Insulin Therapy for Intensive Glycemic Control in Hospital Patients

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Hyperglycemia and diabetes are commonly observed in patients admitted to the hospital. An estimated 13 million Americans have a known diagnosis of diabetes, with type 2 diabetes accounting for 90% to 95% of all diagnosed cases. An additional 5.2 million Americans have diabetes but are unaware of their condition.[1] The rising prevalence of diabetes is leading to an increasing number of hospital admissions for the management of cardiovascular disease, stroke, and other conditions in which diabetes is an underlying comorbidity and diagnosis.[1–4] In addition, persons admitted to the hospital may have unrecognized diabetes or present with illness-related hyperglycemia.[4] Up to 12% of all patients admitted to hospitals have hyperglycemia but no history of diabetes prior to admission.[5] A prospective study of 1034 consecutively hospitalized patients found that 37.5% of all hyperglycemic medical patients (n = 66) and 33% of all hyperglycemic surgical patients (n = 48) were admitted without a formal diagnosis of diabetes.[6] Diabetes remained undiagnosed throughout the hospital stay in 93% of these cases, despite mean peak blood glucose levels of 299 mg/dL and documentation of more than 1 elevated blood glucose level in two thirds of patients. Overall, up to 60% of patients who are hospitalized with blood glucose levels greater than 125 mg/dL are subsequently found to have diabetes upon further testing.[7]

Failure to recognize and address hyperglycemia in hospital patients has been shown to adversely affect patient outcomes, including increasing morbidity and mortality and prolonging hospital stays. To achieve optimal outcomes, physicians must have a clear understanding of the causes, implications, and strategies for managing hyperglycemia in the hospital. Specifically, targeted blood glucose control increasingly is being recognized as a crucial component of management in the hospital setting. This article discusses outcomes data that support more aggressive approaches to blood glucose control in hospital patients and reviews recommendations from national guidelines that address intensive treatment of hyperglycemia and diabetes in the hospital.[4]

TAKE HOME POINTS

- Hyperglycemia is clearly associated with increased mortality and morbidity in hospital patients; insulin therapy to control blood glucose to target levels has been shown to improve clinical outcomes, including mortality and morbidity.
- Target blood glucose levels in the hospital are ≤ 110 mg/dL in the intensive care unit and ≤ 180 mg/dL in non–critical care units.
- Insulin requirements in illness are typically higher than in health, even when the patient is not eating.
- Insulin is recommended for treatment of hyperglycemia in the hospital.
- Components of the physiologic insulin regimen for the hospital patient are basal insulin, nutritional insulin, and correction-dose insulin.
- Avoid use of sliding-scale insulin alone, as it is associated with increased rates of hypoglycemia and hyperglycemia.

CAUSES OF HYPERGLYCEMIA IN HOSPITAL PATIENTS

Hyperglycemia that is observed upon or during hospitalization does not necessarily indicate the presence of diabetes.[4] Acute stress or injury, such as a myocardial infarction, stroke, trauma, or surgery, may cause elevations in counter-regulatory hormones (ie, glucagon, catecholamines, glucocorticoids, growth hormone), cytokines, and other inflammatory mediators, which leads to enhanced hepatic glucose production, lipolysis, proteolysis, and accelerated muscle catabolism.[4,8,9] These metabolic changes, in turn, can elevate blood glucose, free fatty acids, ketones, and lactate. Impairment of insulin secretion may also occur in response to

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glucose toxicity, further compounding the tendency for hyperglycemia to occur.

Hyperglycemia that occurs during hospitalization also may be iatrogenic. Glucocorticoids are well known to affect carbohydrate metabolism, causing hyperglycemia of varying degrees of severity.[4,10] Glucocorticoids induce increases in plasma glucose through a number of mechanisms, including enhanced hepatic glucose production, enhanced glycogenolysis, impaired cellular glucose uptake, and induction of insulin resistance.[4,10,11] Other commonly prescribed medications that can cause hyperglycemia include vasopressors, thiazide diuretics, calcium channel blockers, β-blockers, protease inhibitors, thyroid hormones, cyclosporine, phenytoin, and niacin.[4,10,12]

