Journal of Diabetes Science and Technology
Volume 5, Issue 3, May 2011

REVIEW ARTICLE

Intensive Insulin Therapy in Critically Ill Hospitalized Patients: Making It Safe and Effective

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Abstract

Intensive insulin therapy (IIT) for hyperglycemia in critically ill patients has become a standard practice. Target levels for glycemia have fluctuated since 2000, as evidence initially indicated that tight glycemic control to so-called normoglycemia (80–110 mg/dl) leads to the lowest morbidity and mortality without hypoglycemic complications. Subsequent studies have demonstrated minimal clinical benefit combined with greater hypoglycemic morbidity and mortality with tight glycemic control in this population. The consensus glycemic targets were then liberalized to the mid 100s (mg/dl).

Handheld POC blood glucose (BG) monitors have migrated from the outpatient setting to the hospital environment because they save time and money for managing critically ill patients who require IIT. These devices are less accurate than hospital-grade POC blood analyzers or central laboratory analyzers.

Three questions must be answered to understand the role of IIT for defined populations of critically ill patients: (1) How safe is IIT, with various glycemic targets, from the risk of hypoglycemia? (2) How tightly must BG be controlled for this approach to be effective? (3) What role does the accuracy of BG measurements play in affecting the safety of this method? For each state of impaired glucose regulation seen in the hospital, such as hyperglycemia, hypoglycemia, or glucose variability, the benefits, risks, and goals of treatment, including IIT, might differ.

With improved accuracy of BG monitors, IIT might be rendered even more intensive than at present, because patients will be less likely to receive inadvertent overdosages of insulin. Greater doses of insulin, but with dosing based on more accurate glucose levels, might result in less hypoglycemia, less hyperglycemia, and less glycemic variability.

J Diabetes Sci Technol 2011;5(3):755-767

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Abbreviations: (A1C) hemoglobin A1c, (AACE) American Association of Clinical Endocrinologists, (ACP) American College of Physicians, (ADA) American Diabetes Association, (BG) blood glucose, (CID) critical-illness-induced dysglycemia, (FDA) Food and Drug Administration, (ICU) intensive care unit, (IIT) intensive insulin therapy, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation, (POC) point-of-care, (TGC) tight glycemic control

Keywords: critical care, glucose, glucose monitoring, glucose variability, hyperglycemia, hypoglycemia, insulin, intensive, intensive care unit, point of care

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Introduction

In the United States, more than one in five hospitalizations are for people with known diabetes.[1] An additional one in five hospitalizations is for people with elevated hemoglobin A1c (A1C) levels on admission who were not previously known to have diabetes.[2,3] Transient hyperglycemia, even without a diagnosis of established diabetes, occurs frequently in critically ill hospitalized patients.[4,5] Hyperglycemia from any cause is associated with worse outcomes in proportion to the elevations in blood glucose (BG) levels.[6–10]

Intensive insulin therapy (IIT) is defined as delivering frequent or continuous doses of intravenous insulin that are intended to achieve tight glycemic control (TGC), which is currently defined by most intensivists as BG levels no more than 150 mg/dl. Intensive insulin therapy has been proposed as the treatment of choice for hyperglycemia in critically ill hospitalized patients.[11] This approach is controversial because of concerns about whether IIT is both safe and effective and whether barriers to its effective use must be overcome. No prospective trials have been conducted stratifying the effects of IIT on hyperglycemic patients with diabetes and with stress-induced hyperglycemia.

The term critical-illness-induced dysglycemia (CID) has been proposed to describe various states of glucose dysregulation seen in the hospital, such as hyperglycemia, hypoglycemia, and glucose variability.[12] For each of these three types of dysregulation, multiple risk factors might be responsible,[13] and for each disease, which is an example of CID, the benefits, risks, and goals of therapy, including IIT, might differ. Furthermore, even with appropriate application of IIT to critically ill intensive care patients, when these patients reach a lower level of acuity and transfer to a lower acuity hospital ward, they will still require glycemic management that is appropriate for their new, less acute status.

Controversies

Three significant controversies surround the use of IIT for defined populations of critically ill hospitalized patients with hyperglycemia: (1) How safe is IIT, with various glycemic targets, from the risk of hypoglycemia? (2) How tightly must BG be controlled for this approach to be effective? (3) What role does the accuracy of BG measurements play in affecting the safety of this method? Addressing these three controversies, respectively, involves (1) determining the safety of IIT for defined hospital outcomes, (2) setting appropriate glycemic effectiveness goals for inpatients, and (3) defining adequate performance of BG monitoring technology in the hospital. This article analyzes these three controversies by reviewing the safety and effectiveness of IIT as well as the performance of currently available glucose monitoring technology that is used for treating hyperglycemia in critically ill patients.

