



Glycemic control and insulin therapy in sepsis and critical illness

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Abstract

Objective: To review the literature about the pathophysiology of hyperglycemia and glycemic control in children and adults with sepsis and critical illness.

Sources: Non-systematic survey of the medical literature using MEDLINE and terms hyperglycemia, glycemic control, intensive insulin therapy, sepsis and intensive care. Articles were selected according to their relevance based on the authors' opinion.

Summary of the findings: Hyperglycemia is frequent in critically ill children and it is associated with worsened outcome. In adults, there is no consensus on the efficacy and safety of glycemic control. We describe the possible mechanisms involved in glucose toxicity and the beneficial effects of glycemic control. Initial studies showed that use of insulin to achieve glycemic control reduced morbidity and mortality in adult intensive care; however, recent studies have failed to confirm these findings. Importantly, it is evident that glycemic control is associated with increased incidence of hypoglycemia. The efficacy of glycemic control has not yet been studied in critically ill children.

Conclusion: Glycemic control is a novel therapeutic option in critical care. Conflicting evidence in adults means that before we apply this approach to pediatrics it will need to be assessed in clinical trial.

J Pediatr (Rio J). 2007;83(5 Suppl):S128-136: Hyperglycemia, glycemic control, glucose level, insulin therapy, intensive care, pediatric.

Introduction

Carbohydrate metabolism is essential for survival. Shortage of carbohydrate (i.e., hypoglycemia) is a severe threat to homeostasis and triggers the stress response. If persistent, hypoglycemia leads to irreversible cellular dysfunction, tissue/organ failure, and eventually death.¹ In children, hypoglycemia is well recognized as a clinical hazard and actively prevented in a wide range of situations (e.g., newborn babies, children with diabetes, fasting preoperative children). In contrast, hyperglycemia has a very different role and its effect in acute illness is not completely understood. Until recently, except for diabetics, hyperglycemia was rarely considered clinically relevant in children. New studies in adults and children, however, have raised concerns regarding possible deleterious effects of hyperglycemia.²⁻⁶ Children with sepsis are

known to have high glucose level, and evidence of hyperglycemia is associated with worsened outcome.⁵ In this article we describe mechanisms underlying stress hyperglycemia and their possible pathophysiologic effects. We also describe and discuss the current evidence for glycemic control in acute illness in both adults and children with sepsis.

Sepsis, glucose metabolism and the stress response

In sepsis, homeostasis is threatened by invading microorganisms. The body reacts to this challenge by mounting a complex response: first, prioritizing energy supply to vital organs; second, increasing the organism's aptitude to fight the invading microbe; and third, stimulating return to homeostasis. This response was first described by Hans Selye in 1936

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Suggested citation: Branco RG, Tasker RC, Garcia PC, Piva JP. Glycemic control and insulin therapy in sepsis and critical illness. *J Pediatr (Rio J)*. 2007;83(5 Suppl):S128-136.

doi 10.2223/JPED.1710

as the general adaptation syndrome (GAS).^{7,8} Several neuroendocrine and inflammatory mediators are involved in this process, and hyperglycemia is an important feature of the acute changes that occur during this response. In the acute phase of the GAS, or the stress response, neuroendocrine stimulation yields high circulating levels of glucagon, growth hormone, catecholamines, and glucocorticoids. These hormonal changes (also known as the counter-regulatory response) and an increase in pro-inflammatory cytokines, i.e., interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, are important factors leading to hyperglycemia. The pathophysiologic mechanism involves changes in carbohydrate metabolism (e.g., peripheral insulin resistance, increased hepatic glycogenolysis, and increased gluconeogenesis) aimed at redirecting energy supply to vital organs (Figure 1).⁹