Enteral and total parenteral nutrition (TPN) supplements also contribute to hyperglycemia in the hospitalized patient.[9,13] Hyperglycemia in patients given enteral nutrition is commonly due to the high levels of carbohydrates contained in these formulas, which generally account for 45% to 92% of their calories.[9] Hospital patients given TPN have been shown to experience critical hyperglycemia (blood glucose > 400 mg/dL) at rates more than 2-fold higher than patients who do not receive TPN.[13] The degree of hyperglycemia associated with TPN appears to vary based on patient age, severity of illness, and the rate of dextrose infusion.[4,13–15] Aging exaggerates the blood glucose increases that accompany TPN. Glucose levels during TPN also have been shown to increase in concordance with severity of illness across a variety of medical and surgical conditions.[13,15] There is some evidence that limiting dextrose infusion rates to below 5.0 mg/kg per minute and providing patients with daily lipid infusions to meet estimated caloric needs may reduce the incidence of hyperglycemia associated with TPN.[14]

HYPERGLYCEMIA AND POOR CLINICAL OUTCOMES

An association between hyperglycemia and increased mortality and morbidity in hospital patients is supported by a large body of observational data. A recent study investigating the relationship between hyperglycemia and outcomes in medical and surgical patients admitted to a community teaching hospital found that patients with no prior history of diabetes and admission or in-hospital hyperglycemia (fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL) had a significantly higher rate of in-hospital mortality (16%) than patients who were normoglycemic (mean blood glucose, 108 mg/dL; 1.7%).[5] Patients with in-hospital hyperglycemia also had increased length of hospital stay, higher admission rates to intensive care units (ICUs), and a greater likelihood of discharge to an extended care facility.

Observational studies in acute myocardial infarction (AMI) have revealed that hyperglycemia is associated with an increased risk of in-hospital mortality and poor cardiovascular outcomes (eg, congestive heart failure, cardiogenic shock).[5,16,17] Hyperglycemia during the immediate postoperative period following cardiac surgery is known to increase risk for deep sternal wound infection in patients undergoing cardiac surgery. These infections, in turn, result in increased mortality, length of stay, number of trips to the operating room, and cost of hospitalization.[4,18,19] Furthermore, several recent observational studies of acute stroke patients have demonstrated that hyperglycemia is associated with increased mortality as well as increased infarct size, poor functional recovery, longer hospital stay, and higher inpatient costs.[8,20,21]

BENEFITS OF TARGETED BLOOD GLUCOSE CONTROL

A small but growing number of prospective clinical trials provide evidence that intensive targeted blood glucose control using insulin therapy in the hospital improves clinical and health care economic outcomes. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study[22,23] was a prospective, randomized controlled trial that investigated the impact of intensive insulin therapy (IIT) on patient mortality in 620 patients with diabetes and AMI.[22] Patients were randomized to receive either intensive treatment with an intravenous (IV) insulin infusion followed by multidose subcutaneous (SC) insulin therapy for at least 3 additional months (n = 306), or conventional treatment with insulin given only if clinically indicated (n = 314). During the first 24 hours following treatment, blood glucose levels decreased from 277.2 mg/dL to 172.8 mg/dL in the IIT group and from 282.6 mg/dL to 210.6 mg/dL in the conventional treatment group ($P < 0.0001$).[22] The 1-year mortality rate in the IIT group was reduced by 29% compared with the conventional treatment group (18.6% versus 26.1%; $P = 0.027$). This effect persisted after 3.4 years of follow-up (33% versus 44%; $P = 0.011$; **Figure 1**) and was most pronounced among patients who had not received prior insulin treatment and those at lower risk for cardiovascular disease.[23]

A follow-up trial failed to replicate the key result of DIGAMI 1, namely that insulin-glucose infusion followed by insulin-based long-term glucose control reduces patient mortality following AMI.[24] It did confirm that glucose level is a strong independent predictor of mortality following AMI.[24] The study design of DIGAMI 2 may have contributed to the negative result, as neither

