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In Brief

Hyperglycemia in the inpatient setting has been linked to poor outcomes. There is evidence that careful management of hyperglycemia in the acute care setting can decrease lengths of stay, morbidity, and mortality. In unstable, critically ill patients, blood glucose excursions are most effectively controlled through the use of continuous intravenous insulin infusion protocols. However, barriers remain to the acceptance and successful implementation of protocol-driven initiatives to achieve normoglycemia. A multidisciplinary team approach can help overcome staff misconceptions and fears regarding tight glycemic management in hospitalized patients.

Continuous Intravenous Insulin: Ready for Prime Time

Nancy J. D'Hondt, RPh, CDE

Rationale for Continuous Insulin Infusion

Stress-induced hyperglycemia is a commonly encountered problem in the acute-care setting. Elevated blood glucose levels in critically ill patients may result from the presence of excessive counterregulatory hormones and high levels of tissue and circulating cytokines. These metabolic changes can result in increased insulin resistance and a failure to suppress hepatic gluconeogenesis. Thus, hyperglycemia may be present even in inpatients without a diagnosis of diabetes. Studies have shown an association between hyperglycemia and an increased risk of infection, sepsis, renal failure, congestive heart failure, stroke, and neuropathy.[1–6] The recognition of hyperglycemia as a contributor to poor outcomes has provided the rationale to pursue tight glycemic control.

The key to effectively controlling hyperglycemia is to identify early patients who have or are at risk of developing elevated blood glucose levels and to initiate appropriate therapy in a timely manner to maintain near-normoglycemia. Insulin is the therapy of choice for management of hyperglycemia in hospitalized patients. Sliding-scale insulin regimens consisting of four to six daily injections of short- or rapid-acting insulin for a given degree of hyperglycemia are often used. However, sliding-scale algorithms are implemented without regard to nutritional intake or preexisting insulin administration

and do not allow for individualization based on a patient's sensitivity to insulin. Thus, sliding scales do not provide a physiological approach to insulin management. Variable-rate continuous insulin infusion (CII) is the best method to address the rapidly changing needs of critically ill, unstable, or surgical patients. Unlike the unpredictable sliding-scale approach, this therapeutic option allows for continual titration of insulin levels to match a patient's constantly changing requirements.[7,8]

Clinical Trials

Before 2001, hyperglycemia was hypothesized to be a beneficial adaptive response in acutely ill patients, and blood glucose values > 200 mg/dl were not uncommon. Since that time, several key studies have disproved that notion and confirmed the detrimental effects of uncontrolled hyperglycemia in the acute-care setting. This information has prompted a paradigm shift in the approach to inpatient glycemic management.

In November 2001, van den Berghe et al.[1] published the results of a landmark trial in the *New England Journal of Medicine*. This was the first prospective, randomized, controlled study to look at inpatient intensive insulin therapy. These investigators compared the use of intensive insulin therapy (to maintain blood glucose targets of 80–110 mg/dl) to conventional treatment (to maintain blood glucose between 180 and 200 mg/dl) in 1,548 surgical intensive care unit (ICU) patients receiving mechanical ventilation. The near-normal glucose levels achieved resulted in considerable reductions in several end points, including length of stay, sepsis, dialysis, and in-hospital mortality. This intervention spurred additional studies to explore the effects of intensive insulin therapy in ICUs.

A prospective, observational study published in 2004 by Furnary et al.[9] sought to level the playing field between patients with and without diabetes in the cardiac surgery arena. These investigators were the first to show that one could eliminate the inherent disadvantage faced by diabetic patients receiving coronary artery bypass grafting by using CII and lower blood glucose targets before, during, and for three full days after surgery. Another study published that same year by Krinsley[6] not only corroborated the findings of van den Berghe et al. and Furnary et al. but also further expanded proof of the benefits of tight glucose control to the noncardiac surgery population.

