

Glucose control in critical care

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Abstract

Glucose control among critically-ill patients has been

a topic of considerable attention for the past 15 years. An initial focus on the potentially deleterious effects of hyperglycemia led to a series of investigations regarding intensive insulin therapy strategies that targeted tight glycemic control. As knowledge accumulated, the pursuit of tight glycemic control among critically-ill patients came to be seen as counterproductive, and moderate glycemic control came to dominate as the standard practice in intensive care units. In recent years, there has been increased focus on the importance of hypoglycemic episodes, glycemic variability, and pre-morbid diabetic status as factors that contribute to outcomes among critically-ill patients. This review provides a survey of key studies on glucose control in critical care, and aims to deliver perspective regarding glycemic management among critically-ill patients.

Key words: Glycemic control; Critical care; Blood sugar in intensive care unit; Diabetes in intensive care unit; Glycemic control

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Core tip: Glucose control among critically-ill patients has been an area of active research and considerable controversy in the past 15 years. This review provides a practical guide to the evidence, with a survey of the key studies that have informed current perspectives and clinical guidelines related to glycemic management among the critically ill. The article shows why initial enthusiasm for tight glycemic control waned as evidence accumulated favoring more modest glucose goals. The article also summarizes recent work investigating the importance of hypoglycemic episodes, glycemic variability, and pre-morbid diabetic status on morbidity and mortality in the intensive care unit.

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INTRODUCTION

In 2001, van den Berghe *et al.*^[1] reported results from a single-center, prospective, randomized controlled trial in Leuven, Belgium, and changed the way that blood glucose was managed in intensive care units (ICUs) throughout the world. Prior to the publication of this first Leuven study, glycemic control among critically-ill patients received scant attention, either at the bedside or in academic journals. The overwhelmingly favorable results of the study - which, among critically-ill surgical patients, found a remarkable mortality benefit from the use of intensive insulin therapy targeting normoglycemia - sparked strong interest in glycemic management in the ICU. Intensive insulin therapy quickly became the standard of care in both medical and surgical ICUs. However, as has been the experience in many facets of critical care, promising initial single-center results were not duplicated in subsequent trials. The publication of the NICE-SUGAR trial in 2009, which reported that intensive insulin therapy may actually result in increased mortality among critically-ill patients, served as a major bookend to the era of tight glycemic control as a pillar of ICU management^[2].

Nonetheless, interest in defining optimal glycemic control among critically-ill patients has continued. In the years that have followed the publication of the NICE-SUGAR trial, investigations have focused on establishing which factors of glycemic control and dysregulation most affect patient outcomes in the ICU. It has been increasingly recognized that hypoglycemia, glycemic variability, and premorbid diabetic status are all important considerations to be taken into account when approaching the glycemic management of a critically-ill patient.

This review aims to provide a survey of the key studies that have informed the changes in thinking in the past 15 years as regards glucose control in critical care. It explores the basis of the initial enthusiasm for, and subsequent skepticism of, intensive insulin therapy in the ICU. It also aims to provide perspective regarding major issues of glycemic management among critically-ill patients: hyperglycemia, hypoglycemia, glycemic variability, and premorbid diabetic status.

HYPERGLYCEMIA

Elevated blood sugar levels are commonly seen among critically ill patients, including those without a known history of diabetes. There are many reasons why patients undergoing treatment for critical illness develop hyperglycemia, and these reasons include both effects of endogenous stress responses and byproducts of medical interventions. Inflammatory cytokines and stress hormones, including cortisol and epinephrine, serve to inhibit insulin release and promote insulin resistance, thereby naturally increasing blood glucose levels by stimulating gluconeogenesis and glycogenolysis while impeding glucose uptake by peripheral tissues^[3,4]. Many

medical therapies further promote hyperglycemia, including the administration of exogenous catecholamines and corticosteroids, the infusion of dextrose for the purpose of suspending intravenous medications or providing parenteral nutrition, and even bedrest, which in and of itself may serve to impair glucose uptake in skeletal muscles^[5,6].