Hyperglycemia in children with sepsis and critical illness

Historically, hyperglycemia was considered to be an adaptive response to stress and little was known about its incidence and clinical associations in children with sepsis and critical illness. One problem was the likely possibility that our treatment (e.g., exogenous administration of catecholamines, corticosteroids, intravenous dextrose and nutrition) may contribute or be an additional cause of hyperglycemia. We have therefore recently studied glucose levels in 57 children with septic shock who failed to respond to fluid resuscitation and found that the glucose level was very high (mean peak glucose 214 ± 98 mg/dL).⁵ The peak glucose level was not associated with the use of corticosteroids, nutrition, or intravenous dextrose. In all, only 7% of the children had all of their glucose measurements within normal limits (60 to 110 mg/dL), and 51% had at least one glucose measurement above 178 mg/dL. We found that non-survivors had higher glucose level during their illness when compared to survivors. There was also an association between the highest glucose level and mortality (Figure 2). Moreover, the effect of glucose level on mortality was independent of age, premorbid nutritional state, and risk of mortality at admission.⁵ These

results suggest that hyperglycemia may affect outcome of children with sepsis, and raised the question as to whether these children would benefit from some therapy (such as insulin) to lower their glucose level. Similar results to ours have also been reported by others studying critically ill children.^{3,4,10-12} Srinivasan et al.⁴ studied 152 children requiring mechanical ventilation and vasoactive support and found an 86% prevalence of hyperglycemia (peak glucose > 126 mg/dL). There was also an association between mortality and both the highest glucose level and the duration of hyperglycemia. Wintergerst et al.,¹⁰ in a larger retrospective study, evaluated glucose level in 1,094 children and found that both hyperglycemia and hypoglycemia were associated with worsened outcome. Furthermore, individual variation in glucose had a strong association with mortality. Table 1 describes the main studies that have evaluated the association between glycemic level and mortality in critically ill children. Studies in other groups of children needing intensive care (e.g., traumatic brain injury,¹³ burns,¹⁴ cardiac surgery,¹⁵ and necrotizing enterocolitis¹⁶) have also shown an association between high glucose level and worsened outcome. In bronchiolitis, where mortality is low, high glucose level is associated with markers of inflammation and severity of illness.¹¹

Mechanism of glucose toxicity

The cellular mechanisms underlying the association between hyperglycemia and worsened outcome are poorly understood. However, insights from in vitro studies when applied to the clinical features of patients with hyperglycemia and glycemic control studies raise possible hypotheses concerning glucose toxicity in acute stress. For example, the lipid bilayer membrane of the cell only allows glucose to enter via one of the family of glucose transporters. The main group conveys glucose by facilitated diffusion and consists of GLUT-1, 2, 3, and 4. Each of the GLUT proteins has distinct substrate specificities, kinetic properties, and tissue distribution that dictate their functional role.¹⁷ GLUT-1 is widely expressed and present in high concentrations in brain, erythrocytes, and endothelial cells. It provides basal glucose uptake – Michaelis-Menten constant (Km) for glucose of 20 mmol/L – under physiological conditions, and under hyperglycemic conditions it is

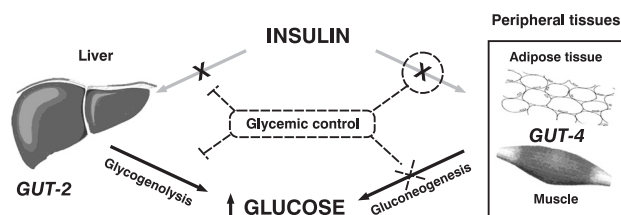


Figure 1 - Mechanism of stress-induced hyperglycemia. Changes occurring during stress (dark solid lines) cause insulin resistance (X) in the liver (stimulating glycogenolysis) and in peripheral tissues (reducing glucose uptake and stimulating gluconeogenesis). Insulin therapy (dashed lines) reverses peripheral but not hepatic insulin resistance