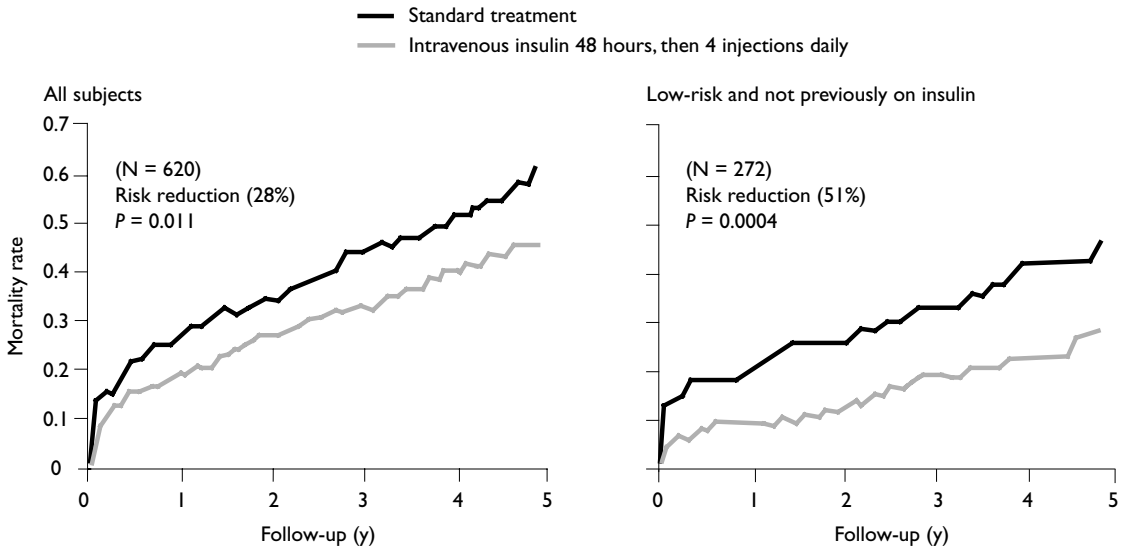

Figure 1. Mortality after acute myocardial infarction is reduced with intensive insulin therapy. (Adapted with permission from the BMJ Publishing Group. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI [Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction] Study Group. BMJ 1997;314:1512–5.)

tight blood glucose control nor a significant difference in blood glucose levels between intervention and control groups was attained.[25]

In a landmark prospective, randomized controlled trial, van den Berghe et al[26] investigated the impact of intensive targeted blood glucose control on clinical outcomes in 1548 critically ill adults admitted to a surgical ICU who were receiving mechanical ventilation. Among the patients admitted to the ICU, 63% had undergone cardiac surgery and 37% were admitted for noncardiac indications. These patients were randomized to receive either IIT targeting blood glucose to less than 110 mg/dL or conventional therapy targeting blood glucose to 180 to 200 mg/dL. Patients receiving conventional therapy were treated with IV insulin only if blood glucose levels exceeded 215 mg/dL. Mean blood glucose level was 103 mg/dL in the IIT group and 153 mg/dL in the conventional treatment group ($P < 0.001$). Mortality during ICU stay was 43% lower in the IIT group compared with the conventional treatment group (4.6% versus 8.0%; $P < 0.04$; **Figure 2A**). For each 20 mg/dL elevation in blood glucose over 100 mg/dL, the risk of death during ICU care increased by 30% ($P < 0.001$). Furthermore, IIT reduced rates of overall in-hospital mortality by 34% (**Figure 2B**). It also reduced in-hospital rates of bloodstream infections by 46% ($P < 0.003$), acute renal failure requiring dialysis or hemofiltration by 41% ($P < 0.007$), requirement for red cell transfusions by 50% ($P < 0.001$), and critical-illness polyneuropathy by 44% ($P < 0.003$). These findings demonstrate that substantial reductions in morbidity and mortality can be achieved in critically ill patients treated with IIT targeted to maintain blood glucose levels at or below 110 mg/dL.

Further emerging data appear to support the value of targeted blood glucose control in the ICU setting. Krinsley[27] evaluated a protocol for administration of IIT in adult patients admitted to a medical-surgical ICU. This study examined 800 consecutive admissions following institution of the protocol and 800 historic controls. The goal of intensive therapy was to maintain blood glucose below 140 mg/dL. Following initiation of IIT using an insulin drip when 2 consecutive blood glucose readings greater than 200 mg/dL were obtained, mean blood glucose levels were lowered from 152.3 mg/dL to 130.7 mg/dL ($P < 0.001$). Intensive control reduced the number of cases of new renal insufficiency by 75% ($P = 0.03$), the number of patients requiring packed red blood cell transfusions by 29.3% ($P = 0.002$), hospital mortality by 29% ($P = 0.002$), and ICU length of stay by 11% ($P = 0.01$). These data are consistent with those of the van den Berghe et al[26] study.