Determining the Effects of Hyperglycemia on Hospital Outcomes

Stress Hyperglycemia

In hospitalized patients, hyperglycemia may occur because of a combination of increased production of catabolic hormones, increased hepatic gluconeogenesis, and resistance to the peripheral and hepatic actions of insulin.[14] Excessive administration of glucose can also give rise to hyperglycemia. Stress hyperglycemia, compared with the hyperglycemia of diabetes, appears to confer a higher risk of mortality,[12] possibly because of differences in the pathophysiology and the natural history of these two states of hyperglycemia.[15] In a retrospective observational study for a high A1C cohort, however, survivors showed a trend toward higher glycemia; whereas in a lower A1C cohort, survivors showed a trend toward lower glycemia. This study generated a hypothesis that glucose levels that are considered safe and desirable in patients without diabetes might be undesirable and too low for patients with diabetes who have chronic hyperglycemia.[16]

Until the 21st century, stress hyperglycemia was thought to promote cellular uptake of glucose in non-insulin-dependent tissues and provide a buffer against hypoglycemia-induced brain damage. Moderately elevated BG levels were considered to be beneficial.[17] Stress hyperglycemia associated with BG levels as high as 160–200 mg/dl was regarded as not requiring treatment.[18]

Benefits of Glycemic Control

Tight glycemic control of a study population was first administered in the nonrandomized, observational, prospective, ongoing Portland Diabetes Project, which began in 1992. In this trial, cardiac surgery patients with diabetes received intravenous insulin to control

BG levels.[19] A series of three articles by Furnary and colleagues[20–22] between 1997 and 2003 reported the benefits of glycemic control in this study population. The first article presented an observational study showing that the incidence of postoperative wound infections in diabetic patients was reduced after implementation of a protocol to maintain mean BG levels below 200 mg/dl in the immediate postoperative period. Data were collected by retrospective chart review. Glucose control lowered the risk of sternal wound infection in patients with diabetes after implementation of a protocol to maintain mean BG levels below 200 mg/dl in the immediate postoperative period.[20] In the second article, a prospective sequentially controlled trial of an intensive insulin protocol of intravenous insulin every 1–2 h intended to maintain BG between 150 and 200 mg/dl was compared with control therapy of subcutaneous insulin every 4 h intended to maintain BG levels at or below 200 mg/dl. The intensive protocol, compared with the control protocol, resulted in lower daily mean glucose levels, starting on the day of surgery as well as on each of the first three postoperative days. In the continuous intravenous insulin infusion group, there was a significant reduction in the incidence of deep sternal wound infections compared with the subcutaneous intravenous insulin infusion group (0.8% versus 2.0%, $p = .01$).[21] In the third article, the same two insulin protocols were compared in a prospective sequential evaluation conducted on heart surgery patients with diabetes. The observed mortality with continuous insulin infusion was significantly lower than with subcutaneous insulin administration (2.5% versus 5.3%, $p < .0001$).[22]

In 2001, the benefits of IIT intended to correct hyperglycemia, compared with standard subcutaneous insulin therapy, were noted to extend also to hyperglycemic patients without a known history of diabetes. That year, a landmark study by Van den Berghe and colleagues[23] in Leuven, Belgium, compared morbidity and mortality of IIT (BG goal 80–110 mg/dl, which the authors considered to represent normalization of glucose levels, with intravenous insulin initiated at a BG level exceeding 110 mg/dl) against conventional therapy (BG goal 180–200 mg/dl, with intravenous insulin initiated at a BG level exceeding 215 mg/dl) in critically ill hyperglycemic surgical intensive care unit (ICU) patients. Intensive insulin therapy resulted in both lower ICU and lower in-hospital mortality. Other benefits of IIT in this Leuven study[23] included decreases in mechanical ventilation duration and incidences of bloodstream infections, acute renal failure, critical illness polyneuropathy, and transfusion requirements. Hypoglycemia (defined as a BG level of ≤40 mg/dl) occurred in 39 of the 765 subjects in the IIT group and in 6 of the 783 subjects in the conventionally treated group. No p value was reported for this difference. Two subjects treated with IIT reported hypoglycemia associated with sweating and agitation, but there were no instances of hemodynamic deterioration or convulsions. No neuropsychological testing or long-term follow-up assessments of the hypoglycemic subjects were reported. The subjects in the Leuven study received a large percentage of their calories parenterally (intravenously).

A later study in 2006 by Van den Berghe's group[24] in Leuven, using a similar IIT regime in medical ICU subjects, did not reduce the mortality overall, but it did reduce morbidity in the IIT subjects and also reduced mortality in a subset of subjects who remained in the ICU for three or more days. In this second Leuven study, the prevalence of severe hypoglycemia was greater in the IIT arm than in the control treatment arm, but the hypoglycemic episodes in both treatment groups were not associated with any adverse clinical consequences.