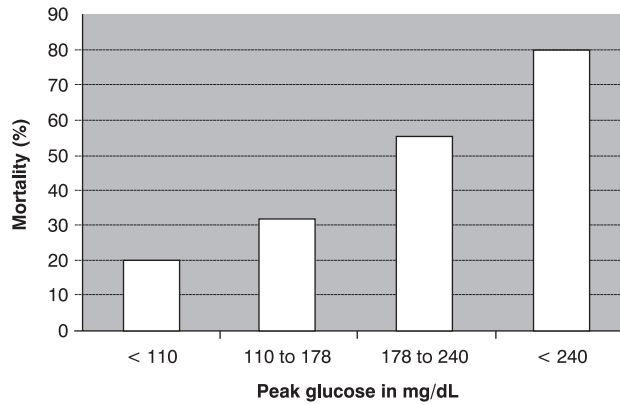


Figure 2 - Mortality according to peak glucose band in children with septic shock⁵

down-regulated to reduce uptake. GLUT-2 is a low affinity/high capacity transporter (Km 42 mmol/L) present in kidney, small intestine, liver and pancreatic beta cells. It works as a glucose sensor in pancreatic cells due to its efficiency as a glucose carrier. GLUT-3 is a high-affinity glucose transporter (Km 10 mmol/L) present in neurons. GLUT-4 is a high-affinity (Km 2-10 mmol/L) insulin-responsive glucose transporter present in skeletal muscle, cardiac muscle and adipose cells.¹⁷ In stress, inflammatory mediators upregulate expression of GLUT-1 and GLUT-3 transporters, thereby increasing glucose uptake in a wide variety of cells.^{18,19} These changes may overcome the normal physiologic down-regulation of GLUT-1 in hyperglycemia, which exposes cells to high uptake of glucose and, most likely, glucose toxicity. Different distributions of glucose transporters may account for the difference in hyperglycemia-induced mitochondrial abnormalities observed in liver and skeletal muscle cells.²⁰

During normal aerobic metabolism of glucose, the mitochondrial respiratory chain produces small amounts of superoxide, which are later detoxified by manganese superoxide dismutase (MnSOD). In hyperglycemia, superoxide production is increased which, in association with nitric oxide (increased in stress), forms peroxynitrite. The latter induces nitration of mitochondrial complexes I and IV, MnSOD, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and voltage-dependent anion channel. These changes will ultimately have detrimental effects (e.g., suppressed mitochondrial electron transfer chain; impaired detoxification of superoxide; shuttle of glucose into toxic pathways, and increased apoptosis) and suggest that hyperglycemia can be toxic to cells (Figure 3).^{20,21} Systemically, hyperglycemia directly influences the stress response. It increases the level of early proinflammatory cytokines (TNF-alpha, IL-1, IL-6), impairs neutrophil chemotaxis and phagocytosis, and decreases microvasculature responsiveness.^{20,22}

Glycemic control in adult intensive care: the Leuven studies

In 2001 Van den Berghe et al. described the use of insulin to treat hyperglycemia and normalize blood glucose level (80-110 mg/dL) in a large randomized controlled trial performed in a single surgical intensive care unit (ICU).⁶ This trial, known as the Leuven study, challenged the concept that hyperglycemia is an adaptive change in stress and should be tolerated in the critical illness. In this study, glycemic control was associated with a 42% relative reduction in ICU mortality (8% mortality in the control group and 4.6% in the insulin group). It also reduced episodes of bloodstream infection (46%), acute renal failure (41%), red-cell transfusion (50%), and critical-illness polyneuropathy (44%). This study triggered a renewed interest in glycemic control in adult ICU. However, there were several concerns about the possible limitations of this study.

