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Perioperative Glucose Control

What Is Enough?

TYPE 2 diabetes mellitus, impaired fasting glucose/impaired glucose tolerance, and stress-induced hyperglycemia (SIH) are ubiquitous in the adult population and represent major public health concerns.[1] Almost 10% of adult Americans have type 2 diabetes mellitus, an additional 20–25% have impaired glucose tolerance/impaired fasting glucose, and an unknown number develop SIH. Upwards of one third of affected patients are unaware of the presence of dysglycemia and its systemic effects.[1] Projections predict a continued, dramatic increase in the incidence and prevalence of type 2 diabetes over the next several decades, with its deleterious impact on quality of life and life expectancy. In this issue of ANESTHESIOLOGY, Drs. Lipshutz and Gropper address the impact of dysglycemia on perioperative management.[2]

Patients with diabetes require acute and critical care, procedural interventions, and hospitalizations more commonly than those with normal glucose tolerance.[3] When patients with diabetes require hospitalization or undergo certain procedures, they sustain greater morbidity and mortality.[4] Studies from this decade have shown that a minimalist approach to glucose control in selected perioperative and critically ill patient populations is unwarranted, and improved glucose control leads to less morbidity and better outcomes,[4–6] particularly in those with SIH.[7] Key questions remain unanswered. How tight should glycemic control be? Are all hyperglycemic patients at equal risk for morbid and lethal events at a given degree of dysglycemia? What is the incidence and degree of morbidity when tight glycemic control (TGC) is universally applied? Identification of the dysglycemic patient and application of reliable glucose monitoring and glucose management techniques to a proper endpoint are crucial to achieving adequate perioperative glucose control. Identification of new-onset glucose intolerance in the perioperative patient should be followed by appropriate referral to the patient's primary care provider for ambulatory unstressed diabetes testing.

Drs. Lipshutz and Gropper emphasize that the current data reporting the benefits in reducing morbidity and mortality in intensive care unit patients using intensive insulin therapy to provide TGC be interpreted with care in light of risks reported when this approach is applied universally. They comment on the potential differences in glucose control and outcome related to type 1 *versus* type 2 diabetes or SIH, the effect of glucose variability during the course of intense monitoring and therapy, and the current risk-benefit data on TGC in various populations. They caution about extrapolating intensive care unit studies directly to the perioperative patient. We would go a step further and caution against a sudden call for intraoperative normalization of blood glucose (80–110 mg/dL; 4.4–6.1 mmol). Additional data should be obtained before implementing rigid perioperative standards of glucose management while tying reimbursement for care of the hyperglycemic perioperative patient to potentially unsubstantiated goals.[8–10]

This thorough review briefly comments on the importance of glucose monitoring, quality control of bedside glucose measurements *versus* laboratory techniques, and attempts at developing continuous and closed loop systems to control glucose. The reliability of glucose measurements is important to remember when controlling glucose levels during the dynamic perioperative period. Practical pitfalls in glucose monitoring secondary to sample site and source, technique of monitoring, impact of concurrent pathophysiologic states and interfering substances such as nonglucose sugars, and various medications are now recognized.[11–13]

The source of glucose monitoring, point-of-care device, blood gas analyzer, or central laboratory evaluation may explain some of the conflicting results reported when intensive insulin therapy and TGC protocols are instituted.[11–13] Point-of-care glucose monitoring using finger-stick capillary blood, the most common approach to perioperative evaluation, is based on application of ambulatory technology using photoreflectometry or electrochemical reaction. The Food and Drug Administration mandates a ± 20% agreement between the point-of-care device and laboratory gold standard.§ Differences between laboratory and point-of-care–derived values are particularly important in intensive care unit patients who are anemic, hypothermic, or hypoperfused. Potentially critical disagreements between the central laboratory value and point-of-care measurement may lead to inappropriate insulin management.[11–13] Certain operative patients, particularly those in shock or actively hemorrhaging, are likely to be affected.

Multidisciplinary teams should develop glucose control protocols, set reasonable goals for control, monitor the effectiveness of controlling glucose, and recognize

This Editorial View accompanies the following article: Lipshutz AKM, Gropper MA: Perioperative glycemic control: An evidence-based review. ANESTHESIOLOGY 2009; 110:408–21.

Accepted for publication November 7, 2008. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

§ U.S. Food and Drug Administration. Diabetes Information. Available at: http://www.fda.gov/diabetes/glucose.html. Updated June 14, 2005. Accessed November 5, 2008.

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and carefully monitor patients at high risk for hypoglycemia.[14–17] The latter is especially important during the perioperative period, when early signs of hypoglycemia may be masked due to the administration of sedatives, analgesics, and anesthetics. The University of California, San Francisco group and others have reported their success with such an approach.[14–17] Nonetheless, given concerns over reports of hypoglycemia with intensive insulin therapy that range from 5–18.7% and increased mortality when hypoglycemia (glucose < 40 mg/dL; 2.2 mmol) develops in critically ill patients, cautious application of TGC in the perioperative period should be the norm until more data are forthcoming.[4,5,18,19] Further, the effort and resources required to maintain TGC are significant, and the potential for long-term morbidity secondary to hypoglycemia-induced neuropsychologic compromise has not been well studied.

The implications of establishing practice guidelines and applying them globally[17] to complex perioperative populations that range from patients with neuroischemia, neurotrauma, cardiac compromise, and sepsis, to name but a few, are significant. Adding the variables discussed in this review, prior diabetes, type 1 *versus* type 2, SIH, and a host of others such as obesity, age, and other end-organ compromise further complicate the potentially premature call for routine TGC in the perioperative period. The wisdom of applying glucose management standards to pay for performance remains to be proven and can be potentially dangerous at present and should await additional data. The application of these standards might even be dangerous to unique patients, and their use must await further study in diverse patient populations.

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE SUGAR) Trial‖ completed enrollment of 6100 patients in August 2008.[20] Although an ICU trial, it is multicenter, international, prospective, and randomized, and it is the largest trial of its kind. It has the potential to further guide therapeutic interventions in patients with a broad spectrum of illnesses, including those in the perioperative period.

The development of a prospective multi-institutional database evaluating the incidence and evidence-based management of hypoglycemia or hyperglycemia across the heterogeneous perioperative population would address some major public health concerns. This database would facilitate identification of previously undiagnosed surgical patients with diabetes, aid in determination of the incidence and natural history of SIH in perioperative patients, and provide data on the impact of glycemic management and quality of long-term care of specific subsets of patients, including those undergoing primary neurologic, cardiac, or traumatic surgery. Unfortunately, at present, other than epidemiologic screens such as the National Health and Nutrition Examination Survey,# there is no program, federally or privately funded, available to generate such information. Hopefully, the drive for evidence-based medical care could facilitate such a vehicle to examine this and other important perioperative diagnoses and management strategies such as use of β-blockers, indication for statin administration, and application of genomic diagnostics to stratify care and optimize outcome.

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David S. Warner, M.D., and Mark A. Warner, M.D., Editors

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Perioperative Glycemic Control

An Evidence-based Review

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Hyperglycemia in perioperative patients has been identified as a risk factor for morbidity and mortality. Intensive insulin therapy (IIT) has been shown to reduce morbidity and mortality among the critically ill, decrease infection rates and improve survival after cardiac surgery, and improve outcomes in acute neurologic injury and acute myocardial infarction. However, recent evidence of severe hypoglycemia and adverse events associated with IIT brings its safety and efficacy into question. In this article, we summarize the mechanisms and rationale of hyperglycemia and IIT, review the evidence behind the use of IIT in the perioperative period, and discuss the implications of including glycemic control in national quality benchmarks. We conclude that while avoidance of hyperglycemia is clearly beneficial, the appropriate glucose target and specific subpopulations who might benefit from IIT have yet to be identified. Given the potential for harm, inclusion of glucose targets in national quality benchmarks is premature.

