# Intensive Insulin Therapy in Critical Care Settings

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**Abstract:** Hyperglycemia in hospitalized patients has been shown to increase both morbidity and mortality, regardless of the presence of preexisting diabetes. In order to achieve recommended glycemic goals, many patients require the use of intravenous insulin therapy in the critical care setting. Following the publication of a landmark trial evaluating the benefits of intensive insulin therapy in critically ill patients, a worldwide increased effort to achieve strict glycemic control has ensued. Maintaining blood glucose levels between 80 and 110 mg/dL has been shown to improve outcomes such as mortality and infectious complications in critically ill patients, while also decreasing length of hospital stay and healthcare expenditures. However, achieving strict glycemic control has proven to be a challenge for many institutions, partly due to the prevalence of hypoglycemia. As demonstrated by studies which have been terminated prematurely due to increased risk for hypoglycemic episodes, the benefits versus risks of intensive insulin therapy must be weighed carefully. Patients receiving continuous infusions of insulin require close monitoring, which may increase workload for intensive care unit staff. In an effort to balance the risks and benefits of intensive insulin therapy, many hospitals are incorporating standardized protocols and using an interdisciplinary approach toward patient care.

**Key Words:** Critical illness, hyperglycemia, insulin.

## INTRODUCTION

Hyperglycemia is common among critically ill patients and presents a challenge to clinicians in this setting. Several studies have demonstrated that hyperglycemia is strongly correlated with adverse outcomes, particularly higher mortality [1-3]. Following myocardial infarction, hyperglycemia has been associated with an increased risk for inpatient mortality, as well as the development of heart failure and cardiogenic shock [4]. A similar relationship exists between intraoperative hyperglycemia and complications following cardiac surgery, with higher mortality among hyperglycemic patients [5]. In addition to its effects on mortality, hyperglycemia has been linked to other complications, such as longer length of intensive care unit (ICU) stay and overall hospital stay. Elevated blood glucose levels have also been associated with infectious morbidity and an increased need for prolonged mechanical ventilation [6-9].

Interestingly, the link between hyperglycemia and adverse clinical outcomes is not limited to patients with preexisting diabetes. A retrospective analysis of critically ill patients has revealed that even modest hyperglycemia is associated with increased in-hospital mortality [10]. Regardless of the presence of diabetes, acute illness stressors, often related to infection or surgery, may increase insulin resistance due to rising concentration of counter-regulatory hormones [11]. Furthermore, the use of medications such as corticosteroids, vasopressors, enteral or parenteral nutrition, or infusion of dextrose-containing fluids frequently contributes to hyperglycemia [12]. Efforts to maintain strict glycemic control should be applied in an attempt to improve clinical outcomes among all critical care patients, irrespective of the presence or absence of diabetes.

In order to provide guidance to clinicians managing hyperglycemia in critical care settings, the American Diabetes Association (ADA) recommends maintaining blood glucose levels less than 140 mg/dL, with ideal levels as close to 110 mg/dL as possible [13]. In contrast, the American Association of Clinical Endocrinologists (AACE) recommends maintaining blood glucose levels below 110 mg/dL, while the Surviving Sepsis Campaign suggests goals of less than 150 mg/dL [14,15]. Despite slight variations in recommendations from these organizations, a clear consensus exists regarding the emphasis of maintaining glycemic control in the critical care setting.

In order to meet glycemic goals, many patients require intravenous insulin infusions [13]. In fact, most studies examining intensive insulin therapy in the ICU utilize continuous insulin infusions. This approach offers flexibility in adapting to complex patients with rapidly changing insulin requirements and is more proactive than traditional sliding scale insulin regimens. Although sliding scale insulin regimens are commonly employed at many institutions, limited evidence exists to either support or refute the efficacy of this practice [16]. Sliding scale insulin is an antiquated approach which reacts to existing hyperglycemia, whereas proactive therapy may be more appropriate to minimize prolonged elevation of blood glucose. Despite the potential benefits of aggressive hyperglycemia management, sliding scale insulin

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regimens are commonly utilized in the hospital setting and often do not achieve adequate glycemic control [17].