First, the study involved mostly postoperative, cardiac surgical patients. Second, the nutritional protocol used in the ICU involved large amounts of intravenous glucose and early parenteral/enteral nutrition, which does not reflect the practice in most ICU. Third, glycemic control resulted in a higher incidence of hypoglycemia (0.8% in controls and 5.1% in the insulin group) and hypoglycemia was associated with an increased risk of death (odds ratio = 3.2). Last, mortality in the control group was higher than expected from the severity of illness of the group. Egi et al.²³ have studied this issue in a matched sample from Australian ICU and found that the incidence of sepsis and mortality in their cohort (2.2% mortality) was significantly lower than that reported in the Leuven study (8% mortality in the control group and 4.6% in the insulin group). These authors, therefore, suggested caution when applying glycemic control to other hospitals or countries where patient mix and comorbidity can be different.

In 2006 Van den Berghe et al. reported a second large randomized controlled trial of glycemic control, this time in a

Table 1 - Summary of reports on glucose level and outcome in pediatric critical care

Author (year) [Design]	Population (n, casemix)	Incidence of hyperglycemia	Outcome associations	Comments
Branco et al. (2005) ⁵ [prospective cohort]	Dopamine resistant Septic shock (n = 57)	> 110 mg/dL: 93% > 178 mg/dL: 51%	Peak glucose level (during all PICU stay) was an independent fac- tor associated with mortality. Glucose > 178 mg/dL had 2.59 relative risk for death.	Small cohort High mortality cohort Few glucose measurements/ patient
Srinivasan et al. (2004) ⁴ [Retrospective cohort]	Children requiring mechanical ventilation and vasoactive support (n = 152)	> 110 mg/dL: 93% > 126 mg/dL: 86%	Peak glucose level (at 24 h and 48 h) was an independent factor as- sociated with mortality. Glucose > 150 mg/dL had a 2.96 odds ratio for death.	Retrospective – potential selection bias
Wintergerst et al. (2006) ¹⁰ [Retrospective cohort]	All children admitted to ICU (medical + surgical) (n = 1,094)	> 110 mg/dL: 86.7% > 150 mg/dL: 61% > 200 mg/dL: 35.2%	Peak glucose and glucose in the highest quintile were associated with higher mortality. Hypoglycemia and glucose variability were also associated with higher mortality.	Retrospective – potential selection bias
Faustino et al. (2005) ³ [Retrospective cohort]	All children admitted to PICU(n = 942)	> 120 mg/dL: 75% > 150 mg/dL: 50.1% > 200 mg/dL: 26.3%	Peak glucose at 24 h and within 10 days were as- sociated with higher mortality. Glucose 150 mg/dL in the first 24 h had a 2.5 rela- tive risk of death; and within 10 days a relative risk of 4.13	Retrospective – potential selection bias No risk adjustment
Van Waardenburg (2006) ¹² [prospective cohort]	Children with MS and MSS (MSS = 10, MS = 6)	In MS: > 110 mg/dL: 42.2%* > 140 mg/dL: 13.6%* > 200 mg/dL: 0* In MSS: > 110 mg/dL: 57%* > 140 mg/dL: 23.3%* > 200 mg/dL: 3.1%*	Hyperglycemia cor- related with severity of illness (r = 0.833) (using physiologic stability index) Children with MSS had hypoinsulinemic hyperglycemia.	Small cohort Very specific population

