



# ENDOCRINOLOGÍA

## The Evolving Paradigm of Hyperglycemia and Critical Illness

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It is fascinating to observe how the approach to the diagnosis and treatment of a particular medical condition evolves over time. The treatment of hyperglycemia in the setting of critical illness represents one such example. It has been known for years that critically ill patients become hyperglycemic for a number of different reasons. Alterations in glucose metabolism including insulin resistance are common. There are numerous adaptive responses, such as increased catecholamine secretion, and elevations in serum cortisol and glucagon, that can also result in hyperglycemia. As a medical student some 20 years ago, hyperglycemia was viewed as more of an epiphenomenon. Though frequently observed in the ICU, most physicians did not think that it was directly pathogenic. This resulted in a *laissez faire* approach to treatment. In general, I was taught then to keep the blood glucose (BG) level at < 300 mg/dL with occasional doses of relatively small amounts of subcutaneous insulin.

As our knowledge base expands, this attitude is clearly changing. Data have gradually accumulated demonstrating that for specific medical and surgical diagnoses, a tighter control of hyperglycemia improves morbidity, mortality, and other outcome measures in both diabetic and nondiabetic patients. For example, a review article (1) concluded that the mortality risk increased 3.9-fold in a group of nondiabetic patients with acute myocardial infarction whose BG levels were in a range from 109.8 to 144 mg/dL. In a cardiac surgical model, mortality correlated with BG level in a dose-dependent manner with the lowest mortality occurring in the group with a mean postoperative BG level of < 150 mg/dL (2). There is an increase in serious infections including sepsis, pneumonia, and wound infections in postoperative diabetic patients with elevated BG levels (3). Mortality and functional recovery after acute stroke correlated with BG in a nondiabetic patient group (4). In an important study, Van den Berghe et al (5) concluded that using insulin to maintain BG levels at 110 mg/dL in critically ill patients in a surgical ICU reduced morbidity and mortality, bloodstream infections, acute renal failure requiring dialysis or hemofiltration, and critical illness polyneuropathy. A recent study (6) showed that mean and maximum BG values were significantly higher among nonsurvivors in a heterogeneous group of critically ill general medical, surgical, and cardiac patients. In this study, the lowest hospital mortality occurred in patients with a mean BG of 80 to 99 mg/dL and increased progressively as BG values increased.

The precise pathophysiology behind the complications associated with hyperglycemia in critical illness extends beyond the simple elevation in BG level. Insulin inhibits inflammatory growth factors, which may be important in acute myocardial infarction. Insulin also inhibits lipolysis, and elevated free fatty acids have been associated with poor outcomes and cardiac arrhythmias. The stimulation of endothelial nitric oxide synthase by insulin leads to arterial vasodilation and other effects on oxidation. Immunologic function is affected in several different ways. Hyperglycemia has been associated with impaired leukocyte chemotaxis, impaired phagocytosis, decreased Ig function, and complement fixation (7).

Some believe that the beneficial effects are due more to glycemic control than to insulin per se. Using intensive insulin therapy, Van den Berghe et al (8) showed that normoglycemia could be safely attained in 24 h. Metabolic control, as reflected by normoglycemia, was thought to be the cause of the beneficial effects, rather than the insulin dose (8). In a single-center observational study, Finney et al (9) in fact concluded that increased insulin administration is positively associated with death in the ICU, regardless of the prevailing BG level, again suggesting that glycemic control accounts for the mortality benefit. It could be that higher insulin needs are simply a marker of increased disease severity, with resultant higher mortality.



I believe that the current article by Cely et al in CHEST (page 879) complements the literature. In a carefully performed prospective study, they categorized patients as having normal or abnormal baseline glucose control, based on history and hemoglobin A1C (Hgb A1C) levels. They demonstrated that even in patients with normal glucose homeostasis at baseline, hyperglycemia during critical illness is common. Furthermore, among patients with normal Hgb A1C levels, those in the lower range of normal at presentation had less hyperglycemia during critical illness than those in the higher range of normal. The inclusion of patients in whom Hgb A1C level was not assessed would not have altered their conclusions. Those patients differed primarily on the need for blood transfusion, which should not have directly affected BG level. The study might be criticized for including only patients with APACHE (acute physiology and chronic health evaluation) II scores of 12. However, the same relationships with hyperglycemia and critical illness seem to hold true among a "less sick" critically ill population as well.