This review will examine the evidence supporting strict glycemic control in critically ill patients, as well as discuss clinical applications for clinicians who practice in the intensive care setting.

## EVALUATION OF THE LITERATURE

Increased focus on the importance of strict glycemic control in the ICU is primarily based on results from two large randomized controlled trials which demonstrated morbidity and mortality benefits with intensive insulin therapy. The first of these trials, a landmark study performed in Belgium, examined the effects of intensive insulin therapy in a surgical ICU setting [18]. Over 1500 mechanically ventilated patients were randomized to receive either intensive insulin infusion or conventional therapy. Target blood glucose levels in the intensive insulin group were 80 to 110 mg/dL, with patients achieving a mean blood glucose level of 103 mg/dL. In contrast, patients receiving conventional therapy had target levels between 180 and 200 mg/dL, averaging a blood glucose level of 153 mg/dL. Only 13% of the patients included in this study reported a past history of diabetes, indicating that other causes of hyperglycemia were present.

In the intention-to-treat population, strict glycemic control lowered ICU mortality (absolute risk reduction [ARR] 3.4%, p=0.005) and in-hospital mortality (ARR 3.7%, p=0.01) when compared to conventional therapy. The impact of intensive insulin therapy increased with the duration of ICU stay, with the greatest benefit in ICU and in-hospital mortality observed among patients requiring intensive care for five or more days (ARR 9.6 and 9.5%, respectively). In addition to the significant mortality benefit observed among patients receiving intensive insulin therapy, this group also demonstrated decreased rates of bloodstream infections, anemia, new renal injury, and critical-illness-related polyneuropathy. Patients in this group were also less likely to require prolonged mechanical ventilation and intensive care. Along with improvements in mortality and morbidity, the use of an intensive insulin regimen demonstrated a significant reduction in health care costs [19].

The potential benefits of intensive insulin therapy in this trial were well-recognized. Nevertheless, it is also important to consider the adverse effects of continuous intravenous insulin infusion, particularly hypoglycemia. Defined in this study as a blood glucose level of less than 40 mg/dL, hypoglycemia occurred in 5.1% of patients in the intensive treatment group, as compared with 0.8% in the conventional treatment group. Although this trial was limited to a single center in a surgical ICU, its findings prompted subsequent efforts to further examine the role of intensive intravenous insulin therapy in the critical care setting.

To expand upon the findings of this landmark trial involving surgical ICU patients, a second large randomized, controlled trial attempted to find a similar benefit among medical ICU patients [20]. The same intravenous insulin titration protocol was used, although this patient population was generally less healthy as compared to those in the previous study involving surgical ICU patients. Medical ICU patients in the intensive insulin therapy group achieved mean blood glucose levels of 105 mg/dL, as compared to 160 mg/dL in the conventional treatment group.

Although no difference in mortality was observed between patients receiving intensive insulin or conventional therapy, among those patients remaining in the ICU for 3 or more days, intensive insulin therapy was associated with a reduction in hospital mortality (ARR 9.5%, p=0.009) and ICU mortality (ARR 6.8%, p=0.05). Patients in the intensive insulin group also demonstrated improvements in morbidity, as shown by accelerated weaning from mechanical ventilation, shorter hospital and ICU stays, and less renal injury.

In both the medical ICU patients and the surgical ICU patients evaluated in the previous study, the intensive insulin groups had an approximate six-fold increase in hypoglycemic events, though the risk in medical ICU patients was more pronounced (18.7% compared to 3.1% in conventional group, p=0.001). Of note, no serious adverse clinical outcomes were attributed to hypoglycemic episodes in either study [18,20].

