

**Intensive Glucose Management in Critically Ill Patients
Improves Patient Outcomes**

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Pharmacy Practice Paper
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Background:

Hyperglycemia, defined as random blood glucose concentrations greater than 200 mg/dL (adapted from the American Diabetes Association [ADA] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus)¹, is common in critically ill patients with and without diabetes. Hyperglycemia, once considered to be an appropriate response to stress, is now being recognized as a predictor of negative outcomes including mortality. Hyperglycemia is common in critically ill hospitalized patients, and it is associated with adverse outcomes, such as increased length of stay in the Intensive Care Unit (ICU), increased risk of infections and increased morbidity and mortality. Within the last ten years it has been suggested that the hyperglycemia observed during stress may contribute to the morbidity and mortality in the ICU.

Stress-induced hyperglycemia, described in 5 to 30% of critically ill patients, is believed to be secondary to increased levels of stress hormones.² During acute illness, stress hormones are produced which increase insulin resistance by increasing hepatic glucose production and decreasing peripheral glucose uptake.³ Over the short term, hyperglycemia can adversely affect fluid balance and immune function, and it can promote inflammation.⁴ Hyperglycemia negatively affects many body systems, including the cardiovascular (acute myocardial ischemia, cardiogenic shock, arrhythmias), neuromuscular (polyneuropathy), immunologic (immunosuppression, nosocomial infections) and cerebral (ischemic stroke), and also impairs wound healing. In critically ill patients, besides maintaining euglycemia, insulin has beneficial multi-factorial actions in each of these body systems, as well as in wound healing.²

The prevalence of diabetes in hospitalized adult patients is not known, however, more than 50% of hospitalized patients with hyperglycemia do not have a diagnosis of diabetes.⁵ The adverse consequences of chronic hyperglycemia in diabetic patients are well known. Two landmark studies performed in the mid 1990s, The Diabetes Complication Control Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), proved that tight blood glucose control decreases the micro-vascular complications of both Type 1 and Type 2 diabetes up to nearly 70%.³ Likewise, two recent significant studies, the Leuven study by Van den Berghe and the Diabetes Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Trial, have overturned traditional approaches in critical care diabetes management.³ These recent studies have confirmed that intensive glucose management of hyperglycemia, via continuous insulin infusions, reduces mortality in a largely non-diabetic, critically ill population. Furthermore, management of hyperglycemia through the use of insulin infusion protocols is becoming a new standard in critical care.

The purpose of this paper is to review the literature supporting intensive glucose management and the implementation of insulin infusion protocols to achieve improved patient outcomes.

Literature Evaluation:

Several studies have established the benefits of strict glycemic control in critically ill hospitalized patients. The first of these is the final paper of the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Trial by Malmberg, et al. This final paper published in May 1997 reported the long-term mortality data.⁶ The DIGAMI Study by Malmberg, et al, was a multi-center double-blinded, prospective, randomized trial that took place in 19 Coronary Care Units (CCUs) across Sweden, from January 1990 to December 1993. All patients were followed up prospectively for one year; after one year the patients were followed up by their physician. On July 31, 1995, the vital status of all patients was checked and verified by the physician responsible for the study in each participating center.⁷ The study included a total of 620 patients with established Type 1 and Type 2 Diabetes, as well as patients with either newly diagnosed Type 2 Diabetes or stress hyperglycemia.⁶ The patients were randomly allocated to standard (control) treatment or to insulin treatment. The standard treatment group, which included 314 patients, did not receive insulin unless clinically indicated; the insulin treatment group, which included 306 patients, received an insulin-glucose infusion according to a predefined protocol for at least 24 hours, followed by subcutaneous insulin four times daily for at least three months.⁷ The goal blood glucose level was a range between 126 and 180 mg/dL.⁸ Both groups received conventional management of their acute myocardial infarction, with no significant differences in the use of thrombolytics, aspirin, beta-blockers or ACE inhibitors between the two groups.⁶ The primary outcome measure was long-term all cause mortality.⁷ The mean follow up period was 3.4 years.⁷ The DIGAMI Trial showed a 30% reduction in mortality at 1 year in the insulin treatment group (18.6% vs. 26.1%, $p < 0.027$).⁶ This reduced mortality was maintained at the mean follow up period of 3.4 years, with 33% (102 patients) in the insulin treatment group versus 44% (138 patients) in the standard treatment group ($p = 0.011$).⁶ (Table 1) The absolute reduction in risk of mortality was 11%, which equates to one life saved for every nine patients treated via the DIGAMI protocol.⁶ This absolute risk reduction of insulin-glucose infusion and long-term insulin compare well with other interventions that are considered standard practice in the management of patients with diabetes following AMI.⁶

