In Brief

Clinical studies have shown that maintaining normal blood glucose (BG) levels improves clinical outcomes in critically ill patients. However, achieving glycemic control in the hospital is difficult because it requires intensive nursing efforts, including frequent BG monitoring and complex intravenous insulin infusion protocols (IIPs). This article describes the successful implementation of a nurse-driven IIP that safely and effectively controls BG levels in critically ill patients. The authors then review some of the practical lessons they learned during this process, focusing on key issues that affect the ability of physicians and nurses to successfully implement such an IIP.

Selling Root Canals: Lessons Learned From Implementing a Hospital Insulin Infusion Protocol

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Strictly defined as blood glucose (BG) ≥ 126 mg/dl, hyperglycemia occurs in the majority of critically ill patients.[1,2] For decades, hyperglycemia has been associated with poor outcomes in a wide variety of clinical settings. Following acute myocardial infarction,[3,4] stroke,[5,6] cardiac surgery,[7] and admission to the intensive care unit (ICU),[8] hyperglycemia has been associated with excess morbidity and mortality. In one community hospital study,[9] hyperglycemia in previously nondiabetic patients predicted a ninefold increased risk for in-hospital mortality (16.0 vs. 1.7%). Moreover, once these hyperglycemic patients required admission to an ICU, their mortality rates skyrocketed to nearly one in three.

Several mechanisms have been proposed in an attempt to define *causal* relationships between hyperglycemia and adverse clinical outcomes. In addition to precipitating osmotic diuresis, reducing cardiac output, and impairing tissue perfusion,[10] hyperglycemia also impairs the body's normal responses to stress and infection. For example, high circulating glucose levels lead to nonenzymatic glycosylation of immunoglobulins and complement, dampening the immune re-sponse.[11,12] Hyperglycemia has also been directly implicated in leukocyte function abnormalities, including defective chemotaxis,[13] cell adherence,[14] and phagocytosis.[15] Aside from high BG levels, insulin therapy itself seems to exert a number of convergent anti-inflammatory effects at both the cellular and molecular levels.[16,17]

Evidence Favoring Strict Glycemic Control in the Hospital Setting

In the 1990s, large, randomized, controlled trials demonstrated the value of controlling chronic hyperglycemia in *outpatients* with diabetes.[18,19] However, until recently, there were few published data regarding the impact of glycemic control on *short-term* clinical outcomes in the hospital setting. In the mid-1990s, Malmberg et al.[20,21] reported that inpatient use of an intravenous (IV) insulin-glucose infusion, followed by intensive outpatient glycemic control, reduced mortality following acute myocardial infarction in diabetic patients. Subsequently, in diabetic patients undergoing cardiac surgery, Furnary et al.[22–24] demonstrated reductions in both deep sternal wound infections and overall mortality following their introduction of an evolving insulin infusion protocol (IIP). In 2004, Grey and Pedrizet[25] also reported that strict glycemic control reduced the incidence of nosocomial infections in their surgical ICU.

In November 2001, publication of what has become known as "the Leuven study" in the *New England*

Journal of Medicine[2] dramatically altered the landscape of inpatient glucose management. In this landmark article from Leuven, Belgium, Van den Berghe et al.[2,26] presented results from a large, prospective, randomized controlled trial of intensive insulin therapy in ICU patients, reporting a dramatic 42% reduction in ICU mortality. This study, targeting an aggressive BG target of 80–110 mg/dl, also reduced patients' needs for antibiotics, red blood cell transfusions, renal replacement therapy, and prolonged ventilatory support, and it significantly lowered the incidence of critical illness polyneuropathy. Based largely on the Leuven study, on a subsequent consensus statement from the American College of Endocrinology,[27] and on a recent technical review from the American Diabetes Association,[28] there has recently been a dramatic national shift in emphasis toward improving glycemic control in the hospital setting.