Meta-Analyses of Intensive Insulin Therapy in Critically Ill Patients

A meta-analysis of studies using IIT to achieve TGC (goal less than 150 mg/dl) compared with usual care (glucose goal and method of insulin administration could vary between studies) was published in 2008 (29 randomized controlled trials totaling 8432 patients).[25] The authors concluded that, in critically ill adult patients, TGC is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia. Among the 27 trials that presented mortality data as an endpoint, 16 favored tight control and 11 favored usual care. The relative risk reductions were statistically significant (at a 95% confidence interval) in only 2 of the 16 studies that favored tight control and none of the 11 studies that favored usual care. The only beneficial outcome from tight control was demonstrated by a significantly reduced risk for septicemia; however, this benefit was limited to surgical ICU patients and not medical ICU patients.

A second meta-analysis of TGC (goal no more than 150 mg/dl) in 2009 (26 trials totaling 13,567 subjects) concluded that IIT significantly increased the risk of hypoglycemia six-fold and conferred no overall mortality benefit among critically ill patients.[26] This analysis suggested that IIT, compared with control therapy, might benefit patients admitted to surgical ICUs with a resulting mortality risk ratio of 0.63 (95% confidence interval 0.44–0.91) but would not benefit patients admitted to medical ICUs or mixed medical–surgical ICUs.

A third meta-analysis of TGC (goal 80–110 mg/dl) in 2010 (7 randomized controlled trials totaling 11,425 subjects) concluded that there was no evidence to support the use of IIT in medical or surgical ICU patients fed orally.[27] The analysis revealed that TGC did not reduce the 28-day mortality, the incidence of sepsis, or the requirement for renal replacement therapy. The incidence of hypoglycemia was significantly higher in patients randomized to TGC. There was a statistically significant relationship between the proportion of calories provided parenterally and mortality. The authors speculated that excessive parenteral glucose in the absence of IIT leads to hyperglycemia and increased cellular glucose uptake, which, in turn, is associated with increased mortality. They also concluded that TGC is associated with a high incidence of hypoglycemia and an increased risk of death in patients not receiving parenteral nutrition.

A fourth meta-analysis of TGC (goal no more than 150 mg/dl) in critically ill patients (26 trials totaling 13,567 subjects) was reported in late 2010. This study assessed whether IIT has a differential effect in critically ill patients with either a surgical diagnosis or a medical diagnosis.[28] This study reanalyzed the 2009 meta-analysis data[26] and categorized the surgical and medical subgroups by the type of patient rather than type of ICU, as was done in the prior study. The authors classified every subject from mixed medical–surgical ICUs as either medical or surgical and combined these subjects' data with data from subjects already classified as being in either a medical or surgical ICU. The mortality data were then reanalyzed for all the medical and surgical subjects. The authors concluded that, although there had been statistical heterogeneity in the surgical subgroups, with some trials demonstrating significant benefit and others demonstrating significant harm, no surgical subgroup consistently benefited from IIT. Therefore, this reanalysis of the 2009 meta-analysis concluded that IIT has not been shown to reduce mortality in either critically ill surgical patients or medical patients.

A fifth meta-analysis of TGC (target glucose below 120 mg/dl) was reported in 2011 for hospitalized patients in multiple hospital settings (21 randomized controlled trials comprising 14,768 patients), including ICU, perioperative care, myocardial infarction, and stroke or brain injury settings.[29] Intensive insulin therapy was not associated with benefit for short-term mortality (28-day, hospital, or ICU mortality). No evidence of benefit from IIT was reported in any hospital setting, and the clearest evidence for lack of benefit was demonstrated in ICU settings. The risk for IIT-associated hypoglycemia was increased in all hospital settings. Based on the specified lower limit for inclusion, the first Leuven study was excluded. The authors concluded that: (1) there is no consistent evidence to demonstrate that IIT targeted to strict glycemic control compared with less strict glycemic control improves health outcomes in hospitalized patients; and (2) IIT is associated with an increased risk for severe hypoglycemia. See **Table 1** for a summary of the five meta-analyses of IIT for critically ill patients with hyperglycemia.

Multicenter Studies

Since 1996, two large multicenter randomized controlled trials of in-hospital IIT have been halted. The European

Table 1.
Meta-Analyses of Randomized Controlled Trials of Intensive Insulin Therapy for Critically Ill Patients with Hyperglycemia[a]

First author	Year	Number of trials	Number of subjects	Type of subjects	BG target (mg/dl)	Risk of hypoglycemia	Risk of morbidity
Wiener[25]	2008	29	8432	SICU and MICU	<150 mg/dl	Increased	No ↓ in SICU, no ↓ MICU, no ↓ mixed MICU/SICU
Griesdale[26]	2009	26	13,567	SICU, MICU, and mixed SICU/MICU	≤150 mg/dl	Increased	Yes ↓ SICU, no ↓ MICU, no ↓ mixed MICU/SICU
Marik[27]	2010	7	11,425	SICU and MICU	80–110 mg/dl	Increased	No ↓ in any subjects
Friedrich[28]	2010	26	13,567	SICU, MICU, and mixed SICU/MICU	≤150 mg/dl	Increased	No ↓ SICU and no ↓ MICU
Kansagara[29]	2011	21	14,768	SICU, MICU, mixed SICU/MICU, MI, and brain	<120 mg/dl	Increased	