To further evaluate the benefits of intensive insulin therapy in various subpopulations of ICU patients, data from the two trials discussed previously were combined in a pooled dataset analysis [21]. Overall hospital mortality for the medical and surgical ICU was lower among individuals receiving intensive insulin therapy (ARR 3.2%, p=0.04). Compared to patients attaining blood glucose levels between 110 and 150 mg/dL, those with values exceeding 150 mg/dL had higher mortality rates (odds ratio [OR] 1.38, 95% CI 1.1-1.8). Furthermore, mortality was lower with blood glucose levels less than 110 mg/dL (OR 0.77, 95% CI 0.61-0.96), illustrating the importance of achieving strict glycemic control. The pooled data is consistent with results from the individual trials and demonstrated the highest reduction in mortality among patients remaining in the ICU for three or more days (ARR 7.8%, p=0.002). Subgroup analyses also revealed efficacy among patient populations with the following conditions: cardiovascular, respiratory, or gastrointestinal/ hepatic disease or surgery; active malignancy; and sepsis upon ICU admission. Interestingly, no survival benefit was observed among patients with a history of diabetes, although morbidity was significantly reduced.

Other clinical trials have also examined the use of intensive insulin therapy in the critical care setting, although the results are difficult to interpret and generalize due to significant limitations. A small prospective, randomized controlled study performed in a general surgical ICU population found that intensive insulin therapy reduced the incidence of nosocomial infections [22]. However, because this study included only 61 patients, power was insufficient to detect any difference in mortality.

Subsequently, a large observational study evaluated the effects of implementing a protocol targeting tight glycemic control in a heterogeneous ICU patient population [23]. In medical and surgical ICU patients (n=800), intravenous insulin was administered to patients with two or more consecutive blood glucose values exceeding 200 mg/dL. Following initiation of the protocol, the mean blood glucose value

**Table 1. Main Features of Clinical Trials Evaluating Tight Glycemic Control in the ICU Setting**

| Trial | Study Design | Patients | Comparator Groups | Findings | Comments |
|---|---|---|---|---|---|
| Van den Berghe *et al.* (*N Engl J Med* 2001) [18] | Single center prospective, randomized controlled trial | Surgical ICU patients receiving mechanical ventilation (N = 1548) | Intensive insulin therapy: Target blood glucose (BG) 80-110 mg/dL (mean 103 mg/dL)<br>Conventional therapy: Target BG 180-200 mg/dL (mean 153 mg/dL) | Mortality: Decreased in intention to treat and target group 5-day ICU stay<br>Morbidity: Decrease in bloodstream infections, acute renal failure requiring dialysis or hemofiltration, median number of red-cell transfusions, hyperbilirubinemia, and critical-illness-related polyneuropathy | History of diabetes in 13% of the patients<br>Hypoglycemia (blood glucose <40 mg/dL) occurred in 5.1% of patients in the intensive treatment group, as compared with 0.8% in the conventional treatment group |
| Van den Berghe *et al.* (*N Engl J Med* 2006) [20] | Single center prospective, randomized controlled trial | Medical ICU patients (N = 1200) | Intensive insulin therapy: Target BG 80-110 mg/dL (mean 105 mg/dL)<br>Conventional therapy: Target BG 180-200 mg/dL (mean 160 mg/dL) | Mortality: Decreased in target group (≥3 days in ICU) but no difference in intention-to-treat population<br>Morbidity: Decrease in myopathy, critical-illness-related polyneuropathy/mypotathy, new kidney injury, hyperbilirubinemia, duration of mechanical ventilation, ICU stay, and hospital stay | Same intravenous insulin titration protocol was used as in [17]<br>Patient population was generally less healthy as compared to previous study involving surgical ICU patients [17]<br>Potentially due to lack of power, no mortality benefit was observed in the intention-to-treat population<br>Hypoglycemia (blood glucose <40 mg/dL) in intensive insulin group was more pronounced compared to conventional group (18.7% versus 3.1%, $p<0.001$) |
| Van den Berghe *et al*. (*Diabetes* 2006) [21] | Meta-analysis of two previous studies [18,20] | Medical and surgical ICU patients (N = 2748) | Intensive insulin therapy: Target BG 80-110 mg/dL (mean 105 mg/dL)<br>Conventional therapy: Target BG 180-200 mg/dL (mean 152 mg/dL) | Mortality: Decreased in intention to treat and target group ≥3 days in ICU<br>Morbidity: Decrease in new kidney injury, critical-illness-related polyneuropathy<br>Subgroup Analyses: Efficacy present in the following subroups of patients: cardiovascular, respiratory, or gastrointestinal/hepatic disease or surgery; active malignancy; sepsis | Effects on mortality were most striking in patients remaining in the ICU for three or more days (ARR 7.8%, $p=0.002$)<br>Despite increased risk for hypoglycemia, no detectable clinical consequences of this adverse effect |
| Grey et al (*Endocr Prac* 2004) [22] | Single center prospective, randomized controlled trial | Surgical ICU patients (N = 61) | Intensive insulin therapy: Target BG 80-120 mg/dL (mean 125 mg/dL)<br>Conventional therapy: Target BG 180-220 mg/dL (mean 179 mg/dL) | Mortality: No difference between groups<br>Morbidity: Decrease in nosocomial infections | Small study<br>Inadequately powered to detect a difference in mortality<br>Surgical ICU patients only |