Yale IIP: Implementation

In early 2002, at the Yale-New Haven Hospital, we sought to standardize and improve glycemic control for our critically ill patients. Although effective IIPs had been previously published,[2,20,22,23,29–31] we felt that existing IIPs were disadvantaged either by overly conservative BG targets or by providing only "guidelines" for insulin management without truly automating IV insulin therapy. In clinical practice, we found that these IIPs required constant physician supervision, limiting their practical utility.

We therefore designed our own IIP, incorporating the three elements used by experienced endocrinologists to guide IV insulin therapy: *1*) the current BG level, *2*) the "velocity" of glycemic change, and *3*) the current insulin infusion rate. The protocol is shown in Figure 1. Our specific goal was to create a protocol that could be safely and effectively implemented by an ICU nursing staff with minimal need for ongoing physician supervision. In October 2002, following a series of 45-minute nursing inservice training sessions, we implemented the Yale IIP in our hospital's medical ICU (MICU). The details of the protocol's implementation have been previously published.[32]

To summarize our initial findings, the Yale IIP was employed 69 times in 52 MICU patients, 56% of whom had pre-existing diabetes. Despite frequent use of therapies known to worsen hyperglycemia,[33] including enteral nutrition (65% of patients), corticosteroids (52%), and vasopressors (25%), the IIP performed admirably. From a mean BG (± SD) level of 299 ± 96 mg/dl at insulin drip initiation, target BG levels (100–139 mg/dl) were reached within an average of 9 hours. As shown in Figure 2, BG levels then remained extremely stable. Once glucose levels fell within the target range, 66% of subsequent hourly BG values fell within a clinically desirable range of 80–139 mg/dl. Of 5,808 recorded hourly BG readings, only 20 (0.3%) fell below 60 mg/dl, with no clinically significant adverse events. The Yale IIP performed equally well in diabetic and nondiabetic patients and represented a significant improvement from the glycemic control observed in our ICU's historical controls.

To confirm the generalizability of the Yale IIP, we also documented its use in two cardiothoracic ICUs (CTICUs), one at the Yale-New Haven Hospital and the other in a nearby community teaching hospital, the Hospital of Saint Raphael.[34] Glycemic control in the two CTICUs was slightly superior to that observed in our MICU, with 73% of hourly BG values falling in a clinically desirable range of 80–139 mg/dl. As in the MICU, the IIP performed equally well in diabetic and nondiabetic patients. Notably, the protocol performed just as well in the community teaching hospital as in our academic tertiary care center.

Based on this experience, we have concluded that the Yale IIP is safe and effective in achieving glycemic control in ICU patients in a variety of clinical and hospital settings, regardless of patients' prior diabetes status. The IIP produces only rare and clinically insignificant episodes of hypoglycemia and can be easily implemented by an ICU nursing staff with minimal requirements for ongoing physician input.

Breaking Down Barriers to IIP Implementation

Largely because of the extra workload created by IIPs, convincing clinicians and nurses to employ these tools is not a simple task. While implementing our IIP at the Yale-New Haven Hospital, we learned some important practical lessons, which we believe will be helpful to other hospitals seeking to implement protocols for intensive glycemic control. Below, we present five of the most important lessons from a physician's point of view:

1. Educate your nursing allies.
2. Recruit and educate clinician allies in each unit.
3. Dispel the myths of hypoglycemia.
4. Encourage forethought and troubleshooting.
5. Don't forget to answer the ever-present question, "Now what?"

1. Educate your nursing allies.

From the very beginning, it is essential to recruit ICU nurses as *allies* against hyperglycemia, as opposed to "forcing" them to conform with a new hospital "policy." An IIP significantly increases the nursing workload. Openly acknowledging this fact is an important part of forming a functional physician-nurse alliance.

At our hospital, we found that once our nurses understood the purpose and potential benefits of the IIP, they were eager to use it (and in many cases sought to expedite its use), despite the extra work it created. During our 45-minute nursing inservice trainings, we spent half of each session simply justifying use of the IIP, by presenting specific results from the Leuven study and other key studies demonstrating the value of inpatient glycemic control. In oral and written feedback following these inservices, our nurses responded very favorably to this approach. Specifically, many of the nurses reported that they never really understood why hyperglycemia mattered. This lack of exposure was clearly a primary reason for our nurses' initial resistance to implementing an IIP.