HYPERGLYCEMIA has been identified as a risk factor for perioperative morbidity and mortality. In 2001, Van den Berghe *et al.* published the first Leuven study, a randomized controlled trial (RCT) of more than 1500 surgical intensive care unit (ICU) patients in which intensive insulin therapy (IIT) (target blood glucose [BG], 80–110 mg/dL) reduced in-hospital mortality by 34% when compared to standard therapy (target BG, 180–200 mg/dL) and significantly decreased morbidity, including bloodstream infections, acute renal failure, red-cell transfusions, and critical-illness polyneuropathy.[1] Other studies have shown that tight glycemic control during cardiac surgery is associated with decreased infection rates and improved survival,[2–5] that postoperative glycemic control in cadaveric renal transplantation decreases allograft rejection,[6] and that intensive insulin improves outcomes in the setting of acute neurologic injury[7,8] and acute myocardial infarction.[9] Widespread implementation of IIT in the perioperative period ensued on the basis of these data; the Joint Commission (formerly known as JCAHO) has included postoperative BG in cardiac surgical patients in its core measure set,‡ and the Centers for Medicare & Medicaid Services (CMS) has included it in the Surgical Care Improvement Project (SCIP).§ The data from SCIP will yield evidence-based guidelines and national benchmarks and may eventually be used in pay-for-performance (P4P) programs in which a portion of reimbursement for patient care depends on the attainment of certain quality benchmarks.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

This article is accompanied by an Editorial View. Please see: Fahy BG, Sheehy AM, Coursin DB: Perioperative glucose control: What is enough? ANESTHESIOLOGY 2009; 110:204–6.

More recently, however, there has been considerable controversy over the safety and efficacy of IIT. The second Leuven study showed that medical ICU patients may not benefit from IIT in the same way as their surgical counterparts,[10] and two studies were stopped early by data safety monitoring boards due to the high incidence of severe hypoglycemic events (BG $\leq$ 40 mg/dL) and other serious adverse events.[11,12] Intraoperative IIT during cardiac surgery may increase the incidence of death and stroke.[13] Furthermore, the use of insulin, in general, is not without its risks: along with anticoagulants, opiates, potassium chloride, and hypertonic saline, insulin is considered a "high-alert medication," one that has the highest risk of causing injury when misused.[14]

Given the inconclusiveness of the data and the potential for harm, it is unclear if adequate evidence exists to support the widespread adoption of IIT, not to mention its inclusion in quality measures and P4P programs. This review intends to summarize the pathophysiology and mechanisms of hyperglycemia and insulin therapy, review the

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Received from the Department of Anesthesia and Perioperative Care, University of California, San Francisco, California. Submitted for publication May 21, 2008. Accepted for publication October 2, 2008.

Mark A. Warner, M.D., served as Handling Editor for this article.

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‡ Joint Commission. Specifications Manual for National Hospital Quality Measures, April 2008. Available at: http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Current+NHQM+Manual.htm. Accessed July 12, 2008.

§ MedQIC Surgical Care Improvement Project Program Information. Available at: http://www.qualitynet.org/dcs/ContentServer?cid=1136495755695&pagename=Medqic%2FOtherResource%2FOtherResourcesTemplate&c=OtherResource. Accessed July 19, 2008.

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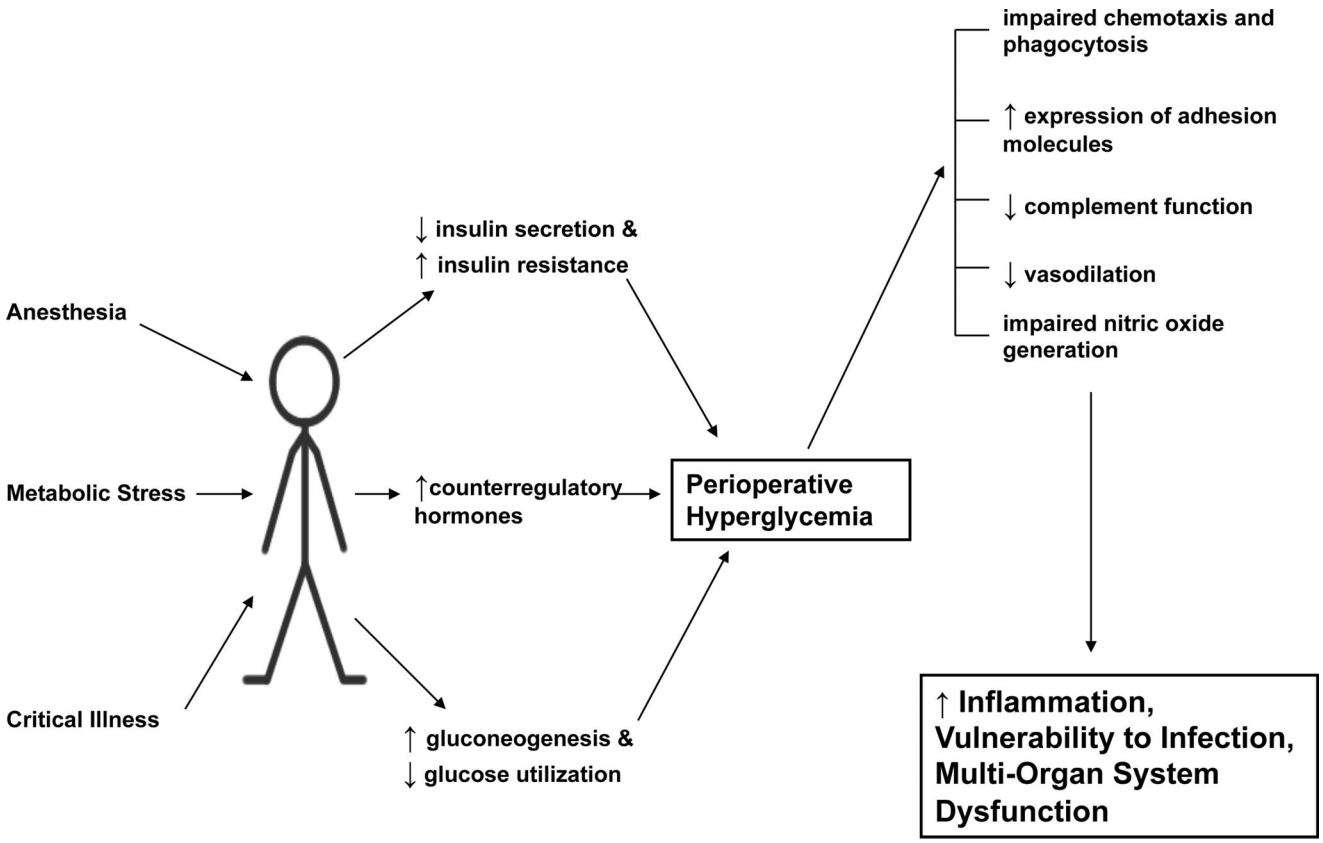

Fig. 1. Pathophysiology of hyperglycemia. Anesthesia, metabolic stress, and critical illness lead to metabolic derangements, resulting in hyperglycemia. Hyperglycemia is associated with increased inflammation, susceptibility to infection, and organ dysfunction.

evidence behind the use of IIT in the perioperative period (intraoperatively, postoperatively, and in the ICU), and discuss the implications of the inclusion of glycemic control in Joint Commission core measures, SCIP, and P4P for practicing anesthesiologists and intensivists.

Materials and Methods

We searched MEDLINE and the Cochrane Library for RCTs, observational studies, review articles, meta-analyses, and editorials on IIT in the perioperative period. We evaluated articles published between January 1, 1999 and January 31, 2008, and we limited our search to articles published in the English language. The following search terms were used: *intensive insulin, glycemic control, glucose control, hyperglycemia, intraoperative, intensive care, critically ill,* and *postoperative.* Bibliographies of all relevant articles from the search were examined manually for additional articles. We also searched for and reviewed abstracts published in meeting proceedings as well as information on relevant ongoing clinical trials from ClinicalTrials.gov. We focused primarily on studies in which mortality was the primary endpoint; however, studies evaluating infectious complications will also be discussed in brief. Given the wealth of literature on this topic, we will focus on the major influential studies that have implications for the clinical decision-making of practicing anesthesiologists: well-designed, adequately powered prospective observational studies and RCTs. Retrospective studies were also included when their analysis was robust and/or topic novel to the literature.