Prior to the publication of the first Leuven trial^[1], many practitioners viewed moderately severe hyperglycemia among critically ill patients to be either an epiphenomenon or an adaptive response, not warranting significant concern or intervention^[7]. However, as observational studies accumulated linking hyperglycemia to negative in-hospital patient outcomes, this permissive attitude began to change^[8-11]. Hyperglycemia was coming to be seen as complication worthy of physician attention. For example, a retrospective study of 1826 patients admitted to a mixed ICU in Stamford, Connecticut serving medical, surgical, and coronary patients reported reduced survival among those with elevated mean blood glucose levels, with a stepwise effect resulting in higher mortality as mean blood glucose levels rose^[8]. Compared to patients who survived to hospital discharge, those who died had higher initial (175 mg/dL vs 151 mg/dL), mean (172 mg/dL vs 138 mg/dL), and maximum (258 mg/dL vs 177 mg/dL) blood glucose levels. In-hospital mortality was 9.6% among those with a mean blood glucose of 80-99 mg/dL, 29.4% among those with a mean blood glucose of 180-199 mg/dL, and 42.5% among those with a mean blood glucose greater than 300 mg/dL.

Observations such as these raised concern that acute hyperglycemia was itself contributing to poor outcomes, potentially by leaving affected patients susceptible to at least some of the consequences that have long been observed among chronic diabetics, including high infection rates, poor wound healing, and polyneuropathy^[1,5]. Laboratory studies have also raised concerns about the possible deleterious effects of acute hyperglycemia, as hyperglycemia has been shown to cause injury to a variety of cell types that exhibit insulin-independent glucose uptake, including endothelial cells, hepatocytes, and renal tubular cells^[12-16].

The repeated observation that hyperglycemia is associated with worse outcomes among critically ill patients, together with the theoretical harms of acutely elevated blood glucose levels, represents the basis for focusing on glycemic control in the intensive care setting. However, the possibility remains that elevated blood glucose levels are actually beneficial to the critically ill individual, and that stress hyperglycemia is an appropriate and adaptive response to life-threatening illness, as no randomized trial investigating glycemic control has studied the effect of truly permissive hyperglycemia^[17]. Potential benefits of hyperglycemia in the critically ill individual include promotion of glucose delivery in the face of ischemic insults (down an enhanced glucose diffusion gradient), with insulin resistance favoring redistribution of available glucose

stores toward cells of the immune and nervous systems, and away from peripheral tissues^[17]. Recent observational studies have provided some support for this view, reasserting the possibility that hyperglycemia is simply a marker of illness severity. For example, a recent retrospective study of 7925 consecutive critically ill patients admitted to three mixed ICUs in Australia showed that while hyperglycemia was associated with in-hospital mortality, once lactate levels were considered, there was no independent association between hyperglycemia and mortality^[18]. This finding was consistent with a previous retrospective study, which found that among a cohort of septic nondiabetic adult patients, hyperglycemia noted on initial presentation did not increase mortality risk unless accompanied by concurrent hyperlactatemia^[19]. Such observations present a useful reminder that our understanding of the effects of hyperglycemia remains incomplete.

Our ability to identify patients most likely to suffer harm from hyperglycemia also remains incomplete. Several studies have concluded that the association between hyperglycemia and in-hospital mortality is attenuated among those with pre-existing diabetes mellitus, with some even failing to demonstrate any association at all^[11,20-23].

MAJOR INVESTIGATIONS OF GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS

Concern about the potentially deleterious effects of hyperglycemia in critically ill patients has motivated multiple randomized controlled trials investigating glycemic management in ICUs^[1,2,24-32]. This section serves to review the major trials regarding this subject, exploring the evidence that underlay the initial enthusiasm for, and subsequent skepticism of, intensive insulin therapy for glycemic normalization among critically ill patients. Key features of the trials are summarized in Table 1.