**(Table 1. Contd….)**

| Trial | Study Design | Patients | Comparator Groups | Findings | Comments |
|---|---|---|---|---|---|
| Krinsley et al (*Mayo Clin Proc* 2004) [23] | Observational study | Medical and surgical ICU patients (N = 1600) | Intensive insulin protocol: Target BG <140 mg/dL if 2+ consecutive BG levels over 200 mg/dL (mean 131 mg/dL) Historical control: Treatment of hyperglycemia was not standardized in baseline period (mean 152 mg/dL) | Mortality: Decreased compared to baseline Morbidity: Decrease in length of ICU stay, incidence of new kidney injury, need for transfusion, and healthcare costs | Retrospective review of patients admitted to a medical/surgical ICU before and after the implementation of a protocol advocating more strict glycemic control Use of historical controls in a non-randomized design |
| GLUCONTROL [24] | Prospective, randomized controlled, multicenter trial | Medical and surgical ICU patients (N = 855) | Intensive insulin protocol: Target BG 80-110 mg/dL (mean 118 mg/dL) Historical control: Target BG 140-180 mg/dL (mean 147 mg/dL) | | Trial halted early due to hypoglycemia Results presented at international symposium No formal publication Lack of statistical power to detect difference in mortality |
| VISEP Brunkhorst et al (*N Engl J Med* 2008) [26] | Multicenter, prospective, randomized, open-label, two-by-two factorial study | Multidisciplinary ICU patients with sepsis / septic shock (N=537) | Intensive insulin therapy: Target BG 80-110 mg/dL (mean morning glucose 112 mg/dL) Conventional therapy: Target BG 180-200 mg/dL (mean morning glucose 151 mg/dL) | Mortality: No difference between groups Morbidity: No difference between groups | Increased risk for severe hypoglycemia (≤40mg/dL), resulting in early termination of the trial Lack of statistical power to detect difference in mortality |

among ICU patients fell from 152 mg/dL to 131 mg/dL, with a 53% reduction in the percentage of blood glucose values 200 mg/dL or higher. Compared to the historical control group (n=800), hospital mortality during the protocol period decreased from 20.9 to 14.8% (ARR 6.1%, p=0.002). The study also revealed the following improvements: decreased ICU stay, reduced incidence of new renal injury, decreased need for transfusions, and reduced health care costs. Of note, achievement of lower blood glucose levels did not result in an increased risk for hypoglycemia.