The landmark study by Van den Berghe, et al., was a large, prospective, randomized controlled trial that took place in a single center in Leuven, Belgium, from February 2000 to January 2001. This study included 1,548 patients admitted to a Surgical Intensive Care Unit (SICU) on mechanical ventilation, whose baseline clinical and demographic characteristics were similar at randomization. The patients were randomly assigned to receive conventional treatment or intensive insulin treatment. In the conventional treatment group, which included 783 patients, a continuous insulin infusion was started only if the blood glucose level exceeded 215 mg/dL, and the goal blood glucose level was between 180 and 200 mg/dL. In the intensive insulin treatment group, which included 765 patients, a continuous insulin infusion was started only if the blood glucose level exceeded 110 mg/dL, and the goal blood glucose level was between 80 to 110 mg/dL.⁹ The primary outcome measure was death from any cause during intensive care. Secondary outcome measures were in-hospital death; the number of days in the ICU and the need for prolonged intensive care (more than 14 days) or readmission; the need for mechanical ventilation, dialysis, or inotropic or vasopressor support; critical-illness

polyneuropathy; markers of inflammation; bloodstream infection and use of antibiotics for more than 10 days; transfusion requirements; and hyperbilirubinemia.⁹ (Table 1) In the conventional treatment group, the morning blood glucose level was maintained at an average level of 153+/-33 mg/dL; in the intensive insulin treatment group, the morning blood glucose level was maintained at an average level of 103+/-19 mg/dL ($p<0.001$).⁹ In this study, 35 patients (4.6%) in the intensive insulin treatment group died during intensive care, compared with 63 patients (8%) in the conventional treatment group (unadjusted $p=0.005$). This represents an apparent risk reduction of 42%; however, after adjusting for repeated interim analyses, the median unbiased estimate of the reduction in mortality was 32% ($p<0.04$).⁹ The observed reduction in mortality with intensive insulin therapy occurred exclusively among patients receiving intensive care for greater than 5 days, with 10.6% (22 patients out of 208) in the intensive insulin treatment group versus 20.2% (49 patients out of 243) in the conventional treatment group ($p=0.005$).⁹ Furthermore, intensive insulin therapy reduced the length of stay (LOS) in the ICU but not the overall LOS in the hospital. The average LOS in the ICU for both arms was 3 days ($p=0.2$); however, only 11.4 % (87 patients) in the intensive insulin treatment group required greater than 14 days of intensive care compared to 15.7% (123 patients) in the conventional treatment group ($p=0.01$).⁹ The incidence of bloodstream infections was also reduced in the intensive insulin treatment group, with 4.8% (37 patients) in the intensive insulin treatment group versus 7.8% (61 patients) in the conventional treatment group ($p=0.003$).⁹ Thus, regardless of whether the patients had a history of diabetes, the use of intensive insulin therapy to maintain blood glucose at a level that did not exceed 110 mg/dL greatly reduced mortality in the ICU, in-hospital mortality, and morbidity among critically ill patients in the ICU.⁹