The original Leuven study, reported by van den Berghe *et al.*^[1] in 2001, was the first major prospective trial to investigate the effects of tight glycemic control in critically ill patients. This was a prospective, non-blinded, randomized controlled trial of 1548 mechanically ventilated adult patients admitted to a single surgical ICU in Leuven, Belgium. A majority of the patients (63%) had undergone cardiac surgery. Prior to admission, 13% of patients had been diagnosed with diabetes mellitus, and 5% had been maintained on insulin therapy. Upon ICU admission, patients were randomly assigned to receive either "intensive" or "conventional" insulin therapy. For all patients, insulin was delivered *via* a continuous infusion, and glycemic monitoring was performed *via* measurements of whole-blood glucose of arterial blood samples, collected every one to four hours. For patients in the intensive insulin therapy group, insulin infusions were started if measures of blood glucose exceeded 110 mg/dL, and the infusions were titrated to maintain

blood glucose in the range of 80 to 110 mg/dL. By contrast, for patients in the conventional therapy group, insulin infusions were only started if measures of blood glucose exceeded 215 mg/dL, and the infusions were titrated to maintain blood glucose in the range of 180 to 200 mg/dL. All patients received intravenous glucose for the first 24 h of ICU admission, after which feeding continued *via* total parenteral, total enteral, or combined enteral and parenteral nutrition. All patients reverted to conventional blood glucose management upon discharge from the ICU. During their ICU stays, 98.7% of patients in the intensive insulin therapy group required insulin infusions, and the targeted blood glucose level was achieved, with a mean blood glucose of 103 mg/dL. Among patients in the conventional insulin therapy group, only 39.2% required insulin infusions, and the mean blood glucose was 153 mg/dL. The results of the study strongly favored the intensive insulin therapy group, with observed benefits in terms of both morbidity and mortality. In-ICU mortality was 4.6% in the intensive insulin therapy group compared to 8.0% in the conventional insulin therapy group ($P < 0.04$), and the survival benefit persisted to hospital discharge, with an absolute risk reduction of in-hospital mortality of 3.7% (7.2% vs 10.9%; $P = 0.01$), largely due to a reduction in deaths attributed to sepsis. Compared to patients in the conventional insulin therapy group, those receiving intensive insulin therapy also experienced reduced rates of renal replacement therapy, prolonged mechanical ventilation, and extended ICU stays. The overwhelmingly positive results from the first Leuven study were in many ways practice-changing, and it informed investigations into glycemic management of critically ill patients for the ensuing decade, and beyond.

The next major prospective trial came from the same group in Belgium, and was again a single-ICU study^[24]. In this second Leuven study, 1200 adult patients admitted to a medical ICU were studied. The study included only patients who were unable to take oral nutrition upon ICU admission, and who were anticipated to require at least 3 d of intensive care. Patients were randomized to intensive vs conventional insulin therapy groups, with stratification according to diagnostic categories. Thresholds for initiation of insulin therapy and target blood glucose levels for the two groups were identical to what had been used in the first Leuven study^[24]. In stark contrast to the findings of the previous trial, the second Leuven study showed no overall mortality benefit to intensive insulin therapy, as both ICU and in-hospital mortality rates were similar among patients in the intensive and conventional insulin therapy groups. However, the authors reported a statistical difference in in-hospital mortality among the subset of patients who actually received at least 3 d of ICU care, as had been intended at the time of their inclusion in the study. Among this subset of 767 patients who stayed in the ICU for at least 3 d (of whom 386 received intensive insulin therapy and 381 received conventional insulin therapy), in-hospital mortality was

Table 1 Summary of major randomized controlled trials investigating the use of intensive vs conventional insulin therapy in critically-ill patients