In 2006, van den Berghe published results from her study on glycemic control in a medical ICU.[2] Her findings again showed reductions in morbidity similar to the previous surgical ICU study. A subgroup analysis revealed mortality benefits only in the intensive treatment group who had an ICU stay of > 3 days. Since publication of this study, several questions have been raised with regard to the safety and efficacy of intensive interventions, as well as appropriate blood glucose targets.

van den Berghe subsequently pooled the data set from the two earlier studies and revealed an overall reduction in hospital mortality for all patients from 23.6 to 20.1% and from 37.9 to 30.1% in patients remaining in the ICU for at least 3 days. Morbidity end points, such as polyneuropathy, kidney injury, and critical illness, were reduced by one-half. In addition, the impact of maintaining glucose levels near normal increased with time in both the medical and surgical populations. Pooling the data from these two studies created the statistical power to show the benefits of intensive insulin therapy on morbidity and mortality in the mixed medical/surgical patient population.[10]

Recent studies have questioned the safe administration of intensive insulin therapy.[11,12] Investigators of the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial[11] closed the study prematurely because a nearly sixfold increase in severe hypoglycemia occurred in the two intensively treated arms. The Glucontrol trial[12] was also stopped early because of protocol violations and unacceptable rates of hypoglycemia in the intensive therapy group. Applicability of these studies in evaluating tight glycemic control in the ICU is questionable. Both trials demonstrated limitations in study design, and enrollment was vastly underpowered to draw any definitive conclusions.

Today, there is overwhelming evidence to support the management of hyperglycemia in acutely ill patients.[1–7] However, barriers remain to the widespread acceptance of tight glycemic initiatives, and questions such as who will benefit most, what the glycemic targets should be, and for which patient populations remain to be answered. Further research is needed to more fully indentify best practices for implementing tight glycemic control in the acute-care setting.

Organizational Recognition of Tight Glycemic Control

Several organizations now support the use of tight glycemic control; however, questions remain regarding the appropriate blood glucose targets. Today, both the American Diabetes Association (ADA) and the American College of Endocrinology (ACE) support keeping blood glucose levels in ICU patients as close to 110 mg/dl as possible. For noncritically ill patients, it is recommended that glucose levels not exceed 180 mg/dl[13,14] (Table 1). The ACE guidelines recommend CII therapy for patients whose glucose levels must be brought under control promptly, including those who are critically ill or on prolonged NPO (nothing-by-mouth), nutritional status.[14]

The Joint Commission recently proposed tight glucose control for the critically ill as a core quality-of-care measure for all U.S. hospitals that participate in the Medicare program.[15] The Institute for Healthcare Improvement, together with an international initiative by several professional societies including the American Thoracic Society, is promoting a care "bundle" for severe sepsis that also includes intensive glycemic control.[16]

CII Versus Sliding Scale

In critically ill patients, insulin is necessary to achieve a reduction in blood glucose levels. Using intravenous (IV) insulin in the absence of glucose lowering will have no effect on outcomes. The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study[17] demonstrated that, in patients suffering an acute myocardial infarction regardless of a history of diabetes, IV insulin therapy for 24 hours followed by intensive subcutaneous therapy for ≥ 3 months improved long-term survival. The follow-up DIGAMI 2 study[18] was designed to evaluate the relative benefit of long-term tight glycemic management. Although the investigators failed to demonstrate significant differences in glucose control and mortality among the three treatment arms, they did illustrate the association between

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Table 1. ADA and ACE Recommendations for Inpatient Blood Glucose Targets[13,14]

Patient Population	ADA	ACE
ICU/Critically Ill	As close to 110 mg/dl as possible and generally < 140 mg/dl	110 mg/dl
Regular Units (Noncritical)	< 126 mg/dl fasting < 180–200 mg/dl random	110 mg/dl preprandial 180 mg/dl maximum

higher glucose levels and increased risk of death. Thus, merely administering insulin without lowering glucose levels will not improve outcomes.

CII is the only delivery method specifically developed for inpatient use and is preferred over the subcutaneous route for several clinical indications (Table 2). The only type of insulin that should be given intravenously is human regular insulin. There is no advantage to using rapid-acting analogs in preparing insulin infusions because the rate of absorption is no longer a factor when administering insulin intravenously and can only result in added costs to the institution.