The only report of a prospective treat-to-target intervention in stroke patients is the Glucose Insulin in Stroke Trial (GIST).[28] This study examined the safety of glucose, insulin, and potassium (GIK) infusion in treating stroke patients to a target glucose of 72 to 126 mg/dL. Lowering plasma glucose with GIK infusion was not

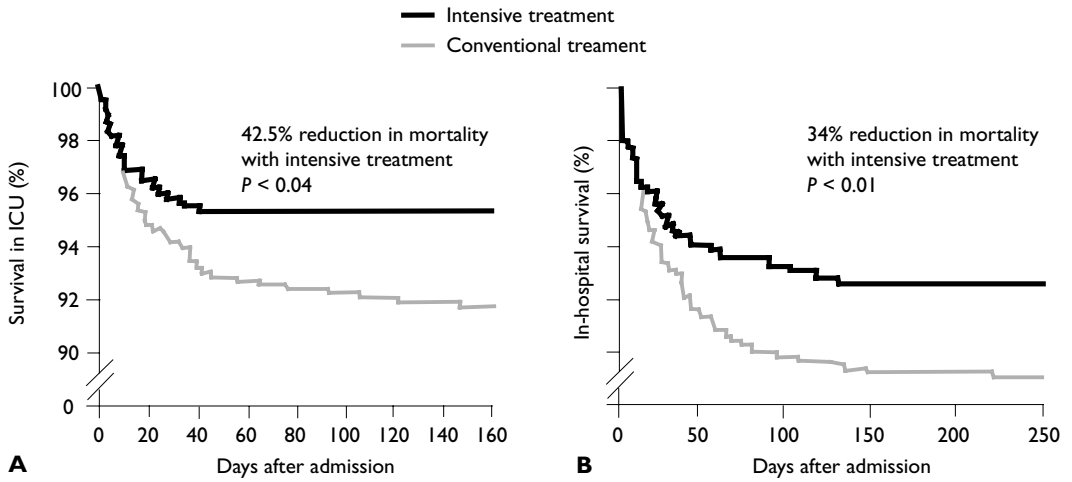

Figure 2. Cumulative survival for critically ill patients receiving intensive insulin treatment versus conventional treatment in patients discharged alive (**A**) from the intensive care unit (ICU) and (**B**) from the hospital. (Adapted with permission from van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67. Copyright © 2001 Massachusetts Medical Society.)

associated with significant risk of hypoglycemia or excess mortality in patients with acute stroke and mild-to-moderate hyperglycemia, opening the door for further studies in which targeted blood glucose control can be examined to determine impact on stroke outcomes.

The impact of intensive targeted blood glucose control on development of deep sternal wound infections and patient mortality has been explored in a prospective study of patients with diabetes who underwent open heart surgery between January 1987 and 1997.[18] Those who were operated on after August 1991 were treated with continuous IV insulin during the perioperative period, targeting maintenance blood glucose levels in the range of 150 to 200 mg/dL. Prior to this time, SC insulin was used to treat hyperglycemia.[18,19] Compared with SC insulin therapy, targeted IV insulin therapy decreased blood glucose levels for the first 2 days after surgery (177 ± 30 mg/dL versus 213 ± 41 mg/dL; $P <$ 0.001) and significantly reduced the incidence of deep sternal wound infections (1.5% versus 2.4%; $P < 0.02$).[19] Observed mortality was 2.5% (65/2612) in the IV insulin group versus 5.3% (50/942) in the SC group ($P <$ 0.001). A positive correlation between postoperative blood glucose levels and mortality was observed, with the lowest mortality rates seen among patients with levels below 150 mg/dL.[29] Furthermore, a recent analysis of data from this group found that despite the relative expense of insulin therapy, an overall cost savings was achieved.[30] Treatment with targeted IV insulin therapy in cardiac surgery patients was associated with an overall cost savings of $680 per patient, with most savings attributed to decreased costs for treatment of wound infections and shorter hospital stays.[30]

In summary, evidence from numerous observational studies demonstrates that hyperglycemia in hospital patients is associated with negative outcomes.[18,19,26,27] Furthermore, intensive targeted glucose control with insulin therapy has been shown in several landmark studies to reduce patient mortality and morbidity related to infection, septicemia, kidney failure, red blood cell transfusions, and polyneuropathy.[18,19,26,27] It has also been shown to lead to shorter ICU and hospital stays.[27,30] The DIGAMI and van den Berghe et al studies are considered to provide level A evidence in support of intensive glucose control in the management of hyperglycemia and diabetes in hospital patients.[4,22,23,26,31]