Trial	Study population	Number of patients enrolled	Target blood glucose in the intensive insulin therapy group (mg/dL)	Target blood glucose in the conventional insulin therapy group (mg/dL)	Key mortality findings	Key morbidity findings
First Leuven Trial, 2001 ^[1]	Single-center; surgical ICU	1548	80-110	180-200	Reduced ICU and in-hospital mortality in the intensive insulin therapy group	Reduced incidence of bloodstream infection, acute renal failure, red cell transfusion, and critical-illness neuropathy in the intensive insulin therapy group. Increased occurrence of severe hypoglycemia in the intensive insulin therapy group
Second Leuven Trial, 2006 ^[24]	Single-center; medical ICU	1200	80-110	180-200	No mortality difference	Reduced incidence of newly acquired kidney injury, reduced duration of mechanical ventilation, and reduced lengths of ICU and hospital stays in the intensive insulin therapy group. Increased occurrence of hypoglycemia in the intensive insulin therapy group
Arabi <i>et al</i> ^[25] , 2008	Single-center; mixed ICU, including medical, surgical, and trauma patients	523	80-110	180-200	No mortality difference	Increased occurrence of hypoglycemia in the intensive insulin therapy group
Brunkhorst <i>et al</i> ^[26] , 2008	Multicenter; mixed ICUs; all patients with severe sepsis or septic shock	537	80-110	180-200	No mortality difference	No difference in the mean score for organ failure. Increased occurrence of severe hypoglycemia in the intensive insulin therapy group
De La Rosa Gdel <i>et al</i> ^[27] , 2008	Single center; mixed ICU, including medical, surgical, and trauma patients	504	80-110	180-200	No mortality difference	Increased occurrence of severe hypoglycemia in the intensive insulin therapy group
Preiser <i>et al</i> ^[28] , 2009	Multicenter; medical and surgical ICU patients	1078	79-110	140-180	No mortality difference	Increased occurrence of severe hypoglycemia in the intensive insulin therapy group
NICE-SUGAR Trial, 2009 ^[2]	Multicenter; medical and surgical ICU patients	6104	81-108	144-180	Increased 90-d mortality in the intensive insulin therapy group	Similar between-group markers of morbidity, with the exception of an increased occurrence of severe hypoglycemia in the intensive insulin therapy group
Annane <i>et al</i> ^[29] , 2010	Multicenter; all patients with septic shock	509	80-110	180-200	No mortality difference	Increased occurrence of severe hypoglycemia in the intensive insulin therapy group
Coester <i>et al</i> ^[30] , 2010	Single center; all patients with severe traumatic brain injury	88	80-110	< 180	No mortality difference	No difference in neurologic outcomes. Increased occurrence of hypoglycemia in the intensive insulin therapy group
Green <i>et al</i> ^[31] , 2010	Single center; mechanically-ventilated neurologic patients	81	80-110	≤ 150	No mortality difference	No difference in neurologic function at 90 d. Increased occurrence of hypoglycemia and severe hypoglycemia in the intensive insulin therapy group
Macrae <i>et al</i> ^[32] , 2014	Multicenter; medical and surgical pediatric patients	1369	72-126	180-216	No mortality difference	No difference in ventilator-free survival. Increased occurrence of severe hypoglycemia in the intensive insulin therapy group

ICU: Intensive care unit.

43.0% in the intensive therapy group, compared to 52.5% in the conventional therapy group ($P = 0.009$). While an interesting finding, this subset analysis suffered from a lack of real-world applicability (even the authors were unable to accurately predict which patients would require extended ICU stays) and a loss of balanced diagnostic categorization (likely biasing the results). While no mortality benefit to intensive insulin therapy was identified, secondary analyses of patient morbidity found reduced rates of acquired kidney injury, reduced durations of mechanical ventilation, and reduced lengths of ICU and hospital stay among patients in the intensive insulin therapy group compared to those in the conventional insulin therapy group.