In addition to educating the nurses, it is important to anticipate and plan for the three most common practical complaints offered by ICU nurses when implementing the IIP. These complaints sound something like the following:

- *"With all of the patients on insulin drips, I can never find the glucose meter. I probably spend an hour each day just looking for the $/*)&#! glucose meter."*
- *"By the time I find the glucose meter, check the blood sugar, document it, and adjust the insulin drip, I've already lost 10 minutes out of every hour. My patients are too sick; I just can't afford that kind of time commitment."*
- *"After 2 or 3 days on the insulin drip, my patients' fingers look like hamburger meat."*

The following insulin drip protocol is intended for use in hyperglycemic adult patients in an ICU setting, but is not specifically tailored for those individuals with diabetic emergencies, such as diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar states (HHS). When these diagnoses are being considered, or if BG≥ 500 mg/dL, an MD should be consulted for specific orders. Also, please notify an MD if the response to the insulin drip is unusual/unexpected, or if any situation arises that is not adequately addressed by these guidelines.

INITIATING AN INSULIN DRIP

1) INSULIN INFUSION: Mix 1 U Regular Human Insulin per 1 cc 0.9 % NaCl. Administer via infusion pump (in increments of 0.5 U/hr).
2) PRIMING: Flush 50 cc of Insulin/NS drip through all IV tubing, before infusion begins (to saturate the insulin binding sites in the tubing)
3) TARGET BLOOD GLUCOSE (BG) LEVELS: **100-139 mg/dL**
4) BOLUS & INITIAL INSULIN DRIP RATE: Divide initial BG level(mg/dL) by 100, then round to nearest 0.5 U for bolus AND initial drip rate
   Examples: 1) Initial BG = 325 mg/dL: 325 ÷ 100 = 3.25, rounded ↑ to 3.5: IV bolus 3.5 U + start drip @ 3.5 U/hr.
   2) Initial BG = 174 mg/dL: 174 ÷ 100 = 1.74, rounded ↓ to 1.5: IV bolus 1.5 U + start drip @ 1.5 U/hr.

FINGERSTICK (FS) BLOOD GLUCOSE MONITORING

1) Check FS hourly until stable (= 3 consecutive values in target range)
2) Then check FS q 2 hours; once stable x 12-24 hours, FS checks can be spaced to q 4 hours if:
   a) No significant change in clinical condition AND b) No significant change in nutritional intake
3) If ANY of the following occur, consider the temporary resumption of hourly FS monitoring, until BG is again stable (= 2-3 consecutive BG values in target range).
   a) Any change in insulin drip rate (i.e. BG out of target range)
   b) Significant changes in clinical condition
   c) Initiation or cessation of pressor therapy
   d) Initiation or cessation of renal replacement therapy (hemodialysis, CVVH, etc.)
   e) Initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, etc.)

CHANGING THE INSULIN DRIP RATE

If BG < 50 mg/dL:
D/C INSULIN DRIP — **Give 1 Amp (25 g) D50 IV; recheck BG q 15 minutes**
⇒ When BG ≥ 100 mg/dL, wait 1 hour, then restart insulin drip at 50% of original rate

If BG 50-74 mg/dL:
D/C INSULIN DRIP — **If symptomatic (or unable to assess), give 1 Amp (25 g) D50 IV; recheck BG q 15 minutes**
If asymptomatic, give 1/2 Amp (12.5 g) D50 IV or 8 ounces Juice; recheck BG q 15-30 minutes
⇒ When BG ≥ 100 mg/dL, wait 1 hour , then restart drip at 75% of original rate

If BG ≥ 75 mg/dL:
STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL

STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for INSTRUCTIONS:
[Note: If the last BG was measured 2-4 hrs before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL and the BG at 4PM is now 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is –30 mg/dL ÷ 2 hours = -15 mg/dL/hr.]

