization.

Predictor Variables

Because of the significant impact on safety, the hypoglycemia rate for level I (BG at 69 mg/dl or less) and level II (BG at 53 mg/dl or less) was included in the analysis. This was defined as the number of hypoglycemic measurements out of the total measurements taken. GC was measured as maximum BG, minimum BG, mean BG, and mean morning BG (defined as BG measurements between 0400 and 0800) and percent of glucose checks within the target range (140–180 mg/dl). IR was measured by the total insulin dosage for the 14 days study period, mean insulin dose per day, and 14-day MM delta. GV was measured in several methods, including standard deviation, variance, delta, percent coefficient of variation, ADRR, and MAGE, all described in the literature.

Statistical Analysis

Pre-analysis data screening was done to address any data quality issues before performing the statistical tests. Categorical variables are displayed as absolute and relative frequencies. Normally distributed continuous variables are reported with mean and standard deviations. Continuous variables that are not normally distributed are reported with a median and quartiles. Differences in proportions were compared using

chi-square or Fisher exact tests. Welch's t-test was chosen to compare the mean of groups where equal variances could not be assumed. Spearman's rho was selected for correlation analysis because data for one or more variables were expressed in ranks or categories. Spearman's correlation is applicable when the data is not normally distributed [25]. The Benjamini-Hochberg procedure was utilized to decrease the false positive rate or type I error when performing the correlation analysis. Benjamini-Hochberg procedure is often preferred over a Bonferroni correction as Bonferroni tends to be overly conservative, increasing the risk of Type-II error [26].

Logistic regression analysis was performed when assessing dichotomous DVs, and linear regression was used for continuous DVs. The Wald statistic was used to determine significance for logistic regression and has an associated P-value. As the literature supports, the researcher anticipated the revised Baux score (RBS) to have significant multicollinearity and a close association with the DVs. Because of this influence on outcomes, a stepwise approach was used for regression analysis.

A 95% confidence interval was used when reporting odds ratios. Statistical significance was reported at a P-value of 0.05 or less. IBM SPSS Statistics for Windows, Version 25.0 (SPSS Corp, Armonk, NY) was used for most analyses. Additionally, R studio was used to compute ADRR and MAGE using the "iglu" package for interpreting data from continuous glucose monitors [27, 28].

RESULTS

A total of 136 patients were analyzed for his study, with an overall mortality rate of 16.9%. Demographic data from the sample are presented in Table 4.1. As a group,

the mean age was 41.73, and the mean burn size was 36.2% TBSA. As expected with burn injury research, more males were included than females. After factoring in inhalation injury for the RBS calculation (positive in 43 cases, 32%), a mean RBS of 83.26 was shown in the sample. When survivors and nonsurvivors were compared, significant differences existed for the various severity measures of injuries like injury severity score (ISS), TBSA, and inhalation injury, as expected (see Table 4.2). The RBS, however, just missed statistical significance.

Table 4.1. Patient Demographics, n=136

Variable	Result
Age (years; *mean* ± *SD*)	41.73 ± 16.09
Gender	Male 116 (85.3%) Female 20 (14.7%)
BMI	29.38 ± 6.54
TBSA	36.16 ± 16.66
RBS	83.26 ± 25.47
ISS	19.45 ± 12.55
LOS	34.53 ± 26.02
Mortality	Dead 23 (16.9%) Alive 113 (83.1%)
Discharge location	
Home	30 (22.1%)
Home with services	16 (11.8%)
Inpatient rehabilitation	45 (33.1%)
Skilled Nursing	10 (7.4%)
Long Term Acute Care	8 (5.9%)
Hospice	4 (2.9%)
Death	23 (16.9%)

BMI = body mass index; TBSA = total body surface area; RBS = revised Baux score; ISS = injury severity score; LOS = length of stay

A total of 46,763 BG measurements, 31,723 insulin dosages, and 21,367 MMs were analyzed for this study. Mean glucose for the sample was 157.9 mg/dl, with mean

morning BG slightly lower at 151.8 mg/dl. The collaborative hypoglycemia rate was 0.77% (70 episodes total) for level I (BG < 70 mg/dl) and 0.21% (39 episodes) for level II (BG < 54 mg/dl). The overall percent of glucose measurements in the target range was 33.3, lower than expected.

Table 4.2. Comparison of Severity of Injury by Outcome using Chi-Square, n=136

	Lived	Died	P value
LOS	36.23 ± 26.12	26.17 ± 24.32	0.024*
Inhalation Injury	29 (25.7%)	14 (60.9%)	0.001*
TBSA	32.94 ± 13.08	51.97 ± 22.77	0.003*
ISS	17.19 ± 10.09	30.52 ± 17.15	0.006*
RBS	76.44 ± 20.74	116.75 ± 19.50	0.057

LOS = length of stay; TBSA = total body surface area; ISS = injury severity score; RBS = revised Baux score; * $p < 0.05$

Of the 136 patients, 15 had a history of diabetes mellitus (DM) on admission, with 11 utilizing an oral anti-diabetic regimen and 2 utilizing injection of insulins for treatment. Three patients had never been diagnosed with DM and were diagnosed based on A1C upon admission. These patients were started on a comprehensive diabetes treatment plan prior to discharge if they survived. A comparison was made of survivors versus nonsurvivors according to baseline characteristics. Most demographics showed no differences in the groups. However, a greater percentage of patients with DM died, this finding approached significance but just missed (see Table 4.3). Our sample's average hemoglobin A1c for the patients diagnosed with diabetes was 7.6 ± 1.76 as opposed to those without DM 5.4 ± 0.40, a significant difference ($p < 0.001$).

Table 4.3. Comparison of Demographic Factors by Outcome using Chi-Square, n=136

	Lived	Died	P value
Age (years; mean ± SD)	39.14 ± 14.97	54.44 ± 15.63	0.221
Male Female	94 (81%) 19 (95%)	22 (19%) 1 (5%)	0.124
BMI	29.39 ± 6.55	29.37 ± 6.64	0.492
Diabetic	12 (10%)	4 (25%)	0.080
HbA1c	5.60 ± 0.84	6.3 ± 1.70	0.118

BMI = body mass index; HbA1c = hemoglobin A1c

Because of the mortality differences in patients with DM, we compared the treatment parameters for patients with and without DM (see Table 4.4). A Welch's *t*-test was performed to compare the means of the patients with and without diabetes. Despite the same protocols and procedures, almost all GC, GV, and IR variables were worse for the patients with diabetes when compared to those without diabetes. The only areas that showed similar results were the percentage of BG measurements within the target range and the hypoglycemia rates. Overall, staff had a considerably more difficult time controlling patients' BG in those with DM. However, the percentage of measurements the BG was in the target range remained the same.