The mortality benefits realized in the first Leuven study and the morbidity benefits realized in the second sustained considerable enthusiasm for tight glycemic control in critically ill patients for the next several years, with widespread adoption of intensive insulin protocols in medical and surgical ICUs, despite occasional voices urging caution^[33,34]. However, a series of studies published in 2008 and 2009, culminating with the NICE-SUGAR trial, severely tempered this enthusiasm^[2,25-28]. The first of these trials, reported by Brunkhorst *et al.*^[26], involved patients with severe sepsis or septic shock admitted to multidisciplinary ICUs in 18 academic tertiary hospitals in Germany. This was a two-by-two factorial trial, and patients were randomized to receive either intensive or conventional insulin therapy for glycemic control (with protocols similar to those used in the two Leuven studies^[1,24]) and either hydroxyethyl starch or modified Ringer's lactate for fluid resuscitation. The use of intensive insulin therapy was terminated after the first safety analysis, due to a nearly six-fold increased frequency of hypoglycemia in the intensive insulin group, including a high proportion of severe hypoglycemic events that were classified as life-threatening and requiring prolonged hospitalization. Among the patients studied, there was no documented benefit to intensive insulin therapy, as there were no statistical differences in rates of mortality, rates of acute renal failure or renal replacement therapy, use of vasopressor medications, number of ventilator-free days, or length of ICU stay.

Several subsequent studies conducted in a variety of settings similarly failed to demonstrate clear benefits to tight glycemic control in critically ill patients, but consistently highlighted an increased risk of hypoglycemia among patients treated with intensive insulin protocols^[2,25,27,28]. Arabi *et al.*^[25] reported a prospective trial wherein they randomized 523 medical, surgical, and trauma patients admitted to a single ICU in Riyadh, Saudi Arabia to intensive or conventional insulin therapy, and found no between-group differences in mortality, ICU or hospital lengths of stay, rates of renal replacement therapy, durations of mechanical ventilation, or frequencies of infectious complications, but patients in the intensive insulin group experienced much higher rates of hypoglycemia. Similar negative findings with respect to measures of mortality and morbidity were

reported by De La Rosa Gdel *et al.*^[27] in their study of 504 medical, surgical, and trauma patients admitted to a single ICU in Medellin, Colombia and randomized to intensive or conventional insulin therapy, though again, rates of hypoglycemia were much higher in the intensive insulin group. A subsequent multinational trial, involving patients admitted to 21 medico-surgical ICUs in 7 countries, also failed to identify meaningful benefits to tight glycemic control^[28]. This study, which again randomized patients to intensive or conventional insulin therapy, was ultimately underpowered, as it was prematurely stopped due to a high rate of unintended protocol violations. However, among the 1078 patients studied, there were no between-group differences in mortality, and the only differences in measures of morbidity were higher rates of hypoglycemia among patients in the intensive insulin therapy group and a slight reduction in vasopressor/inotrope use in the conventional insulin therapy group.

On the heels of these four consecutive negative studies^[25-28], the landmark NICE-SUGAR trial was reported, which remains the most comprehensive study of glycemic control strategies among ICU patients performed to date^[2]. The NICE-SUGAR study included 6104 medical and surgical patients admitted to ICUs at 42 hospitals in Australia, New Zealand, Canada, and the United States. All patients were anticipated to require at least 3 d of ICU care, were expected to be unable to eat for at least 2 d, and had an arterial line in place as part of their routine ICU management. As with previous studies, patients were randomized to intensive or conventional insulin therapy groups, but the target blood glucose range of the conventional insulin therapy group was lower than it had been in the Leuven studies^[1,24], based on updated practice surveys. In the intensive insulin therapy group, the target blood glucose range was 81 to 108 mg/dL, while in the conventional insulin therapy group, the target blood glucose was 180 mg/dL or less, with insulin administration reduced and then discontinued if blood glucose levels fell below 144 mg/dL. As had been the case in Leuven studies^[1,24], blood glucose monitoring was performed every one to four hours, and the use of arterial rather than capillary blood samples for this purpose was encouraged. The majority of patients in both treatment groups received insulin therapy (97.2% of those in the intensive insulin therapy group and 69.0% of those in the conventional insulin therapy group). The mean time-weighted blood glucose level in the intensive group was 115 mg/dL, while it was 144 mg/dL in the conventional group. The primary study endpoint was 90-d all-cause mortality, which was 2.6% higher in the intensive than in the conventional insulin therapy group (27.5% vs 24.9%, $P = 0.02$). Subgroup analyses suggested no differences in treatment effects for comparisons of medical and surgical patients, patients with and without preexisting diabetes, and patients with and without severe sepsis. With the exception of rates of severe hypoglycemia, markers of morbidity did not differ according to treatment groups,

as there were similar between-group ICU and hospital lengths of stay, durations of mechanical ventilation, frequencies and durations of renal replacement therapy, rates of new organ failure, and occurrences of positive blood cultures. Severe hypoglycemia (defined as a blood glucose level less than or equal to 40 mg/dL) occurred in 6.8% of the patients in the intensive insulin therapy group vs 0.5% of those in the conventional therapy group ($P < 0.001$).