[a] SICU, surgical ICU; MICU, medical ICU; MI, myocardial infarction; brain, acute cerebrovascular accident or brain injury

Glucontrol study was launched in 2002 by the working group on metabolism and nutrition of the European Society of Intensive Care Medicine and was endorsed by the European Critical Care Research Network.[30] Twenty-one ICUs participated. Mixed medical–surgical ICU patients were randomized to receive either IIT (target glucose 80–110 mg/dl) or conventional treatment (target glucose 140–180 mg/dl). The study was halted in 2006 because of a high rate of unintended protocol violations consisting of high proportions of glucose values outside of the target ranges. The proportions of BG values in the target ranges at the time of the interim analysis were 27.8% in the intensive group and 54.8% in the conventional group. It should be noted that the protocol did not specify a particular method for monitoring glucose. The rate of hypoglycemia was higher in the intensive group than in the conventional group (8.7% versus 2.7 %, $p < .0001$). Intensive care unit mortality was similar in the two groups. The failure to consistently achieve target levels of glycemia in this trial and other trials of IIT raises a question as to whether the higher incidence of hypoglycemia in IIT (versus conventional therapy) was due to protocol violations or whether it was an inherent risk of IIT to meet tight glycemic targets. In the former case, the problem lies not with IIT, but with its execution, and in the latter case, the need for higher glycemic targets would be demonstrated.[31]

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis or VISEP study was a German multicenter trial conducted at 18 academic tertiary hospitals, which began recruiting in 2003.[32] The trial was a two-by-two factorial design comparing randomized ICU patients with severe sepsis to either IIT or conventional therapy and either 10% pentastarch or modified Ringer's lactate for fluid resuscitation. Intensive insulin therapy was terminated early in 2005 because of an increased number of hypoglycemic events, compared with conventional insulin therapy (12.1% versus 2.1%, $p < .001$). The morbidity and mortality rates did not differ significantly between the IIT and conventional therapy groups.

The benefits of IIT were further thrown into question in 2009 when the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was completed.[33] This study was the first completed multicenter mixed-patient ICU population study that adequately addressed the issue of TGC versus conventional glucose control and the effects of hypoglycemia. This trial included 6104 subjects and compared outcomes in critically ill patients receiving either IIT (target glucose of 81–108 mg/dl) or conventional glucose control (target glucose below 180 mg/dl). The mean BG levels achieved were 107 mg/dl in the intensive group and 144 mg/dl in the conventional group. This study demonstrated a significant increase in the mortality from cardiovascular causes in the IIT arm compared with the conventional group, and there was no significant difference in morbidity between the two groups in terms of renal replacement therapy or number of days of mechanical ventilation. Methodological differences have been proposed to account for the observed differences in mortality and morbidity between the first Van den Berghe and NICE-SUGAR studies.[34,35] See **Table 2** for a list of these methodological differences.

Another large multicenter study, the Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults or COIITSS study reported in 2010 that, compared with conventional insulin therapy, IIT did

Table 2.
Methodological Differences between the First Van den Berghe and NICE-SUGAR Studies

Protocol feature	Van den Berghe study of 2001[23]	NICE-SUGAR study[33]
Number of sites	1	41
Number of subjects	1548	6104
Diagnoses of subjects	Only surgical	Surgical and medical
Comparator glycemic target range (mg/dl)	180–215	140–180
Source of blood	Arterial	Arterial and capillary
Instrument for measuring BG	Blood gas analyzer	Multiple instruments
Simultaneous measurement of potassium with each glucose measurement	Yes	No
Portal of intravenous insulin delivery	Central venous intravenous line	Peripheral intravenous line
Route of feeding	Mostly parenteral	Mostly enteral
Data points that fell within target glycemia in the study group	70%	<50%

not improve in-hospital mortality among patients who were treated with hydrocortisone for septic shock.[36] Although the potential benefits of IIT have generally not been realized in mixed-patient ICU populations, the benefits of IIT are nevertheless being studied for specific subpopulations of ICU patients. No results of the effects of IIT on outcomes for hospitalized non-ICU patients have been reported from randomized controlled trials, although observational studies have demonstrated poor outcomes linked to hyperglycemia.[37]

Risks of Insulin Therapy in the Hospital

Insulin is a powerful drug that is known to be associated with adverse drug reactions in hospitalized patients. An evaluation in 2010 of almost 50 million claims from Medicare and privately insured patients identified the drugs most frequently associated with reports of adverse drug reactions in the hospital. Insulin was in the top 12.[38] According to the U.S. Pharmacopeia, compared with other medications, insulin is twice as likely to result in harm if it is involved in a medication error, and these errors are most commonly due to omission or improper dosing of insulin.[39] Careful patient monitoring is needed to prevent hypoglycemia when IIT is administered.