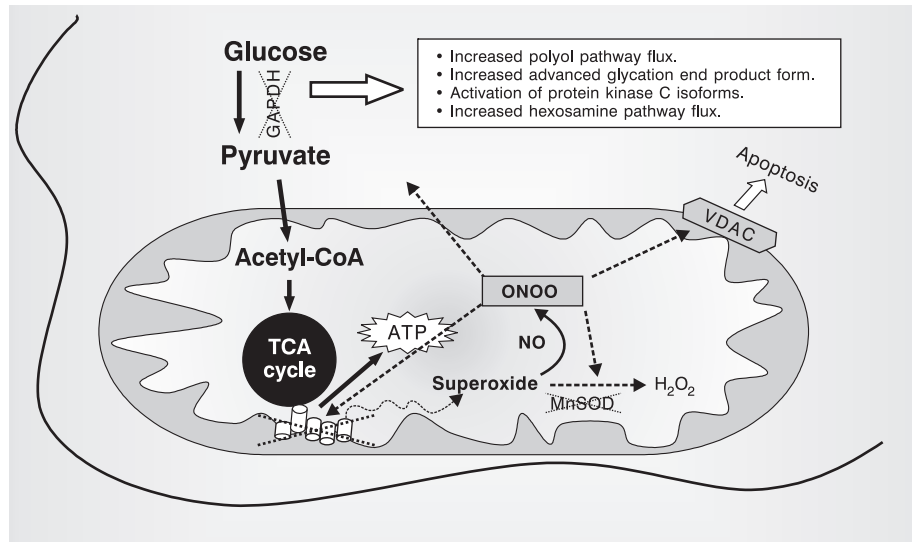
ICU = intensive care unit; MS = meningococcal sepsis; MSS = meningococcal septic shock; PICU = pediatric intensive care unit.

* Expressed as percentage of the total number of glucose measurements.

Children with diabetes mellitus were excluded from all studies.

medical ICU.² This trial, the Leuven medical study, showed that while glycemic control did not reduce overall mortality (40% in the control group and 37.3%, $p = 0.33$) it did reduce morbidity (i.e., reduced incidence of renal impairment, shortened duration of mechanical ventilation, length of ICU and hospital stay). In patients who stayed in ICU longer than 3 days mortality was reduced from 38.1% in the control group to 31.3% in the treatment group ($p = 0.05$). The reduction in morbidity was even more evident in the subgroup analysis.

Incidence of blood stream infection, however, was not reduced. In common with the surgical study there were limitations and concerns regarding the nutritional protocol, the mortality in the control group, and the incidence of hypoglycemia. The medical study also raised additional concerns in regard to safety. First, in patients who stayed in ICU for less than 3 days, glycemic control was associated with increased mortality (18.8% in the control group and 26.8% in the insulin group, $p = 0.05$). This increased mortality in the glycemic



Acetyl-CoA = acetyl coenzyme A; ATP = adenosine triphosphate; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; H₂O₂ = hydrogen peroxide; MnSOD = manganese superoxide dismutase; NO = nitric oxide; ONOO = peroxynitrite; TCA = tricarboxylic acid; VDAC = voltage-dependent anion channel.

Detailed pathophysiology of glucose toxicity

A common pathway for hyperglycemia-induced cell injury is the formation of intracellular reactive oxygen species accumulation (ROS). High glucose levels increase electrochemical potential difference generated by the proton gradient in mitochondrial respiratory chain, leading to a prolonged life of superoxide-generating electron transport intermediates, inducing accumulation of ROS. Once intracellular ROS accumulates, four mechanisms can induce cell injury:

(1) Increased polyol pathway flux: hyperglycemia results in increased enzymatic conversion of glucose to the polyalcohol sorbitol, with concomitant decrease in nicotinamide adenosine dinucleotide phosphate (NADPH) and glutathione, enhancing cellular sensitivity to oxidative stress. Hyperglycemia-induced overproduction of superoxide significantly inhibits glucose-6-phosphate dehydrogenase, inhibiting the pentose phosphate pathway that is required for providing reducing equivalents to the antioxidant defense system.

(2) Increased advanced glycation end product (AGE) formation: glucose, although one of the least reactive reducing sugars, can react with a free amino group to form an adduct commonly referred as a Schiff base, which formation is relatively fast and highly reversible. However, Schiff bases can be rearranged originating an Amadori product (in a reaction that is much faster than the reverse reaction). Therefore, Amadori glycation product tends to accumulate on proteins, initiating the processes of advanced glycation. AGE arise from autooxidation of glucose to glyoxal, decomposition of the Amadori product to 3-deoxyglucosone, and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal. Glyoxal, methylglyoxal, and 3-deoxyglucosone are reactive intracellular dicarbonyl that react with amino groups of intracellular and extracellular proteins to form AGE. Production of intracellular AGE precursors interferes with target cell integrity by modifying protein function or by inducing receptor-mediated production of reactive oxygen species, which have been shown to cause changes in gene expression.

