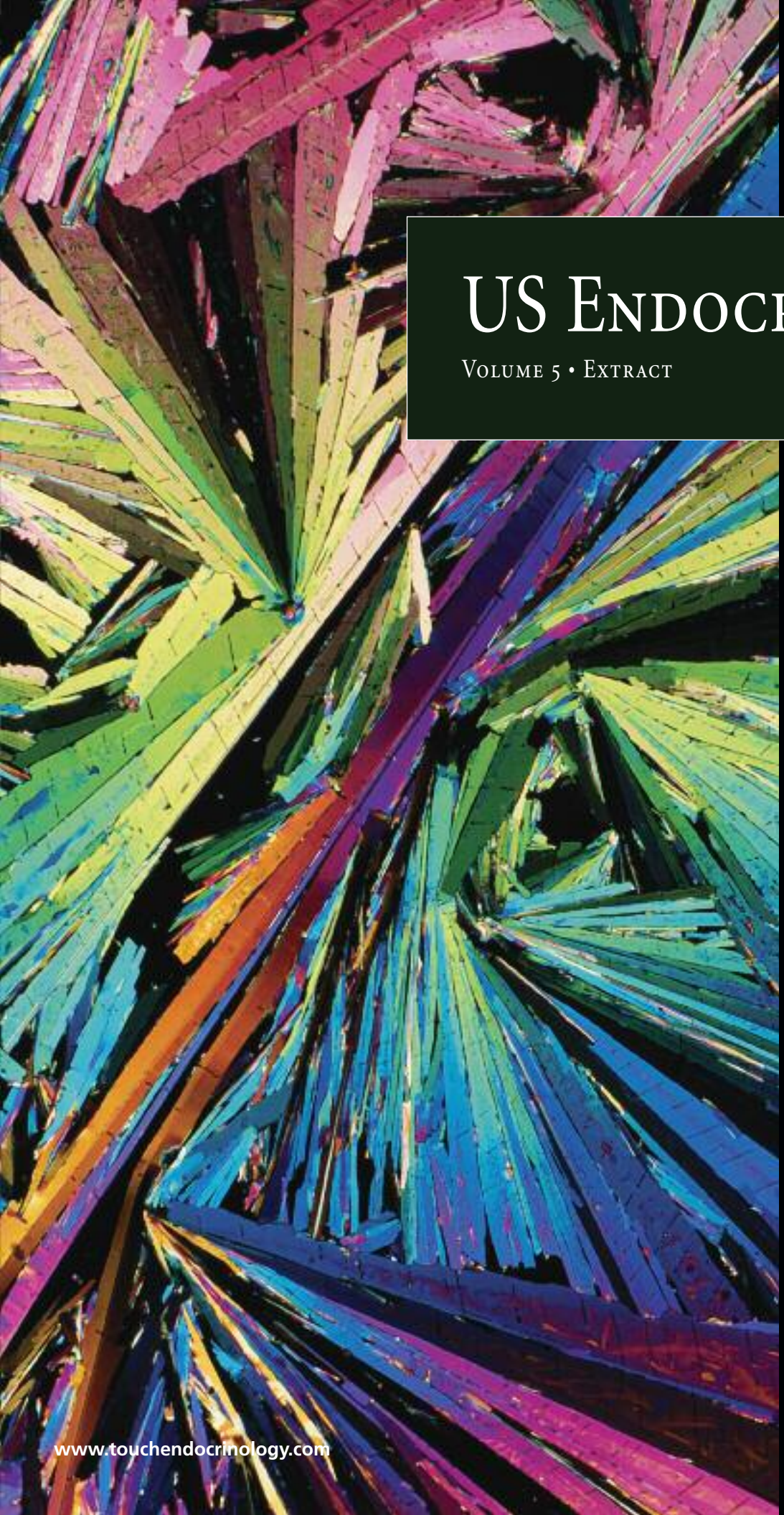

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Glucose Control in the Critically Ill Patient Utilizing Computerized Intravenous Insulin Dosing

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Abstract

Hyperglycemia and hypoglycemia in the critically ill patient are associated with increased morbidity and mortality. Numerous studies have investigated the benefits of glucose control in the critically ill patient receiving intravenous insulin. Tight glucose control (blood glucose 80–110mg/dl) in this patient population has been difficult to achieve. When accomplished, it has been accompanied by an increased risk of hypoglycemia and in some studies increased mortality. Computer-guided glucose management systems (CGGMS) offer an alternative to paper protocols for the attainment of improved glucose control in critically ill patients requiring intravenous insulin. CGGMS provide a way to achieve improved glucose control with reduced hypoglycemia while reducing insulin infusion calculation errors and standardizing insulin therapy, thus improving patient safety.