Table 4.4. Comparison of Glucose Control in Patients with DM and without DM using Welch's *t*-test, n=136

	Diabetes	No Diabetes	P-value
% Hypoglycemia Level I (<70 mg/dl)	1.76 ± 0.02	0.61 ± 0.01	0.063
% Hypoglycemia Level II (<54 mg/dl)	0.57 ± 0.01	0.14 ± 0.004	0.205
%BG In Target Range	32.46 ± 0.08	33.48 ± 0.11	0.648
BG Maximum	447.50 ± 72.31	361.02 ± 141.79	< 0.001**

BG Minimum	53.61 ± 25.48	64.82 ± 22.84	0.230
BG Mean	179.21 ± 26.96	154.24 ± 18.94	0.001*
BG Mean Morning	168.79 ± 28.12	148.83 ± 20.11	0.010*
BG Delta	393.89 ± 73.17	296.20 ± 153.54	< 0.001**
BG % COV	36.67 ± 0.05	29.78 ± 0.08	< 0.001**
BG SD	65.86 ± 15.68	46.63 ± 15.44	< 0.001**
ADRR	31.56 ± 10.69	14.43 ± 7.95	< 0.001**
MAGE	112.03 ± 31.02	75.63 ± 32.10	< 0.001**
14-Day Insulin total	2141.47 ± 1678.23	691.07 ± 1031.87	0.001*
Total # Insulin Doses	171.55 ± 94.66	76.48 ± 75.21	< 0.001**
14-Day Mean Insulin/Day	152.96 ± 119.87	49.36 ± 73.70	0.001*
14-Day Delta of MM	0.22 ± 0.14	0.18 ± 0.10	0.157

DM = Diabetes Mellitus; BG = blood glucose; % COV = percent coefficient of variation; SD = standard deviation; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion; MM = mathematical multiplier
* $p < 0.05$; ** $p < 0.001$

A comparison of infection and infection sources by mortality was also made. Infection during the hospitalization, especially infection in the first 14 days, was significantly associated with mortality (see Table 4.5). Specifically, a respiratory source of infection was associated with mortality over other culture sources.

Table 4.5. Comparison of Infection by Outcome using Chi-Square, n=136

	Lived	Died	P value
Infection during the hospitalization	70 (61.9%)	22 (95.7%)	0.002*
Infection in the first 14 days	59 (52.2%)	21 (91.3%)	0.001*
Positive culture, blood	14 (12.4%)	4 (17.4%)	0.519
Positive culture, respiratory	44 (38.9%)	18 (78.3%)	0.001*
Positive culture, urinary tract	7 (6.2%)	1 (4.3%)	0.732
Positive culture, wound	23 (20.4%)	3 (13.0%)	0.416

* $p < 0.05$

Correlation

Mortality was associated with the percent of BG in the target range, mean BG, mean morning BG, ADRR, the 14-day insulin total, and the mean insulin per day (Table 4.6). Discharge location was closely associated with almost every IV, excluding some of the measures of GV. Total LOS was closely related to measures of GC and IR but did not correlate with GV measures except BG delta. Infection during the hospitalization was associated with GC and IR measures. Specifically, infection in the first 14 days of hospitalization was associated with the percent of BG in the target range and IR measures. Most notably, culture-positive infection of the respiratory tract was linked to hypoglycemia, GC, IR, and one of the GV measures (BG delta). The many measures of GV did not contribute to much of the variance in the model overall. The researcher also examined correlation coefficients for possible multicollinearity. In the Spearman's rho correlation, none of the variables had a correlation coefficient greater than 0.8. The maximum correlation coefficient in the data set was 0.450, decreasing the threat of multicollinearity. Multicollinearity was evaluated more closely with the regression model using the calculated tolerance. Overall, many significant correlations were found and then included in the regression analysis.

Table 4.6. Spearman's rho Correlations Among Independent and Dependent Variables, n=136

Independent Variable	Dependent Variable	Correlation Coefficient	P-value	Benjamini-Hochberg Critical Value (i/m)/Q
% Hypoglycemia	Discharge Location	0.23	0.007	0.026*

Level I (<70 mg/dl)	Total LOS	0.297	0.000	0.003*
	Respiratory Culture +	0.175	0.042	0.112
% Hypoglycemia Level II (<54 mg/dl)	Discharge Location	0.249	0.003	0.014*
	Total LOS	0.358	0.000	0.000*
	Infection LOS	0.174	0.042	0.111
	Respiratory Culture +	0.25	0.003	0.014*
BG Maximum	Discharge Location	0.299	0.000	0.003*
	Total LOS	0.376	0.000	0.000*
	Infection LOS	0.174	0.043	0.110
	Respiratory Culture +	0.188	0.029	0.077
BG Minimum	Discharge Location	-0.276	0.001	0.006*
	Total LOS	-0.528	0.000	0.000*
	Infection LOS	-0.207	0.016	0.048*
	Infection 14 days	-0.172	0.045	0.114
	Respiratory Culture +	-0.258	0.002	0.011*
BG Mean	Death	0.29	0.001	0.004*
	Discharge Location	0.315	0.000	0.001*
BG Mean Morning	Death	0.313	0.000	0.002*
	Discharge Location	0.316	0.000	0.001*
% BG in Target Range	Death	0.289	0.001	0.004*
	Discharge Location	0.403	0.000	0.000*
	Total LOS	0.229	0.007	0.026*
	Infection LOS	0.228	0.008	0.025*
	Infection 14 days	0.266	0.002	0.008*
	Respiratory Culture +	0.273	0.001	0.006*
BG Delta	Discharge Location	0.322	0.000	0.001*
	Total LOS	0.45	0.000	0.000*
	Infection LOS	0.202	0.018	0.053*
	Infection 14 days	0.194	0.024	0.066
	Respiratory Culture +	0.228	0.007	0.025*
ADRR	Death	0.269	0.002	0.007*
	Discharge Location	0.386	0.000	0.000*
MAGE	Discharge Location	0.241	0.005	0.019*
14 Day Mean Insulin/Day	Death	0.205	0.016	0.048*
	Discharge Location	0.319	0.000	0.001*
	Total LOS	0.236	0.006	0.021*
	Infection LOS	0.215	0.012	0.037*
	Infection 14 days	0.229	0.007	0.026*
	Respiratory Culture +	0.277	0.001	0.006*
Total # Insulin Doses	Discharge Location	0.311	0.000	0.002*
	Total LOS	0.321	0.000	0.001*

