



Glycemic control in the hospital: How tight

Consider the latest evidence as you explore the controversial issue of glycemic control in critically ill patients.

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PATIENTS WITH DIABETES are often our most challenging. Although diabetes isn't usually the reason that patients are admitted to the hospital, it's the fourth most common comorbidity. Half of patients with type 1 and 2 diabetes will face surgery in their lifetime.¹

During hospitalization, up to 12% of patients who don't have a history of diabetes will develop hyperglycemia, which is defined as a fasting blood glucose over 126 mg/dL or a random glucose over 200 mg/dL. Surprisingly, these patients will have a nearly 18-fold increased risk of in-hospital mortality compared with the 3-fold risk experienced by patients known to have diabetes.² Recent studies have demonstrated that better glycemic control can greatly reduce mortality, morbidity, and hospital costs.¹

So how tight should glycemic control in hospitalized patients be? Based on recent studies, the answer to that question remains controversial. This article will explore this issue and present current best practices for caring for a patient in the hospital who has diabetes or hyperglycemia.

Why "sweet" patients go sour

Physiologic metabolic responses to acute injury and stress can even cause hyperglycemia in hospitalized patients who don't have diabetes. Conditions such as a myocardial infarction, stroke, surgery, trauma, pain, and sepsis often

should it be?

cause the release of biological mediators and counter-regulatory hormones that promote hyperglycemia. See *Liver under stress*.

When hyperglycemia persists, a state of glucose toxicity may occur that can blunt beta cell insulin secretion, causing further hyperglycemia.¹ To make matters worse, the potent stress hormone cortisol also impairs insulin receptors, making the patient more insulin resistant. Stress-induced hyperglycemia may contribute to an 18-fold increase in mortality.²

The vicious cycle of stress-induced hyperglycemia, hypoinsulinemia, and insulin resistance can lead to altered inflammatory and coagulation responses, resulting in macrovascular and microvascular damage. The flood of inflammatory cytokines promotes neutrophil dysfunction, oxidative stress, endothelial dysfunction, and a prothrombotic tendency.³

It's little wonder that patients with hyperglycemia are prone to impaired wound healing, sepsis, cardiac reperfusion injury, and a greater risk of tissue and organ damage. Hyperglycemia also increases the risk of polyneuropathy, dyslipidemia, and infection. Research has revealed that when blood glucose increases to over 200 mg/dL for 2 hours, the postsurgical risk of infection can increase tenfold.⁴

Hospitalized patients are also more vulnerable to hyperglycemia because of

fluids and medications they receive. Glucose-containing I.V. fluids, corticosteroids, vasopressors, and parenteral and enteral nutrition can all promote higher glucose levels. Other pharmacologic culprits include diuretics, antipsychotics, sympathomimetics, cyclosporine, and propofol.⁵

Benefits of blood glucose control

A landmark study by Van den Berghe in 2001 supported tight glycemic control in postoperative patients and led to urgent revamping of hospital insulin protocols throughout the United States.⁶ Van den Berghe and her team found that mortality was reduced by 34% in cardiac surgery patients whose glucose levels were tightly controlled between 80 and 110 mg/dL with an insulin infusion, compared with patients whose levels were maintained merely under 200 mg/dL via conventional intermittent subcutaneous insulin therapy.

Tighter insulin control also resulted in a reduction in bloodborne infections, acute renal failure, polyneuropathy, and blood transfusion requirements. Reduced mortality was found primarily in those spending more than 5 days in the ICU.

Other studies of patients in cardiovascular and surgical ICUs substantiated the use of very tight glycemic control. These studies also showed

a reduced risk of postoperative atrial fibrillation.⁴

Evidence to the contrary

But many hospitals changed their protocols again based on more recent research suggesting that tight glycemic control may not benefit every acutely ill patient—and in fact may significantly increase both hypoglycemia and mortality. The Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study of intensive versus conventional glucose control in critically ill patients demonstrated the drawbacks of tight glycemic control.⁷ This multicenter trial included 6,100 critically ill patients with hyperglycemia.