Large randomized controlled IIT trials of medical and surgical hyperglycemic patients, as well as subset analyses from these trials, have not clearly identified any groups who have benefited from this approach.[25–28] Furthermore, the subset analyses have generally not been powered to look for such associations. For patients with diabetes undergoing heart surgery, the benefits of IIT have been shown to exceed the risks in nonrandomized trials.[19] For many types of critically ill hyperglycemic patients, the morbidity associated IIT, which is an increased incidence of hypoglycemia, appears to outweigh the benefits of TGC, such as the glycemic levels that weretargeted in the single-center Leuven protocols.[40] Therefore, for every critically ill hospitalized hyperglycemic patient, a decision to deliver IIT must balance the potential benefit of this approach (the prevention of hyperglycemic complications) against the safety of this approach (the risk of inducing hypoglycemia). It is unclear whether hypoglycemia is a cause of adverse outcomes or whether this state is a marker for more severe intercurrent disease. Treatment decisions will be influenced by patients' diagnoses at admission, their risk factors for morbidity and mortality, the aggressiveness of the IIT protocol, and the hospital team's experience in delivering such care.

Setting Appropriate Glycemic Goals for Inpatients

Consensus Guidelines for Inpatient Glycemic Control

The first Leuven study was well received by the endocrinology community.[41] In 2004, three years after this study was published, the American College of Endocrinology and the American Association of Clinical Endocrinologists (AACE) developed a set of consensus guidelines for inpatient glycemic control. Their upper limits for glycemic targets were 110 mg/dl in the ICU, 110 mg/dl fasting for non-critical-care patients, and 180 mg/dl as a maximal level.[42] The American Diabetes Association (ADA) first reported recommended goals for BG levels in the hospital in 2005. Their recommendations specified that, for critically ill patients, BG levels should be kept as close to 110 mg/dl as possible and generally below 180 mg/dl and, for non-critically ill patients, premeal BG levels should be kept as close to 90–130 mg/dl as possible and postprandial glucose levels should be kept below 180 mg/dl.[43] Subsequently, new evidence was reported that disputed the benefits of very tight glycemic control of hospitalized diabetic patients and suggested that this type of approach might lead to unsafe hypoglycemia.

The Endocrine Society issued a statement on the day that the NICE-SUGAR study was published in 2009. This society made two points. First, near-normalization of blood sugar does not clearly improve outcomes in all critically ill hyperglycemic ICU patients, and there is even a suggestion that such an approach may worsen outcomes. Second, looser control of hyperglycemia, i.e., target BG of 144–180 mg/dl, is a reasonable, and perhaps preferable, option in this particular group of very sick patients.[44]

The AACE and the ADA responded to the publication of the NICE-SUGAR data and developed a set of updated recommendations for inpatient hyperglycemia later in 2009. These two organizations reported their conclusions simultaneously in their associations' own publications.[45,46] These latest recommendations no longer advocated IIT as had been the case for the AACE and the ADA, respectively, in 2004 and 2005. See **Table 3** for the 2009 AACE/ADA consensus recommendations for treatment of hyperglycemia of inpatients. This latest set of consensus recommendations is currently well received. No significant evidence has emerged since this report was issued to make it likely that yet another set of glycemic targets will be recommended in the near future.

Table 3.
American Association of Clinical Endocrinologists and American Diabetes Association Consensus Recommendations for Treatment of Hyperglycemia of Inpatients

	Critically ill patients	Non-critically ill patients
Threshold for initiating insulin therapy	Persistent hyperglycemia of 180 mg/dl or greater	Already on insulin
Target glucose level	140–180 mg/dl	Premeal <140 mg/dl and postmeal <180 mg/dl
Preferred route of insulin administration	Intravenous with frequent glucose monitoring	Subcutaneous with basal, nutritional, and correction components

On February 15, 2011, the American College of Physicians (ACP) presented a guideline for the use of IIT for the management of glycemic control in hospitalized patients with hyperglycemia.[47] The ACP recommended (1) not using IIT for strict BG control in non-surgical/medical ICU patients with or without diabetes mellitus, (2) not using IIT to normalize BG in surgical/medical ICU patients with or without diabetes mellitus, and (3) aiming for a target BG level of 140 to 200 mg/dl if insulin therapy is used in surgical/medical ICU patients. The ACP guideline authors allowed that the evidence is not sufficient to give a precise range for BG levels, but they nevertheless concluded that target values of 140 to 200 mg/dl are a reasonable option in ICU patients because insulin therapy targeted at BG levels 140 to 200 mg/dl is associated with similar mortality outcomes as IIT targeted at BG levels of 80 to 110 mg/dl, and this higher target range is associated with a lower risk for hypoglycemia. The ACP authors stated that published studies do not provide sufficient information to determine whether allowing BG levels to even increase above the range of 180 to 200 mg/dl is associated with similar outcomes to those seen at lower target levels.