IV insulin delivery offers many advantages over subcutaneous insulin delivery. It eliminates the need for multiple injections, allows for more accurate dose administration, has more predictable kinetics, and provides a quick response to rapidly changing glucose levels. IV administration also has the advantage of accomplishing adequate control with smaller insulin doses. These properties result in continuous, safe, and effective maintenance of blood glucose values within a narrow therapeutic window.[7,19,20]

Lazar et al.[21] showed that the hourly administration of subcutaneous sliding-scale insulin resulted in an average postoperative blood glucose level of 267 mg/dl. In contrast, the use of a dynamic scale IV insulin infusion in the Portland Protocol[22] resulted in a composite 3-day blood glucose value of 122 mg/dl, an impressive 145 mg/dl difference. Data supporting the efficacy and safety of sliding-scale insulin are lacking. No clinical study has documented the benefit of a sliding-scale regimen, and in retrospective and nonrandomized studies, sliding-scale insulin has been associated with higher rates of both hyperglycemia and hypoglycemia.[23]

The unpredictability in absorption of subcutaneous insulin in intensive care patients makes it an inappropriate option for intensive insulin therapy. ICU patients experience changes in volume and subcutaneous tissue perfusion that could dramatically affect absorption kinetics. These physiological changes could potentiate glucose variability resulting in an increased risk of hyper- or hypoglycemia.

Several protocols, algorithms, and standardized order sets have been developed to guide CII therapy. The best protocols incorporate several data elements including the current blood glucose level, previous blood glucose level, and current infusion rate. These factors are used to adjust insulin infusion rates based on an evaluation of velocity of change in glucose levels, rather than relying on absolute blood glucose levels alone.

Variability and Rate of Change

In the outpatient setting, research has shown that fluctuations in blood glucose levels can lead to increased cellular damage, resulting in a higher incidence of complications.[24,25] Glucose variability is a factor that has also been associated with poor outcomes in the inpatient setting. A recent study by Al-Dorzi et al.[26] found that predictors of glycemic variability in critically ill patients include age, diabetes, and daily dose of insulin. Study results showed that increased variability was associated with higher inpatient mortality and suggested glucose range as an independent predictor of nosocomial infection.

IV insulin protocols should incorporate insulin sensitivity as the basis for adjustments in IV drip rates. Rate of change is the parameter that best facilitates evaluation of insulin sensitivity. This variable allows for adjustments in insulin infusion rates based on comparison of sequential blood glucose values and the present infusion rate. Using rate of change when initiating CII facilitates quicker adjustment of insulin infusion rates to compensate for the degree of insulin resistance; this results in a shortened time-to-target window. Sudden shifts in glucose levels during maintenance insulin infusion usually reflect modifications in therapy or nutrition, or a change in clinical status. Dramatic variations should alert care providers to the need for adjustments in the rate of infusion that will again stabilize blood glucose levels. Rate of change is one variable that should be incorporated into every CII protocol because it allows for the safer, more effective administration of IV insulin.

Protocol-Driven Insulin Infusion Therapy

In providing for safe and effective administration of IV insulin, it is imperative to have a framework—a formal protocol—from which to operate. When given intravenously, insulin has a rapid onset and short duration of action, allowing for precise titration. This titration requires careful, scheduled, and accurate monitoring, as well as appropriate response by care providers according to the parameters of the given protocol. Protocol-driven insulin delivery will establish appropriate practice guidelines, control variability among patients, standardize performance, and provide for evaluation of outcomes.

Institutional Support

When changing an accepted practice, there are several key steps involved in transitioning from thought to application. The first is to ensure administrative support. Without institutional backing, implementation of tight glycemic control will prove to be difficult. Proof of both financial and clinical benefits will be required to obtain the assistance of all interested parties—hospital, physicians, staff, and patients. The evidence supporting the use of intensive insulin therapy is abundant. Several studies have shown improved outcomes, including significant reductions in complications, lengths of stay, and mortality.[1–8] Clinical data demonstrate considerable morbidity and mortality benefits from normalizing glucose levels in hyperglycemic patients, and as a result, several leading organizations have endorsed

Table 2. Common Indications for IV Insulin Therapy[13,14]