Pathophysiology of Hyperglycemia

Hyperglycemia is a common response to critical illness and metabolic stress.[15,16] Figure 1 summarizes the pathophysiology of hyperglycemia. Stress-induced release of counterregulatory hormones cortisol, glucagon, epinephrine, and growth hormone leads to upregulation in hepatic gluconeogenesis and glycogenolysis despite hyperinsulinemia and compromised insulin-regulated peripheral glucose uptake.[17–20] Interestingly, total body glucose uptake is increased but occurs primarily in insulin-independent tissues such as the brain and red blood cells.[18,20] Glucose uptake and glycogen synthesis in skeletal muscle is decreased, primarily due to a defect in the glucose transporter-4 (GLUT4).[21] Historically, hyperglycemia in critical illness was considered a beneficial adaptation intended to supply energy to vital organs. However, evidence that hyperglycemia is an independent risk factor for morbidity and mortality in the perioperative period refutes this notion.[1,2,10,22] Although the adaptive rationale for the hyperglycemic response is not well understood, acute hyperglycemia has many deleterious

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effects, including decreased vasodilation, impaired reactive endothelial nitric oxide generation, decreased complement function, increased expression of leukocyte and endothelial adhesion molecules, increased cytokine levels, and impaired neutrophil chemotaxis and phagocytosis, leading to increased inflammation, vulnerability to infection, and multiorgan system dysfunction.[23] IIT ameliorates some of the injurious effects of hyperglycemia by reducing endothelial activation *via* decreased circulating levels of ICAM-1 and E-selectin,[24] protecting hepatocyte mitochondrial ultrastructure,[25] stimulating peripheral glucose uptake by increasing transcription of GLUT-4 and hexokinase,[26] normalizing C-peptide and circulating adiponectin levels,[27] and improving the serum lipid profile by increasing low-density lipoprotein and high-density lipoprotein levels while decreasing serum triglycerides.[26]

Hyperglycemic patients have high circulating levels of proinflammatory cytokines, which can lead in turn to organ injury. Most prominent among these cytokines is tumor necrosis factor-α, which is well documented to cause both lung and renal injury.[28] Esposito *et al.* demonstrated increased tumor necrosis factor-α, interleukin-1β, and interleukin-8 plasma levels during acute hyperglycemia, with a reduction in these inflammatory cytokines after insulin administration.[29] The relationship between inflammatory cytokines and glucose metabolism is complex; in fact, hyperglycemia itself could be caused by cytokines *via* induction of peripheral insulin resistance. This association is witnessed clinically; patients with severe sepsis often require high doses of intravenous insulin to maintain normoglycemia.

Until recently, it was unknown whether the benefits of IIT were a result of achieving normoglycemia or due to the therapeutic effects of insulin. Evidence is mounting, however, that the beneficial effects of IIT are due to control of glucose levels rather than administration of insulin. Analysis of results from the first Leuven study found that lower BG rather than insulin dose was related to reduced mortality, bacteremia, critical illness polyneuropathy, and inflammation; however, insulin dose was an independent negative predictor for acute renal failure.[18] In addition, in a single-center, prospective observational study of 531 ICU patients, increased administration of insulin was positively and significantly associated with death, regardless of BG level.[30] A more recent retrospective study of 7285 ICU patients had similar findings: average cumulative insulin administration greater than 100 units per day was associated with an odds ratio for hospital death of 3.8 (95% CI, 1.8–7.7) when controlling for glycemic control.[31] It therefore appears to be the glucose-lowering effects of insulin therapy that are beneficial.

Hypoglycemia can also be detrimental because the brain is an obligate glucose metabolizer. Severe hypoglycemia causes neuronal necrosis *via* increased concentrations in excitatory amino acids, with a predilection for the neurons of the superficial layers of the cortex and the dentate gyrus of the hippocampus; the cerebellum and brainstem are spared injury.[32] Low BG levels also lead to increased secretion of glucagon, epinephrine, growth hormone, and cortisol. In diabetic patients, hypoglycemia is associated with neurogenic and neuroglycopenic symptoms, including seizure, coma, or even death.[33] Case reports describe seizures and coma after severe, prolonged hypoglycemia in ICU patients; however, little is known about the effects of short-term accidental hypoglycemia in this population.[34]

Effects of IIT by Patient Population

The Critically Ill. Van den Berghe *et al.* performed a single-center, RCT of 1548 surgical ICU patients receiving mechanical ventilation comparing IIT (target BG, 80–110 mg/dL) to conventional treatment (insulin given for BG $>$ 215 mg/dL; target BG, 180–200 mg/dL). IIT reduced overall in-hospital mortality by 34% and significantly decreased the incidence of bloodstream infection, acute renal failure requiring dialysis or hemofiltration, red-cell transfusion, and critical-illness polyneuropathy. IIT also decreased the duration of mechanical ventilation and ICU length of stay (LOS).[1] Patients with an ICU stay longer than 5 days had a larger mortality benefit compared to those with shorter stays.

The incidence of hypoglycemia (BG $\leq$ 40 mg/dL) was 5.1% in the IIT group *versus* 0.8% in the conventional treatment group, without any evidence of hemodynamic deterioration or convulsions. A preplanned subanalysis of the cardiac surgery patients in this study performed 4 yr after ICU admission showed that the number of posthospital discharge deaths was similar in the two study groups, reflecting maintenance of the acute survival benefit with IIT (although, interestingly, at the expense of decreased quality of life).[35]

Of note, however, the first Leuven study was performed at a single center and was unblinded. The majority of patients (63%) were recovering from cardiac surgery. Patients received intravenous glucose on arrival to the ICU[36] and a significant but unquantified percentage of calories through parenteral nutrition, which is known to cause hyperglycemia and insulin resistance.[37] Notably, the nurse-to-patient ratio in the study was 1-to-1, higher than most ICUs, and nurses were also assisted by a study physician who was not otherwise involved in clinical care. The high-level staffing interventions likely limited the incidence and magnitude of hypoglycemia. Furthermore, the mortality of cardiac surgery patients in the control group was quite high, and some even argue that the extremely high relative risk reduction in mortality stretches biologic plausibility.[36] Based on these limitations, it is unclear if the results of this study are generalizable to other surgical ICUs, much less medical ICUs or operating rooms.

A before-after study of IIT in a 14-bed mixed medical-surgical ICU at a community hospital compared the morbidity and mortality of 800 patients admitted imme-

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diately before implementation of the protocol and 800 patients after.[22] Approximately two thirds of patients were medical patients, and one third were surgical. This protocol, which was less strict than the Leuven study in its treatment goal (target BG, 80–140 mg/dL), was associated with a 29% decrease in hospital mortality. There also was a significant reduction in ICU LOS, incidence of renal insufficiency, and number of red blood cell transfusions. The incidence of infections and hypoglycemic episodes (BG $<$ 40 mg/dL) were unchanged. Although this study was limited by its noncontrolled, nonrandomized design, it suggested that the findings of the first Leuven study might be reproducible.

In 2006, Van den Berghe *et al.* published the results of the second Leuven study, an RCT comparing IIT (target BG, 80–110 mg/dL) and conventional therapy (insulin given for BG $>$ 215 mg/dL; target BG, 180–200 mg/dL) in 1200 medical ICU patients.[10] Although IIT decreased ICU and hospital LOS, ventilator days, and incidence of kidney injury, it did not reduce mortality in the intention-to-treat analysis. In subgroup analysis of patients with an ICU LOS $\geq$ 3 days, IIT was associated with a decrease in mortality from 53 to 43%; conversely, there was a trend toward increased mortality in the group of patients with ICU stays shorter than 3 days. Importantly, patients requiring longer ICU stays could not be identified *a priori*. Hypoglycemia (BG $\leq$ 40 mg/dL) was more common in the IIT group, occurring in 18.7% of patients compared with 3.1% of patients in the conventional group, and it was an independent predictor of death in multivariate analysis. This trial, therefore, provided the first clue of the potential hazards associated with IIT and highlighted the potential consequences of hypoglycemia but was unable to specify the mechanism of harm.