The 200 mg/dl upper limit of the target range for IIT advocated by the ACP was not well received by three organizations composed of mostly endocrinologists. The AACE and the ADA released a joint statement in response to the ACP guideline. They maintained that an upper limit of 180 mg/dl is safe and justified by data on benefits of glycemic control and the harms of uncontrolled hyperglycemia.[48] The Endocrine Society also responded to the ACP guideline and also expressed support for an upper target level of 180 mg/dl to minimize an increased risk of infections, longer hospital stays, and mortality associated with BG levels above 180 mg/dl.[49]

Glycemic Variability

Glycemic variability is a factor related to BG levels that has been proposed to be a risk for complications.[50] Glycemic variability has been found to be associated with an increased risk of mortality;[51,52] however, an analysis of the two Leuven studies revealed that this IIT intervention decreased mean glucose levels and mortality but did not decrease glycemic variability.[53] There is no clear agreement on the best measure for expressing glycemic variability[54] and no clear consensus on an ideal degree of glycemic variability in hospitalized critically ill patients.[55]

Hospital Factors

The shifts in targeted glycemic levels—initially toward and later away from intensive glucose control—reflect a dearth of high-quality outcomes data in the field of hospital management of diabetes. It appears that the net benefits of intensive control will have to account for not only potentially improved hospital outcomes but also an inevitable increase in the incidence of hypoglycemia.[56] An important factor that must be accounted for when a hospital sets out to provide IIT in the ICU is the time resource needed for nurses to monitor BG levels frequently in order to dose insulin frequently and monitor the safety and effectiveness of this type of intervention. For example, at the University of California at San Francisco Medical Center, it has been estimated that each BG determination requires 7 minutes of nursing time, and a nurse caring for two patients on an intensive insulin protocol would spend approximately 2 hours of a 12-hour shift to monitor patients, obtain samples, perform tests, and intervene.[57]

For any particular hospital to adopt consensus guideline target BG levels into local protocols, the hospital's staff must consider: (1) their own mix of patients according to diagnoses and tolerance of hypoglycemia; (2) their available staffing for delivering IIT; (3) current limitations of laboratory and regulatory science for accurately monitoring glucose levels and using this information to determine insulin doses; and (4) the evolving nature of best practices for management of diabetes in the hospital.

Improving the Performance of Blood Glucose Monitors in the Hospital

Methods for Measuring Blood Glucose in the Intensive Care Unit

Achievement of target levels of glycemia requires timely and accurate measurement of glucose levels. The central laboratory can provide the most accurate results[58] but is generally unable to turn around specimens sufficiently

quickly for hourly adjustments of insulin dosages. Measurements can also be made at or near the bedside by point-of-care (POC) handheld BG monitors or by nonhandheld hospital-grade POC blood analyzers.

Point-of-care glucose monitoring instruments include: (1) handheld BG monitors that are marketed in the hospital environment unchanged from the home product; (2) handheld BG monitors that have been repackaged as hospital-specific products with the same measurement technology and special data management systems; or (3) hospital-grade blood analyzer devices such as blood gas analyzers or BG analyzers, which are not handheld and also not intended for self-monitoring of blood glucose.[59] Specimens for blood analyzers are not transferred onto strips as with handheld BG monitors. A specimen to be assayed by a blood analyzer may be sampled from a syringe, which is typical for arterial blood gas analyzers that also measure glucose. A specimen to be assayed by a blood analyzer may also be sampled from a collection tube (either as whole blood or, following centrifugation, as a plasma specimen), which is typical for dedicated glucose analyzers. Almost all hospital ICUs use either POC handheld BG monitors or hospital-grade arterial blood analyzers to measure glucose, because they provide rapid readings, which are critically important for patient care.

Arterial blood gas analyzer instruments located in the ICU have been demonstrated to deliver greater accuracy than handheld BG monitors.[60,61] There is little data available regarding the performance of any handheld POC devices in the low glucose range where it is important to measure glucose accurately.[60] An advantage of using a blood gas analyzer (compared with a handheld glucose monitor) for POC glucose monitoring is the simultaneous availability of a potassium measurement with each sample. Insulin induces a shift of potassium from the extra-cellular to the intracellular compartment, which can lead to hypokalemia and subsequently life-threatening arrhythmia. Undetected hypokalemia may have possibly contributed to the excess cardiovascular deaths in NICE-SUGAR and other trials of IIT that did not measure glucose exclusively with blood gas analyzers.[34]

Handheld Blood Glucose Monitors

Handheld POC monitors offer many advantages over blood analyzers,[62] and they are used by most hospital ICUs far more frequently than blood analyzers for measuring glucose rapidly. **Table 4** lists these advantages. The use of handheld POC instruments, compared with blood analyzers, saves time, money, and effort.

