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COMMENTARY

The Future Is Now: Software-Guided Intensive Insulin Therapy in the Critically Ill

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Abstract

Since the development of intensive insulin therapy for the critically ill adult, tight glycemic control (TGC) has become increasingly complicated to apply and achieve. Software-guided (SG) algorithms for insulin dosing represent a new method to achieve euglycemia in critical illness. We provide an overview of the state of SG TGC with an eye to the future. The current milieu is disorganized, with little research that incorporates newer variables of dysglycemia, such as glycemic variability. To develop and implement better algorithms, scientists, programmers, and clinicians need to standardize measurements and variables.

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Introduction

Glycemic control in critically ill patients has become an important element of care owing to the discovery that stress hyperglycemia, when severe, is a strong risk factor for death.[1,2] Studies demonstrating that hyperglycemia is an independent marker of mortality and morbidity have spurred research into how to better control hyperglycemia in the critically ill.[1–3] A decade after Van den Berghe and coauthors[4] reported the benefits of tight glycemic control (TGC) in critically ill surgical patients, controversy about how aggressively to correct hyperglycemia, and the best method for doing so, continues, particularly in nonsurgical patients. Despite Van den Berghe's studies in surgical, medical, and pediatric intensive care unit populations, larger multicenter randomized controlled studies have not been able to reproduce her observations when the experimental group target glucose range is below 110 mg/dl.[4–10] As a result, a consensus statement by the American Association of Clinical Endocrinologists and the American Diabetes Association currently recommends a glucose level goal of 140 to 180 mg/dl.[11] However, as data accumulate, experts acknowledge that moderate glycemic control between 110 and 180 mg/dl, when carefully applied to treat or prevent severe hyperglycemia while avoiding severe hypoglycemia (<40 mg/dl), can reduce mortality and morbidity in the intensive care unit. Further, morbidity and mortality decrease as the upper limit is lowered from 180 mg/dl, though it is unknown at what point benefit ceases. At our institution, for example, we have a target range in our surgical intensive care units of 95 to 135 mg/dl, with hypoglycemic events less than 1%. Both the American Association of Clinical Endocrinologists and the American Diabetes Association note that, even within their suggested range, greater benefit may be achieved at the lower glucose level.[11]

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Abbreviations: (GRIP) Glucose Regulation for Intensive Care Patients, (GV) glycemic variability, (IIT) intensive insulin therapy, (MPC) model predictive control, (PID) proportional integral derivative, (SG) software guided, (TGC) tight glycemic control

Keywords: computerized decision support system, hyperglycemia, intensive insulin, software, tight glycemic control

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Moreover, it appears that absolute glucose concentrations that are very high or very low are not the only factors contributing to the harm of dysglycemia in the critically ill. Glycemic variability (GV) has been shown to be an important risk factor in the critically ill.[12–18] When studies use different parameters and algorithms for intensive insulin therapy (IIT), the medical community's ability to interpret results in ways that can improve bedside practice is hindered. Limitations of our current technology exacerbate this. Additionally, closer scrutiny of these studies uncovers methodological flaws and insulin dosing protocol violations.[19,20] Disappointing protocol adherence is not unique, with studies repeatedly demonstrating a nurse adherence rate of less than 50%.[21,22] It is noteworthy that the paper-based protocol in the NICE-SUGAR trial, for example, was six pages long and involved 56 "action codes."[9] For all these reasons, research has failed to yield a consensus target glucose range in the critically ill, let alone a superior method and algorithm for treatment of hyperglycemia and GV. The result has been myriad target ranges and paper and software insulin dosing protocols with a paucity of evidence to support one methodology over the other. How do we tangibly move forward in research and practice, incorporating well-studied, cutting-edge technological developments?

As control of dysglycemia in the critically ill becomes more complicated and studies demonstrate the difficulties of adherence to paper-based protocols, software-guided (SG) IIT has shown promise as a superior method for maintenance of euglycemia. Though a nascent field of study with few outcomes data, SG IIT appears to be tighter, faster, and less variable, with less hypoglycemia compared with paper-based IIT protocols.[23–30]

Software algorithms can be divided into three groups. The simplest type of software is heuristic, converting paper-based protocols into a software program. While computerizing protocols reduces errors and improves adherence, the simplicity of paper-protocols is still a limiting factor.[31–34] Computerizing the Leuven protocol was as safe and effective as the paper protocol but still relied on a single daily glucose measurement and did not take GV into account.[35,36] The simplicity of heuristic conversions does not take advantage of the ability of SG IIT to utilize increasingly complex algorithms for better control with minimal increases in staff work flow.