	Infection LOS	0.228	0.008	0.025*
	Infection 14 days	0.257	0.003	0.011*
	Respiratory Culture +	0.3	0.000	0.003*
14 Day Delta of MM	Death	0.205	0.016	0.049*
	Discharge Location	0.319	0.000	0.001*
	Total LOS	0.236	0.006	0.022*
	Infection LOS	0.215	0.012	0.038*
	Infection 14 days	0.229	0.007	0.026*
	Wound Culture +	-0.294	0.008	0.026*

LOS= length of stay; BG = blood glucose; SD = standard deviation; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion
* significant after Benjamini-Hochberg procedure

Prediction of Outcomes

Almost every GC variable was predictive of mortality in the logistic regression models (see Table 4.7). For GV, only the delta of BG values had significance. None of the measures of IR showed any significant impact on mortality after controlling for the revised Baux score. Interestingly, though hypoglycemia was reported to increase mortality in many studies, the hypoglycemia rate did not show significance in any regression analyses for outcomes in this data set. A link has been suggested between hypoglycemia and GV, which proved true in our data with a significant correlation between every measure of GV and hypoglycemia in the sample. All significant prediction equations were verified with Hosmer and Lemeshow test to ascertain the goodness of fit and were non-significant, indicating a good fit.

Table 4.7. Logistic Regression of Predictors of Mortality after Controlling for Revised Baux Score, n=136

Variable	Odds Ratio	P value	95% Confidence Interval	
			Lower	Upper

BG Maximum	0.992	0.028*	0.985	0.999
BG Minimum	1.048	0.004*	1.015	1.082
BG Mean	1.053	0.025*	1.007	1.102
BG Mean Morning	1.052	0.010*	1.012	1.094
BG Delta	0.991	0.012*	0.985	0.998
ADRR	1.025	0.451	0.961	1.093
MAGE	1.000	0.998	0.976	1.024
14 Day Mean Insulin/Day	1.003	0.354	0.997	1.009
Total # Insulin Doses	0.996	0.265	0.989	1.003

BG = blood glucose; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion
* $p < 0.05$

When predicting LOS using a linear regression model, the glucose maximum and minimum in the first 14 days of hospitalization and the delta of BG showed the most significant impact (see Table 4.8). The total number of insulin doses, a measure of IR, also had a significant influence. For all significant relationships, the tolerance was assessed and found well above the acceptable standard (> 0.10), indicating it is unlikely multicollinearity influenced the findings.

Table 4.8. Linear Regression of Predictors of Length of Stay after Controlling for Revised Baux Score, n=136

Variable	Beta Coefficient	P value	95% Confidence Interval	
			Lower	Upper
BG Maximum	0.377	<0.001**	0.041	0.102
BG Minimum	-0.454	<0.001**	-0.678	-0.327
BG Mean	-0.140	0.120	-0.373	0.044
BG Mean Morning	-0.161	0.069	-0.386	0.014
% BG in Target Range	0.117	0.185	-13.855	71.135
BG Delta	0.427	<0.001**	0.047	0.103
ADRR	-0.153	0.112	-0.858	0.090
MAGE	-0.095	0.270	-0.201	0.057
14 Day Mean Insulin/Day	-0.004	0.963	-0.052	0.050
Total # Insulin Doses	0.226	0.012*	0.016	0.123

14 Day Delta of MM	0.057	0.614	-43.328	72.857

BG = blood glucose; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion; MM = mathematical multiplier
* $p < 0.05$; ** $p < 0.001$

Neither infection at any point in time during the hospitalization or infection in the first 14 days of hospitalization could be predicted by any of the variables for GC, IR, or GV. None of the regression models for predicting culture-positive blood infection or urinary tract infection were significant. After breaking down culture-positive infection in the first 14 days into subcategories of blood, respiratory, urine, and wound, the only regression analysis with any significance was from the wound (see Table 4.9). The minimum BG and 14-day change in the MM were significant predictors for wound infection. Even though culture-positive respiratory infection seemed to be most clinically significant, impacting mortality according to our sample, no prediction equations proved significant. Total insulin doses showed a trend in predicting culture-positive respiratory infection ($p = 0.052$, $CI = 1.000–1.009$).

In the sample, 80 patients had a culture-positive infection in the first 14 days of hospitalization, and 92 had an infection during hospitalization. This indicates that a culture-positive infection in the first two weeks seems to predict infection overall. The most frequent date of culture-positive infection was hospital Day 9 for blood, 2 for respiratory, 4 for urinary tract, and 8 for the wound. Infection from a respiratory source was far more common than any other source ($n = 62$, 46%), with wounds being the second most common ($n = 25$, 18%). It is important to note that when performing bronchoscopy to diagnose inhalation injury in the first 24 hours, cultures were routinely

taken, and treatment initiated if they were positive for any microbial growth other than normal respiratory flora. This could explain the discrepancy in the date of onset for culture-positive respiratory infection.

Table 4.9. Logistic Regression of Predictors of Culture Positive Wound Infection after Controlling for Revised Baux Score, n=136

Variable	Odds Ratio	P value	95% Confidence Interval	
			Lower	Upper
BG Maximum	1.000	0.897	0.996	1.003
BG Minimum	0.978	0.043*	0.957	0.999
BG Mean	0.986	0.210	0.963	1.008
BG Mean Morning	0.981	0.088	0.959	1.003
% BG in Target Range	1.704	0.804	0.025	114.060
BG Delta	1.000	0.846	0.997	1.003
ADRR	0.982	0.470	0.933	1.032
MAGE	0.990	0.207	0.974	1.006
14 Day Mean Insulin/Day	0.996	0.229	0.990	1.003
Total # Insulin Doses	0.998	0.537	0.993	1.004
14 Day Delta of MM	0.000	0.036*	0.000	0.590

BG = blood glucose; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion; MM = mathematical multiplier
* $p < 0.05$

Significant predictors of discharge disposition were found in mean morning BG and in the percent of BG measurements in the target range (see Table 4.10). The most common discharge location was inpatient rehabilitation (n = 45, 33%) followed by home (n = 30, 22%), then home with home care services (n = 16, 12%).