The study by Finney, et al., was a single-center, prospective observational study conducted in London, England over a period of six months, from January 2002 to June 2002. This study included 531 patients newly admitted to the adult ICU for cardio-respiratory surgery and medicine, but only 523 patients underwent glycemic control analysis. The patients had similar demographic and admissions characteristics. In this study, six bands of glycemic control were prospectively defined and each band defined a range of blood glucose values. Since during a single admission patients will have glucose levels that fall into several bands, the amount of time each patient spent within each of the six bands was computed. For each glucose band the percentage of time spent in that band was categorized into three groups so that each subgroup contained the same number of people.¹⁰ The objective of this study was to determine whether blood glucose level or quantity of insulin administration is associated with reduced mortality in critically ill patients. The goal blood glucose level was a range between 90 to 145 mg/dL using a continuous insulin infusion.¹⁰ The primary endpoint was ICU mortality. Secondary endpoints were hospital mortality, ICU and hospital LOS, and predicted threshold glucose level associated with risk of death.¹⁰ (Table 1) Odds ratios (ORs) of death were expressed relative to the tertile that spent the most time in a specific glucose band.¹⁰ In all glucose bands, increased insulin administration was associated with a significantly increased risk of death ($OR>1$), indicating that glucose control rather than administration of exogenous insulin was the dominant factor in improving mortality.¹⁰ The results of this study suggest that patients who spent less time in higher glucose bands were less likely to die than those who spent the most time there. In higher glucose bands, a shorter duration of exposure was associated with predicted ORs of death less than 1

($p=0.18-0.34$); whereas in lower glucose bands, a shorter duration of exposure was associated with predicted ORs of death greater than 1 ($p=0.2-0.41$).¹⁰ Thus, this study concluded that control of glucose levels rather than absolute levels of exogenous insulin account for the reduced mortality associated with intensive insulin therapy; and that a threshold level of less than 145 mg/dL may be adequate.¹⁰

The study by Krinsley compared the outcomes of 800 patients admitted consecutively to the ICU immediately before institution of the glucose management protocol (February 23, 2002 through January 31, 2003) to those of the first 800 patients admitted after institution of the protocol (February 1, 2003 through January 10, 2004).¹¹ The setting was a 14-bed medical-surgical ICU in a community teaching hospital in Stamford, Connecticut. The glycemic management protocol was written by a multidisciplinary group of physicians and nurses, and it is a nurse-driven protocol, whereby nurses administer insulin without a physician's order based on the parameters of the protocol. The goal of the protocol is to maintain blood glucose levels lower than 140 mg/dL. Continuous insulin infusion is used if the blood glucose exceeds 200 mg/dL on two successive occasions; subcutaneous regular insulin is used for lower blood glucose levels.¹¹ There was no significant difference noted between the patients' demographic and clinical characteristics. The primary outcome measure was effect of the protocol on glycemic control. Secondary outcome measures were new renal dysfunction after ICU admission, transfusion requirements, bloodstream infections acquired in the ICU, hospital mortality, and LOS in the ICU.¹¹ The glycemic management protocol led to significantly improved glucose levels with a significant increase in hypoglycemia. The mean blood glucose level for the baseline group was 152.3 mg/dL compared to 130.7 mg/dL in the treatment group.¹¹ Hospital mortality decreased 29.3% during the protocol period, with 118 patients (14.8%) in the treatment group versus 167 patients (20.9%) in the baseline group ($p=0.002$).¹¹ Mean LOS in the ICU decreased from 3.58 days in the baseline group to 3.19 days in the treatment group ($p=0.11$).¹¹ There was no significant difference in the number of patients with bloodstream infections between the two groups (27 patients in the baseline group versus 21 patients in the treatment group).¹¹ (Table 1) The protocol resulted in significantly improved glycemic control and was associated with decreased mortality and LOS in the ICU in a diverse population of critically ill adult patients, thus supporting the implementation of this intervention as a standard of care for critically ill patients.¹¹

Gabbanelli, et al., conducted a retrospective clinical study involving 412 patients admitted to the ICU of a University Hospital in Ancona, Italy, between December 18, 2000 and February 20, 2002. All patients were assigned to five groups based on the type of critical illness (neurologic disease, respiratory disease, general surgery, cardio-circulatory insufficiency, and others) on admission. The baseline characteristics of the patients were similar. The goal blood glucose level was a range of 180 to 200mg /dL. The blood glucose levels were measured at the time of admission and daily at 2 to 4 hour intervals. According to the internal protocol, when the blood glucose level exceeded 180 mg/dL an insulin bolus was administered or a continuous insulin infusion was started, according to the judgment of the attending physician.¹² Regardless of the reason for admission into the ICU, all five groups showed higher ICU mortality in patients with increased mean blood glucose levels; a total of 74 patients, corresponding to an observed mortality of 18%.¹² Moreover, it was determined that in patients in whom the mean