To address concerns regarding the potential harms of IIT, Van den Berge *et al.* performed an analysis of a pooled dataset of the two Leuven RCTs.[38] IIT reduced morbidity and mortality in the intention-to-treat group and long-stayers, with no evidence of harm in short-stayers. These effects were independent of parenteral feeding, thereby refuting the possibility that the mortality benefit of IIT in the first Leuven study was from antagonization of the side effects of parenteral feeds. Maintaining BG below 150 mg/dL was most important in reducing mortality, but additional survival benefit was achieved with BG less than 110 mg/dL, which was also necessary to protect the kidney and nervous system. Hypoglycemia was more common in the IIT group (11.3 *vs.* 1.8%); it is unclear if this caused any harm.

Several studies since have examined risk factors and outcomes of hypoglycemia in critically ill patients. A retrospective cohort study by Vriesendorp *et al.* associated hypoglycemia (BG $<$ 45 mg/dL) with continuous venovenous hemofiltration, history of diabetes, sepsis, inotropic support, and a decrease in nutrition without insulin adjustment.[39] A nested case control study of the same patient population showed no association between hypoglycemia and mortality.[34] Krinsley *et al.* identified diabetes, septic shock, renal insufficiency, mechanical ventilation, severity of illness, and IIT as independent risk factors for hypoglycemia (BG $<$ 40 mg/dL) in a case-control analysis.[40] Multivariate regression in this study identified hypoglycemia as an independent predictor of mortality (odds ratio = 2.28; P = 0.0008). Thus, the issue of hypoglycemia and mortality in the ICU remained unresolved.

Recently, two RCTs of IIT were stopped early due to safety concerns given a high incidence of severe hypoglycemia and serious adverse events. In the European GLUCONTROL trial, mixed medical-surgical ICU patients were randomized to receive either IIT (target BG, 80–110 mg/dL) or conventional treatment (target BG, 140–180 mg/dL).‖ The study was halted in May 2006 after enrollment of only 1,101 patients out of a planned 3,500 due to increased incidence of hypoglycemia in the IIT group (9.7 *vs.* 2.7%), with evidence of an associated increase in mortality. Further analysis negated the concern over increased mortality but showed no survival benefit of IIT over conventional therapy.[41] Likewise, the VISEP trial, a two-by-two factorial trial that randomized ICU patients with severe sepsis to either IIT or conventional therapy and either 10% pentastarch or modified Ringer lactate for fluid resuscitation was stopped at the first planned safety analysis.[11] A total of 537 patients were evaluated. At 28 days, there was no difference in the rate of death, but the rate of severe hypoglycemia (BG $<$ 40 mg/dL) was significantly higher in the IIT group (17.0 *vs.* 4.1%), and the episodes were more likely to be classified as life-threatening and to require prolonged hospitalization. However, this study has been criticized for a number of reasons. First, it was markedly underpowered by a factor of more than 10 to reproduce the findings of the Leuven studies.[42,43] Second, the goal of normoglycemia was achieved in only 50% of the patients in the IIT group, placing the quality of glycemic control and adherence to the protocol into question and highlighting the importance of cautious implementation.[44]

A recent meta-analysis of 29 randomized trials of IIT *versus* conventional glucose control in adult intensive care patients showed no statistically significant difference in hospital mortality, even when stratified by glucose goal or intensive care unit setting.[45] IIT was associated with decreased risk of septicemia in surgical ICU patients, but at the cost of an over fivefold increase in the risk of hypoglycemia (BG $\leq$ 40 mg/dL). Although this meta-analysis may have been underpowered to detect the difference in mortality observed (21.6% *vs.* 23.3% in the IIT and conventional therapy groups, re-

‖ Glucontrol study: Comparing the effects of two glucose control regimens by insulin in intensive care unit patients. Available at: http://clinicaltrials.gov/ct/gui/show/NCT00107601. Accessed July 18, 2008.

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spectively), it still serves an important role in the literature; it acts as an "effectiveness study" of the effects IIT in everyday practice.[46]

A summary of the major studies evaluating IIT in the critically ill can be found in table 1.

Intraoperative IIT. Although the vast majority of the literature on IIT has been in the ICU population, the safety and efficacy of intraoperative IIT has also been evaluated. Interest in intraoperative insulin therapy (table 2) initially focused on the cardiac surgery population, based on evidence of the mortality benefit of glucose-insulin-potassium mixtures in patients with acute myocardial infarction[9](recently questioned in the CREATE-ECLA trial, which showed no mortality benefit from high dose glucose-insulin-potassium)[47] and stroke,[48] and the link between hyperglycemia and infection among people with diabetes in this population.[49–52] The rationale for using glucose-insulin-potassium focused on the cardioprotective effects of the mixture *via* promotion of glucose as the primary myocardial energy substrate, decrease in circulating free fatty acid levels, increase in myocardial membrane stability, and promotion of cell survival.[53] Early studies of intraoperative insulin in cardiac surgical patients, therefore, did not identify glycemic control as a desired endpoint[54–56]; as such, they were unable to assess the relationship between hyperglycemia and morbidity and mortality.

The Portland Diabetic Project, a prospective, nonrandomized, interventional research study, has been investigating the relationship between hyperglycemia and morbidity and mortality in cardiac surgical patients since 1987.[57] In 2003, Furnary *et al.* analyzed data from the project and published a before-after study of IIT (with changes in BG targets and expansion of protocol to include intraoperative insulin occurring during the study period) *versus* subcutaneous insulin (target BG $<$ 200 mg/dL) in diabetic patients undergoing coronary artery bypass grafting (CABG), which showed a 57% reduction in mortality.[2] However, this study was limited by its nonrandomized design and resulting heterogeneous study groups, changes in the protocol during the study period, and the potential for temporal bias due to a 14-yr study period.

A more recent before-after study showed that intraoperative IIT (target BG 150–200 mg/dL) followed by postoperative IIT (target BG $<$ 140 mg/dL) in diabetic patients undergoing surgical myocardial revascularization reduced mortality by 72% in a multivariate regression analysis using propensity scores.[58] Ouattara *et al.* showed that poor intraoperative glycemic control was associated with severe in-hospital morbidity in diabetic cardiac surgery patients.[3] In this population, four consecutive intraoperative BG levels greater than 200 mg/dL were associated with an adjusted OR for morbidity of 7.2 as compared to patients without hyperglycemia. A prospective, randomized trial of glucose-insulin-potassium initiated intraoperatively with a target BG of 125–200 mg/dL compared to standard therapy (target BG $<$ 250 mg/dL) also in diabetic CABG patients showed a survival advantage, decreased LOS, and decreased wound infection rates.[59] This study was limited by lack of blinding and potential undertreatment in the standard therapy arm. Several retrospective studies have provided further evidence of the effect of intraoperative hyperglycemia on outcomes.[4,5]

However, a recent RCT of both diabetic and nondiabetic patientss undergoing on-pump CABG compared intraoperative IIT (target BG 80–100 mg/dL) with conventional treatment (target BG $<$ 200 mg/dL) and showed no reduction in perioperative morbidity and mortality.[13] In fact, there was a statistically significant increase in the incidence of stroke in the IIT group and a trend toward increased mortality.

Unfortunately, data on intraoperative glucose control in noncardiac surgical patients is lacking.

Postoperative IIT. Several studies have evaluated the effects of hyperglycemia in the postoperative period. Glycemic control is known to decrease the risk of wound infection in diabetics after cardiac surgery. Analysis of 1585 diabetic patients undergoing cardiac surgery before and after the implementation of an insulin protocol (target BG $<$ 200 mg/dL) revealed a significant decrease in the incidence of deep wound infection (2.4 to 1.5%).[49] Furnary *et al.* had similar results in a prospective study of 2467 patients with the same BG goal; IIT was associated with a 66% decrease in deep sternal wound infection.[50] In a retrospective analysis by Golden *et al.*, postoperative hyperglycemia was an independent predictor of infectious complications in diabetic patients undergoing coronary artery bypass surgery.[52] A more recent retrospective review also showed mortality benefit in this population[51]; however, diabetic patients were the only subgroup in the Leuven studies to show no mortality benefit from IIT.[1,10]

Studies on the effects of postoperative hyperglycemia outside of the diabetic cardiac surgery population and the critical care population are lacking. One retrospective cohort study by Vriesendorp *et al.* found elevated postoperative glucose levels to be an independent risk factor for infection in patients undergoing infrainguinal vascular surgery.[60] In addition, in a prospective randomized pilot trial comparing IIT (target BG 80–120 mg/dL) to conventional treatment (target BG 80–220 mg/dL) in patients with aneurysmal subarachnoid hemorrhage status after surgical clipping, IIT was associated with decreased infection rate (42 to 27%) but no difference in the incidence of vasospasm, neurologic outcome, or mortality.[7] The frequent use of intraoperative dexamethasone, which is known to further increase glucose levels,[61,62] could make postoperative glycemic control harder to achieve in this patient population.