Table 4.10. Linear Regression of Predictors of Discharge Disposition after Controlling for Revised Baux Score, n=136

Variable	Beta Coefficient	P value	95% Confidence Interval	
			Lower	Upper

BG Maximum	0.018	0.780	-0.002	0.002
BG Minimum	0.055	0.401	-0.006	0.016
BG Mean	0.115	0.084	-0.001	0.023
BG Mean Morning	0.132	0.043*	0.000	0.024
% BG in Target Range	0.155	0.017*	0.535	5.391
BG Delta	0.009	0.897	-0.002	0.002
ADRR	0.074	0.301	-0.013	0.042
MAGE	0.030	0.640	-00.006	0.009
14 Day Mean Insulin/Day	0.099	0.132	-0.001	0.005
Total # Insulin Doses	0.020	0.765	-0.003	0.004
14 Day Delta of MM	0.147	0.099	-0.503	5.748

BG = blood glucose; ADRR = average daily risk range; MAGE = mean amplitude of glycemic excursion; MM = mathematical multiplier
* $p < 0.05$

All patients received enteral nutrition support per burn center standards of practice, with most reaching goals within 72 hours of admission. In the study group, 74 (54%) were on an insulin infusion at some time in the first 14 days of admission. Patients who were only on intermittent insulin injections were not included in the analysis of the MM. The average day of initiation for the insulin infusion was 5.7 (*range* = 1–13), with the most common being day 4. The presence of insulin infusion was more common in patients that died (74%) versus those that survived (50%), which was significant (p = 0.039). The highest delta of BG occurs on hospital day 8 for the sample. The highest insulin infusion multipliers occurred on Days 7 through 12. Similarly, insulin dosing rises steadily until day nine then remains elevated throughout at least the first 14 days. The timing of operations in relation to BG values was not included in the analysis but may have proven beneficial considering cessation of nutrition prior to procedures may have played a role in GC.

DISCUSSION

This study shows that GC impacts mortality and other outcome measures, more so than IR or GV. The diagnosis of diabetes did impact the survival and discharge disposition of patients in an otherwise well-matched sample. This mortality impact was in opposition to previous research [17]. Diabetes did not, however, show significant correlations with any of the other outcomes or measures of severity of the injury. After comparing the patients with diabetes and those without, it became clear that despite similar percentages of BG measurements inside the target range, patients with DM had significant difficulties with BG control. The diabetes group had higher mean BG and mean morning BG as one would expect. The substantial worsening in GV and IR showed in the diabetes group was notable. Several other authors have shown that increasing GV and worsening IR even in the face of adequate GC contributes to mortality [5, 14, 16, 18, 29, 30]. The findings from our study demonstrate that effect in this group of DM patients. The mortality impact may also be influenced by end-organ changes associated with DM.

Measures of overall GC were most closely associated with outcomes in this study, including mean BG, mean morning BG, maximum BG, minimum BG, and percent BG measurements inside the target range. This was consistent with literature across critical care supporting blood GC within various target ranges, improves survival [19, 20, 24, 31]. The overall percentage of the BG measurements inside the target range was 33.3% in this sample, a number that would be considered “high variability” by other research standards [16]. Other research reports indicate a 50% mean of BG measurement inside

the target range in their samples. To see differences in GV or IR, it is possible that one must achieve GC first. Centers who achieve target glucose a greater percentage of the time may see differences in the nuances of GV or IR measures in their outcomes hidden in this sample. Additionally, the timing of GC was not accounted for in the study but is essential in burns considering the mortality benefit when control is achieved earlier in the hospitalization [31].

This study showed that GV measures correlate with infection. However, when analyzed using logistic regression, GV could not be used to predict infection. Previous research examined daily fluctuations in relation to the timing of sepsis and found that GV was a more meaningful indicator than glucose measurements or insulin dosing [14]. The study reported here did not delve into daily measurements but rather total GV over the first 14 days of hospitalization. It is possible that daily fluctuations would still have proven significant. Consistent with Pisarchik's work, the delta of the BG showed the strongest correlation with infection for our sample [14].

Research has shown that GV, measured by the percent of BG measurements outside the target range, is associated with higher mortality [16]. This would be the inverse of the current study variable of percent BG measurements inside the target range, essentially measuring the frequency of achieving the target range. Pidcoke et al. utilized a glucose target of 80–110 mg/dl [16]. Group comparisons were made based on low variability or achieving glucose target more significant than 50% of the measurements and high variability where patients were inside the glucose target less than 50% of the measurements. Chi-square comparisons were made, and significant differences in

mortality were found among their groups. The current research supported a correlation between the percent of measurements inside the target range and mortality. Still, that relationship did not prove significant when assessing prediction using regression and controlling for revised Baux score. A critical difference in the two studies is the glucose target range with much tighter control in the Pidcoke et al. study [16]. The overall hypoglycemia rate is not reported by Pidcoke et al. but may have played a role, as they stated in their report.

One other positive aspect of the delta of BG levels for assessing GV is that it can be ascertained in real-time during hospitalization. Standard deviation and other measures are completed post hoc. One of the primary goals of burn nursing is to identify any threats to life and intervene rapidly. An electronic health record could easily accommodate a simple warning system if a change in BG for any given 24 hours is greater than a chosen threshold. A more in-depth look at daily fluctuations specifically targeted to identify sepsis is warranted. The researcher suggests prospective studies should be used to evaluate this potential advancement in early warning systems. Alternatively, early recognition of GV could also result in treatment algorithms to augment existing GC strategies. Continuous nutrition support with as few interruptions as possible may limit the risk of GV from dramatic changes in nutrient delivery. Rather than the traditional method of ceasing all enteral nutrition at midnight before all operations, it has been shown safe in some cases to continue tube feeding right up until or sometimes throughout the operation. This decision must be made in collaboration with

the anesthesia team. Medications to decrease glucose absorption may also prove beneficial to reduce the effects of GV from enteral glucose loading.

Ali et al. correctly identified that GV correlated with hypoglycemia in their extensive data set [12]. After recognizing hypoglycemia, treatment typically revolves around the rapid administration of glucose, often resulting in rebound hyperglycemia. GV has been independently associated with sepsis, as has hypoglycemia. The two variables may be congruent symptoms of the same problem.

Another interesting finding in this study was the minimal impact of hypoglycemia on outcomes measures. No relationship was found between hypoglycemia and death in our sample. Hypoglycemia did correlate with infection, specifically infection with a respiratory source and hospital length of stay. This center uses moderate glycemic control parameters and, as such, has a very low hypoglycemia rate (0.87% were less than 70 mg/dl; 0.26% were less than 54 mg/dl; calculated with the total number of readings as the denominator). Bearing in mind the most significant downside to tight glycemic control is hypoglycemia, this centers combination of moderate GC and a low hypoglycemia rate may prevent any mortality effect from surfacing.