Whether you practice in an academic university setting or a private practice community hospital setting, this and many other studies concerning hyperglycemia and critical illness raise the following questions. What should be the standard of care? Who should make that determination? Like other common problems in medicine, there is no one single study or expert group that sets a standard. It is a process that evolves to a consensus over time. In this instance, it is significant that many different medical disciplines including cardiology, endocrinology, critical care, and cardiac and general surgery, all are coming to similar conclusions. These studies have been published in a wide variety of both general and specialty journals. Researchers are looking more toward evidence-based medicine than to the time-honored method of simply following the historical practices of our attending physicians. Although some controversy remains, the preponderance of the ever-growing literature supports an aggressive approach to the treatment of hyperglycemia during critical illness.

What should the standard approach be? While any single cutoff value by definition is arbitrary, I believe we should aim for a BG level that is as near to normal as is safe and practical. Hospitals across the country are evaluating intensive IV insulin protocols to achieve these goals. As physicians, we must understand the added burden and responsibility this places on the bedside nurse. Although a concern, the incidence of significant hypoglycemia as a complication of treatment has not been commonly seen. We must also be cognizant that other interventions such as vasopressors, steroids, and enteral and parenteral nutrition may exacerbate hyperglycemia, mandating closer observation of these patients. [\(10\)](#)

What should be the target BG level? I do not believe that there is yet a consensus on that question. Van den Berghe et al<sup>5</sup> have argued for a BG level of 110 mg/dL, while others have endorsed a more conservative value up to 139 mg/dL [\(7\)](#) or even higher if the patient is not in a critical care unit. The College of Critical Care Medicine recently recommended [\(11\)](#) maintaining a BG level of < 150 mg/dL in patients with severe sepsis. It may not be correct to think that in the presence of an elevated BG level during critical illness there is a single threshold value below which all patients can avoid hyperglycemic complications. My bias, although difficult to prove, is that a "safe" upper limit of BG for any individual critically ill patient may vary, depending on their baseline glucose homeostasis, the presence or absence of preexisting diabetic complications, and other factors that influence gluconeogenesis, glycolysis, and insulin resistance. This would be

analogous to different ranges of CNS autoregulation of blood flow in hypertensive vs nonhypertensive patients. When a patient presents with hypertensive crisis and CNS bleeding, we may aim for a different goal BP, depending on the presence or absence of preexisting hypertension.

Like any good study, this article raises more questions. Should all ICU patients have Hgb A1C levels measured? The data does not support that at this time. It is also not known whether every single ICU patient requires tight glucose control. Some think that the benefit accrues to those staying > 5 days in the ICU, and strict control may not be needed in those with shorter lengths of stay. [\(12\)](#) I hope that the next several years will reveal more details about underlying mechanisms. As Finney and Evans have commented,[\(13\)](#) although BG can be easily measured at the bedside, it may be a surrogate marker for another metabolic parameter. As discussed previously, some studies have suggested that the BG level itself, not the use of insulin, may be the more important factor. In that light, other agents are being explored to control BG levels. Glucagon-like peptide 1 is an insulinogenic and glucagonostatic gut hormone that normalizes BG levels in patients with type 2 diabetes. Because its action is dependent on glucose, hypoglycemia does not develop. A small study of eight patients concluded that glucagon-like peptide-1 can reduce BG concentrations in patients with type 2 diabetes after major surgery. [\(14\)](#) This requires a continuous infusion, and whether or not this study will have applications to a wider variety of nondiabetic critically ill patients remains to be seen. In conclusion, the majority of the current evidence supports the tight



control of BG levels in most critically ill patients. As the study by Cely et al shows, baseline glucose homeostasis plays a role. Standardized IV insulin protocols developed by multidisciplinary teams offer the best chance for control with low rates of hypoglycemia. The use of sliding scale subcutaneous insulin alone should be discouraged. It is not supported by the literature and results in higher rates of hyperglycemia. [\(15\)](#) Finally, the threshold maximum BG value accepted in the critically ill patient may vary depending on clinical circumstances.