blood glucose levels were greater than 141.7 mg/dL, the probability of death was higher than in the group of patients in whom a strict blood glucose control was maintained.¹² The patients from each group were further categorized into Group A, which included 273 patients and in which the mean blood glucose level was less than 141.7 mg/dL; and Group B, which included 139 patients and in which the mean blood glucose level was 141.7 mg/dL or greater.¹² There were 37 deaths in both groups, thus in Group A the mortality rate was 13.55%, and 26.62% in Group B (p=0.0014).¹² (Table 1) Thus, this study demonstrated an increase in mortality when the mean blood glucose level exceeded 141.7 mg/dL, confirming the importance of avoiding hyperglycemia.

Clinical Recommendations:

The current practice in most hospitals is that physicians allow moderately elevated blood glucose levels, usually in the range of 150 to 200 mg/dL, in patients in the acute care setting; and when hyperglycemia is treated in the hospital setting, it is usually treated with a subcutaneous Regular Insulin sliding scale. However, the sliding scale approach to maintain euglycemia is not always appropriate¹³, especially in critically ill patients. Insulin infusions tend to be underutilized, and are typically not started until blood glucose levels are greater than 350 mg/dL for several hours.¹³ Within the last ten years, several studies have established the benefits of strict glycemic control in critically ill hospitalized patients (Table 1), and some studies have also proven that administration of a continuous insulin infusion is an effective way to achieve tight control of blood glucose.^{6,9}

Based on this emerging clinical evidence, increasing efforts are made worldwide to maintain strict glycemic control in critically ill patients.¹⁴ Furthermore, these efforts are the driving force towards the development of standardized Insulin Infusion Protocols (IIP) that are practical and easily implemented by ICU nurses without the need of frequent physician input. A study conducted by Goldberg, et al, at the Yale New Haven Hospital designed an IIP that was easily implemented by the MICU nursing staff without the need for ongoing physician input (Table 2). The goal blood glucose level of the IIP was 100 to 139 mg/dL. The primary outcome measure was blood glucose levels. With the mean blood glucose level at the start of the IIP at 299+/-96 mg/dL, the mean time to reach target blood glucose level was 10.1+/- 4.6 hours.¹⁴ In addition, out of 5,808 subsequent hourly blood glucose values only 20 values (0.3%) were below 60 mg/dL, none of which resulted in clinically significant adverse events.¹⁴

A study by Kanji, et al. conducted at a Canadian hospital evaluated the efficiency and safety of a nurse-managed IIP in critically ill patients (Table 2). The interventional cohort received an insulin infusion adjusted using a standardized protocol targeting a blood glucose level of 81 to 110 mg/dL. The study endpoints related to glucose control, safety and nursing workload.¹⁵ This study showed that target blood glucose levels were achieved more rapidly in the interventional cohort, at 11.3+/-3.7 hours compared to 16.4+/-12.6h in the control group (p=0.028).¹⁵ Furthermore, the IIP was found to be safe as evidenced by a four-fold decrease in patients experiencing severe hypoglycemia in the interventional cohort (4% vs. 16%, p=0.046).¹⁵ In addition, the nursing workload increased significantly with the IIP, as approximately 35% more blood glucose measurements were required.¹⁵

Another study conducted in Canada was by Chant, et al., which also evaluated the effectiveness, safety, and associated patient outcomes of a nurse-directed IIP to achieve a target blood glucose level of 90 to 144 mg/dL.¹⁶ (Table 2) The study's primary endpoint was morning blood glucose level, which was measured by the hospital's central laboratory. The interventional group's mean morning blood glucose level was 128+/-32 mg/dL versus 176+/-50 mg/dL in the control group ($p<0.001$).¹⁶ Also, the time to achieve goal blood glucose levels was faster in the interventional group, with median time of 15 hours compared to 66 hours in the control group ($p<0.0001$).¹⁶ However, the rate of hypoglycemia was more frequent in the interventional group, with 3.8% compared to 2.2% in the control group ($p=0.004$).¹⁶ This study demonstrated that intensive blood glucose control is achievable using a standardized nurse-driven IIP.¹⁶