- Diabetic ketoacidosis and hyperglycemic hyperosmolar state
- General preoperative, intraoperative, and postoperative care
- Postoperative period after cardiac surgery
- Critical illness
- Uncontrolled hyperglycemia during high-dose corticosteroid therapy
- Labor and delivery
- Prolonged NPO nutritional status in patients who are insulin deficient
- Myocardial infarction or cardiogenic shock
- Dose-finding strategy before conversion to subcutaneous insulin therapy
- Stroke
- Post-organ transplantation

the implementation of uniform standards for managing elevated glucose levels in the inpatient setting.[11,12,27]

The cost of maintaining normoglycemia is minimal compared to the costs associated with the outcomes of failing to address hyperglycemia. Several cost analyses have been conducted. A financial analysis of the first study by van den Berghe et al.[28] showed that surgical patients receiving intensive insulin therapy had a mean length of stay of 6.6 days and a cost savings of 2,638 Euros (> $4,000) per patient. This figure is based on quantification of ICU days and the costs of mechanical ventilation, transfusions, antibiotics, inotropes, and vasopressors. The cost savings are attributable to reduced length of stay in the ICU and to reductions in morbidity, such as renal failure, transfusions, ventilator support, and sepsis.

Krinsley conducted a similar analysis of costs associated with implementation of intensive insulin management.[29] This study attempted to quantify the individual components of the total cost of care. Reductions included ICU hours by 17.2%, time on a ventilator by 19%, laboratory costs by 24.3%, pharmacy costs by 16.7%, and imaging costs by 5%. An overall annualized cost savings was reported to be $1.34 million based on patients receiving intensive insulin therapy with a mean length of stay of 3.4 days in the ICU.

Cost analyses of the Portland Protocol have also been published.[30] It is estimated that the extra cost per patient of implementing this protocol is approximately $170. The net return on investment to the hospital in overall prevented deep sternal wound infections and length-of-stay savings total $4,638 for each cardiac patient treated with a full 3 days of IV insulin, compared to those treated with subcutaneous insulin therapy.

Glycemic Management Team

In today's hospital culture, integration of services is necessary for the successful management of patient care. Tight glycemic control initiatives require an interdisciplinary team approach to establish hospital pathways, promote a culture of safety and efficacy, and provide ongoing professional education. Members of the team should include a "champion" and all key stakeholders and relevant hospital services. ACE recommends the use of a multidisciplinary team that would ideally include personnel from the medical staff, nursing, case management, pharmacy, nutrition services, dietary, laboratory, quality improvement, information systems, and administrative divisions.[31] Each member of the team brings necessary knowledge, skills, and perspectives to the initiative. A team approach will aid in designing and coordinating strategies for appropriate protocol development, staff education, implementation, and evaluation.

In studying the impact of a diabetes team intervention, Koproski et al.[32] found that patients with a primary diagnosis of diabetes who received intervention had an average 2-day reduction in length of stay. If diabetes was a secondary diagnosis, the median length of stay decreased by 0.5 days, and the readmission rate at 3 months after discharge was less than half of that seen in the control group.

The multidisciplinary team approach to the identification and management of inpatient hyperglycemia facilitates communication, implementation, and feedback. These dynamics will result in systems for better delivery and coordination of care, leading to improved patient outcomes. Failing to integrate patient care services will create barriers to effective glucose control. Benchmarks are needed to evaluate the effectiveness of a multidisciplinary team.

Protocol Selection

Numerous published protocols are available, ranging from simple to complex. It is important to assess an institution's present inpatient practices to determine the most appropriate fit for the specific culture. Table 3 lists some key elements to consider when adopting or developing a protocol.

A good protocol will provide the operational framework from which to standardize practices and metrics. Protocols should streamline the clinical decision-making process. Important variables to consider when evaluating existing protocols would be time to target, amount of time spent in target range, flexibility, and incidence of adverse events. Ideally, the time to target should be minimized without increased risk of hypoglycemia. Slow-titration algorithms may subject patients to long periods of hyper- or hypoglycemia.[33] A protocol yielding low glucose variability and high incidence of time spent in target range demonstrates that it can maintain stable blood glucose levels over time. Flexibility pertains to the ability to adjust the protocol to meet the needs of the patient population or to overcome institutional barriers. Consideration of the ability to change initiation glucose levels and target ranges based on evidence and acceptance are important. Additionally, a low incidence of severe hypoglycemia is crucial to the successful adoption and implementation of the protocol.