Following the overwhelmingly negative results of the NICE-SUGAR study, Annane *et al.*^[29] reported on the use of intensive vs conventional insulin therapy in patients with septic shock being treated with corticosteroids, hypothesizing that this subset of ICU patients may benefit from intensive insulin therapy, even if a general ICU population does not. A total of 509 patients treated in 11 ICUs in France were randomized to intensive or conventional insulin therapy, according to the treatment protocols used in the first Leuven study^[1]. Here again, there were no between-group differences in measures of patient mortality or morbidity, with the exception of an increased rate of severe hypoglycemia among patients in the intensive insulin therapy group. Subsequently, randomized controlled trials investigating intensive insulin therapy among mechanically ventilated neurologic patients, patients with severe traumatic brain injuries, and critically ill pediatric patients have all failed to demonstrate a clinical benefit to tight glycemic control^[30-32].

In summary, following the publication of the two single-center Leuven studies^[1,24], the preponderance of evidence has strongly indicated that the use of intensive insulin treatment with the goal of tight glycemic management in critically-ill patients at best provides no benefit over moderate or lax glycemic control, and at worst results in markedly increased rates of severe hypoglycemia and possibly even increased mortality^[2,25-29].

HYPOGLYCEMIA

As clinicians and investigators have grappled with the results of the NICE-SUGAR trial and of other negative studies regarding the use of intensive insulin therapy in critically-ill patients^[2,25-32], several potential explanations have been proposed to account for the lack of demonstrable benefit for tight glucose control. The proposed explanations have targeted either the rationale for intensive insulin therapy (positing that hyperglycemia may be beneficial, or that exogenous insulin may be harmful), or the execution of the strategy (suggesting that the labor-intensive focus on tight glycemic control distracts from other considerations, or that the benefits of normoglycemia have been obscured by an inability to avoid hypoglycemia)^[4,35]. This final consideration—that hypoglycemic complications negate the potential benefits of tight glycemic control—has gained widespread acceptance, and has important implications for future study of glycemic management among critically-ill patients. Hypoglycemia has been a commonly-reported

occurrence among the patients treated with intensive insulin therapy in major trials, and severe hypoglycemia (defined as a blood glucose level less than 40 mg/dL) has occurred in up to 28% of these patients^[4]. It was not initially clear whether the increased rate of hypoglycemia experienced among patients treated with a tight glycemic control strategy was problematic. In the first Leuven study, severe hypoglycemia was reported to have occurred 6.6-fold more commonly among patients in the intensive insulin therapy group, but no clinically-significant outcomes were associated with its occurrence in any of the patients, and the issue of hypoglycemia was not addressed in the manuscript's discussion^[1].

By the time the NICE-SUGAR trial was reported, the frequency of hypoglycemic episodes among patients treated with intensive insulin regimens had become a significant concern. It was recognized that hypoglycemia could theoretically be harmful to patients by means of a number of different mechanisms, including irreversible neuronal damage, autonomic instability, cardiac arrhythmia, and alteration of inflammatory responses^[36,37]. The relationship between hypoglycemia and mortality was examined in a post-hoc analysis of the NICE-SUGAR trial^[37]. For the purpose of this analysis, severe hypoglycemia was defined as a recorded blood glucose level of 40 mg/dL or less, while moderate hypoglycemia was defined as a recorded blood glucose level in the range of 41 to 70 mg/dL. Among the 6026 patients analyzed, severe hypoglycemia occurred in 3.7% of individuals, while moderate hypoglycemia occurred in an additional 45.0%. Hypoglycemic episodes were much more common among those patients in the intensive insulin therapy group, with this group accounting for 93.3% of severe hypoglycemia and 82.4% of moderate hypoglycemia. The occurrence of hypoglycemia was strongly associated with an increased risk of death, with moderate hypoglycemia associated with a 40% increase in adjusted mortality risk, and severe hypoglycemia associated with a doubling of this risk. While these data do not prove a causal relationship between hypoglycemia and mortality, they do support the possibility that it was the increased frequency of iatrogenic hypoglycemic episodes that accounted in some measure for the excess mortality observed among patients treated with intensive insulin therapy in the NICE-SUGAR trial.