(3) Activation of protein kinase C (PKC) isoforms: hyperglycemia results in increased enzymatic conversion of glucose to sorbitol, which is metabolized to fructose by sorbitol dehydrogenase, increasing the ratio NADH/NAD⁺. This results in oxidized triose phosphates with de novo synthesis of diacylglycerol (DAG). Increased DAG content activates PKC.

(4) Increased hexosamine pathway flux: under usual metabolic conditions, 2-5% of glucose entering cells are directed into the hexosamine pathway. During hyperglycemia, however, the increased nutrient availability shunts the excess glucose the hexosamine pathway. The end product of this pathway, UDP-N-acetylglucosamine, is the substrate for the glycosylation of intracellular transcription factors, affecting the expression of many genes. This pathway has been associated with endothelial and microvascular dysfunction.

Figure 3 - Mechanisms of glucose toxicity. Adapted from Rolo & Palmeira²¹ and van der Berghe²⁰

control group, early on, suggests that hyperglycemia is temporarily well tolerated, and perhaps beneficial to survival. Second, hypoglycemia was an independent risk factor for death, and glycemic control increased the incidence from 3.1% in the control group to 18.7% in the insulin group. Hypoglycemia was particularly evident in patients with sepsis, with an overall incidence of 11.4% (2.9% in control group and 19.6% in the insulin group). Whether the association between hypoglycemia and higher mortality reflects a consequence of hypoglycemia, or the higher risk of mortality in these patients, is still a matter of discussion. Nevertheless, hypoglycemia

should be avoided and glycemic control should not be implemented without extreme vigilance of glucose levels.

Physiologic effects of glycemic control in adults

The Leuven studies were followed by a series of studies aimed at evaluating the mechanism underlying benefit of glycemic control. Most of them were performed using groups of patients from the original Leuven studies. The first question raised was whether the benefit was a consequence of improved glycemic control, or a direct result of insulin infusion. A retrospective analysis,²⁴ and studies in animal models,²⁵ suggest that glycemic control is responsible for most of

the benefit. However, it is likely that both factors – glycemic control and insulin therapy – have important physiologic roles and the clinical benefit may only be seen when both interventions are used.

Experimentally, glycemic control using insulin has anti-inflammatory effects. Insulin suppresses nuclear factor kappa beta (NF- κ B) regulated pathways, thereby inhibiting production of TNF- α , macrophage migration-inhibitory factor, and superoxide generation.²⁶ In patients, glycemic control reduced C-reactive and mannose-binding lectin.²⁷ Clinically, dyslipidemia is frequent in adult critical care and changes in triglycerides and increased high density lipoprotein (HDL) are associated with severity of illness. Use of insulin to achieve glycemic control reverses hypertriglyceridemia and increases HDL levels.²⁸ Glycemic control also prevents endothelial dysfunction²⁹ and reduces insulin resistance in peripheral tissues, but not in the liver.^{28,30,31} (Figure 1).