Another trial marked by limitations is GLUCONTROL, a prospective, randomized, controlled, multicenter trial [24]. This study investigated the effects of strict glycemic control in a mixed critical care patient population. An intensive insulin therapy regimen was used to target blood glucose levels between 80 and 110 mg/dL. However, an interim analysis revealed that this target was only met in approximately 25% of patients, most likely related to unintentional protocol violations [25]. Furthermore, the rate of hypoglycemia was considered unacceptably high (10%). Thus, after considering these limitations, the steering and safety committee decided to stop enrollment in this trial. It is important to note, however, that the rate of hypoglycemia was comparable to other studies in the medical and surgical ICU [18,20].

As with the GLUCONTROL study, the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was also marred by an unacceptable rate of hypoglycemia [26]. Designed as a four-arm trial, the intent of this study was to compare two types of fluid resuscitation while also evaluating the efficacy and safety of intensive insulin therapy in patients with severe sepsis and septic shock. At the first planned safety analysis, the intensive insulin arm was halted due to significantly higher rates of hypoglycemia, defined by a blood glucose level less than 40 mg/dL, among patients treated with intensive insulin therapy compared to conventional therapy (17% versus 4.1%, $p<0.001$). Following premature discontinuation of the insulin arm of the trial, there was no significant difference in 90-day mortality between intensive and conventional insulin treatment groups.

To support the use of intensive insulin therapy in the critical care setting, a meta-analysis of 35 clinical trials has provided additional evidence showing a mortality benefit compared to conventional treatment (relative risk [RR] 0.85, 95% CI 0.75-0.97) [27]. Specifically, a subgroup analysis demonstrated improved mortality in the surgical ICU setting (RR 0.58, 95% CI 0.22-0.62). However, none of the trials included in this meta-analysis involved patients from the medical ICU, thus limiting the ability to generalize results to all patient care settings. Anticipated results from the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial may more clearly define the benefits of intensive insulin therapy in critical care settings [28].

## CLINICAL APPLICATIONS

Despite evidence to support maintaining target blood glucose levels in critically ill patients, unfortunately, several barriers to achieving these goals remain [29]. Reluctance to incorporate measures for strict glycemic control may be due to fear of hypoglycemic events or to skepticism among clinicians regarding its beneficial effects. Other potential barriers include limited hospital resources and complex educational efforts required to initiate change in practice standards.

While the support for intensive insulin therapy in the medical and surgical ICU setting is primarily based on two large randomized controlled trials, limitations of other clinical studies help to illustrate the inherent challenges of incorporating these measures into standard practice. As shown by the GLUCONTROL and VISEP trials, the risk of hypoglycemia is substantial and remains a valid concern among clinicians. Furthermore, the unintentional protocol violations in the GLUCONTROL trial point to the difficulty in achieving and maintaining strict glycemic control, especially in the absence of adequate education for healthcare providers.

According to the AACE/ADA Task Force on Inpatient Diabetes, fear of hypoglycemia has been cited as a universal barrier to achieving tight glycemic control among critically ill patients [29]. The risk for adverse events, particularly hypoglycemia, is an important consideration in the critical care setting. In particular, as demonstrated in one study, hypoglycemic symptoms are often difficult to recognize in critical care settings [30]. While most of the studies discussed previously have demonstrated an increased risk for hypoglycemia, the clinical consequences of this adverse event are not yet clear. In these previously discussed landmark trials, hypoglycemic episodes were transient and did not appear to result in other serious clinical sequellae. However, the incidence of hypoglycemia did coincide with a higher risk of death (corrected OR 3.2 and 2.9 in the surgical and medical ICU, respectively) [18,20]. In addition, the VISEP study revealed that hypoglycemia was an independent risk factor for death (hazard ratio 3.31, 95% CI 2.23-4.9) [26]. Therefore, it is possible that hypoglycemia may have neutralized, to some extent, the survival benefit demonstrated in these trials. On the other hand, rather than acting as an independent risk factor for death, the presence of hypoglycemia may have merely identified patients at risk for dying [31]. A recent nested-case control study has established no causal link between death and hypoglycemia in the ICU [32]. Nonetheless, based on current available data, it is impossible to determine the true clinical implications of hypoglycemia among ICU patients receiving intensive insulin therapy. In the future, accurate continuous glucose monitoring systems may become routinely used in critical care settings and could play a significant role in the prevention and management of hypoglycemia.