This possibility has been supported by other retrospective studies investigating the relationship between hypoglycemic episodes and mortality among ICU patients. In a review of 4946 patients admitted to two ICUs in Australia, Egi *et al.*^[38] found that 22.4% of patients experienced at least one episode of hypoglycemia, defined as recorded blood glucose of less than 82 mg/dL. The patients were analyzed in six bands, according to the level of their lowest recorded blood glucose, and it was shown that the severity of hypoglycemia was independently associated with in-hospital mortality. In a separate single-center review of 5365 consecutive patients admitted to a mixed medical-

surgical ICU, the occurrence of even one episode of severe hypoglycemia was seen to be independently associated with mortality, both by case-control and by multivariable logistic regression analyses^[39].

To a significant extent, a desire to avoid inducing hypoglycemia has motivated the move away from treating ICU patients with intensive insulin protocols^[40]. It should be noted that the focus on avoiding hypoglycemia leaves the door open to future reconsideration of the benefits of tight glycemic control. If the problem with intensive insulin therapy is mainly an inability to avoid hypoglycemic episodes, one can imagine that the development of better glucose monitoring technologies and glycemic control algorithms (if they allow for severe reductions in the incidence of hypoglycemia) could result in improved outcomes with a tight glycemic control strategy. In recent years, the development of continuous glucose monitoring systems has received significant attention along these lines, but the benefits of continuous glucose monitoring have not yet been established^[41-43].

GLYCEMIC VARIABILITY

In recent years, it has increasingly been recognized that glycemic variability is a dimension of significant importance among critically-ill patients, independent of the acute highs and lows of blood glucose measurements in the ICU. The potential significance of glycemic variability among ICU patients was first raised by Egi *et al.*^[44], in a retrospective observational study of 7049 patients who had been admitted to four hospitals in Australia. For the purposes of this study, a patient's glycemic variability was defined as the standard deviation of the arithmetical mean of the entire set of glucose measurements during that individual's ICU stay. The authors found that glycemic variability was an independent predictor of mortality, and that the glycemic variability was actually a stronger predictor of ICU mortality than the mean glucose concentration. A subsequent single-center retrospective observational study of 3252 ICU patients in the United States confirmed and extended these findings, again demonstrating that this measure of glycemic variability was a strong independent predictor of mortality, even after excluding patients who had experienced severe hypoglycemia^[45].

As glycemic variability has been further considered among ICU patients, definitions have changed. Defining glycemic variability as the standard deviation of the mean of all blood glucose measurements has fallen out of favor, as starkly different glycemic patterns can generate identical mean glucose and standard deviations^[46]. Multiple other measures of glycemic variability have been described, including coefficient of variation, glycemic lability index, mean absolute glucose change, and mean amplitude of glycemic excursion^[47,48]. No gold standard for measuring glycemic variability has been established, but multiple studies utilizing these more complicated metrics have confirmed that glycemic variability is

independently associated with mortality among ICU patients^[23,46,48,49].

Whether glycemic variability is a cause of poor patient outcomes or is simply a marker of severe illness is not known. However, several lines of evidence have suggested that glycemic variability causes oxidative stress, enhances cell apoptosis, and impairs endothelial function^[45,46]. Therefore, it is plausible that glycemic variability causes harm to critically-ill patients, and that optimal glycemic control in the ICU would aim to minimize glycemic variability. As with avoiding hypoglycemia in the ICU, it is hoped that advances in glycemic monitoring and corresponding glucose control algorithms will reduce the extent of glycemic variability, but at least one early study has failed to show that existing means of continuous glucose monitoring would reduce glycemic variability^[47].