In the NICE-SUGAR study, patients were randomized to either intensive glucose control (with an insulin infusion and a target blood glucose of 80 to 108 mg/dL) or to conventional glucose control (with an insulin infusion

Liver under stress

Under stress, the liver produces and releases glucose in response to glucocorticoids (cortisol), catecholamines (epinephrine), growth hormone, and cytokines (interleukin-6, interleukin-1, and tumor necrosis factor-alpha). As a result, protein and fat are catabolized and blood glucose surges.³

started for blood glucose over 180 mg/dL and discontinued when blood glucose dropped below 140 mg/dL). Intermittent doses of subcutaneous insulin were then used to maintain blood glucose below 180 mg/dL. Patients in the intensive glucose control group experienced six times as many incidents of severe hypoglycemia as those conventionally treated with insulin. More alarming, critically ill patients in the intensive glucose control group were 14% more likely to die during the 90-day study period.⁷

Based on these findings, the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) have jointly recommended a revised glucose target of 140 to 180 mg/dL for the majority of critically ill patients. In noncritically ill patients, a premeal glucose target below 140 mg/dL in conjunction with a random glucose less than 180 mg/dL is generally preferred. A lower blood glucose target may be used in stable patients with a prehospital history of tight blood glucose control. See *Suggested glucose targets in the hospital*.

Other medical societies are awaiting further analysis of the NICE-SUGAR results before rendering their verdicts. Some experts believe that the result will be a customized approach that tailors insulin therapy to individual patients during their hospitalization.⁸

Insulin therapy decisions

Many hospitals have or are adopting protocols for improved glycemic control. Subcutaneous and I.V. insulin are still the treatment of choice for hospitalized patients with significant hyperglycemia. Oral hypoglycemic agents are problematic in these patients with

severe hyperglycemia due to unreliable absorption, metabolism, and impaired excretion of the drugs. In addition, many of these patients are N.P.O., which increases their risk of hypoglycemia.

Outside of a critical care or step-down unit, hospitalized patients who require insulin may receive intermittent subcutaneous insulin therapy. Clinicians should consider this therapy for any patient whose blood glucose levels rise above 180 mg/dL in the fasting (preprandial) and postprandial state.⁸

In all critically ill patients who are hyperglycemic, an I.V. insulin infusion is preferred because subcutaneous insulin injections may be absorbed erratically in patients who have hypotension or generalized edema or are receiving vasopressors. Given I.V., insulin can be quickly adjusted to prevent wide variations in blood glucose levels and reduce the risk of hypoglycemia.

Patients at greatest risk for significant hyperglycemia are those undergoing major cardiovascular surgery and organ transplants, those with decompensated diabetes (such as diabetic ketoacidosis and hyperglycemic hyperosmolar state), those in cardiogenic shock or renal failure, and those receiving high steroid doses. These patients often have impaired insulin metabolism and fluctuating insulin needs. See *Does your patient need an I.V. insulin infusion?*

IMPORTANT POINT: An insulin infusion must be initiated in all critically ill patients who have type 1 diabetes.

Managing insulin infusions can be time-consuming and challenging, especially if your institution doesn't have an insulin infusion protocol. A nation-

al trend may remedy this situation: Research has demonstrated the safety benefits of standard insulin infusion protocols.⁹

Making a case for protocols

Insulin infusion protocols have helped patients achieve target glucose levels and can improve communication between nurses and prescribers. To be effective, the protocol should incorporate an algorithm that can be easily adapted to individual patient responses, get the patient to goal quickly with minimal hypoglycemic risk, and be used hospital-wide. Many insulin protocols found online or in medical books or journals can be adapted for use in your own hospital. The Yale Insulin Infusion Protocol is one example.¹⁰

Whatever insulin protocol you use, be prepared to make adjustments depending on how insulin resistant your patient is. The hourly insulin requirement for a patient with type 2 diabetes who weighs 270 pounds (122.5 kg) is usually quite different from that of a patient with type 1 diabetes who weighs 140 pounds (63.5 kg).