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS*
		BG ↑ by > 50 mg/dL/hr	BG ↑	↑ DRIP by "2Δ"
	BG ↑ by > 25 mg/dL/hr	BG ↑ by 1-50 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	↑ DRIP by "Δ"
BG ↑	BG ↑ by 1-25 mg/dL/hr, BG UNCHANGED, *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 1-50 mg/dL/hr	BG ↓ by 26-75 mg/dL/hr	NO DRIP CHANGE
BG UNCHANGED *OR* BG ↓ by 1-25 mg/dL/hr	BG ↓ by 26-50 mg/dL/hr	BG ↓ by 51-75 mg/dL/hr	BG ↓ by 76-100 mg/dL/hr	↓ DRIP by "Δ"
BG ↓ by > 25 mg/dL/hr *see below***	BG ↓ by > 50 mg/dL/hr	BG ↓ by > 75 mg/dL/hr	BG ↓ by > 100 mg/dL/hr	HOLD DRIP x 30 min, then ↓ DRIP by "2Δ"

**D/C INSULIN DRIP; √BG q 30 min; when BG ≥ 100 mg/dl, restart drip @75% of original

***CHANGES IN DRIP RATE ("Δ") are determined by the current drip rate:**

Current Drip Rate (U/hr)	Δ = Rate Change (U/hr)	2Δ = 2X Rate Change (U/hr)
< 3.0	0.5	1
3.0 - 6.0	1	2
6.5 - 9.5	1.5	3
10 - 14.5	2	4
15 - 19.5	3	6
20 - 24.5	4	8
≥ 25	≥ 5	10 *(Consult MD)*

Figure 1. Yale IIP (Reprinted with permission from Ref. 32)

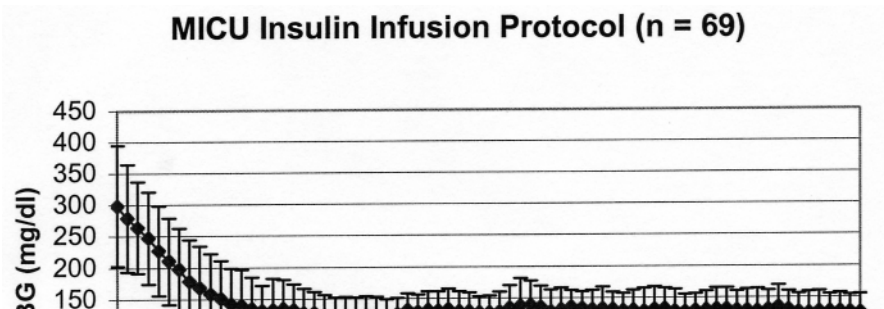

Figure 2. Performance of the Yale IIP in the MICU (data points represent the first 72 hours of insulin infusion). All BG levels shown as the means ± SD.

Solutions to these problems are readily available. The nursing workload can be lessened significantly through the purchase of additional glucose meters; newer devices yielding rapid results are preferred. Recruiting nurses' aides to share in the burden of frequent BG monitoring is also recommended. Additionally, since arterial, venous, and capillary glucose levels usually differ by < 10%, alternate sources of blood, such as central venous catheters and arterial lines, may sometimes be employed for hourly sampling. At our institution, we simply recommend standardizing the source of blood—in other words, using a single source of blood for a given nursing shift—to avoid systematic errors in glucose measurement. Of course, frequent accessing of indwelling catheters may increase the risk for infection.

At Yale-New Haven Hospital, once these important nursing issues were addressed, the ICU nurses rated our IIP quite highly. In the MICU, 73% of the nurses rated the IIP as either "very easy" or "somewhat easy" to use, 86% rated it as either "very effective" or "somewhat effective," and 75% felt that the IIP was "an overall improvement" compared with previously available, nonstandardized hospital insulin infusion orders.[32] Other Yale ICUs, including the CTICU and coronary care unit, have employed the IIP with equal success.

By empowering ICU nurses to manage BG levels, overall nursing time spent on glycemic control may actually be reduced. That is, IIPs dramatically reduce the need to page physicians (and to wait for physicians to return their pages) for specific insulin orders.