Glycemic control in adult intensive care: confirmatory studies

So far, only a few studies have been able to reproduce the findings of the Leuven studies. The first was a small randomized controlled trial (61 patients) targeting normoglycemia (80-120 mg/dL) in a general surgical ICU.³² It reduced blood glucose levels (179 mg/dL in the control group and 125 mg/dL in the study group) and decreased the incidence of nosocomial infection. However, the incidence of hypoglycemia (< 60 mg/dL) was increased (32 vs. 7.4%). Krinsley et al.³³ reported a large trial (n = 1,600) comparing a prospective cohort treated with insulin (aiming to keep glucose below 140 mg/dL) with a retrospective cohort where only glucose levels above 200 mg/dL were treated. The prospective cohort had lower mean glucose levels, lower hospital mortality (14.8 versus 20.9%), reduced ICU stay and reduced need for red blood cell transfusion, when compared to the historical cohort. The number of hypoglycemic glucose measurements (glucose below 40 mg/dL) was unchanged in the two periods (0.34 versus 0.35%). Last, Bilotta et al.³⁴ studied a small cohort (n = 78) of neurosurgical ICU patients with subarachnoid hemorrhage. They found reduced infection rate in the glycemic control group (27 versus 42% in the control group) but no changes in other outcomes (i.e., incidence of vasospasm, mortality, and neurological outcome after 6 months).

In contrast to these confirmatory studies, two studies planned as large randomized controlled trials evaluating the effect of glycemic control in adults were stopped prematurely. In 2005 a German study with combined interventions, aimed at evaluating the efficacy of volume substitution and insulin therapy in severe sepsis (VISEP),³⁵ was stopped because of concerns about hypoglycemia. The glycemic control arm of the study had an excess of hypoglycemia (12.1% in glycemic control and 2.1% in the control group). The mortality was not significantly different between the groups (n =

488; mortality 29.5% in glycemic control and 32.8% in control group). The Glucontrol study was a multicenter European randomized controlled trial comparing glycemic control at two different levels, 80 to 110 mg/dL (glycemic control group) and 140 to 180 mg/dL (control group). The study planned to enroll 3,500 patients in order to detect a 4% reduction in mortality.³⁶ However, the study was stopped after recruiting only 1,082 patients because target glycemic control was not achieved (blood glucose was 118 mg/dL) in the glycemic control group, and because the incidence of hypoglycemia was excessive (8.6% in the glycemic control and 2.4% in the control group).³⁷ Mortality was not significantly different between the two groups (16.9% in the glycemic control and 15.2% in the control group).^{38,39} Another large randomized controlled trial in adult critical care is currently underway. The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation [NICE-SUGAR] study plans to enroll 6,100 patients in Australia and Canada.⁴⁰ It also compares two glycemic control levels, 81 to 108 mg/dL and 144 to 180 mg/dL. So far, the researchers have recruited more than 3,000 patients.

Controversies in glycemic control in adult ICU

The inconsistency between the benefit of glycemic control observed in the Leuven studies and the early stopping of two large trials (VISEP and Glucontrol) because of hypoglycemia has fueled an ongoing debate about glycemic control. For some investigators, the results of the Glucontrol study suggest that there is no difference between targeting glucose levels 80 to 110 mg/dL and 140 to 180 mg/dL, and that the risk of achieving the lower target far outweighs any potential benefits.^{38,41} This suggestion is, however, debated by others who believe the glucose level in the intervention group of the Glucontrol study (118 mg/dL) was too high and only approximately 25% of the patients would have a mean glucose below the 110 mg/dL target. The “negative” result of the trial therefore only emphasizes to them the importance of achieving normoglycemia.^{37,38}

A second controversy regards the subgroup that may benefit from glycemic control. There are clear differences in the Leuven medical and surgical studies. While the medical study failed to prevent deaths,² the surgical study showed a remarkable 44% relative reduction in mortality.⁶ Moreover, evidence from observational studies in surgical ICU is more forthcoming than in medical ICU.^{32,42} However, the underlying mechanisms proposed for the action of glycemic control do not provide a reason why there should be a difference between surgical and medical patients. It also appears that diabetics do not necessarily benefit from glycemic control in critical illness, whether surgical or medical.^{37,43}

The consensus opinion is that glycemic control increases the incidence of hypoglycemia, that hypoglycemia is more frequent in patients with more severe diseases (particularly sepsis), and that hypoglycemia is associated with an increased

risk of death.^{37,44} However, mortality associated with insulin-induced hypoglycemia is not as high as with spontaneous hypoglycemia. Insulin-induced hypoglycemia may, therefore, only identify patients with high risk of dying, and not represent an independent risk factor.^{37,44} Nevertheless, even if hypoglycemia has a negative effect on outcome, debate exists as to whether the benefit of glycemic control may overcome any risks associated with hypoglycemia.