Patients with type 2 diabetes tend to be more insulin resistant than patients with type 1 diabetes. Patients who are obese also tend to have greater insulin resistance and require higher insulin infusion rates.

The insulin infusion protocol used should allow for these variations in insulin resistance. When the patient has more insulin resistance, you'll need to use greater incremental insulin doses when titrating the infusion rate up or down.

An effective insulin infusion protocol should be user friendly, giving you greater autonomy to adjust infusion rates to meet the patient's glucose targets. Nurses at your hospital should provide their input for the design and implementation of any hospital-approved insulin infusion standard.

Starting the insulin infusion

When an infusion is ordered, the pharmacy will typically mix regular human insulin or aspart (NovoLog) in 0.9%

Suggested glucose targets in the hospital

Patients	Fasting/preprandial	Postprandial	Labor and delivery
Critical (ICU)	140 mg/dL*	180 mg/dL	Not applicable
Noncritical	110-140 mg/dL	180 mg/dL	Not applicable
Pregnancy	100 mg/dL	120 mg/dL	100 mg/dL

* The healthcare provider may aim for tighter control in select cases, but glucose levels under 100 mg/dL are rarely needed.

Source: American Diabetes Association and American Association of Clinical Endocrinologists.

sodium chloride solution for a final insulin infusion concentration of one unit of insulin per milliliter. Other rapid-acting insulins, lispro (Humalog) and glulisine (Apidra), aren't yet approved by the FDA for in-hospital insulin infusions. However, they may be used for intermittent subcutaneous therapy.

Before starting the infusion, flush the I.V. tubing with 30 to 50 mL of insulin infusion (depending on the length of the tubing) to saturate insulin-binding sites within the tubing. Be aware of "dead space" in central venous access devices that may delay actual insulin infusion into the bloodstream. Whether or not to give the patient an initial I.V. insulin bolus is determined by the patient's initial blood glucose reading. Bolus dose recommendations vary within institutions and among protocols.

The Yale Insulin Infusion Protocol, one of many published protocols, recommends giving an insulin bolus if the patient's initial blood glucose is 150 mg/dL or more.¹⁰ (This target may change as research continues.)

Other insulin protocols determine infusion rates based on the patient's weight. Expect higher infusion rates in patients undergoing cardiac surgery or receiving high-dose steroids, and in those with significant preexisting insulin resistance.

Along with an insulin infusion, patients with hyperglycemia will need a tandem I.V. infusion, preferably of 5% dextrose and 0.45% sodium chloride solution or 0.9% sodium chloride solution at a rate commensurate with their fluid needs. This allows another infusion site through which to deliver extra fluid volume or infuse other I.V. medications. In patients with type 1 diabetes, the tandem I.V. must be a dextrose solution because these patients are particularly prone to hypoglycemia.

Most patients receiving an insulin infusion also require potassium administered via the tandem infusion. Insulin drives potassium into cells, especially into muscle and liver cells, dramatically reducing serum potassium levels.

Does your patient need an I.V. insulin infusion?

Here are some common indications for I.V. insulin infusions:

- diabetic ketoacidosis and hyperglycemic hyperosmolar state
- critical illness or injury
- myocardial infarction, cardiogenic shock, and stroke
- postoperative cardiac surgical care
- general perioperative care, intra-abdominal surgery, and organ transplantation
- prolonged N.P.O. status in patients with type 1 diabetes
- parenteral nutrition
- hyperglycemia during high-dose corticosteroid therapy
- labor and delivery
- to help determine a patient's total daily insulin requirements before initiation of an outpatient subcutaneous insulin regimen.

Source: Clement S, Braithwaite SS, Magee MF, et al.; American Diabetes Association. Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27(2):553-591.

Monitor serum potassium levels regularly.

Monitoring parameters

Hourly blood glucose checks and infusion rate readjustments are labor-intensive, but a well-written insulin infusion protocol can help you achieve patient-glucose goals and minimize the risk of hypoglycemia. Infusion rates should be increased, decreased, or stopped temporarily based on blood glucose readings and the prescribed algorithm.