Obstetrical IIT. Data on the use of IIT in the setting of obstetrical anesthesia focuses on patients with gesta-

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Table 1. Studies of Intensive Insulin Therapy (IIT) in the Critically Ill

Study	Design	Patient Population	Primary Endpoint	Major Findings
Van den Bergh, *et al.*[1]	Single-center RCT, partially blinded of IIT (target BG, 80–110 mg/dL) *vs*. conventional treatment (insulin infusion if BG > 215 mg/dL, with target BG 180–200)	1,548 surgical ICU patients receiving mechanical ventilation	Death from any cause during intensive care	IIT reduced mortality in the ICU from 8.0 to 4.6% ($P < 0.04$), in-hospital mortality by 34%, bloodstream infections by 46%, ARF requiring dialysis or hemofiltration by 41%, red-cell transfusions by 50%, and polyneuropathy by 44%
Van den Berghe *et al.*[10]	Single-center RCT of IIT (target BG, 80–110 mg/dL) *vs*. conventional treatment (insulin infusion if BG > 215 mg/dL; with target BG, 180–200 mg/dL)	1,200 patients admitted to medical ICU believed to need intensive care for at least 3 days	Death from any cause in the hospital	No reduction in in-hospital mortality in intention-to-treat analysis. Among patients who stayed in ICU for ≥ 3 days, there was a decrease in mortality from 52.5 to 43% ($P = 0.009$) in the treatment group; among those staying < 3 d, treatment group mortality was greater
Van den Berghe *et al.*[38]	Pooled dataset analysis of 2 RCTs comparing IIT (target BG, 80–110 mg/dL) to conventional treatment (insulin infusion if BG > 215 mg/dL; target BG, 180–200 mg/dL)	Pooled data of 2,748 medical and surgical ICU patients from 2 RCTs	Goals to investigate harm in brief treatment in mixed population, identify subgroups who may not benefit from IIT, to determine optimal target BG, and to study hypoglycemia	IIT decreased mortality in intention-to-treat group (20.4% *vs*. 23.6%; $P = 0.04$); short-stayers had no difference in mortality; mortality was higher with BG > 150 mg/dL and lower with BG < 110 mg/dL compared to BG 110–150 mg/dL; patients with diabetes showed no benefit; hypoglycemia was more likely with target BG < 110 mg/dL and was not associated with morbidity
Krinsley[22]	Before-after study of intensive glucose management protocol (target BG < 140 mg/dL maintained with SC insulin unless BG > 200 mg/dL on two successive fingersticks	1,600 patients in university-affiliated community hospital mixed medical/surgical ICU	Hospital mortality	After implementation of the protocol, hospital mortality decreased 29.3% ($P = 0.002$), LOS in ICU decreased 10.8% ($P = 0.01$), incidence of new renal insufficiency decreased 18.7% ($P = 0.04$), and red-cell transfusions decreased 18.7% ($P = 0.04$); there was no significant change in the incidence of hypoglycemia.
Finney *et al.*[30]	Single-center, prospective observational study of effects of glycemic control and insulin administration	531 patients admitted to mixed medical/surgical ICU	ICU mortality	Increased administration of insulin was associated with increased ICU mortality (OR 1.02; $P < 0.001$) in normoglycemic patients (BG 111–144 mg/dL)
Krinsley and Grover[40]	Retrospective database review and case-control analysis of risk factors for severe hypoglycemia (BG < 40 mg/dL) before and after implementation of tight glycemic control protocol (target BG, 80–140 mg/dL, then 80–125 mg/dL)	102 patients in medical/surgical ICU with severe hypoglycemia from a series of 5365 patients	N/A	Treatment in tight glycemic control period is an independent risk factor for severe hypoglycemia, and severe hypoglycemia is an independent predictor of mortality (OR 2.28; $P = 0.0008$)
Toft *et al.*[109]	Prospective before-after study of IIT (target BG 80–110 mg/dL) *vs*. conventional therapy (target BG < 216 mg/dL)	271 noncardiac ICU patients	ICU mortality	Study was underpowered, but it showed a trend toward reduced mortality and decreased incidence of infection. Hypoglycemia was significantly more common in the IIT group (14% *vs*. 4%)
Ingels *et al.*[35]	Preplanned subanalysis of cardiac surgery patients from first Leuven study	970 patients admitted to the ICU after cardiac surgery	4-years all-cause mortality and number of post-hospital discharge deaths	Mortality at 4 years was similar among groups; among patients staying in ICU at least 3 days, mortality at 4 years was lower for IIT group (23% *vs*. 36%); post-hospital discharge deaths were similar; increased survival among long-stayers was associated with decreased perceived quality-of-life
Brunkhorst *et al.*[11]	Multicenter 2×2 factorial trial, randomly assigning patients to IIT or conventional therapy and either 10% pentastarch or modified Ringer lactate	Analysis of patients with severe sepsis or septic shock admitted to multidisciplinary ICUs at 18 hospitals: n = 488 for insulin arm, n = 537 for fluid arm	Death at 28 days and mean score for organ failure	Stopped early for safety reasons; no difference in rate of death or mean score for organ failure at 28 days; rate of severe hypoglycemia (BG < 40 mg/dL) was higher in treatment group (17% *vs*. 4.1%; $P < 0.001$), as was rate of serious adverse events (10.9% *vs*. 5.2%, $P = 0.01$)
GLUControl Trial*	Single-blinded, multicenter, RCT of IIT (target BG 80–110 mg/dL) *vs*. conventional therapy (target BG 140–180 mg/dL)	Goal to enroll 3500 patients; stopped after 1,101 medical/surgical ICU patients at 21 hospitals completed the study	ICU Mortality	Stopped early for safety reasons and a high rate of protocol violations; incidence of severe hypoglycemia increased in treatment arm (8.6% *vs*. 2.4%; $P < 0.001$); no difference in all-cause mortality or LOS

* Glucontrol Study: Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients. Available at: http://clinicaltrials.gov/ct/gui/show/NCT00107601. Accessed July 18, 2008.

ARF = acute renal failure; BG = blood glucose; ICU = intensive care unit; IIT = intensive insulin therapy; LOS = length of stay; OR = operating room; RCT = randomized controlled trial; SC = subcutaneous.