An additional study that evaluated the efficacy and safety of a nurse-driven IIP was conducted by Taylor, et al. in a Missouri hospital. (Table 2) The study periods were not contiguous to allow multidisciplinary input into logistical and safety issues in each protocol before its implementation¹⁷, thus the study consisted of three phases. The first phase of the study did not have a unit-wide goal blood glucose level; the goal blood glucose level at the second phase was a range of 120 to 150 mg/dL; and, the third phase had a goal blood glucose level of 80 to 110 mg/dL.¹⁶ The endpoints in this study were protocol effectiveness and safety, and nursing compliance.¹⁷ This study demonstrated a successive significant decrease in the average daily blood glucose levels from Phase I (190 mg/dL) to Phase II (163 mg/dL) to Phase III (132 mg/dL) ($p<0.001$).¹⁷ When the nurse-driven IIP was instituted in Phase II, the number of hours to achieve a blood glucose level of less than 150 mg/dL decreased to 7.4 hours, compared to 14.1 hours during the physician-directed management in Phase I.¹⁷ However, the length of time to achieve the goal blood glucose level was not decreased additionally in the more aggressive Phase III protocol (7.2 hours).¹⁷ Moreover, the incidence of severe hypoglycemia did not differ between physician-directed insulin infusions or either nurse-driven IIP (range 1.1% to 3.4%, $p>0.05$).¹⁷ This study showed that implementation of a nurse-driven IIP led to a more rapid and more effective blood glucose control in critically ill surgical patients compared with physician management.¹⁷

In light of the evidence provided by these studies, the new standard in critical care is the management of hyperglycemia through the use of IIPs. As always, the first step in the development or implementation of a new practice is education. Although the Critical Care physicians and the Hospitalists at this facility are well aware of the improved outcomes of intensive glucose management in critically ill patients, many of the General Practice physicians are still unaware of it. Through the use of the hospital's Newsletter, which is a monthly two-sided, one-page information sheet of topics relating to this facility, the physicians at the hospital can learn of this new treatment strategy for hyperglycemia. In addition, poster-boards about intensive glucose management and the use of continuous Insulin infusions can be placed at the main entrances of the hospital so that the physicians and nurses see it on their way in and out of the facility. Furthermore, via a Chart Note (Figure 1) this new practice in critically ill patients can be communicated to the physicians by placing them in appropriate patients' charts.

In general, both physicians and nurses can be educated about this new standard in critical care by providing in-services at the facility where the studies supporting the benefits of

intensive glucose management are presented, as well as the studies supporting the use and implementation of IIPs. As for the Critical Care nurses that will be using these IIPs, they can be provided in-services specifically targeting the safety and utilization of these protocols, since their workload will be greatly increased due to the larger number of blood glucose measurements that will be required. The Critical Care pharmacist at this hospital has facilitated the implementation of the IIPs currently used by two of the Critical Care physicians by participating in their development and assisting the nurses with any questions that arise. The two IIPs currently used at this hospital use a goal blood glucose level of 100 to 130 mg/dL, which is easier to achieve and more practical to maintain.

In addition, hospitals with Critical Care pharmacists will have an advantage over those without one, because the pharmacists can play a key role in the implementation and the supervision of the IIPs.¹⁸ An article in *Pharmacy Practice News* describes four ways that pharmacists can lead the way towards an IIP in the ICU. First, pharmacy can be the one to lead the initiative towards developing an IIP. Second, it is important for the pharmacists to communicate well with the nurses, since nursing will be carrying the majority of the workload. Third, the pharmacists can help develop a safe, effective and easy-to-use IIP upon discharge from the ICU to the floor and from the floor to the home. Fourth, the pharmacists can be involved in the quality assurance of the IIP to identify problems and revise the protocol if necessary.¹⁸ The ultimate goal would be for each hospital to develop their own practical, safe and easy-to-use nurse-driven IIP, dependent upon their patient population, as a multi-disciplinary team consisting of physicians, nurses and pharmacists.