Among the measures of IR, the mean insulin per day and the total number of doses administered per day correlated with outcomes the most. For patients specifically on an insulin infusion, the delta of the MM correlated with outcomes as well. This study was not designed to assess daily changes in insulin dosing to identify sepsis in real-time. Consistent with the ABA sepsis criteria, increasing insulin dosing or very high insulin infusion rates may signal infection [23]. One group determined that a rise in insulin

dosing occurred 48 hours before clinical signs of sepsis [30]. This increase happened before any vital sign changes. The premise of early recognition of IR stems from the now-standard management of the hyperglycemic patient. Though differences exist between institutions in the minutia of managing hyperglycemia, most centers have protocols to treat hyperglycemia aggressively with intermittent insulin or continuous insulin infusion. As hyperglycemia worsens, insulin treatment rises in response. A patient's hyperglycemic response may be blunted when aggressive treatment is underway. Recognizing the rapid escalation of insulin dosing may be a better measure of sepsis than hyperglycemia alone. Some studies suggest IR is associated with mortality even when BG is controlled within the target range [5]. Enough data exists to warrant a prospective design to tease out dosing changes that signal increasing IR, which may be an important prognostic indicator. Considering the advancements in closed-loop insulin infusion systems, algorithms could be put in place to identify incremental dosing changes signaling worsening IR. This may also prove to be an essential part of early warning systems in the future.

Infection, as expected, was significantly associated with mortality. For burn patients that survive resuscitation, infection is the number one cause of death [32]. It then follows that early recognition and prediction of sepsis is a crucial priority for burn care providers. The investigator anticipates that using technology to aid in predicting and early identification of sepsis will be a significant focus for health innovation in the coming years. Ideally, we can use the information already stored in the electronic health record to form algorithms for this early warning system. It is difficult to compare

outcomes from other studies considering the standards of care in centers across the nation differ. A recent literature review by this author (pending publication) found that almost no consistency exists in target glucose rates, measures of hypoglycemia, how researchers measure GV, and how, if at all, researchers assess IR across burn centers.

Strengths and Limitations

We recognize limitations to this study that merit discussion. The single-center design may limit the applicability of the findings. Correlation cannot identify causation, especially in a retrospective analysis, so these findings should be hypothesis-generating. Though the standard of care for the burn center is to provide continuous enteral nutrition support, there are times when enteral nutrition may be stopped for operations, procedures, or intolerance. This analysis did not include the timing of enteral nutrition cessation in relation to any BG measurements. Additionally, a broad definition of culture-positive infection was utilized, and the analysis did not account for device days. Lastly, it is essential to note that the last year assessed in this study window was amidst the global pandemic when stressors and workload on nursing staff were overwhelming.

Strengths include a large number of glucose measurements, insulin dosages, and MMs included in the analysis. The statistical methodology of using a stepwise approach to control for the revised Baux score was a strength to identify the variables' influence above and beyond what the severity of injury dictates. Anemia can impact glucose readings on point-of-care glucose monitoring devices; the burn center utilizes restrictive transfusion practices consistent with evidence-based practice. To ameliorate the impact

of anemia, the burn center uses a four-channel bedside glucose monitor utilizing whole blood samples, which is more accurate in the face of low hemoglobin.

CONCLUSION

This study concludes that achieving GC within the target range is paramount to other nuances of GC. Patients with diabetes are significantly more difficult for the burn team to manage. After GC is achieved, additional nuances of GV or IR may prove to be essential additions to a GC strategy for burn critical care. Prospective studies remain an unfulfilled need for definitive determination of best practices. Technological advances directed towards the early identification of sepsis by tracking various GC parameters warrant investigation immediately, especially using data already existing in the electronic health record.

Considering the specialized care necessary for managing critically ill, burn-injured patients, the lack of consistency in this crucial area is startling. To achieve the goal of developing technology solutions to address these challenges of GC, early identification of mortality risk, and early recognition of sepsis, homogeneity in treatment algorithms will be fundamental. Calls for prospective studies in burns to identify best practices remain unfulfilled two decades after the GC discussion began following the groundbreaking work from Leuven [19].

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CHAPTER V

IMPLICATIONS, RECOMMENDATIONS, AND CONCLUSIONS

Burn care is an important specialty area in critical care nursing. GC is essential for all critical care areas, perhaps even more so for burns considering their heightened risk of infection. A comprehensive literature review was performed by the researcher, where several gaps in the literature were discovered. The researcher ascertained that glycemic control is comprised of many factors that play a role, not just the glucose target. Future research endeavors should be focused on optimizing glycemic control, using clinical decision support mechanisms to track GC parameters, identifying the best measure of GV, and investigating novel strategies to augment GC. Monitoring and benchmarking hypoglycemia and correcting inaccurate point-of-care glucometer results are important evidence-based practice initiatives that burn teams should endeavor to implement forthwith.

The purpose of this study was to investigate the relationship between glycemic variables, insulin dosing, and outcomes in a critically ill population of adults with burn injury. Specifically, the researcher examined the ability of GC, GV, and IR to predict clinical outcomes (mortality, length of stay, and discharge disposition) and infectious complications. This was the first study of its kind to compare the prediction capabilities and the effects of all three of these variables at once. Findings from this study may be used to identify relationships that are important to managing the burn-injured patient. The

results may help clinicians narrow down the best method to track performance and guide critical care decisions regarding all aspects of GC. In addition, results can be used to identify or mitigate the stress response causing hyperglycemia, create better treatment strategies for IR to prevent complications, and optimize burn management to aid the patient in restoring balance using holistic nursing care. Most importantly, this research should be hypothesis-generating for future prospective studies to identify best practices and potentially implement decision support using existing technology or other methods to identify mortality risk and complications early.

The NSM proved to be a good fit for this research centering on the imbalance of GC. The NSM focuses on the stressor, reaction, and intervention processes that pair well with burn injury, glucose dysregulation, and treatment using insulin, other medications, and nursing interventions. Nursing interventions targeted towards the restoration of euglycemia were the primary intervention under investigation.

The research methodology resulted in a large, well-matched group of burn-injured patients where survivors and nonsurvivors had similar demographics. Prior work informed the research to develop a data collection tool and statistical analysis plan that effectively answered the research questions. The electronic data query created by the researcher resulted in a robust data set for analysis quickly.

Research Question 1

What is the relationship between GC (GC), IR (IR), GV (GV), mortality, and infection in critically ill, burn-injured patients?

Several vital relationships were identified with the correlation analysis of the large data set. GC did correlate significantly with mortality. Discharge location correlated significantly with almost every IV, excluding some of the measures of GV. Total length of stay correlated with measures of GC and IR but did not correlate with GV measures except BG delta. Infection during the hospitalization was associated with GC and IR measures. Most notably, culture-positive infection of the respiratory tract was linked to hypoglycemia, GC, IR, and one of the GV measures (BG delta). A link has been suggested between hypoglycemia and GV, and that proved true in the data with a significant correlation between every measure of GV and hypoglycemia in the sample. Overall, many significant correlations were found and then included in the regression analysis.