Hourly blood glucose monitoring is recommended until three consecutive glucose values are in the target range. If changes aren't expected in hemodynamic parameters or glucose-altering therapies, such as use of vasopressors, steroids, and nutritional support, you can reduce blood glucose checks to every 2 hours. If glucose levels remain at target for 6 consecutive hours, decrease blood glucose monitoring to every 4 hours.

Obtaining accurate glucose measurements is essential for safe insulin therapy. Use caution when interpreting results of point-of-care (POC) glucose meters. Discrepancies can be found among capillary, venous, and arterial blood, with arterial glucose values approximately 5 mg/dL higher than capillary samples and 10 mg/dL higher than venous samples.⁵

Finger-stick measurements are adequate for most noncritically ill patients. For critically ill patients, you may need to obtain a blood sample from an

indwelling vascular catheter despite the associated increased risk of infection. If your POC glucose measurement doesn't correlate with the patient's clinical status, send a blood sample for lab analysis.

IMPORTANT POINT: **Finger-stick blood glucose values may be inaccurate in patients on vasopressors and in those who are edematous or in shock. False high values are found in the presence of low hematocrits, high bilirubin, and severe lipemia. False low values are found with high hematocrit and hypoxic states. Avoid finger-stick testing in critically ill patients with these conditions.**

Immediately stop the insulin infusion if the patient's blood glucose is less than 70 mg/dL. If the patient is symptomatic or has a blood glucose below 50 mg/dL, give an ampule (25 grams) of 50% dextrose as ordered and recheck blood glucose levels every 15 minutes. In some acute care settings, glucagon may be administered I.M. or subcutaneously.

Patients with hypoglycemia who aren't symptomatic and whose blood glucose level is over 50 mg/dL may be treated with 12.5 grams of 50% dextrose or, if they're not N.P.O., 4 to 6 ounces of orange or grape juice (120 to 175 mL). Once blood glucose rises above 90 mg/dL, the insulin infusion may be restarted but at 50% to 75% of the previous rate. Notify the prescribing healthcare provider of any hypoglycemic episode and document it in the medical record.

Stopping the insulin infusion

Once the patient's blood glucose level remains stable for 12 to 24 hours, the insulin infusion may be discontinued. Stopping the infusion doesn't mean the end of insulin therapy; however, the patient may need ongoing therapy with subcutaneous basal (intermediate or long-acting) insulin and bolus (short-acting) insulin.

Basal insulin therapy controls glucose the patient continually produces via hepatic gluconeogenesis. Bolus doses correct blood glucose surges and cover food intake. Bolus insulin choices include regular, aspart, lispro, and glulisine.

Basal insulin is given once or twice a day in doses sufficient to control blood glucose between meals, overnight, and in the fasting state. Basal insulin (glargine, detemir, or NPH) is required if the patient has needed more than 0.5 units/hour to maintain target blood glucose or if the patient has type 1 diabetes.^{3,11}

IMPORTANT POINT: Patients with type 1 diabetes must receive basal insulin in addition to bolus insulin doses to reduce the risk of ketoacidosis.

The dose for both basal and bolus insulin can be determined by the amount of insulin infused over the previous 6 to 24 hours. Eighty percent of the calculated 24-hour insulin infusion

dose may be given subcutaneously in a split basal-to-bolus ratio of 50:50 or 60:40. Most patients with type 2 diabetes need a higher percentage of basal insulin.^{3,12}

You must give a subcutaneous rapid-acting insulin 30 to 60 minutes before stopping the infusion. Otherwise, blood glucose levels will rise quickly. This can put the patient with type 1 diabetes at enormous risk for ketoacidosis and death, because infused insulin is cleared from the body in as little as 5 minutes. Basal insulin (glargine or detemir) is often given approximately 3 hours before the infusion is discontinued because their onset of action is slower.¹² See *Insulin action: A matter of timing*.