Keywords

Hyperglycemia, hypoglycemia, tight glucose control, computer-guided glucose management system, intravenous insulin

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Inpatient hospital hyperglycemia is associated with increased morbidity and mortality.[1,2] This is particularly true in the critically ill patient admitted to the intensive care unit (ICU).[3–9] Critically ill patients who require ICU care for more than five days have as high as a 20% risk of death and significant morbidity.[10] Hyperglycemia associated with insulin resistance is commonly encountered in the critically ill patient and is seen not only in those patients with pre-existing diabetes but also in those patients with undiagnosed diabetes and those with stress hyperglycemia.[11] Retrospective and *post hoc* analysis of large randomized controlled studies of intensive insulin therapy in the ICU suggests that patients with newly discovered hyperglycemia are at a greater mortality risk than patients with euglycemia or those with a previous diagnosis of diabetes.[1,12] Adverse outcomes have been reported in various critically ill populations.[3–5,8,9] In several patient populations, improved morbidity and mortality has been reported at blood glucose ranges defined as 'tight' (glucose 80–110mg/dl) or those below 140mg/dl.[3,4] Areas of controversy and discussion are ongoing related to the appropriate blood glucose goals in critically ill patients, as well as how and when to measure blood glucose and what the most appropriate glucose and study metrics should be.[13–16] The one consistent finding with the highest statistical significance in all outcome studies is the increase in the incidence of hypoglycemia associated with glucose control.[3–6,17] The contribution of 'hypoglycemic events' to outcomes associated with glycemic control protocols remains a topic of interest and major concern.[16] Until studies are completed with the same, near-zero hypoglycemia incidence randomized to different target goals, the optimum target glucose range is likely to always be dependent on the method of control.

Background

Numerous studies have investigated the benefits of glycemic control in critically ill patients.[3–9,18,19] A retrospective study in a mixed medical–surgical ICU investigated a heterogeneous patient population with a treatment blood glucose goal of <140mg/dl. A significant improvement in mortality and morbidity was demonstrated compared with those patients with blood glucose >140mg/dl.[18] Hyperglycemia and hypo-glycemia affect the prognosis of hospitalized patients with diabetes and cardiac disease, and cardiovascular surgical patients.[8,19,20] Hyperglycemia on admission in the patient with acute coronary syndrome or myocardial infarction (MI) has been associated with increased mortality,[19] whereas reduction of glycemia is associated with improved outcomes.[21] Optimal clinical outcomes were shown to be associated with mean glucose values between 100 and 140mg/dl for those patients with acute coronary syndrome,[19] who displayed higher mortality associated with glucose levels lower than 100mg/dl or with mean blood glucose levels increasing above 140mg/dl, albeit increasing at a less steep rate per mg/dl. Cardiovascular surgical patients with diabetes and hyperglycemia have decreased wound infections and morbidity with improved glucose control.[8]

Three major prospective, randomized, controlled trials (RCT) of over 1,000 critically ill ICU patients have been reported in the medical literature.[3–5] Perhaps the seminal study was that of Van den Berghe and

Table 1: Glycemic Targets in Hospitalized Patients

Surgical critical care patients	140–180mg/dl
Medical critical care patients	140–180mg/dl
General medical–surgical patients	100–180mg/dl Pre-meal <140mg/dl Random <180mg/dl