One unexpected finding was the relationship between a diagnosis of diabetes and mortality. Despite the same protocols and procedures, the patients with diabetes showed worse GC, more GV, and increased IR when compared to those without diabetes. The only area that showed similar results was the percentage of BG measurements within the target range. Though the burn center has a minimal hypoglycemia rate, the patients with diabetes had substantially more episodes of hypoglycemia. Overall, staff had a substantially more difficult time controlling patients' BG in those with DM.

Research Question 2

Which variables (GC, IR, GV, or all) are most predictive of mortality and infection in critically ill burn-injured patients?

In the logistic regression models, almost every GC variable was predictive of mortality. For GV, only the delta of BG values had significance. None of the measures of IR showed any significant impact on mortality after controlling for the revised Baux score. Interestingly, though hypoglycemia is reported to increase mortality in many studies, the hypoglycemia rate did not show significance in any regression analyses for outcomes in this data set.

When predicting LOS, the researcher found the glucose maximum and minimum in the first 14 days of hospitalization, and the delta of BG showed the most significant impact. The total number of insulin doses, a measure of IR, also significantly influenced LOS. Neither infection at any point in time during the hospitalization nor infection in the first 14 days of hospitalization could be predicted by any of the variables for GC, IR, or GV. Significant predictors of discharge disposition were found in mean morning BG and in the percent of BG measurements in the target range.

Conclusions

This study showed that GC impacts mortality and other outcomes measures, more so than the sample's IR or GV. The diagnosis of diabetes may have influenced mortaltiy but just missed statistical significance. Diabetes did not, however, show significant correlations with any of the other outcomes or measures of severity of the injury. After comparing the patients with diabetes and those without, it is clear that despite similar

percentages of BG measurements inside the target range, patients with DM had significant difficulties with BG control with considerable worsening of GV and IR. The mortality impact may also be influenced by end-organ changes associated with DM.

Measures of overall GC were most closely associated with outcomes in this study. This is consistent with critical care literature supporting that blood GC within various target ranges improves survival. The findings indicated the overall poor achievement of target glucose. Centers that achieve target glucose a greater percentage of the time may see differences in the nuances of GV or IR measures in their outcomes that are hidden in this sample.

Another interesting finding in this study was the minimal impact of hypoglycemia on outcomes measures. No relationship was found between hypoglycemia and death in our sample. Hypoglycemia correlated with infection, specifically infection with a respiratory source, and hospital length of stay. This center uses moderate glycemic control parameters and, as such, has a very low hypoglycemia rate (0.87% are less than 70 mg/dl; 0.26% are less than 54 mg/dl; calculated with the total number of readings as the denominator). Bearing in mind that the most significant downside to tight glycemic control is hypoglycemia, this center's combination of moderate GC and a low hypoglycemia rate may prevent any mortality effect from surfacing.

Among the measures of IR, the mean insulin per day and the total number of doses administered per day had a positive correlation with outcomes. For patients specifically on an insulin infusion, the delta of the MM positively correlated with outcomes as well. Enough data exists to warrant a prospective design to tease out dosing

changes that signal increasing IR, which may be an important prognostic indicator. Considering the advancements in closed-loop insulin infusion systems, algorithms could be put in place to identify incremental dosing changes signaling worsening IR.

Infection, as expected, was significantly associated with mortality. For burn patients that survive resuscitation, infection is the number one cause of death (Greenhaulgh, 2017). It then follows that early recognition and prediction of sepsis is a crucial priority for burn care providers. The investigator anticipates that using technology to aid in the prediction and early identification of sepsis will be a significant focus for health innovation in the coming years. For example, an electronic health record could easily accommodate a simple warning system if a change in BG for any given 24 hours is more than a chosen threshold. Ideally, the information already stored in the electronic health record can be used to form algorithms for this early warning system.

In conclusion, achieving GC within the target range is paramount to other nuances of GC. Patients with diabetes are significantly more difficult for the burn team to manage. After GC is achieved, other nuances of GV or IR may prove to be essential additions to a GC strategy for burn critical care. Prospective studies remain an unfulfilled need for definitive determination of best practices. Technological advances directed towards the early identification of sepsis by tracking various GC parameters warrant investigation immediately, especially using data already existing in the electronic health record.

Considering the specialized care necessary for managing critically ill, burn-injured patients, the lack of consistency in this crucial area is startling. In order to

achieve the goal of developing technology solutions to address these challenges of GC, early identification of mortality risk, early recognition of sepsis, and homogeneity in treatment algorithms will be fundamental. Calls for prospective studies in burns to identify best practices remain unfulfilled two decades after the GC discussion began following the groundbreaking work from Leuven (Van den Berghue et al., 2001).

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APPENDIX A

IRB APPROVAL - TWU

Texas Woman's University
Institutional Review Board (IRB)
irb@twu.edu
https://www.twu.edu/institutional-review-board-irb/

February 24, 2021

Jennifer Kesey
Nursing - Denton

Re: Exempt - IRB-FY2021-175 Examining the relationship and utility of insulin resistance and glycemic variability to predict mortality and infection in adults with burn injuries

Dear Jennifer Kesey,

The above referenced study has been reviewed by the TWU IRB - Denton operating under FWA00000178 and was determined to be exempt on February 23, 2021.

Note that any modifications to this study must be submitted for IRB review prior to their implementation, including the submission of any agency approval letters, changes in research personnel, and any changes in study procedures or instruments. Additionally, the IRB must be notified immediately of any adverse events or unanticipated problems. All modification requests, incident reports, and requests to close the file must be submitted through Cayuse.

On April 1, 2022, this approval will expire and the study must be renewed or closed. A reminder will be sent 45 days prior to this date.

If you have any questions or need additional information, please contact the IRB analyst indicated on your application in Cayuse or refer to the IRB website at http://www.twu.edu/institutional-review-board-irb/.

Sincerely,

TWU IRB - Denton

Texas Woman's University
Institutional Review Board (IRB)
irb@twu.edu
https://www.twu.edu/institutional-review-board-irb/

April 1, 2021

Jennifer Kesey
Nursing - Denton

Re: Modification - IRB-FY2021-175 Examining the relationship and utility of insulin resistance and glycemic variability to predict mortality and infection in adults with burn injuries

Dear Jennifer Kesey,

The modifications listed below have have been reviewed and approved on March 31, 2021 by theTWU IRB - Denton.
Modifications:

This modification serves to reflect that the study went through a completely separate exempt review through the TTUHSC IRB in Lubbock, TX. The TWU IRB approval and documents have been included in the TTUHSC application for transparency. The TTUHSC IRB approval form has also been uploaded to Cayuse for mutual transparency.