During subcutaneous insulin therapy, check blood glucose before meals and at 3 a.m. You may want to perform a random blood glucose check 2 hours after the patient eats to help you determine if your meal insulin bolus was adequate to keep the blood glucose below 180 mg/dL. For patients who are N.P.O. or on continuous enteral feedings, check glucose levels every 4 to 6 hours.⁸

Glargine (Lantus) is longer-acting than other basal insulin, has no pronounced peak (so it's less likely to cause hypoglycemia), and can be administered once per day. This makes it particularly attractive for hospital use as basal insulin.

When giving bolus insulin with meals, it's best to deliver the bolus immediately after the patient has eaten. That way, the dose can be based on the amount of food actually consumed. Often one unit of rapid-acting insulin per 10 to 15 grams of carbohydrates is given right after the meal, along with a dose to correct a high premeal (preprandial) blood glucose level. The correction dose is determined by the patient's insulin sensitivity and current blood glucose level.³

Insulin sensitivity refers to how much blood glucose levels fall per unit of insulin given. You can calculate insulin sensitivity by adding up the patient's total daily insulin requirement and dividing that amount into 1,500 (for type 2 diabetes) or 1,700 (for type 1 diabetes). If a patient with type 2 diabetes requires a total of 50 units of insulin in a day, then that patient has an insulin sensitivity of 30. Thus, one unit can be expected to drop blood glucose approximately 30 points.^{1,3}

Patients on continuous enteral feedings are best managed with basal insulin (glargine once a day, detemir [Levemir] every 12 hours, or NPH every 8 hours) based on the amount of carbohydrates in their feedings. Bolus insulin is given to correct any hyperglycemia found during the regular glucose monitoring. If the enteral feeding is stopped suddenly, you must check blood glucose hourly to detect any resulting hypoglycemia.^{3,8}

IMPORTANT POINT: Patients are at great risk for hyperglycemia and hypoglycemia when they're transferred from CCUs to medical-surgical or step-down units. Communication is essential.

Oral hypoglycemic agents have no place in the CCU. When the patient transfers to a medical-surgical unit or is preparing for discharge, the health-care provider will determine when to resume use of oral hypoglycemic medications, alone or in combination with insulin.

In patients who have serious comorbidities or who are terminally ill, a less stringent glucose target may be preferred, with diabetes medication

Insulin action: A matter of timing

Type	Onset	Peak	Duration
Rapid acting (bolus)			
Aspart (NovoLog)	10-20 min	1-2 h	3-5 h
Glulisine (Apidra)	10-15 min	30-90 min	<3 h
Lispro (Humalog)	<15 min	30-90 min	<5 h
Short acting (bolus)			
Regular (Humulin R)	40-60 min	2-3 h	4-6 h
Regular (Novolin R)	30 min	2-5 h	8 h
Intermediate (basal)			
NPH (Humulin N)	2-4 h	4-10 h	14-18 h
NPH (Novolin N)	90 min	4-12 h	up to 24 h
Long, "peakless" (basal)			
Detemir (Levemir)	2-4 h	minimal	13-20+ h
Glargine (Lantus)	3-5 h	minimal	22-26 h

adjusted accordingly. Be sure to clarify target glucose levels when your patient's status has changed or the patient is being prepared for discharge.

A sweet ending

Emerging technology may ease the burden of maintaining safe glycemic control. Computer programs are now available that assist in making insulin infusion titrations based on metabolic parameters. In the future, continuous glucose monitors in the hospital will provide real-time monitoring of glucose levels and reduce need for an hourly blood draw.¹³ Patients who use an insulin pump in the outpatient setting may be able to continue using their pump during their hospital stay as long as they're mentally and physically able to do so.⁸

For now, the use of a flexible insulin infusion protocol can help the patient attain safe glucose targets. With knowledge and vigilance, we can keep our sweetest patients from going sour. ✧

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RESOURCES

- American Association of Clinical Endocrinologists. <http://www.aace.com>.
- American Diabetes Association. <http://www.diabetes.com>.

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