Conclusions:

With conditions that predispose patients to hyperglycemia, such as obesity, on the rise in the United States population, critically ill patients are at a higher risk of mortality if they develop hyperglycemia. Hyperglycemia can cause many adverse outcomes in hospitalized patients, including increased risk of infections, increased LOS in the ICU and increased mortality. Within the last ten years studies have shown that intensive glucose management in critically ill patients improves patient outcomes, and that the use of IIPs is a practical, safe and effective way to achieve improved glucose control. Pharmacists can play an important role in the development and implementation of IIPs, as well as help to educate and train the nurses to utilize these protocols.

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Table 1 Summary of Outcomes of Intensive Insulin Control

Study	Study Design	Subjects	Study Location/Duration	Treatment Regimens Evaluated	Outcome Variables Measured and Method of Measurement	Major Findings (Results)
<i>Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus</i> (Malmberg)	Multi-center, double-blinded concealed randomized trial with intention-to-treat	n=620	19 Hospitals in Sweden Mean follow-up was 3.4 years	DM patients were randomized to standard txment (n=314) or to insulin txment (n=306). Standard txment: only given insulin if clinically indicated Insulin txment: given insulin-glucose infusion followed by a multidose subQ insulin regime for at least 3 months Goal BG ~126-180 mg/dL	Primary outcome measure – long term all cause mortality	Mortality at 3.4 years: standard txment – 138 patients (44%); insulin txment – 102 patients (33%) (p=0.011)
<i>Intensive Insulin Therapy in Critically Ill Patients</i> (Van den Berghe)	Prospective, randomized controlled trial at a single center	n=1548	University Hospital of Leuven, Belgium 250 days	Patients on mechanical ventilation were randomized to conventional or to intensive insulin therapy. Conventional txment: insulin CI started only if BG>215 mg/dL & adjusted to keep BG 180-200 mg/dL Intensive txment: insulin CI started only if BG>110 mg/dL & adjusted to keep BG 80-110 mg/dL	Primary outcome measure – death from any cause during ICU stay Secondary outcome measures – in-hospital death, # of days in ICU & need for prolonged (>14 days) in ICU or readmission, need for mechanical ventilation, dialysis or inotropic or vasopressor support, critical-illness polyneuropathy, markers of inflammation, bloodstream infections & use of antibiotics for >10 days, transfusion requirements, & hyperbilirubinemia	Mean AM BG: conventional txment - 153±33 mg/dL; intensive txment - 103±19 mg/dL (p<0.001) Mortality: conventional txment – 63 patients (8%); intensive txment 35 patients (4.6%) (p<0.04---adjusted) LOS: median duration for both arms were 3 days (p=0.2) LOS>14 days in ICU: conventional txment 123 patients (15.7%); intensive txment 87 patients (11.4%) (p=0.01) Bloodstream infections: conventional txment - 61 patients (7.8%); intensive txment – 32 patients (4.2%) (p=0.003)

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<i>Glucose Control and Mortality in Critically Ill Patients</i> (Finney)	Single-center, prospective, observational study	n=531	Royal Brompton Hospital, London, England 6 months (1/02 to 6/02)	Prospectively defined 6 bands of glycemic control with a corresponding defined range of BG values Goal BG 90-145 mg/dL using insulin CI	Primary endpoint was ICU mortality Secondary endpoints were hospital mortality, ICU & hospital LOS, & predicted threshold glucose level associated with risk of death	Results suggest that patients who spent less time in higher glucose bands were less likely to die than those who spent the most time there; a shorter duration of exposure was associated with predicted ORs of death of <1 (p= 0.18-0.34)
<i>Effects of an Intensive Glucose Management Protocol on the Mortality of Critically Ill Adult Patients</i> (Krinley)	Consecutive patients admitted after protocol institution, patients admitted immediately preceding protocol institution	n=1600	Stamford Hospital, Stamford, Connecticut Baseline – between 2/23/02 & 1/31/03 Txment – between 2/1/03 & 1/10/04	Goal of protocol – keep BG<140 mg/dL Insulin CI is used if BG>200 mg/dL on 2 successive occasions; subQ insulin is used for lower BG (Nurse-driven protocol)	Primary outcome measure – effect of the protocol on glycemic control Secondary outcome measures – hospital mortality, new renal dysfunction after ICU admission, transfusion requirements, bloodstream infections acquired in the ICU, & LOS in ICU	Mean BG levels: baseline group – 152.3 mg/dL; txment group – 130.7 mg/dL (p<0.01) Glycemic control: mean BG for baseline group – 152.3 mg/dL; mean BG for txment group – 130.7 mg/dL Mortality: baseline group – 167 patients (20.9%); txment group – 118 patients (14.8%) (p=0.002) Mean LOS in ICU: baseline group – 3.58 days; txment group – 3.19 days (p=0.11) Bloodstream infections: no significant difference; baseline group – 27 patients; txment group - 21 patients
<i>Correlation between hyperglycemia and mortality in a medical and surgical intensive care unit</i> (Gabbanelli)	Retrospective clinical study	n=412	Polytechnic University of Marche, Ancona, Italy 15 months (between 12/18/00 & 2/20/02)	Group A (n=273) – mean BG <141.7 mg/dL; Group B (n=139) –mean BG >141.7 mg/dL Insulin bolus or insulin CI was given once BG >180 mg/dL Goal of protocol – keep BG at or <180-200mg/dL	Primary outcome measure - # of deaths in ICU	Mortality in ICU: Group A – 13.55%; Group B – 26.62% Each group had 37 deaths (p=0.0017)