Proportional-integral-derivative (PID) models are more complicated. The simplest iterations use previous blood glucose values to titrate insulin administration using a dynamic multiplier responsive to insulin sensitivity as judged by changes in glucose for a given insulin dose. These algorithms require little patient-specific information to initiate and allow for real-time adjustments, but they are intensive and may require 18 or more measurements a day.[23,37,38] One open-loop example of this type is the eProtocol-insulin algorithm.[39] Alternatively, the Glucose Regulation for Intensive Care Patients (GRIP) incorporates the derivate aspect of PID controls by using not only the glucose levels and insulin rates, but the change in those values over time.[40,41] Taking into account the rate of change increases the effectiveness of GRIP, even during rapid changes in dextrose administration.[42] This differentiates it from simpler controls, which are limited by measurement rate during rapid changes in glucose level. Overall, however, the PID controls continuously make small adjustments that become more accurate as data accumulate. To date, no algorithm for critically ill adults has used the integral component of PID, though it has been reported in pediatric critically ill patients.[43] Incorporating an integral component could allow a more asymptotic approach to the target glucose range, potentially reducing overtreatment and hypoglycemia. Most academic center protocols that have been reported are a permutation of PID models.[44]

Commercially available software programs are largely PID controls (**Table 1**). Glucommander (Glytec, Greenville, SC), one of the earliest and most well-studied iterations, uses a dynamic multiplier as part of its PID control.[45–50,] GlucoCare (Pronia Medical Systems, Louisville, KY), EndoTool (Hospira, Lake Forest, IL), and GlucoStabilizer (Alere Informatics Solutions, formerly Medical Automation Systems, Charlottesville, VA) are other industrial SG protocols with documented efficacy.[51–54,46]

The newest algorithms fall into the category of model predictive controls (MPCs). By incorporating dextrose administration, insulin sensitivity, age, diabetes diagnosis, and several other patient-specific parameters, these protocols attempt to predict a patient's response to hyperglycemia and IIT.[55] While increasing the number of parameters measured increases the burden of initiation, newer iterations of MPC, such as the enhanced MPC, have increased accuracy while decreasing the sampling rate by up to 50%.[56–59] However, given our limited understanding of dysglycemia and

Table 1.
Commercially Available Software-Guided Intensive Insulin Therapy

Name	Description	Comments
EndoTool	PID	Can be potentially interfaced with existing electronic medical records. Poor data: one article looking only at glucose level.
GlucoCare	PID	Can choose from multiple well-studied protocols, including customizable ones.
Glucommander	PID	Also approved in pediatric populations. Studied in several adult intensive care unit populations.
GlucoStabilizer	PID	Studied in intensive care unit and non-intensive care unit populations.
GRIP	PID	Available for free download. Few studies.
Space GlucoseControl	MPC	Built into proprietary insulin pumps. Well studied.

the factors that influence it in the critically ill, the ability to make accurate predictions of glucose levels and insulin infusion rates is hindered. Inexact estimations of an increasing number of measured parameters, in light of a lack of knowledge of the exact variables to input into a MPC algorithm, can magnify insulin-dosing errors. For example, variability is not well controlled in virtual patient trials.[60,61] Nevertheless, MPCs such as Stochastic Targeted glycemic control and Space GlucoseControl (B. Braun, Melsungen, Germany) show promise with faster entry into the optimum range, minimal hypoglycemia, and, in some cases, decreased workload compared with paper-based protocols.[62–65]

The ideal method for controlling glucose in the intensive care unit is characterized by its ease of use, minimal burden on staff, automated data entry, high adherence rate, and use of a proven algorithm to calculate insulin dosage. It would quickly correct hyperglycemia, consistently maintain glucose within the predetermined optimal range with minimal variability, and not result in episodes of hypoglycemia. This tool would easily interface with other patient measurements and data, be integrated into existing hospital systems to prevent the need for repeated data entry, and also maintain results in a comprehensive, standardized database to facilitate multicenter study.