If you have any questions or need additional information, please email your IRB analyst at irb@twu.edu or refer to the IRB website at http://www.twu.edu/institutional-review-board-irb/.

Sincerely,

TWU IRB - Denton

APPENDIX B

IRB APPROVAL – TTUHSC

TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER

INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS
FWA # 00006767 LUBBOCK IRB #00000096

EXEMPT FROM FORMAL IRB REVIEW

March 23, 2021

PRINCIPAL INVESTIGATOR: John Griswold, MD
STUDY: Examining the relationship and utility of insulin resistance and glycemic variability to predict mortality and infection in adults with burn injuries
IRB #: L21-095
SUBMISSION REFERENCE #: 085622
TYPE OF REVIEW: ADMINISTRATIVE
DATE CLASSIFIED AS EXEMPT: 03/23/2021
APPLICABLE FEDERAL REGULATION: 45 CFR 46.104(d)(4)(iii)

HIPAA WAIVER OF AUTHORIZATION APPROVED

STUDY SUMMARY: The purpose of this study is to investigate the relationship and ability of insulin resistance, glycemic variability, and glucose levels to predict injury severity and infections in adults with burn injuries.
Research Questions:
1. What is the relationship between insulin resistance, glycemic variability, mortality risk, and infection in critically ill, burn-injured patients?
2. Which variables (insulin resistance, glycemic variability, or both) are most predictive of mortality and infection in critically ill, burn-injured patients?
3. Which predictor variable (insulin resistance, glycemic variability, or both) is most sensitive in predicting mortality and/or infection in critically ill, burn-injured patients?
This study is a retrospective review of patients meeting protocol inclusion/exclusion criteria admitted to the burn center at University Medical Center between January 1, 2016 and December 31, 2020. Data from a maximum of 300 subjects may be collected. The study will examine the first 14 days of hospital admission for all included patients. No PHI will be collected on the data sheet but a master list linking medical record numbers and study id numbers will be used and later destroyed at the completion of the study.

REVIEWER COMMENTS: The PI has adequately addressed the stipulations; therefore, this project meets criteria for exemption from formal review by the IRB. Information required to make this determination has been provided by the investigator. All data are in existence at the time of this application for exemption. No identifying information will be recorded on the data sheet. A waiver of individual HIPAA authorization has been requested and found to be appropriate.

RECOMMENDATION: This project is acknowledged as meeting criteria for exemption from formal IRB review in accordance with 45 CFR 46.104(d)(4)(iii). The research may be initiated by the investigators listed on the IRB application.

This application was screened for exempt status according to TTUHSC policies and the provisions of applicable federal regulations. The study was found not to require formal IRB review because the research falls into one of the categories specifically designated as exempt per 45 CFR 46.104(d).

Do not use any subject names or identifiers when presenting or publishing the study results.

There is no expiration date for studies which have been classified as Exempt from formal IRB review.

Study Personnel Currently Approved to Conduct the Research: Jennifer Elizabeth Kesey, MSN

University Medical Center of Lubbock: If this research is to be conducted at University Medical Center (Lubbock) or involves UMC services/resources and/or medical records, the PI will need to contact Ann Purdom, UMC Director of Clinical Research (*ann.purdom@umchealthsystem.com*) or Michael Economidis, UMC Associate General Counsel (*michael.economidis@umchealthsystem.com*) for review and permission prior to initiation of the research.

Reporting: Modifications to this research proposal must be submitted to and acknowledged by the IRB prior to the implementation of the modification. You must report to the IRB any serious problem, adverse effect, or outcome that occurs in conjunction with this project. You are also required to notify the IRB when this study is completed.

The Texas Tech University Health Sciences Center Institutional Review Board is duly constituted (fulfilling FDA requirements for diversity) allows only those IRB members who are independent of the investigator and sponsor of the study to vote/provide opinion on the study, has written procedures for initial and continuing review, prepared written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirement defined in 21 CFR (Code of Federal Regulations) Parts 50 and 56 and ICH (International Conference on Harmonization) guidance relating to good clinical practice.

Please retain this letter with your research records. Research records include all Institutional Review Board submissions and responses and must be kept in the principal investigator's file for a minimum of three (3) years after completion of the study.

The Texas Tech University Health Sciences Center (TTUHSC) IRB Policies and Procedures are available for reference on the TTUHSC Human Research Protection Program Website (https://ttuhsc.imedris.net/).

TTUHSC Lubbock/Odessa Institutional Review Board
3601 4th Street STOP 8146
Lubbock, TX 79430
806-743-4753

APPENDIX C

RESEARCH APPROVAL – UMC

Texas Woman's University
Institutional Review Board
304 Administration Drive
Denton, TX 76204

January 22, 2021

Dear Sir/Madam,

I am writing to express University Medical Center's robust support for the dissertation proposal, "Examining the relationship and ability of insulin resistance and glycemic variability to predict mortality and infection in adults with burn injuries" submitted to Texas Woman's University's Doctor of Philosophy in Nursing Science program by Jennifer Kesey, MSN, RN, FNP-BC, CWS.

The goals of this proposal are synergistic with University Medical Center's vision of optimally managing glucose variability and thereby improving patient outcomes and enhancing patient safety for patients in UMC's Timothy J. Harnar's Burn Center. We applaud her efforts to drive nursing research forward to deliver a solution to an issue within a real-world setting. Nursing Research proposals such as this are highly valued at our Institution and support our Safety/Quality Pillar's goal to become a Highly Reliable Organization in process as well as in practice.

Thank you for involving UMC in this effort. Ms. Kesey's proposal has our full support.

Respectfully,

Ann C. Purdom

Ann C. Purdom, MSN, RN, OCN
Director of Clinical Research
University Medical Center
806.761.0575
ann.purdom@umchealthsystem.com

APPENDIX D

TTUHSC, OPERATING POLICY AND PROCEDURE #56.04

ELECTRONIC TRANSMISSION OF PERSONALLY IDENTIFIABLE INFORMATION AND PROTECTED HEALTH INFORMATION (PHI)

HSC OP: 56.04, **Electronic Transmission of Personally Identifiable Information (PII) and Protected Health Information (PHI)**

PURPOSE: The purpose of this Health Sciences Center Operating Policy and Procedure (HSC OP) is to provide a framework to allow Personally Identifiable Information (PII) and Protected Health Information (PHI) to be securely transmitted over electronic communication networks such as e-mail and the Internet. [1]

REVIEW: This HSC OP will be reviewed on May 1 of each even-numbered year (ENY) by the Institutional Privacy Office and the Information Security Officer, with recommendations for revisions forwarded to the Vice President of Information Technology and Chief Information Officer (CIO) by June 15.