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Table 2. Studies of Intraoperative Intensive Insulin Therapy in Cardiac Surgical Patients

Study	Design	Patient Population	Primary Endpoint	Major Findings
Lazar *et al.*[59]	Prospective randomized trial of intraoperative glucose-insulin-potassium (target BG 125–200) or standard tx (BG < 250)	141 diabetic patients undergoing CABG	Perioperative outcomes	Patients receiving glucose-insulin-potassium have a lover incidence of A-Fib, shorter postop LOS, few recurrent wound infections and improved survival at 2 years
Furnary *et al.*[2]	Before-after study of intraoperative subcutaneous insulin versus continuous insulin infusion (target BG range changed during study period: 150–200 →125–175→100–150 mg/dL)	3,554 diabetic patients undergoing CABG	In-hospital mortality	Continuous insulin infusion was independently predictive against death (OR 0.34; $P = 0.001$), and observed mortality was less than expected by the Society of Thoracic Surgeons' 1996 multivariable risk model (obs/exp = 0.63; $P < 0.001$)
Ouattara *et al.*[3]	Prospective trial of intraoperative intravenous insulin therapy (initiated for BG ≥ 180 mg/dL)	200 consecutive diabetic patients undergoing on-pump CABG	Severe CV, respiratory, infectious, neurologic, and renal in-hospital morbidity	Adjusted OR for severe postoperative morbidity in patients with poor intraoperative glycemic control (defined as 4 consecutive BG > 200 mg/dL) was 7.2 (95% CI, 2.7–19.0)
Gandhi *et al.*[4]	Retrospective observational study with independent variable mean intraoperative BG	409 consecutive cardiac surgery patients	Composite of death and infectious, neurologic, renal, cardiac, and pulmonary complications developing within 30 days of surgery	Intraoperative hyperglycemia is an independent risk factor for complications and death after cardiac surgery (adjusted OR for composite outcome, 1.34 for each 20-mg/dL increase in mean intraoperative BG; 95% CI, 1.10–1.62)
Doenst *et al.*[5]	Retrospective observational study	1,579 diabetic and 4,701 nondiabetic patients undergoing on-pump cardiac surgery	In-hospital mortality	Elevated glucose is an independent predictor of mortality in diabetic (OR 1.20 per 1-mmol increase in BG; $P = 0.0005$) and nondiabetic (OR = 1.12; $P < 0.0001$) patients
Gandhi *et al.*[13]	Open-label, single-center RCT with blinded end point assessment; continuous insulin infusion to keep intraoperative BG 80–100 mg/dL *vs.* conventional treatment (BG < 200 mg/dL)	400 patients undergoing on-pump cardiac surgery	Composite of death, sternal infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure within 30 days after surgery	No difference in number of events between groups; intensive insulin group trended toward more deaths (4 *vs.* 0; $P = 0.061$) and had higher incidence of stroke (8 *vs.* 1; $P = 0.020$)

A-Fib = atrial fibrillation; BG = blood glucose; CV = cardiovascular; CABG = coronary artery bypass graft; GIK = glucose-insulin-potassium; LOS = length of stay; OR = odds ratio.

tional and pregestational diabetes. The goal is to avoid intrapartum maternal hyperglycemia to prevent fetal hyperglycemia and subsequent neonatal hypoglycemia.[63] Maintaining intrapartum normoglycemia (BG < 110 mg/dL) decreases the incidence of neonatal hypoglycemia.[64–66] The American College of Obstetricians and Gynecologists currently recommends a BG target of less than 110 mg/dL during labor and delivery.[67]

Furthermore, maintaining maternal BG below the diabetic range throughout pregnancy may be equally important, given the continuous association between maternal glucose levels below those diagnostic of diabetes and increased birth weight, decreased Caesarean sections, and decreased incidence of neonatal hypoglycemia.[68] Treatment of gestational diabetes with the oral hypoglycemic agent metformin during pregnancy appears to be as effective as insulin therapy in a composite outcome of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-min Apgar score less than 7, or prematurity.[69]

Diabetics *versus* Nondiabetics. To our knowledge, no prospective study has specifically compared the differing effects of IIT on diabetic *versus* nondiabetic patients. Focusing first on the critical care population,

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subgroup analysis from several of the studies discussed above sheds some light on the subject. In the second Leuven study, mortality in the subgroup of diabetic medical ICU patients did not differ by treatment group.[10] In their pooled analysis, Van den Berghe *et al.* demonstrated that IIT reduced mortality in all medical-surgical ICU patients, with the exception of those with preexisting diabetes.[38] However, the lack of effect shown in this subgroup may be explained by the small number of patients included in the analysis and the fact that target BG levels were not reached. In a retrospective case-control study, Rady *et al.* evaluated the influence of individual characteristics on the outcome of IIT in the ICU among diabetic and nondiabetic patients.[31] This study was limited by its design. Patients with BG $>$ 150 mg/dL were treated with insulin therapy, and patients with BG $\leq$ 150 mg/dL were used as controls. As expected, the treatment group had significantly higher severity of illness (as measured by Sequential Organ Failure Assessment), making it hard to compare outcomes. Interestingly, the authors found that mortality among diabetic patients in the therapy group was equal to that of the control group, despite both higher mean glucose values and severity of illness. Mortality among nondiabetic patients in the therapy group was twice as high as that of diabetic patients in the therapy group, despite better BG control (median BG 134 *vs.* 170 mg/dL, respectively). These results suggest that ideal glucose levels for critically ill patients may differ by diabetic status.

Much of the work regarding intraoperative IIT has focused solely on diabetic patients (and has shown benefit; see Intraoperative IIT).[2,3,58,59] A retrospective study by Doenst *et al.* showed that hyperglycemia during CABG was an independent predictor of mortality in both diabetic and nondiabetic patients; the effect size was similar in the two groups.[5] Subgroup analysis of the RCT by Gandhi *et al.* showed no benefit of IIT in diabetic patients in morbidity, mortality, or LOS.[13] Notably, diabetic patients in this study did not achieve BG goals.

It is not clear whether the benefit of IIT differs between type 1 and type 2 diabetic patients. In general, type 1 diabetes is characterized by insulin deficiency due to autoimmune destruction of pancreatic beta cells,[70] and type 2 diabetes is characterized by insulin resistance. However, not all patients with insulin resistance have frank diabetes; indeed, normoglycemia in insulin-resistant patients is initially achieved by increased secretion of insulin. As the disease progresses, though, resistance to insulin at the level of the glucose transporters increases, leading to hyperglycemia and frank diabetes.[21]

Therefore, patients with type 2 diabetes generally require higher levels of insulin than those with type 1 diabetes to achieve the same level of BG control. Given the aforementioned evidence of an association between increased administration of insulin and death, regardless of BG level,[30] it is likely that the two groups will differ in their response to IIT.

Appropriate Glucose Targets

Even among proponents of IIT, controversy exists regarding appropriate BG targets, particularly because aggressive glycemic control targets are associated with increased risk of hypoglycemic events.[40] Existing guidelines on inpatient glycemic control, such as those published in *Endocrine Practice,* the journal of the American Association of Clinical Endocrinologists,[71] should be viewed skeptically. The BG target in the Leuven studies was 80–110 mg/dL; a *post hoc* analysis showed a statistically significant decrease in the risk of morbidity and mortality with decreasing BG levels ($>$150 mg/dL, 110–150 mg/dL, $<$110 mg/dL) in surgical ICU patients. Indeed, they were unable to identify a BG threshold below which no further risk reduction occurred.[18] Golden *et al.* compared patients in each of 4 glucose categories (121–206 mg/dL, 207–229 mg/dL, 230–252 mg/dL, and 253–352 mg/dL) and found that patients in the higher quartiles were at progressively higher risk of infection.[52] Of note, though, is that patients in the lowest quartile of the Golden study still had BG levels higher than the IIT group of the Leuven studies. In a retrospective analysis, Krinsley showed an association between hyperglycemia and increased hospital mortality among medical and surgical ICU patients.[72] Hospital mortality increased with BG; mean and maximum BG values were higher among nonsurvivors than among survivors, even when stratified by APACHE II scores. However, this study was purely observational; no intervention was performed.

Several other studies have also shown significant benefit with higher BG thresholds. For example, Krinsley's before-after study showed a significant decrease in mortality with maintenance of BG less than 140 mg/dL in the critically ill.[22] In their before-after study of diabetic cardiac surgery patients, Furnary *et al.* showed a decrease in mortality with IIT despite a "moving target" of BG during the study time, with the lowest BG goal being 100–150 mg/dL.[2] Several other studies show improved outcomes with BG $<$ 200 mg/dL.[3,50,59]

In addition, there is evidence that variability in the BG concentration, not just BG levels, affects morbidity and mortality. A retrospective study of 7049 patients in 4 mixed medical-surgical ICUs showed that the SD of BG was a significant predictor of ICU and in-hospital mortality (OR = 1.27 per 1 mm; $P = 0.013$; mean BG SD 31 mg/dL and 41 mg/dL in survivors and nonsurvivors, respectively) among both diabetic and nondiabetic patients, and it was an even stronger predictor than mean BG.[73] This finding was confirmed in another retrospective study of septic patients using the glycemic lability index, a measure of glucose variability over time.[74] In this study, patients with increased glycemic lability index but below-average BG had an almost fivefold increase

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in the odds of hospital mortality. Acute changes in BG level are known to have detrimental biochemical effects in diabetic outpatient populations.[75] However, there are insufficient data to determine the optimal SD in BG.