GLUCOSE TARGETS IN THE HOSPITAL

In 2003, in response to accumulating evidence for benefits of intensive targeted glucose control in the hospital, the American Diabetes Association (ADA) convened a Diabetes in Hospitals Writing Group and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) held a consensus conference on hyperglycemia in the hospital. The writing group prepared a technical review that provides a comprehensive overview of the topic, including rationale and strategies for management.[4] This review emphasizes that a key hurdle to aggressive management of diabetes in hospital patients is the tendency to consider hyperglycemia to be secondary in importance to conditions that prompt

admission. The AACE/ACE consensus conference was endorsed by physicians from national organizations representing a broad spectrum of specialists who are stakeholders in the hospital management of diabetes and was co-sponsored by the ADA. Following the consensus conference, AACE/ACE published a position statement on inpatient diabetes and metabolic control.[32]

Unlike previous expert guidelines on diabetes, the AACE/ACE guidelines and the ADA technical review focus on hospital management targets for diabetes during the inpatient stay, recommending target preprandial blood glucose levels below 110 mg/dL and target peak postprandial levels below 180 mg/dL for general medical and surgical patients in the hospital (**Table 1**).[4,32] Target blood glucose levels in the range of 80 to 110 mg/dL are recommended during ICU care.[32] Insulin is recommended as the treatment of choice for control of blood glucose levels in the acute care setting, regardless of diabetes therapy provided prior to admission.[4,32] The following sections review the recommendations from the ADA review.

ROUTES OF INSULIN ADMINISTRATION

Intravenous Therapy

IV insulin therapy is generally considered the treatment of choice for management of hyperglycemia and diabetes during preoperative, intraoperative, and postoperative care in patients with critical illness and/or severely decompensated diabetes, including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state; patients with organ transplantation, cardiogenic shock, and stroke; patients receiving high-dose glucocorticoids; patients during the postoperative period following heart surgery; and patients who are nothing by mouth (NPO) for prolonged periods of time.[4,33,34] Furthermore, studies presented earlier in this review have demonstrated that IV insulin infusion in the coronary and surgical ICUs reduces morbidity and in-hospital and long-term mortality.[18,23,26,29] Patients in these settings often have marked insulin resistance, rapidly changing insulin requirements, generalized edema, and other predisposing factors to impaired perfusion of SC sites, including hypotension and use of vasopressors and/or a need for treatment with enteral feedings. Because IV insulin infusion has a rapid onset of action and can be quickly adjusted or discontinued to minimize the risk of hypoglycemia, it is the preferred therapy for management of hyperglycemia in these settings.[4,33,34] IV insulin infusion is also favored as a dose-finding strategy prior to initiation of SC therapy and during initiation of TPN.[6,34,35]

Table 1. Blood Glucose Targets in the Hospital

Patients	Preprandial	Postprandial	Labor and Delivery
Critical (ICU)	110 mg/dL	110 mg/dL	N/A
Noncritical	110 mg/dL	180 mg/dL	N/A
Pregnancy	100 mg/dL	120 mg/dL*	100 mg/dL

ICU = intensive care unit. (Data from Garber AJ, Moghissi ES, Bransome ED Jr, et al. American College of Endocrinology position statement on inpatient diabetes and metabolic control. Endocr Pract 2004;10 Suppl 2:4–9.)

*1 hour postprandial.

Subcutaneous Therapy

Scheduled or programmed SC insulin therapy (basal and prandial/nutritional insulins) combined with SC correction-dose insulin may be used to achieve and maintain blood glucose goals in most hospitalized patients with diabetes outside of the intensive or critical care setting.[4,34–36] SC insulin therapy is also used as an alternative to IV insulin therapy in hospitals where the ability to use IV insulin therapy is limited. Practical guidelines from the ADA Diabetes in Hospitals Writing Group for the use of SC insulin therapy in hospitalized patients are shown in **Table 2**.[4]

No randomized controlled studies have been done looking at the best method for transitioning a patient from IV insulin therapy to SC insulin. In clinical practice, a fairly wide variety of rules of thumb are applied to calculate starting doses for SC insulin therapy when IV insulin is to be discontinued. While physiologic basal insulin requirement is generally stated to be 40% to 50% of total daily insulin, it is commonly higher in the hospital setting. SC basal insulin starting doses may be calculated based on the IV insulin drip rate, patient weight, and/or known prior SC insulin therapy doses. In addition to basal insulin, nutritional and correction-dose rapid-acting insulin must also be prescribed. There is great interest in developing algorithms for transitioning patients from IV to SC insulin.