Sources: Diabetes Care, *2009;32:1119–31, and* Endocrine Practice, *2009;15(4):353–69.*[16]

colleagues published in 2001.[3] This was a prospective RCT of 1,548 patients treated with intravenous insulin in the surgical ICU of University Hospital in Leuven, Belgium. In the group treated with intensive insulin therapy (IIT) to accomplish tight glycemic control (TGC), defined as a glucose goal of 80–110mg/dl, there was a 34% decrease of in-hospital mortality compared with the conventionally treated group with a glucose goal of 180–200mg/dl. Other measures of morbidity, including sepsis, acute renal failure requiring dialysis, need for blood transfusions, and polyneuropathy, were improved in the IIT group. However, in this study, hypoglycemia (blood glucose levels ≤40mg/dl) occurred in 5.1% of the intensive insulin group and 0.8% of the conventional group.

In 2006, the same group of investigators using the same treatment protocol published their results in 1,200 patients treated in the medical ICU. Unlike the initial study, conducted in a surgical ICU, there was no decrease in hospital mortality during the first three days in ICU in the intensive group (glucose goal 80–110mg/dl). Hypoglycemia, which occurred in 18.7% of patients in the intensive treatment group and 3.1% of the conventional group, was independently associated with a poor prognosis.[4]

In May 2009, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was published in the *New England Journal of Medicine*.[5] This was a randomized, controlled, unblinded study of 6,104 adult patients admitted to medical and surgical ICUs in 42 hospitals, primarily in Australia and New Zealand. The group treated with IIT (glucose goal 81–108mg/dl) achieved a mean glucose level of 115mg/dl, whereas the group treated conventionally (glucose goal 144–180mg/dl) achieved a mean glucose level of 144mg/dl. Hypoglycemia (blood glucose levels ≤40mg/dl) was seen in 6.8% of the intensive group and 0.5% of the conventional group. The primary end-point, mortality at or before 90 days, was 27.5% in the intensive group versus 24.9% in the conventional group (p=0.02). The NICE-SUGAR investigators concluded that intensive glucose control increased mortality among adults in the ICU. A blood glucose target of 180mg/dl or less resulted in lower mortality than did a target of 81–108mg/dl. Contrary to the previous Leuven surgical ICU study,[3] and compatible with the medical ICU study of patients treated for three days or less,[4] the NICE-SUGAR mortality at 90 days was increased in the group treated with IIT, with no decrease in morbidity when compared with the conventional group.

Other smaller studies and meta-analyses have found conflicting results related to mortality and morbidity in ICU IIT-treated (glucose goal 80–110mg/dl) patients.[6,7,13] A consistent observation in these studies is an increase in hypoglycemia in the group treated with IIT (glucose goal 80–110mg/dl).[3–5,13] Severe hypoglycemia is a significant risk in the intensive insulin therapy of critically ill patients and is an independent risk factor for increased morbidity and mortality.[4,22] A potential problem in published large trials is the utilization of the Leuven insulin infusion protocol. In the original van den Berghe paper, the protocol reported an incidence of hypoglycemia (≤40mg/dl) in the IIT group of 5.1 versus 0.8% in the conventional group.[3] Other studies utilizing the same IIT protocol demonstrated an increased incidence of hypoglycemia ranging from 5.1 to 24% in the intensively treated group.[3,4,23] All protocols need to be appropriately applied, but in the literature the Leuven insulin protocol utilization and others have the disadvantage of lack of standardization in application.[23–25] It is unknown whether utilization or application of the Leuven protocol influenced hypoglycemic risk in the reported studies. Although a standard protocol was utilized in NICE-SUGAR, problems with protocol application accounted for a significant number of patients who experienced hypoglycemia.[26] Following review of the literature and pertinent available data, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) issued a consensus statement on inpatient glycemic control.[16] The resultant goals for inpatient glucose control and previous goals are seen in *Table 1*. The committee predicated the basis of the guidelines as: "until further information becomes available, to continue to emphasize the importance of glycemic control in hospitalized patients with critical and non-critical illness while aiming at targets that are less stringent than 80 to 110 mg/dl."[16]

Additional areas of discussion in the evaluation of glucose control and in the methods utilized to attain that control in the critically ill patient involve:

- point-of-care (POC) testing of blood glucose;
- the use or non-use of supplemental caloric administration during IIT; and
- the influence of glucose variability on morbidity and mortality.[15,27–29]

Reliability of POC blood glucose testing is extremely important to patient safety in the hospital setting. Accuracy of POC devices and an understanding of differences in whole blood and plasma glucose measurements are essential. The hospital environment presents the opportunity for multiple confounding factors to be present at once. Variables unique to the patient must be considered, particularly in situations where discrepancies arise between bedside glucose measurement and the clinical presentation.[15]

The use or non-use of IIT with supplemental calories can significantly affect metabolism in the critical care setting as well as blood glucose levels and the amount of infused insulin necessary to attain glucose goals. The cardioprotective, neuroprotective, and antiapoptotic effect of intravenous insulin is realized primarily in the setting of euglycemia versus hyperglycemia.[30] Therefore, this potential variable in critical care therapy must be addressed in treatment and in evaluation of the published literature.

Blood glucose variability in critically ill patients has been identified as a strong independent risk factor for increased mortality in the ICU setting.[27–29] This particular metric is important in the selection of the type of insulin therapy utilized in the ICU and must be considered when evaluating treatment protocols and outcomes.

Computer-guided Glucose Management Systems

The management of critically ill inpatients with hyperglycemia is complex and necessitates an approach that facilitates safe practices

and reduces the risk of errors. Both the over-treatment and the under-treatment of hyperglycemia represent potential safety issues in hospitalized patients with and without diabetes.[1,2,4,22] Various treatment modalities are available to accomplish this goal. They encompass the use of paper protocols and computer-guided glucose management systems (CGGMS).[31–34]

Numerous paper protocols are currently in use to accomplish improved metabolic control in the ICU.[31,32] These insulin infusion algorithms have been reviewed in depth by Braithwaite and Clement.[33] The application of paper protocols is often complex, requiring strict adherence to timing of blood glucose monitoring and the availability of specific patient data. One option in supporting nursing in the application of and adherence to the paper protocol is the application of computer technology, or CGGMS.[34–36] CGGMS algorithms for infusing intravenous insulin include the mathematical equivalent of bedside paper protocols and newer, more complicated mathematical protocols that would be difficult if not impossible to ask the bedside care-giver to perform on a frequent basis. Performing the mathematics in the computer and simply adding an alarm to remind the user of the time the next blood glucose is due would certainly lead to improved protocol performance. In general, these algorithms use a previous blood glucose, insulin infusion rate, current blood glucose, and time interval between testing to assign the next blood glucose, test time, and insulin infusion rate in order to achieve glycemic targets.[33] Shulman and colleagues found computerization of algorithms still may not result in easy attainment of tight glycemic control (glucose 80–110mg/dl), especially during the early stages of infusion.[35] Other investigators, including Kanji, the Specialized Relative Insulin and Nutrition Tables (SPRINT) investigators, and investigators utilizing the Glucose Regulation for Intensive Care Patients (GRIP) system, demonstrated improved target glucose achievement.[25,37,38]

In a recent review of the literature by Eslami and colleagues, 17 peer-reviewed studies on implementation and outcomes using CGGMS for TGC (glucose 80–110mg/dl) are reported. Of the 17 studies, two were prospective RCTs studying fewer than 100 patients, seven were prospective observational or controlled studies, six were retrospective, and two were observational without mention of the study design.[34] As with studies of IIT, studies of CGGMS report on at least one quality indicator that is affected positively; however, the diversity of the studies in terms of case mix, insulin therapy, associated therapies, and indicators used severely hampers study comparisons and prevents valid meta-analysis; a common 'vocabulary' is lacking. This common vocabulary is essential and has been offered as a potential solution for evaluation and comparison of studies.[14,34] There are no randomized studies with different target ranges utilizing CGGMS to control both arms of the study. Basically, all of the randomized studies for target range effect on outcome have used paper protocols with the different target ranges. The most consistent finding of these studies has been a highly significant increase in hypoglycemic incidences in the lower glucose target population. The consequences of this increased incidence of hypoglycemia on outcomes has been associated with increased mortality in some studies.[4,17] This consistent difference in the hypoglycemia incidence has been suggested as offsetting benefit derived from glucose control.[16]