Accuracy of this system depends on tools that are precise enough to measure glucose. Virtually every large study on TGC in the critically ill has allowed the use of point-of-care glucometers that are unreliable at extremes of measurement, differing by up to 32% of central laboratory measurements.[66,67] Further, meters relying on capillary samples are affected by hematocrit, tissue perfusion, and cleanliness of the sample site.[68] Arterial blood should be the preferred sample in the clinical setting. It should be tested in a blood gas analyzer or in the central laboratory. For future investigative studies, glucometers and capillary sampling should not be allowed. Glucometers do not provide a sufficiently reliable measurement, particularly at the extremes of glucose range, to allow use in TGC, regardless of algorithm.

Whether the best model would be a PID control or an MPC is yet to be seen. Model predictive controls are the intuitive, "intelligent" ideal, with algorithms that can predict a response to insulin several hours in advance. However, until we better understand dysglycemia in the critically ill and its variables, we will continue with approximations that require intensive input and frequent sampling to ensure that the predictive model is not veering off the goal path.

While research continues on the best MPC, PID controllers are still an effective workhorse for IIT. By substituting knowledge of the pathophysiology of hyperglycemia in the critically ill with frequent sampling, PID controllers offer an immediate solution for TGC. Nevertheless, the burden on staff, particularly using software that many feel detract from patient bedside interactions, must be acknowledged.[69]

The future of glucose measurement in the intensive care unit—continuous, automated monitoring—promises to be a breakthrough for perfecting PID controllers. In a system where increasing sampling rate increases the accuracy of PID algorithms, continuous monitoring essentially offers an infinite sampling rate. The ability to maintain glucose levels safely, rapidly, and consistently within a target range need not wait for a full understanding of glucose dysregulation.

Early trials of continuous blood glucose monitoring, including some at our own center, are currently underway in Europe and in North America. The less invasive technologies hold the additional allure that continuous monitoring can be expanded to hospital locations with higher patient-to-nurse ratios, such as the surgical and medical wards.

Indeed, the question remains about what happens to these patients requiring IIT once they leave the intensive care units. At our institution, 90% of patients are on the wards, and our unpublished data tracking hyperglycemia reveals severe and frequent hyperglycemia often exceeding a mean blood glucose of 200 mg/dl on several wards, despite implementation of SG IIT in the intensive care units. There are no studies on the effect of hyperglycemia and GV on critically ill patients once they stabilize and are transferred to inpatient wards. Based on early data from non-critically ill, hospitalized patients with type 2 diabetes, the deleterious effects of hyperglycemia and GV persist and are important.[70,71] Glycemic control of ward patients is a poorly addressed field of study. It is likely that glycemic control in the intensive care unit is just the tip of the iceberg.

Software-guided intensive insulin is still in its infancy. There are several products and algorithms from which to choose, but few data on effectiveness or outcomes. Meta-analysis suffers from varied methodology, no standard definition of an optimum range of glucose, different measures of GV, and implementation of a new protocol and software simultaneously, creating a confounding variable.[72] There are no published studies on the effectiveness of SG IIT's ability to control GV. No studies exist examining SG IIT without allowing the use of glucometers. Further, there are no studies comparing two different SG IITs head-to-head. Our lack of understanding coupled with our lack of tools up to our tasks hampers our progress. We should move forward on the assumption that merely creating an SG protocol will result in ill-advised forays, as early evidence demonstrates that designing an efficient, safe SG TGC workflow to which staff will adhere is more complex than paper-based protocols.[69]

While in the long term, SG MPCs may prove to be the most physiologic solution to hyperglycemia in the critically ill, SG IIT based on PID controls is the easiest to implement. With continuous monitoring on the horizon, the ease of use should drastically increase. Automation of data collection and integration of data into existing hospital programming will further ease workflow concerns. But progress cannot happen with the field in its current, nonstandardized disarray. We must continue to push for consensus in measurements and optimal ranges to facilitate robust study and viable comparison. In just over 10 years, we have gone from viewing hyperglycemia as a protective, physiologic response in critical illness to developing complex, computerized algorithms to achieve TGC and minimize or "mitigate against" GV and hypoglycemia. Our software, databases, and measurement tools have not yet caught up with our vision and goals. The question is not whether TGC, minimal GV, and prevention of iatrogenic hypoglycemia are appropriate objectives, but how they are best achieved. We need to consistently measure GV in our IIT studies and develop a standardized measurement of variability to use in investigations. We need to demand that, for now, we forgo use of handheld glucometers in research studies, despite their ease of use clinically. We need to support research into alternatives to point-of-care capillary glucometers and standardize studies of TGC in the intensive care units in such a way that allows the community to compare one algorithm with another. The future is now—we need to marry science, technology, and clinical care in order to achieve these goals.

Disclosures:

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