Measurement of Blood Glucose

To further cloud the picture, there is controversy over how and when to measure BG. A variety of measurement techniques are currently in use, and it is not clear that they are equivalent. For instance, the Leuven studies measured BG using whole undiluted blood and a blood gas analyzer,[1,10] whereas most ICUs rely on point-of-care glucometers that use capillary blood.[37] Recently, Desachy *et al.* examined the accuracy of point-of-care (POC) glucose strip assays for capillary and whole blood, as compared to labortatory results.[76] POC values were considered significantly different from the laboratory value when they disagreed by more than 20%; significant differences were found in 15% of capillary blood samples and 7% of whole blood samples. Hypotension was associated with discrepancy in values. Kanji *et al.* had similar results when comparing three different POC measurements (chemical analysis of arterial blood gas, glucometer analysis of capillary blood *via* fingerstick, and glucometer analysis of arterial blood) with laboratory results.[77] Agreement between POC techniques and laboratory values was low (<80%); perhaps more importantly, agreement was especially dismal during hypoglycemia (26% for capillary blood and 56% for arterial blood using glucometers, and 65% for chemical analysis of blood gas), and the errors tended to overestimate BG levels. A number of other factors, including peripheral hypoperfusion, certain drugs, anemia, and elevated bilirubin or uric acid, have been implicated in affecting POC BG measurements, many of which are commonly seen in crictically ill patients.[78] In a retrospective study comparing bedside glucose to plasma glucose in the ICU, Finkielman and Oyen conclude that bedside glucose provides an "unreliable estimate" for plasma glucose.[79]

BG indices also vary widely. Studies have used admission glucose, maximum daily glucose, mean morning glucose, mean overall glucose, and hyperglycemic index.[75,80,81] This inconsistency is troubling in light of evidence that there is a circadian rhythm of BG values in critically ill patients.[82] Indeed, Egi *et al.* showed that the average morning BG level among critically ill patients was significantly lower than the 24-h average.

Implementation of IIT Protocols

The challenges of IIT implementation in various patient populations are well documented.[83–88] The method of insulin administration and measurement, frequency of BG checks, and protocol design vary widely among the studies, resulting in differing ability to achieve BG targets and incidence of hypoglycemia. Although some studies report ease in achieving normoglycemia,[83] others report BG values within target range as little as 40% of the time.[86] Chaney *et al.* terminated their study of intraoperative IIT in nondiabetic CABG patients due to "unobtainable" glucose goals and unpredictable postoperative hypoglycemic events.[88] A recent systematic review attempted to elucidate the most feasible algorithm for tight glycemic control in the critically ill; this study found that dynamic scale protocols using intravenous insulin infusion, tight glucose targets, frequent BG checks (hourly to every 4 h), and the last two BG values in the algorithm gave the best results in terms of glycemic control to target values and avoidance of hypoglycemia.[89]

A simplified insulin protocol matrix was recently validated at one institution.[90] The matrix specifies necessary changes in insulin dosing based on current and previous BG values. It is promising in that it does not require the same calculations as more traditional IIT protocols, thereby decreasing both the time in administering the protocol and the potential for insulin dosing errors.

We successfully implemented an IIT protocol at the University of California, San Francisco (UCSF) Medical Center in December 2002.[91] UCSF is a 600-bed academic hospital with 60 medical, surgical, cardiac, and neuroscience ICU beds and a typical ICU nurse-to-patient ratio of 1:1.5. Whereas the previous insulin protocol adjusted dose by 0.5 units per hour to achieve BG of 100–200 mg/dL, the IIT protocol aimed to achieve a target BG between 80 and 120 mg/dL *via* adjustment in insulin dosing by 0.2–3.0 units per hour based on both the absolute value and trajectory of glucose concentration. In our opinion, the most important steps in safely implementing an effective IIT protocol are pilot testing and stepwise implementation, which allow rapid response to problems with the protocol. Using these tools, we were able to achieve good glycemic control (median BG, 119 mg/dL) with hypoglycemia (defined as BG < 60 mg/dL) rate of 0.08%. Of note, each glucose determination required 7 min of nursing time; a nurse caring for 2 patients on the insulin protocol would spend approximately 2 h of a 12-h shift monitoring the patient, obtaining samples, performing tests, and intervening. The time intensiveness of this intervention is important to consider, especially when assessing the generalizability of IIT studies such as those performed in Leuven, where staffing was plentiful.

Cost-Effectiveness

The cost-effectiveness of IIT has been evaluated and confirmed in several patient populations. First, cost savings with IIT have been demonstrated in the diabetic inpatient population, regardless of ICU stay.[92] Furnary *et al.* showed decreased costs when IIT was used in diabetic CABG patients.[2] In addition, *post hoc* analysis of several large studies has shown cost-effectiveness in the ICU setting. In a mixed medical-surgical ICU, Krinsley and Jones showed a decrease in ICU and hospital LOS,

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Table 3. Surgical Care Improvement Project Process and Outcome Measures by Category

Infection	
INF 1	Prophylactic antibiotic received within 1 h before surgical incision
INF 2	Prophylactic antibiotic selection for surgical patients
INF 3	Prophylactic antibiotics discontinued within 24 h after surgery end time (48 h for cardiac patients)
INF 4	Cardiac surgery patients with controlled 6 am postoperative serum glucose
INF 5	Postoperative wound infection diagnosed during index hospitalization*
INF 6	Surgery patients with appropriate hair removal
INF 7	Colorectal surgery patients with immediate postoperative normothermia
Cardiac	
Card 2	Surgery patients on a β-blocker before arrival who received a β-blocker during the perioperative period
Card 3	Intraoperative or postoperative acute myocardial infarction diagnosed during index hospitalization and within 30 days of surgery*
Venous thromboembolism	
VTE 1	Surgery patients with recommended venous thromboembolism prophylaxis ordered
VTE 2	Surgery patients who received appropriate venous thromboembolism prophylaxis within 24 h before surgery to 24 h after surgery
VTE 3	Intraoperative or postoperative pulmonary embolism diagnosed during index hospitalization and within 30 d of surgery*
VTE 4	Intraoperative or postoperative deep vein thrombosis diagnosed during index hospitalization and within 30 d of surgery*
Vascular access	
VA 1	Proportion of permanent hospital end-stage renal disease vascular access procedures that are autogenous arteriovenous fistulas
Global	
Global 1	Mortality within 30 d of surgery
Global 2	Readmission within 30 d of surgery
Respiratory†	
Resp 1	Number of days ventilated surgery patients had documentation of the head of the bed being elevated from recovery end date (day 0) through postoperative day seven
Resp 2	Patients diagnosed with postoperative ventilator-associated pneumonia during index hospitalization
Resp 3	Number of days ventilated surgery patients had documentation of stress ulcer disease prophylaxis from recovery end date (day 0) through postoperative day 7
Resp 4	Surgery patients whose medical record contained an order for a ventilator weaning program (protocol or clinical pathway)

From MedQIC. Surgical Care Improvement Project Program Information. http://www.medqic.org/dcs/ContentServer?cid=1122904930422&pagename=Medqic%2FContent%2FParentShellTemplate&parentName=Topic&c=MQParents. Last Accessed July 19, 2008.

*Outcome measures. At this time, only process measures are being collected. † Note the respiratory measures are still under review and may be added at a later date.

ventilator days, and laboratory, pharmacy, and radiology costs, accounting for a total decrease in treatment costs of $1580 per patient.[93] Van den Berghe *et al.* showed a decreased cost of 2638 euros ($4172) in a surgical ICU population receiving IIT.[94] However, the cost-effectiveness of the intervention decreases substantially as the effect size of the intervention decreases. Recent studies showing no mortality benefit and increased incidence of hypoglycemia and serious adverse events are unlikely to demonstrate cost-effectiveness.