2. Recruit and educate clinician allies in each unit.

Recruiting and educating physician allies is equally important for successful IIP implementation. This is best accomplished by presenting the case for strict glycemic control at a critical care conference or at medical/surgical grand rounds. Critical care physicians, like ICU nurses, have traditionally placed little (if any) emphasis on strict glycemic control; in recent years, this climate has changed dramatically. Physicians should also understand that IIPs ultimately ease their workload by reducing the need for constant revision of insulin orders. Although the IIP is nurse-directed, physician reinforcement is essential for maintaining the protocol's nursing "momentum" in the ICUs. On-site physicians are obviously preferred for this role. However, occasional visits from the endocrinology department are extremely useful.

Additionally, physicians and/or hospital administrators should be intimately involved in quality control in the ICUs. Periodic review of glycemic control, as well as scheduled meetings with hospital and nursing administrators, serve to identify and correct problem areas, optimizing the effectiveness of the IIP intervention.

3. Dispel the myths of hypoglycemia.

In most hospital settings, hypoglycemia is a four-letter word. Unrealistic fears of this usually benign condition are rampant. Until recently, based largely on such unfounded fears, medical culture has accepted moderate hyperglycemia as "normal," resulting in an altered sense of what a normal glucose level actually is. When polled about blood glucose levels, many Yale nurses felt that BG levels (mg/dl) in the high 100s and low 200s were optimal because such levels minimized the risk of hypoglycemia while avoiding clinical symptoms. Double-digit BG levels, including normal values between 70 and 99 mg/dl, were viewed as "concerning" and were often treated with either oral carbohydrate intake or even IV dextrose infusions.

During our nursing inservices, when presented with our glycemic target of 100–139 mg/dl, many nurses immediately voiced their concerns about causing hypoglycemia in their patients. Many feared being "blamed" for hypoglycemia events. When informed that recent studies have actually suggested maintaining even lower BG levels of 80–110 mg/dl, most nurses immediately dismissed such targets as unreasonably dangerous. Surprisingly, when we polled these nurses about their own glucose levels, many volunteered numbers in the mid- or high 100s. Some nurses were genuinely surprised to learn that their own BG levels were actually well below 100 mg/dl. Thus, changing nurses' prevailing (but erroneous) definitions of hypoglycemia is a crucial and essential step toward successful implementation of an IIP.

From the physician or hospital administrator standpoint, hypoglycemia also represents an important liability issue because it represents an "act of commission" that may be challenging to defend in the courts.[35] Fortunately, we now have sufficient data to show that clinically significant hypoglycemia is rare when implementing IIPs. In the Leuven study, hypoglycemia occurred in only 5.1% of patients, with no clinically significant adverse events. The "Glucommander" protocol developed by Davidson et al.[36] in the 1980s, resulted in hypoglycemia in just 2.6% of cases.[29] Other published protocols[20,22,23,30,31] have reported less precisely about their rates of hypoglycemia, but none have reported clinically relevant sequelae. At our institution, among 52 MICU patients receiving the IIP, just 0.3% of glucose values fell below 60 mg/dl, and there were *no* clinically significant adverse events.[32] Hypoglycemia was just as rarely observed (0.2%) in our CTICU patients.[34]

In summary, hypoglycemia is uncommon during appropriate utilization of a published IIP, and clinically significant adverse events are very rarely observed.

4. Encourage forethought and troubleshooting.
While IIPs can essentially automate IV insulin infusions, a number of preexisting conditions predictably affect glycemic control. Nurses and clinicians alike must learn to recognize, anticipate, and react to these factors in order to minimize dangerous glycemic excursions. Table 1 lists some of the more important conditions that may predispose patients to hypoglycemia in the hospital.[35]

Ongoing clinical events also have predictable effects on glucose levels. Severity of illness can drastically affect insulin sensitivity. For example, sudden clinical decompensation releases endogenous stress hormones (e.g., cortisol, catecholamines), increasing the risk for hyperglycemia.[37] Alterations in nutrition, such as changes in enteral or parenteral nutrition or NPO (nothing by mouth) status, affect carbohydrate availability. Medication changes, including the initiation or discontinuation of corticosteroids or vasopressors,[33] can also predictably affect BG levels, as do changes in dialysis status.[35] Table 2 summarizes some of the common, clinically relevant changes in clinical status that deserve consideration when adjusting insulin infusions.