According to the ADA 2008 Standards of Medical Care in Diabetes guidelines, existing medical literature supports the use of intravenous insulin infusions in critically ill patients [13]. Although the evidence regarding the role of traditional subcutaneous sliding scale insulin in critical care settings is limited, it is apparent that the use of intravenous insulin is becoming more routine [33]. Many hospitals have incorporated insulin infusion protocols to standardize care for critically ill patients with hyperglycemia. Most published protocols involve titration of insulin infusions based on current blood glucose levels, as well as glycemic trends, in a standard yet individualized approach to patient care. To date, no head-to-head trials have compared the various published insulin infusion protocols, and thus no guidelines exist regarding a preference among these protocols. Continuous quality improvement measures should systematically evaluate the use of established protocols to assess efficacy, safety, and demands on hospital resources.

For any institution implementing a protocol to manage hyperglycemia in the critical care setting, cost remains an important consideration. While insulin infusion protocols often increase nursing staffing requirements, the long-term benefits of hyperglycemia management programs may offset these costs. In addition to improved clinical outcomes, cost savings have been demonstrated by the use of intensive insulin regimens in various inpatient settings. An economic analysis of the effect of an intensive glucose management protocol in critically ill adults has demonstrated a net decrease in healthcare costs by $1,580 per patient per admission [34]. Furthermore, consultation with a diabetes care team has been shown to reduce length of hospital stay by 56%, resulting in an estimated cost savings of $2,353 per patient per admission [35].

Since insulin is considered to be one of the highest risk medications in the inpatient setting, strict monitoring of insulin therapy often requires a team-based, multidisciplinary approach [29]. According to the Institute for Healthcare Improvement *Protecting 5 Million Lives from Harm* campaign, hypoglycemia resulting from inappropriate dosing or insufficient monitoring during insulin therapy is one of three preventable adverse drug events which together account for approximately half of all reported events [36]. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), an accrediting body that defines efficacy and safety standards for United States health-care systems, has recognized hospitals which make outstanding efforts to promote better outcomes across all inpatient settings [37]. JCAHO has identified that the most successful inpatient diabetes programs involve specific staff education, blood glucose monitoring protocols, patient education, and plans for managing hypoglycemia and hyperglycemia.

Support from healthcare providers is absolutely essential to the successful implementation of an insulin infusion protocol. Furthermore, an identified program champion or advocate can help to drive a change in practice [37]. While many clinicians realize the importance of achieving target blood glucose levels, the increased demand on nursing staff is often a barrier to routine use of intravenous insulin regimens. Insulin infusion protocols often rely on nurses to frequently monitor and adjust insulin therapy, and staff education and support are vital when incorporating these protocols into standard medical practice.

## SUMMARY

Hyperglycemia is common among critically ill patients and can increase the risk for adverse outcomes, including death. Implementation of protocols to achieve strict glycemic control in the critical care setting has been shown to reduce mortality, infectious complications, length of hospital stay, and overall healthcare costs. Despite the benefits of intensive insulin therapy, many barriers remain to achieving target blood glucose levels, including fear of hypoglycemia and limited healthcare resources. While intensive insulin regimens have been shown to be cost-effective, successful implementation of these protocols can be challenging for many institutions. A team-oriented, multidisciplinary approach when initiating these services must include adequate staff education and continuous quality improvement in order to provide optimal patient care.

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