The greatest threat to accurate performance of handheld POC blood glucose monitors, whether in the hospital or the outpatient setting, is enzyme degradation, which can occur with either improper storage of strips or use of expired strips. Two factors that can contribute to the problematic accuracy of handheld POC glucose monitors when they are used in the ICU are: (1) misuse of strips by testing samples from arterial or venous sources rather than capillaries, for which they are intended; and (2) the pathophysiology of critical illness that can result in decreased cutaneous perfusion, extremes of hematocrit, oxygenation, and pH, and the use of medications that interfere with the measurement of glucose.[63,64]

Effect of Accurate Blood Glucose Measurement on Insulin Dosing

Many studies of TGC have used handheld POC blood glucose monitor readings for adjusting insulin doses. For example, the pivotal NICE-SUGAR trial specified that "blood samples for glucose measurement were obtained by means of arterial catheters whenever possible; the use of capillary samples was discouraged. Blood glucose levels were measured with the use of point-of-care or arterial blood gas analyzers or laboratory analyzers in

Table 4.
Advantages of Handheld POC Blood Glucose Monitors over POC Blood Analyzers[a]

Feature	Handheld BG monitor[b]	Blood analyzer
1. Space requirement	4 inches	25 inches
2. Weight and portability	4 ounces and portable	70 pounds and stationary
3. Suitability for bedside testing	Yes	No
4. Throughput time per specimen	60 s or more	10 s or less
5. Purchase cost per instrument	$100	$10,000 or more
6. Routine maintenance by technician	Not necessary	Necessary
7. Frequency of malfunctioning	Infrequent	Frequent
8. Calibration frequency	Once per day	Several times per day
9. Standard reference materials	Not necessary	Necessary
10. Blood volume per specimen	1 µl	5 ml

[a] Figures are typical.
[b] Handheld BG monitors have not been approved for use in ICU or acute care settings. The accuracy necessary for acceptable performance by these monitors in ICU or acute care settings is currently under scrutiny by regulatory and standards organizations.

routine use at each center."[34] In the 2008 meta-analysis of TGC, the glucose measurement method was described in only 10 of the 27 studies.[25] The three 2009 and 2010 meta-analyses did not analyze the methods of BG measurement.[26–28] It might be significant that, in the Van den Berghe and colleagues[23] study of 2001, which is the most quoted study demonstrating benefits of TGC, a precise blood gas analyzer (the ABL700 by Radiometer Medical of Copenhagen, Denmark) was used to measure arterial BG. Few hospital ICUs use such accurate, but difficult to maintain (compared with BG monitors), equipment. In a follow-up trial to the Leuven study, also known as the second Leuven study, the same group preferentially used arterial BG measured on a blood gas analyzer, but when arterial blood was unavailable, they also measured capillary blood with a POC hospital blood analyzer.[24]

One important reason why many of the IIT studies failed to deliver decreased hyperglycemia along with no increase in hypoglycemia may be the methods and samples used to measure glucose. Insulin doses, which are determined by a sliding scale based on measured BG levels, can be more or less than the needed amounts if the BG levels are inaccurately measured.[59] Any time that TGC in the hospital is targeted and more intravenous insulin is administered than actually needed, there will be an increased risk of inadvertent iatrogenic hypoglycemia. Improved accuracy of BG monitors, when IIT is delivered, would be expected to result in less hypoglycemia.[65] The source of blood for glucose testing matters. Typically, BG values are highest from arterial, lowest from venous, and in between for capillary specimens.[66] According to the ADA and World Health Organization, venous peripheral plasma is the preferred system for measuring glucose for diagnosing diabetes mellitus.[67] If a sliding-scale insulin dose is based on sampling from the venous compartment and then a sample is obtained from another compartment with higher glucose levels, then the outcome might be an excessive insulin dose resulting in hypoglycemia. This difference between either capillary or arterial BG compared with venous BG is magnified in the postprandial state, during poor perfusion, and with polycythemia.[59]

Two empirical studies compared insulin dose during IIT based on a reference glucose method with insulin dose based on handheld glucose meter values as a primary outcome measure.[68,69] Both studies found that use of these glucose meters resulted in frequent insulin dosing errors. One study concluded that, because only small insulin dosing errors were observed with meters, their use was acceptable.[69] The other study concluded that overestimation of glucose at low glucose values on handheld glucose meters was problematic. In this study, (1) handheld glucose meter analysis of capillary blood, (2) POC handheld glucose meter analysis of arterial blood, and (3) blood gas/chemistry analysis of arterial blood were all compared with central laboratory analysis of plasma. Compared with the reference method, glucose meter analysis of both arterial and capillary blood tended to provide higher glucose values, whereas blood gas/chemistry analysis of arterial blood tended to yield lower glucose values. The magnitude of the differences in the glucose values offered by the different methods of glucose measurement led to frequent clinical disagreements regarding insulin dose titration in the context of an insulin infusion protocol for aggressive glucose control.[68]

Handheld BG monitors are currently approved by the U.S. Food and Drug Administration (FDA) for use both by lay users at home or by health care professionals in clinical settings, including hospitals, for ongoing management of diabetic patients.[61] There is currently no distinction between performance requirements for home use and professional use. The FDA is currently weighing new stricter industry guidelines for BG monitors.[65] Two documents currently under development deal with BG meter performance. One is ISO 15197, "*In Vitro* Diagnostic Test Systems—Requirements for Blood Glucose Monitoring Systems for Self-Testing in Managing Diabetes Mellitus," from the International Organization for Standardization, which addresses BG monitor performance in the outpatient setting. The other is POCT12-A3, "Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities," from the Clinical and Laboratory Standards Institute, which addresses BG monitor performance in hospitals and long-term facilities. The FDA might eventually elect to adopt recommendations from these guidelines in part or in full.