Essential Success Factors for Computer-guided Glucose Management Systems

There are several CGGMS characteristics that are essential. CGGMS can help reduce the risk of insulin infusion calculation errors and standardize insulin therapy. The systems must facilitate the appropriate use of scheduled insulin therapy administered by nursing staff that is educated and knowledgeable in glycemic management. This is essential to attain safe and appropriate levels of glycemic control in the hospitalized ICU patient and achieve maximal benefit of the CGGMS. The CGGMS should be integrated into the workflow of the nursing staff with the clinical decision at the POC. Some systems use computerized ordering systems (computerized physician order entry [CPOE]) as the starting point, with integration of a CGGMS into this system.[38] Others use computers positioned close to the glucose analyzer as the location for nurse–system interaction.[39]

Common features among most CGGMS are that they are stand-alone systems not integrated into other clinical information systems. They are specific to a given patient and furnish management support if the clinical care for the patient is not in accord with protocol. Reminders regarding glucose measurement are received automatically without the need to query and often include audible alarms. The majority of systems receive reminders for insulin infusion rate that require clinicians to ask for advice. In most of the reported studies, the blood glucose is manually entered by the user into a separate CGGMS database. This is due to unavailability of the data electronically or due to lack of connection to the CGGMS. Since intravenous insulin has a short half-life and there is a pharmacodynamic delay in insulin action, any connection between the POC device and the CGGMS will need to be immediate and fail-safe.[33]

In three of the studies reported by Eslami, the data were electronically accessed.[34] Thirty percent of studies reviewed utilized 'if–then' on a varying scale of intravenous insulin. This involves a list of simple rules, with a condition (the 'if') and a conclusion part (the 'then'), and is based on the current blood glucose measurement. The conclusion corresponds to the amount of insulin.[34] The majority of the reviewed studies utilize formula-based protocols relying on a familiar, simple equation (e.g. insulin dose/hour = [blood glucose – 60 x multiplier (insulin sensitivity)].[33,34,40] In a single study, individualized patient modeling was accomplished by using multiple mathematical algorithms.[41] The software up- and downregulates a quadratic insulin dosing relationship based on the entered blood glucose readings from the POC device. Utilization of engineering control mathematics allows consideration of the previous four dose responses to regulate the dosing relationship. In this small, prospective, RCT in a cardiovascular ICU, improved glucose control with a decreased mean time to capture range, and decreased ICU time, were accomplished. Patients spent 84% of their time in the desired range (90–150mg/dl) without an increase in hypoglycemia. Our experience with this system in a larger cardiovascular surgery population has demonstrated improved glycemic control with significant improvement in the incidence of hypoglycemia (unpublished data). Furthermore, the system provides recommended basal–bolus insulin doses when transition to subcutaneous insulin is appropriate.

At present, CGGMS afford an improved approach to facilitate 'tighter' glucose goals with a reduced incidence of hypoglycemia, and in some

systems a reduced nurse and physician workload. Attainment of improved glycemic control in critically ill patients has been reported to be cost-effective.[42] The cost-effectiveness of different CGGMS intuitively would seem to be equal; however, it may vary significantly depending on the system used, and this awaits further study.

As treatment systems for hyperglycemia continue to evolve with utilization of closed-loop glucose monitoring, hypoglycemia, decreased blood glucose variability, and problems with POC blood glucose measurement should continue to improve. This will allow the attainment of improved glucose goals and even greater patient safety, with the hopeful result of decreased morbidity and mortality.

Glycemic control using intravenous insulin has been shown to improve outcomes in critically ill as well as non-critically ill patients. The appropriate control of blood glucose in the ICU is a demanding process complicated by the critical and complex patient who often presents with numerous co-morbid conditions.

Although the entity of tight glucose control is difficult to attain and the evidence-based data cannot be objectively compared, at present the use of CGGMS has introduced a treatment modality that affords an opportunity to accomplish appropriate blood glucose goals utilizing complicated mathematics not amenable to bedside use with the potential of a very low incidence of hypoglycemia and improved patient safety. ■

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