Last, timing of glycemic control is also controversial. Several *in vivo* and *in vitro* studies have shown that short-term hyperglycemia is protective to cardiac myocytes and neurons.⁴⁵⁻⁴⁷ This experimental observation is in keeping with the reduced mortality in control patients with ICU stay shorter than 3 days in the Leuven medical study,² and with the increased mortality of intraoperative glycemic control in patients undergoing cardiac surgery.⁴⁸ However, a post-hoc analysis of the Leuven study showed that the reduced mortality may, in fact, reflect a selection bias; more patients in the control group had treatment withdrawn in the first 3 days.⁴³ Whether short-term hyperglycemia is protective, or whether glycemic control is effective over short periods, remains unanswered.

Glycemic control in pediatric intensive care

Despite the evidence for an association between hyperglycemia and worsened outcome in pediatric intensive care unit (PICU), glycemic control has not been evaluated in critically ill children. There are reasons why this is so. First, the controversies in the adult literature regarding efficacy of glycemic control raises concerns about extrapolating this therapy to children. Second, the increase in hypoglycemia associated with glycemic control is alarming. Third, the large number of children required to evaluate this therapy makes a study difficult to organize, fund, and perform.

Independent of these controversies, glycemic control is used in many adult ICU. Some units, in special surgery and burns, have started to report good results with glycemic control. It is therefore important that we address the question of whether glycemic control is effective in all critically ill children before PICU follow the adult practice and start adopting therapy without formal evaluation. Such assessment is needed because, first, the physiology of critical illness in children differs significantly from the physiology of adults. For example, in children with septic shock cardiac dysfunction is frequent and contributes significantly to death.⁴⁹ In adults with septic shock, vasoplegia is a major feature associated with mortality.⁵⁰ Second, the stress response in children may differ from adults. Hyperglycemia of stress in children with meningococcal shock is associated with low insulin levels, in contrast to peripheral insulin resistance with normal/high insulin levels found in adults.¹² In hypoinsulinemic hyperglycemia, administration of insulin (to reduce glucose level) can cause a precipitous fall in glucose and increase the risk of hypoglycemia. Third, most pathologies found in the PICU are

not present in adult ICU (e.g., bronchiolitis, necrotizing enterocolitis, congenital heart disease) and vice-versa (e.g., myocardial infarct, stroke). Fourth, metabolic regulation and demand in children is very different from adults. Children have developing organs/tissues with different requirements when compared with fully developed adults. Last, premorbid health is very different in children. Adults are constantly exposed to stress-induced changes (e.g., psychological stress, previous injuries), and the allostatic load⁵¹ acquired from these experiences may modulate their acute response to critical illness.

Recently, we have assessed the feasibility and physiology of glycemic control in the PICU in Porto Alegre, Brazil, and in Cambridge, UK. In our experience, normoglycemia is difficult to be achieved, and use of insulin is not without risks.^{52,53} The major factors associated with poor glycemic control and hypoglycemia are: children with hepatic dysfunction and septic shock, delayed gastric emptying, use of catecholamine and hydrocortisone, and alteration in enteral feed or IV glucose infusion.

Conclusion

Glycemic control is an interesting therapeutic option in critical care. Preliminary studies have shown significant benefits using this strategy in adults but further studies are needed to evaluate whether these results can be extrapolated to all adult intensive care. In children there is evidence of an association between hyperglycemia and worsened PICU outcome. However, the efficacy of glycemic control has not yet been studied. Therefore, glycemic control should be restricted to clinical trials. We look forward to the results of studies currently being performed in children and adults, which will help us to better understand this therapy.

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