Table 2 Intensive Insulin Protocol Studies

Study	Study Design	Subjects	Study Location/Duration	Treatment Regimens Evaluated	Outcome Variables Measured and Method of Measurement	Major Findings (Results)
<p><i>Implementation of a Safe and Effective Insulin Infusion Protocol in a Medical Intensive Care Unit</i> (Goldberg)</p>	<p>Data collected prospectively</p>	<p>n=52</p>	<p>Yale New Haven Hospital, New Haven, Connecticut</p> <p>Clinical experience with the IIP started in October 2002</p> <p>Previously collected cohort of 117 patients consecutively admitted to the MICU in March- April 2002</p> <p>All patients were followed until MICU discharge</p>	<p>Insulin infusion protocol (IIP) was designed to be implemented by the MICU nursing staff w/o need for ongoing physician input IIP BG goal – 100-139 mg/dL IIP was recommended for all patients whose BG>200 mg/dL</p>	<p>Primary endpoint - BG levels Secondary endpoints - insulin doses, & relevant clinical interventions (corticosteroids, vasopressor, enteral nutrition, & parenteral nutrition) were collected</p>	<p>Mean BG level at IIP initiation was 299±96 mg/dL & mean time required to achieve target BG levels was 10.1±4.6 hours; IIP facilitated stable glycemic control after target levels were achieved No significant differences between insulin doses & relevant clinical interventions</p>
<p><i>Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose in critically ill adults</i> (Kanji)</p>	<p>Combined retrospective-prospective before-after cohort study</p>	<p>n=100</p>	<p>Ottawa Hospital, Ottawa, Ontario, Canada</p> <p>Data collected both retrospectively & prospectively from June-November 2002</p>	<p>Control cohort – prescribed traditional insulin infusions at discretion of primary physician Interventional cohort – prescribed insulin infusions using a standardized protocol Target BG - 81-110 mg/dL</p>	<p>Endpoints - BG control, safety & nursing workload</p>	<p>Target BG concentrations: achieved more rapidly in the interventional cohort – 11.3+/- 7.9 hours vs. 16.4+/-12.6 hours (p=0.028) Safety: IIP found to be safe as indicated by a 4-fold reduction in patients experiencing severe hypoglycemia in interventional cohort- 4% vs. 16% (p=0.046) Nursing workload: significantly increased, ~35% more BG measurements were required w/IIP (p<0.001)</p>