Future Methods for Measuring and Controlling Blood Glucose Levels

In the future, glucose levels in critically ill hospitalized patients will be measured continuously and automatically in real time.[70,71] Real-time continuous glucose monitors will contain both predictive alarms,[72] for when glucose levels are progressing toward unsafe threshold levels, and threshold alarms,[73] for when glucose levels are actually exceeding predetermined safety threshold levels. This type of technology has been demonstrated to measure glucose levels in critically ill children with a mean absolute relative difference between continuous glucose monitor and BG readings of 15.3%,[74] which

is approximately as accurately as the measurements in outpatients,[75] and to reduce the incidence of hypoglycemia in critically ill patients.[76] Currently, only subcutaneous continuous glucose sensors are FDA approved,[77,78] but in the future, microdialysis-based[79] or intravenous glucose sensors might become available as well.[80]

Intensive insulin therapy can be controlled by printed or computerized algorithms that assign a continuous insulin infusion rate.[81] The dose is determined by various factors, which include the patient's current BG level, weight, and state of insulin resistance, as well as the current insulin infusion rate and the rate of glycemic change. A potentially desirable feature of a computerized hospital insulin delivery system, which could be linked to a continuous glucose monitor, would be a low-glucose shutoff feature. This system would activate to turn off insulin delivery and protect from hypoglycemia in situations where a continuous glucose monitor detects a glucose level below a hypoglycemic safety level. A low glucose insulin delivery shutoff system is currently available as part of a sensor-augmented subcutaneous infusion pump for outpatients.[82] This product is available in Europe but is not approved by the FDA for use in the United States. The ultimate goal for TGC will be a fully closed-loop system, known as an artificial pancreas, which will respond to glucose and nonglucose inputs and deliver a continuously variable and appropriate dose of infused insulin to automatically maintain BG levels in a target range.[83]

Conclusions

Intensive insulin therapy intended to avoid hyperglycemic complications is arguably a laudable goal. The difficulty with adopting this approach is finding a target level of glycemia and a protocol that will be both safe and effective for the patient, and it is not established that TGC can be achieved safely on a routine basis. The first decade of the 21st century has been marked by swings in the consensus recommendations for targets of glycemic control for critically ill patients in hospital ICUs. The 2001 Leuven study demonstrated that glucose levels of 80–110 mg/dl, which are physiologic for non-critically ill patients, can be achieved with lower mortality and morbidity and no increase in severe hypoglycemia. This approach sparked a new enthusiasm to provide critically ill hyperglycemic inpatients with IIT to achieve euglycemia, rather than to simply avoid severe hyperglycemia. Subsequently, many studies failed to replicate the safety and effectiveness of this study. There may have been features of the design and execution of the Leuven protocol that are unique to that hospital and did not translate to the same outcomes at other hospitals.

At the beginning of the first decade of the 21st century, the consensus optimal targets for critically ill inpatients were lowered significantly to the 80–110 mg/dl range from where they had been in the 20th century, which was the low 200s. This sea change in management of diabetes in the hospital was thanks, in large part, to the success of the 2001 Leuven study. Later during the decade, the consensus goals were changed again and raised to the mid 100s (mg/dl) at most hospitals. This reversal was in response to newer data from other hospitals or studies where the low target levels achieved at Leuven in 2001 were associated with hypoglycemic complications and no clinical benefit at the other hospitals. Currently, many endocrinologists and intensivists believe that, if new technology could be developed to permit greater accuracy for glucose monitoring in the ICU, then it might be possible to deliver more IIT in higher doses with lower risks of inadvertent overdosages due to inaccurate glucose readings. This hypothesis will need to be tested empirically when better hospital glucose measurement methods become available.

For critically ill hospitalized patients, specific BG target levels have varied over time as new evidence has accumulated. The underlying goals of IIT for critically ill patients, however, will likely continue to consist of careful implementation of treatment protocols and avoidance of hypoglycemia, hyperglycemia, and glycemic variability.

Acknowledgement:

I thank Douglas B. Coursin, M.D., and Brenda Fahy, M.D., FCCP, FCCM for their assistance in preparing this article.

Disclosures:

Dr. Klonoff is a consultant for C8 Medisensors, Inc.; Insuline Medical Ltd.; LifeScan, Inc.; Medtronic Diabetes; Merck; and Roche Diagnostics.

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