In 2004, Kanji et al.[19] evaluated the efficiency and safety of a nurse-managed insulin infusion protocol in 100 critically ill adults using a target glucose concentration of 81–110 mg/dl. Patients in the control group received subcutaneous and IV insulin titrated to target glucose ranges at the physicians' discretion. The interventional cohort received insulin infusion according to a nurse-managed stardardized protocol. Patients included in the interventional group reached their target range more rapidly and maintained blood glucose concentrations in the target range longer compared to the control group. Several publications and organizations have validated

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Table 3. Elements of a Good Protocol[33,39,43]

- Evidence-based
- Clear and concise
- Easy to implement
- Identifies threshold for initiation
- Nurse-driven
- Based on current blood glucose and rate of change
- Delineates monitoring parameters
- Safe: low risk for hypoglycemia
- Minimizes need for calculations
- Allows for individualization of therapy in special situations
- Includes plan for transitioning to subcutaneous therapy

or endorsed the use of nurse-driven protocols.[34–37]

Hypoglycemia

Although a protocol is designed to be somewhat automated, there remain conditions that could predictably affect glucose control. The fear of hypoglycemia limits the willingness of care providers to adopt lower glycemic targets. Implementation of any tight glycemic control protocol includes a proactive approach to controlling blood glucose while preventing hypoglycemic events. Recognizing predisposing conditions and anticipating those events that could trigger an imbalance between circulating insulin and glucose levels is crucial (Table 4).

Protocols designed with increased frequency in testing for patients at high risk for hypoglycemia will result in a reduced length of time spent in the hypoglycemic state. Insulin infusion protocols allow for titration of IV insulin using small increments of change, thus minimizing the risk of low glucose levels and maximizing options for maintaining tight control.

Hypoglycemia is avoidable, and monitoring of blood glucose is crucial to detecting impending events. Risk reduction requires a protocol designed to prevent occurrences, a management team that that is vigilant in identifying high-risk patients, and an educated staff to implement CII. Measures to minimize errors that could result in sudden changes in glucose levels should be incorporated into the protocol. These include a standardized drip concentration, appropriate priming, suitable monitoring intervals, blood glucose values that trigger corrective measures, and cues to changes in therapy that put patients at risk. Hypoglycemia is a predictable and preventable event and should not create a barrier to achieving euglycemia in the hospital setting.

Point-of-Care (POC) Testing

Protocol implementation relies heavily on directed clinician response to accurate blood glucose measurements. Insulin infusion protocols rely on frequent monitoring and rapid results in blood glucose testing. Hospitals have come to rely on portable monitors as a solution to the need for increased bedside blood glucose testing. Although technology has improved performance of these meters, several factors can affect results. The leading cause of inaccuracy in POC testing is user error.[38] Operator-associated errors include inadequate meter calibration, failure to code correctly, poor meter maintenance, and improper user technique.[39]

Several biological factors have been associated with variations in blood glucose values. Sample source, altitude, triglyceride levels, hematocrit, and the presence of nonglucose sugars can all affect meter results. In steady-state (unfed) conditions, arterial blood glucose concentrations are ~ 5 mg/dl higher than capillary and 10 mg/dl higher than venous concentrations.[40] In some meters, hematocrit values > 60% and < 20% can result in false blood glucose readings.[40]

These drawbacks require careful consideration when selecting a POC testing device. Education, training, and a standardized protocol will drive consistency in practice and minimize error. Institutions should standardize POC testing devices, ensure adequate supplies of glucose meters to meet staff needs, and educate all staff regarding proper device and sampling techniques.

Education Enhances Performance

The understanding and support of those involved in development, initiation, and implementation of any tight glycemic control program is essential to its success. The more staff having a full understanding of the overall picture, the more successful the program will be. A failure to accept the evidence that supports change presents a barrier to achieving euglycemia. A 2004 survey of nurses and physicians conducted by McMullin et al.[41] highlighted lack of knowledge as a failure to incorporate evidence-based medicine into management of hyperglycemia. Recognizing and addressing this potential barrier involves the development of integrated ongoing educational strategies. The rationale is to provide opportunities that will enhance knowledge, improve performance, and offer the support needed to deliver quality care. The benefits of interactive education and performance feedback are listed in Table 5.