PREMORBID DIABETIC STATUS

From the first Leuven study to the NICE-SUGAR trial, all of the major investigations of intensive insulin therapy in critically-ill patients utilized glycemic-control protocols that did not differentiate between diabetic and nondiabetic patients^[1,2,24-28]. Similarly, recent guidelines regarding the use of insulin infusions in the ICU do not advocate altering the approach to glycemic management on the basis of patients' premorbid diabetic status^[40]. However, there is growing evidence that diabetic and nondiabetic patients respond differently to dysglycemia experienced in the ICU.

Krinsley *et al.*^[49] performed a retrospective observational study of 44964 patients admitted to 23 ICUs in 9 countries to determine how diabetic status affected the associations of hyperglycemia, hypoglycemia, and glycemic variability with mortality. While hypoglycemia was associated with an increased risk of mortality among all patients, the diabetic status modulated the impact of both hyperglycemia and glycemic variability. In nondiabetic patients, maintenance of euglycemia was independently associated with a reduced mortality risk, but among diabetic patients, those with a mean glucose of 80 to 110 mg/dL actually had an increased risk of mortality, even when compared only to those with a mean glucose greater than 179 mg/dL. The significance of glycemic variability also seemed to differ according to diabetic status, as a high level of glycemic variability (defined as a coefficient of variability greater than 20%) was independently associated with an increased risk of mortality among nondiabetic patients, but not among those with diabetes.

Similar findings were reported in a subsequent single center retrospective observational study that analyzed glucose and outcome data from 10320 ICU patients^[23]. Again, hypoglycemia was associated with mortality in both diabetic and nondiabetic patients, but outcomes associated with hyperglycemia and glycemic variability differed according to premorbid diabetic status. While hyperglycemia was associated with increased mortality

among the nondiabetic patients, no clear pattern relating elevated mean glucose levels with mortality could be found among the diabetic patients. In addition, glycemic variability (as measured by mean absolute glucose change) was only associated with increased mortality among the nondiabetic patients.

Such differences among diabetic and nondiabetic patients have raised the possibility that future glycemic control protocols for critically-ill patients will differ according to pre-morbid diabetic status, or other markers of insulin resistance, such as metabolic syndrome or non-alcoholic fatty liver disease^[50,51]. However, further studies are needed to better define optimal glycemic management among diabetic patients in the ICU.

CONCLUSION

In the past two decades, glycemic management among critically-ill patients has been a topic of extensive study, leading to significant changes in clinical practice. Intensive insulin therapy was widely adopted following the publication of the first Leuven study^[1], only to be largely abandoned as further knowledge accumulated questioning the benefits of this approach, ultimately culminating with the NICE-SUGAR trial, which found an increased risk of mortality among patients treated with tight, as compared to moderate, glucose control strategies^[2]. Current guidelines regarding glycemic management of critically-ill patients advocate initiating insulin infusions for blood glucose measurements in excess of 150 mg/dL, with the goal of maintaining blood glucose less than 180 mg/dL^[40]. While targeting a blood glucose level less than 180 mg/dL is now widespread (and consistent with the control group in NICE-SUGAR), it should be noted that evidence supporting this goal, as opposed to an even more permissive glycemic control strategy, is lacking.

In recent years, there has been an increased focus on the potential deleterious effects of glycemic variability, though it remains unclear how best to avoid fluctuations in blood glucose levels. In addition, there has been increasing attention given to differences among the glycemic control needs of diabetic and nondiabetic patients.

In coming years, we expect that new glucose monitoring systems will emerge, and that new strategies for maintaining euglycemia (while avoiding hypoglycemic episodes and glycemic variability) will follow. Glycemic management among critically-ill patients remains an area of unsettled medicine.

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