Patient excursions out of the ICU for diagnostic tests or procedures, affectionately known as "field trips," are another commonly encountered issue. Here, frequency of BG monitoring may be affected, and nutrition may be interrupted. At our hospital, we have developed some "tricks" for dealing with field trips, such as calculating ongoing enteral carbohydrate supply for conversion to IV dextrose. For example, consider a patient receiving enteral feeds (containing 30 g of carbohydrate per 240 ml can) at 80 ml/hour, representing 10 g/hour of carbohydrate intake. For a field trip during which enteral feedings are interrupted, one could substitute a D10 drip (10 g/dl) at 100 ml/hour to match the patient's ongoing carbohydrate supply. Because IV dextrose infusions result in slightly higher BG levels than enteral feeds containing equal amounts of carbohydrate, this represents a conservative, rational approach to field trip management.

Table 1. Conditions Predisposing Patients to Hypoglycemia in the Hospital

- Advanced age
- Malnutrition
- Gastrointestinal malabsorption
- Hypoglycemia unawareness
- Renal insufficiency
- Liver disease
- Alcoholism
- Sepsis/shock
- Burns
- Cerebrovascular accident
- Congestive heart failure
- Adrenal/pituitary insufficiency
- Pregnancy
- Polypharmacy (drug interactions)

It is important to recognize that each specific hospital or hospital unit possesses its own unique challenges and patient populations, which may require fine-tuning with regard to IIP implementation. Here, close collaboration with clinicians and nursing staff is key.

5. Answer the ever-present question, "Now what?"
When starting an IIP, one must also address the issue of *stopping* the IIP; that is, of converting IV insulin drips to subcutaneous (SQ) insulin regimens, often for the purpose of transferring patients from the ICU to the general ward. This issue is frequently cited by ICU nurses as a nuisance because it can delay a patient's discharge from the ICU. Two reasonable approaches to this problem have been previously published. Both have been successfully employed in our ICUs.

Employing the methods of Bode et al.,[29] 24-hour insulin requirements may be calculated by extrapolating the last 6–8 hourly rates of IV insulin infusion. Conservatively, 80% of this 24-hour insulin requirement can then be used to calculate a total daily dose of insulin. Then, 50% of the total daily dose can be given as long-acting (twice-daily NPH or once-daily glargine) insulin, while the other half can be given as prandial (rapid-acting) insulin analogs.

Table 2. Changes in Clinical Status That Affect BG Levels

- Change in clinical severity of illness
- Change in nutritional status: NPO, change in enteral or parenteral carbohydrate supply
- Change in medication status: glucocorticoids, vasopressors
- Change in dialysis status

An alternate method, advocated by Abern et al.,[38] suggests taking the latest hourly IV infusion rate, and then providing 8 times that rate as SQ NPH insulin, plus 4 times that rate as SQ regular insulin, with cessation of the IV insulin drip 1–2 hours later. For example, a patient receiving 3 units/hour of IV insulin would receive $3 \times 8 = 24$ units of NPH insulin, plus $3 \times 4 = 12$ units of regular insulin, followed by twice-daily titration of this twice-daily SQ insulin regimen.

To our knowledge, although these strategies are sound and have been used with clinical success, specific BG results associated with their use have not been rigorously reported.

Final Comments
In this article, we have reviewed our encouraging clinical experience with an intensive IIP at the Yale-New Haven Hospital. We have then summarized the lessons we learned while implementing the protocol, emphasizing the key points required to facilitate successful IIP implementation. It is our hope that this work will assist others in fighting the battle against hyperglycemia in the hospital, contributing to improved clinical outcomes for all hospitalized patients.

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