Table 2 Intensive Insulin Protocol Studies

Study	Study Design	Subjects	Study Location/Duration	Treatment Regimens Evaluated	Outcome Variables Measured and Method of Measurement	Major Findings (Results)
<i>Validation of an Insulin Nomogram for Intensive Glucose Control in Critically Ill Patients</i> (Chant)	Prospective study with a retrospective control group	n=86	St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada 21 days	Retrospective control group (n=42) – traditional insulin sliding scales (IV or subQ) were used to control BG levels Prospective nomogram group (n=44) – BG was controlled using an IV insulin infusion at rate specified by nomogram Target BG – 90-144 mg/dL	Primary endpoint - AM BG level Secondary endpoints – frequency of hypoglycemia & severe hypoglycemia, frequency of hyperglycemia, proportion of BG levels w/in target range, # of BG level checks, & time to achieve BG control Also recorded were outcome variables – duration of antibiotic or vasopressor therapy, LOS in ICU, & ICU mortality	AM BG level: control group – mean AM BG 176±50 mg/dL; nomogram group - 128±32 mg/dL (p<0.001) Time to achieve BG control: control group – 66 hours; nomogram group – 15 hours (p<0.0001) BG levels w/in target range: control group – 20%; nomogram group – 52% (p<0.001) Rate of hypoglycemia: control group – 2.2%; nomogram group – 3.8% (p<0.004)
<i>Efficacy and Safety of an Insulin Infusion Protocol in a Surgical ICU</i> (Taylor)	Prepost study design with a single retrospective group & 2 temporally distinct prospective intervention groups	n=166	Barnes-Jewish Hospital, St. Louis, Missouri 3 noncontiguous 6-month periods between 2002 & 2004 (Phase I, II & III) Retrospective data obtained on patients who were on insulin infusions from November 2002 to May 2003 (Phase I) Prospective data obtained on patients on an IIP targeted to keep BG levels 80-110 mg/dL from June 2003 to December 2003 (Phase II) and April to October 2004 (Phase III)	Target BG: Phase I – no unit-wide policy of goal BG level Phase II – 120-150 mg/dL Phase III – 80-110 mg/dL (different IIP used) Phase II: IIP started at BG of 192 mg/dL Phase III: IIP started at BG of 130 mg/dL	Study endpoints – protocol effectiveness & safety, nursing compliance	Protocol effectiveness: significant decrease in average daily BG levels – Phase I – 190 mg/dL; Phase II – 163 mg/dL; Phase III – 132 mg/dL (p<0.001) Protocol safety: incidence of severe hypoglycemia did not differ between Phases (p>0.05) Nursing compliance: Phase III – strict adherence to the protocol occurred in slightly >50% of patient days

Figure 1



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Dear Doctor,

Hyperglycemia, defined as random blood glucose concentrations greater than 200 mg/dL (adapted from the American Diabetes Association [ADA] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus), is common in critically ill patients with and without Diabetes. Hyperglycemia, once considered to be an appropriate response to stress, is now being recognized as a predictor of negative outcomes, including mortality. Several landmark studies, such as the Diabetes Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Trial¹ and the Leuven study by Van den Berghe², have proven that strict glycemic control improves patient outcomes in critically ill patients. Among other benefits, these studies demonstrated a decrease in infections, a decrease in ICU length of stay, and a decrease in mortality with strict glycemic control.

The target blood glucose levels in these studies ranged from 80 to 180 mg/dL; the strictest being Van den Berghe's at 80 to 110 mg/dL. The method by which tight glycemic control was achieved in the studies was via the use of Regular Insulin continuous infusions. These studies have also established that Insulin infusions can be easily and rapidly adjusted to maintain blood glucose concentrations within the desired target blood glucose levels. In addition, since these studies were published several hospitals worldwide have developed and implemented Insulin Infusion Protocols that have proven how practical, safe and easily utilized these protocols can be. The target blood glucose levels in these studies have ranged from 81 to 144 mg/dL.

Until Northeast Baptist Hospital develops its own Insulin Infusion Protocol, Dr. Natalino and Dr. Deal (two in-house Critical Care physicians) have developed and implemented their own Insulin Infusion Protocols that are routinely used by other physicians in this facility. The target blood glucose level of these two protocols is 100 to 130 mg/dL.

If medically appropriate for your patient, please consider a stricter glucose control of your patient Mr. / Mrs. / Ms _____.

This patient's blood glucose levels have been in the range of _____ mg/dL for the past _____ hours / days.

Thank you,

RPh. / Pharm. D.

- 1 Malmberg, K, et al. *Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus*. BMJ 1197;314:1512 (24 May).
- 2 Van den Berghe, G, et al. *Intensive Insulin Therapy in Critically Ill Patients*. N Engl J Med, Vol. 345, No. 19. November 8, 2001.