Implementation: Piloting the Protocol

Piloting is necessary to ensure that the general concepts and details of the protocol are understood and feasible. After extensive educational programs designed to inform and empower staff, the team must decide on a roadmap for implementation.

A stepped approach is one method often used because it allows staff to better acclimate to changes in practice and familiarize themselves with the fundamentals of the protocol. The protocol is initially tested in only one ICU, and possibly only one patient, at a time. Often, based on the amount of supporting literature, the cardiovascular or surgical ICU becomes the chosen unit for initiation. The team must come to agreement with the staff on an acceptable glucose level for initiation and a target glucose range. It is recommended to start with higher target ranges that can be fine-tuned over time to the ultimate goal blood glucose range as the comfort level of the staff increases. Working with nurse management to assure staffing appropriate to the additional time constraints should also be a consideration. Under the guidance and oversight of the glycemic management team, staff can implement the details of the protocol. Through repetition, support, and ongoing communication, staff will increase their familiarity with execution of tight glycemic control protocols and build efficiency in performance. Over time, these new behaviors will become the default rather than the exception.

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Table 4. Conditions That Predispose Patients to Hypoglycemia

- Advanced age
- Changes in nutritional status
- Change in delivery of nutrition or glucose (enteral, parenteral, dialysate)
- Renal failure
- Liver disease
- Concurrent illness (cerebral vascular accident, congestive heart failure, shock, sepsis)
- Ventilator use
- Concurrent medications (β-blockers, quinolones, steroids, epinephrine)
- Infrequent or missed monitoring
- Poor protocol design
- Variation from protocol
- Knowledge deficits of care providers

Table 5. Benefits of Staff Education

- Involves staff in the process
- Builds internal support system
- Dispels myths about risks of tight glycemic control
- Empowers staff to make informed decisions
- Reinforces principles of tight glycemic control
- Recruits clinician advocates
- Assures compliance with the protocol

Should CII be restricted to the ICU?

IV insulin infusion protocols have generally been reserved for the intensive-care setting. Studies to support use of CII have primarily been limited to ICUs. However, patients who could benefit from insulin infusion therapy are not restricted to the intensive-care setting. The use of IV insulin protocols has been widely accepted in the treatment of patients presenting with hyperglycemic hyperosmolar state and diabetic ketoacidosis without a requisite admission to the ICU. Events leading to prolonged hyperglycemia or significant fluctuations in blood glucose levels should not require admission to the ICU for appropriate treatment. Conversely, patients in the ICU who are now clinically stable should not have transfer to a step-down unit or regular medical floor delayed secondary to hospital restrictions regarding IV insulin.

In 2005, a group from Duke University published results of a project evaluating the safety, effectiveness, and feasibility of using an IV insulin algorithm in the general hospital wards.[42] Audit findings indicated that the nomogram for monitoring IV insulin infusion could be used effectively on intermediate-care general medicine units with a nurse-to-patient ratio as high as 1:6.

Expanding implementation of IV insulin protocols requires careful planning, increased education, and evidence to support best-practice measures. For patients who meet criteria for CII but whose clinical status does not warrant admission to or preclude discharge from the ICU, insulin infusion protocols should be developed with looser glycemic targets. Management of hyperglycemia outside the ICU should prove to be a cost-saving measure. Implementation under the guidance of the multidisciplinary team and direction of floor "champions" should be the next step toward better outcomes.

Conclusion: Do No Harm

Today, the intensive management of inpatient hyperglycemia is becoming a standard of care. In unstable or critically ill patients, the adoption of near-normal glycemic targets requires the use of IV insulin infusion protocols. However, institutional and educational limitations have created barriers to the adoption of glycemic targets that will impart the greatest benefit to the inpatient population. The development of protocol-driven programs under the auspices of a multidisciplinary team will best serve to overcome hospital-wide barriers and provide the pathways that will lead to better outcomes for patients experiencing hyperglycemia in the acute-care setting.

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