POLICY/PROCEDURE:

1. Definitions.

   a. Personally Identifiable Information (PII) is information or data about an individual that may be used to distinguish or track the individual's identity or that may be linked to the individual, including, but not limited to, the individual's name, social security number, date of birth, location of birth, mother's maiden name, biometric records, medical information, educational information, financial information, and employment information.

   b. PHI (PHI) is defined in HSC OP 52.02, as individually identifiable health information created, maintained or transmitted by TTUHSC or any other covered entity in any form or medium, including information transmitted orally, or in written or electronic form.

   c. TTUHSC Exchange e-mail is the Microsoft based e-mail system supported by Texas Tech University Health Sciences Center. The primary client software for Exchange email is Outlook and Outlook Web Access. All e-mails ending in "ttuhsc.edu" are routed through TTUHSC Exchange email services.

2. Secure Transmission of PII/PHI through Electronic Means.

   The Health Insurance Portability and Accountability Act (HIPAA) Security Standard requires TTUHSC to "implement security measures to guard against unauthorized access to electronic protected health information that is being transmitted over an electronic communications network". As such, TTUHSC is required to "implement a mechanism to encrypt electronic protected health information whenever deemed appropriate."

   Where other secure means of transmission are available (fax, electronic shared secure files) PII/PHI shall only be transmitted or received over electronic communication networks as outlined in the procedures below.

3. Transmission of PII/PHI through TTUHSC Internal E-Mails.

   TTUHSC has multiple security strategies in place to protect e-mails transmitted through the TTUHSC Exchange email system from unauthorized access from outside the TTUHSC system. PII/PHI transmitted through the TTUHSC Exchange email service, where the sender and recipients' e-mail addresses (including "cc" and blind copies) all end in "ttuhsc.edu", does not need to be encrypted. If any sender or recipient's e-mail address does not end in "ttuhsc.edu",

then the PII/PHI must be encrypted as outlined in paragraph 4 below. Please note, emails sent to "ttu.edu" email accounts are considered internal emails as the same Exchange environment is used for transmission at both institutions. [2]

4. Transmission of PII/PHI through External E-Mails.

Any e-mail containing PII/PHI (either within the body of the message or as an attachment) that is sent from and/or to a non-TTUHSC email address (i.e., IT DOES NOT END IN "ttuhsc.edu") must be encrypted.

In addition, email encryption must take place when sending PII/PHI to other institutions. Emails sent to University Medical Center (UMC) are sent via a dedicated TLS connection which does not require users to input the "[ss]" in the subject line. However, "[ss]' or "[send secure]" is required for email being sent to Covenant Health.

a. Manual Encryption.

TTUHSC currently has a manual encryption system in place to secure PII/PHI that is e-mailed outside the TTUHSC Outlook Webmail system. PII/PHI e-mailed outside the TTUHSC Outlook Webmail system (one or more e-mail addresses do not end in "ttuhsc.edu") must be manually encrypted. To manually encrypt e-mail, one of the following designations MUST BE TYPED INTO THE SUBJECT LINE of the e-mail to be encrypted:

- [ss]; or
- [send secure]

E-mail will not be encrypted if one of these bracketed designations is not manually typed into the subject line of the e-mail. A subject title can be added after either of these designations.

Example: [ss] Medical Records

5. Transmission of PII/PHI through the Internet

PII/PHI transmitted through the Internet must be encrypted or otherwise secured (e.g., use of secure patient portals for each session requiring information be accessed). Any Department and/or School that desires to use the internet to transmit and/or receive PII/PHI is responsible for obtaining written approval from the TTUHSC Privacy Officer and TTUHSC Security Officer confirming that the information is adequately encrypted or otherwise secure.

6. Education & Training

Information and education regarding electronic transmission of PII/PHI shall be provided through the TTUHSC website, live training, and published notices. TTUHSC Information Technology Division shall have information regarding e-mailing of PII/PHI posted at https://hscweb.ttuhsc.edu/it/is/itsolutioncenter/faq/emailencryption.aspx

7. Response to Non-Compliance

The penalty for violation of this policy could result in fines ranging from $50,000 to $1,500,000 to both the individual and the Institution. These violations shall be investigated and addressed by

the TTUHSC Privacy Officer and/or Information Security Officer, who may recommend additional corrective action.

8. Right to Change Policy

TTUHSC reserves the right to interpret, change, modify, amend or rescind this policy in whole or in part at any time without consent of employees. [3][4]

FOOTNOTES:
[1] TAC 202.75
[2] 45 CFR 164.312(e)(1))
[3] 42 CFR 164.312(e)(2)(ii)
[4] 42 U.S.C.1320d–5(a)

APPENDIX E

MANUSCRIPT #1 SUBMISSION ACKNOWLEDGEMENT

A manuscript number has been assigned to AN INTEGRATIVE LITERATURE REVIEW ON GLUCOSE CONTROL, INSULIN RESISTANCE, AND GLYCEMIC VARIABILITY IN PATIENTS WITH BURN INJURIES

em.jbcr.0.75df4c.c4d8878c@editorialmanager.com on behalf of
The Journal of Burn Care & Research <em@editorialmanager.com>

Wed 9/8/2021 20:26

To: Kesey, Jennifer <Jennifer.Kesey@ttuhsc.edu>;

CAUTION: This email originated from outside of TTUHSC. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Kesey,

Your submission entitled "AN INTEGRATIVE LITERATURE REVIEW ON GLUCOSE CONTROL, INSULIN RESISTANCE, AND GLYCEMIC VARIABILITY IN PATIENTS WITH BURN INJURIES" has been been assigned the following manuscript number: JBCR-D-21-00327.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.
The URL is
https://urldefense.com/v3/__https://www.editorialmanager.com/jbcr/__;!!PZU9J6Y!N5RUNbvYUhZFI4I90o75qO4ogUo2HrzRDt5qeyiqta2aEDt9lJWZbqpnPxldyb69I-pI3FA$.

Thank you for submitting your work to this Journal.

Kind regards,

Journal of Burn Care and Research

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APPENDIX F

MANUSCRIPT #2 SUBMISSION ACKNOWLEDGEMENT

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