Policy Implications

The safety, efficacy, appropriate patient population, and cost of IIT are of utmost importance not only because of IIT's potential impact on patient care, but also because of the policy implications of the intervention. In recent years, the Joint Commission and CMS have worked together to develop measures of quality and to align those measures so they are identical; their joint effort resulted in the *Specifications Manual for National Hospital Quality Measures*.# That document contains specific measures for evaluating the quality of care related to clinical conditions and events such as acute myocardial infarction, heart failure, pneumonia, and surgery.

The surgical component, SCIP, was launched in 2006 with the goal of reducing the incidence of surgical complications in the United States 25% by 2010.** The SCIP measures (table 3) call for evidence-based treatment, including appropriate prophylactic antibiotics before surgery, proper hair removal, venous thromboembolism prophylaxis, and head-of-bed elevation for mechanically ventilated patients. SCIP infection measure No. 4 requires cardiac surgery patients to have morning (closest to 0600 h) BG levels less than 200 mg/dL on postoperative days 1 and 2. It is interesting that the Joint Commission and CMS are creating performance measures in

Joint Commission. Specifications Manual for National Hospital Quality Measures, April 2008. Available at: http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Current+NHQM+Manual.htm. Accessed July 12, 2008.

** MedQIC Surgical Care Improvement Project Program Information. http://www.qualitynet.org/dcs/ContentServer?cid=1136495755695&pagename=Medqic%2FOtherResource%2FOtherResourcesTemplate&c=OtherResource. Accessed July 19, 2008.

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controversial areas such as glycemic control. Although the data support avoidance of hyperglycemia in the postoperative period, the data also highlight risk of hypoglycemia and harm, which are known to occur even in the controlled and resource-rich settings of RCTs. Furthermore, with evidence regarding the appropriate target glucose levels lacking, the SCIP goal of less than 200 mg/dL is arbitrary. As discussed in the Measurement of Blood Glucose section above, it is not clear that following morning glucose values is the best way to monitor glycemic control.

Data collected from the SCIP and other quality-improvement programs are currently being used to create evidence-based guidelines and national benchmarks that can be used to create P4P programs. CMS has been devoting increasing amounts of resources into studying and piloting P4P. In a large demonstration project with Premier Hospitals, CMS is set to pay $8.85 million in incentives based on process and outcome measures in five clinical areas. The project was designed to reward top-performing hospitals with bonuses and to penalize hospitals that do not meet a predefined quality threshold.†† Interim analysis of this project has shown significant improvements in quality as defined by preset measures as well as decreased variability in performance among hospitals. Similar incentives and penalties may be put in place with SCIP measures, including glycemic control. Even though leaders in the field of quality and patient safety have recently endorsed the idea of P4P, including a subset of P4P in which CMS will begin withholding payments for serious preventable adverse events,[95] it is obvious that P4P measures must be based on clinical interventions that have a strong evidence base. Pronovost *et al.* argue that P4P is only appropriate when complications are important, measurable, and truly preventable.[96] Given the concerns regarding the safety and efficacy of IIT, it is not clear that glycemic control targets meet this criterion.

Future Directions

Controversy regarding the safety and efficacy of IIT exists, and additional RCTs are needed before definitive recommendations can be made. The Australian and New Zealand Intensive Care Society and the Canadian Critical Care Trials Group completed enrollment of 6105 patients in the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study on August 16, 2008. (Simon Finfer, F.R.C.P., F.J.F.I.C.M., Professor, Royal North Shore Hospital of Sydney, Sydney, Australia, written personal communication, August 21, 2008) A multicenter, open-label RCT, NICE-SUGAR will compare IIT (target BG 81–108 mg/dL) and conventional therapy (target BG 144–180 mg/dL) in a heterogeneous ICU population.‡‡ BG measurements will be obtained from arterial blood using either POC devices or a laboratory; all values < 72 mg/dL will be confirmed by a reference laboratory.[78] The primary endpoint is 90-day all-cause mortality; secondary outcome measures include incidence and severity of hypoglycemia, need for organ support, incidence of blood stream infections, death in ICU, and LOS. The results of this large study should provide important information that will be crucial to the development of definitive recommendations regarding IIT.

In addition, there is increased interest in the role of technology in IIT. Continuous subcutaneous glucose monitoring at home has been shown to be effective in lowering Hemoglobin A1c[97] and decreasing glycemic excursions in adults with type 1 and 2 diabetes. The continuous glucose monitoring device consists of a sensor inserted into the subcutaneous fat of the abdomen to measure glucose by the glucose-oxidase method and transmit the measurement to an external transmitter. Although there are theoretical concerns that subcutaneous edema, hypotension, and vasopressor use could decrease the accuracy and reliability of continuous glucose monitoring in critically ill patients, several studies have validated the use of this system in the ICU *via* Clark Error Grid analysis of the sensor readings and standard glucometer readings performed simultaneously.[98,99] A number of private sector device manufacturers are also developing continuous monitoring devices using blood rather than subcutaneous glucose measurements, which may be promising in the perioperative setting.[100]

Evaluation of automation of the insulin infusion protocol is also underway. Rood *et al.* studied the use of a computerized algorithm that provides guideline-based advice within preexisting decision support software and found that the computer-based protocol improved insulin-dosing guideline compliance and decreased the incidence of BG values outside the target range.[101] Plank *et al.* tested a fully automated model predictive control algorithm, a technology that has been used successfully in outpatients with diabetes.[102] Model predictive control treatment was associated with a significantly higher percentage of time within the BG target range with no hypoglycemic events.

The ultimate goal of these technological advances is the creation of closed-loop glucose control. A closed-loop system couples continuous glucose monitoring with an IIT algorithm and an automatic intravenous infusion pump, thereby acting like an artificial pancreas. Several studies have evaluated the use of closed-loop systems in diabetic outpatients and in critically ill patients.[103–107] Unfortunately, due to sensor reading devi-

†† Centers for Medicare and Medicaid Services. Premier Hospital Quality Demonstration. Available at: http://www.cms.hhs.gov/HospitalQualityInits/35_hospitalpremier.asp. Accessed July 19, 2008.

‡‡ Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR STUDY). Available at: http://clinicaltrials.gov/ct2/show/NCT00220987?spons=%22Australian+and+New+Zealand+Intensive+Care+Society+Clinical+Trials+Group%22&spons_ex=Y&rank=2. Accessed July 19, 2008.

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ations and poor performance in achieving glycemic targets, more work is required before this technology becomes a reality.

Conclusion

Although it is clear that hyperglycemia is harmful, there is currently insufficient evidence to support the routine use of tight glycemic control (target BG 80–110 mg/dL) in the operating room or the ICU. With careful, stepwise implementation of IIT protocols, maintaining BG less than 150 mg/dL and reducing BG variability may be both safe and effective. It is likely that there are subpopulations of patients that would benefit from tighter glycemic control (BG 80–110 mg/dL). Until these populations are identified, however, the newly elucidated risk of hypoglycemia and serious adverse events cannot be ignored. If IIT is implemented, careful monitoring of hypoglycemic episodes and dosing errors is imperative. Including BG targets as a core measure in the SCIP program and using BG targets in P4P initiatives before the appropriate target BG values and benefiting patient populations are well-defined is inappropriate and may create more harm than good.

Perhaps more importantly, the experience with immediate and widespread acceptance of IIT after the publication of only one incompletely blinded single-center study suggests that we may need to redefine the idea of evidence-based medicine and be more hesitant to change the standard of care. The controversy over perioperative β-blockade substantiates this idea; the use of β-blockers in at-risk patients in the perioperative period was enthusiastically adopted after two studies showed benefit, but preliminary results from the PeriOperative Ischemic Evaluation (POISE) trial show an increase in the risk of death and stroke in the treatment group.[108]

Furthermore, the inclusion of BG targets in national quality and patient safety initiatives highlights how difficult it is to identify and define measures of quality in healthcare. As we enter an era in which Medicare plans to augment or withhold payments on the basis of quality of care delivered, it will be important for anesthesiologists and intensivists alike to take part in defining and redefining standard of care in both the operating room and ICU.

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