PHYSIOLOGIC INSULIN REPLACEMENT WITH SUBCUTANEOUS THERAPY

Programmed Insulin Therapy

Physiologic insulin replacement attempts to mimic normal insulin secretion patterns and is used in the outpatient setting to meet an individual's basal and prandial insulin requirements. Because hospitalized patients may not be taking discrete meals, physiologic insulin dose requirements are referred to as *basal* and *nutritional* insulin needs in the hospital. Programmed or scheduled insulin

Table 2. ADA Practical Guidelines for Hospital Use of Subcutaneous Insulin

	Scheduled Insulin Option(s)			
Clinical Setting	**Basal**	**Prandial/Nutritional**	**Correction-Insulin Option(s)**	**Comments**
Eating meals	Int-I or LA-I	Reg-I or rapid-I before meals	Reg-I or rapid-I	Insulin drip is treatment of choice in severely decompensated type 1 diabetes, with or without DKA and in type 2 diabetes with hyperglycemic hyperosmolar state
Not eating	Int-I or LA-I	N/A	Reg-I or rapid-I	
Perioperative or periprocedural				
Will eat post-op or postprocedure	Int-I or LA-I glargine	When resumes eating, restart prior doses of reg-I or rapid-I	Until resumes eating, reg-I or rapid-I	Usual insulin doses given the night prior to surgery
Will not eat (ie, major surgery)	Reg-I, rapid-I, int-I, or LA-I	N/A	Until resumes eating, reg-I or rapid-I	Where a prolonged postoperative NPO period is anticipated (ie, cardiothoracic cases), insulin drip is recommended
ICU	If NPO and/or clinically unstable, reg-I or rapid-I If eating, continue int-I or LA-I	If NPO, N/A If eating, reg-I or rapid-I	Reg-I or rapid-I	Insulin drip is treatment of choice for decompensated diabetes in the ICU setting, including coronary care and surgical ICU
Enteral tube feeding				
Continuous	24 h: int-I or LA-I Daytime only: int-I	Reg-I or rapid-I During tube-feeding delivery period only: reg-I or rapid-I	Reg-I or rapid-I	Nutritional insulin requirements met with programmed doses of reg-I or rapid-I
Bolus	24 h: int-I or LA-I Daytime only: int-I	Reg-I or rapid-I During bolus delivery period only: reg-I or rapid-I	Reg-I or rapid-I	
TPN	N/A	N/A	Reg-I or rapid-I	Use SC insulin with caution with TPN
Transition to oral intake	Int-I or LA-I	Reg-I or rapid-I	Reg-I or rapid-I	Postprandial target blood glucose < 180 mg/dL
High-dose glucocorticoid therapy	Int-I or LA-I	Reg-I or rapid-I	Reg-I or rapid-I	High-dose glucocorticoids raise insulin requirements

ADA = American Diabetes Association; DKA = diabetic ketoacidosis; ICU = intensive care unit; Int-I = intermediate-acting insulin (neutral protamine Hagedorn or lente); LA-I = long-acting insulin (glargine or ultralente); NPO = nothing by mouth; rapid-I = rapid-acting insulin (lispro or aspart); reg-I = regular insulin. (Adapted with permission from Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals [published errata appear in Diabetes Care 2004;27:856 and 2004;27:1255]. American Diabetes Association Diabetes in Hospitals Writing Committee. Diabetes Care 2004;27:553–91. Copyright © 2004 American Diabetes Association.)

therapy, consisting of basal and prandial/nutritional insulin, supplemented with correction-dose insulin is generally preferable to administering sliding-scale insulin for controlling blood glucose levels.[4,36]

The term *basal insulin requirement* refers to exogenous insulin per unit of time necessary to prevent unchecked gluconeogenesis and ketogenesis. *Nutritional insulin requirements* tend to be broader than prandial insulin requirements. Nutritional requirements refer to insulin necessary to cover IV dextrose, TPN, enteral feedings, and/or discrete meals and must accommodate fluctuations in appetite and/or changes in feeding status that commonly accompany illness, hospitalization, surgery, and/or procedures.[4] Illness- or stress-related insulin requirements are often an additional consideration in hospitalized patients and refer to the amount of insulin needed to meet the insulin resistance that accompanies acute illness, surgery, and the use of drugs that elevate blood glucose levels.[4,35,36] The presence of additional nutritional and illness-related factors in hospital patients increases insulin requirements.

Correction- or supplemental-dose insulin is used to

treat hyperglycemia that occurs before or between meals in patients receiving scheduled insulin or to correct hyperglycemia in the NPO patient or the patient who is being treated with a scheduled insulin regimen and is not eating discrete meals (**Figure 3**). If correction-dose insulin is needed at bedtime, it should be administered at a reduced dose compared with other times of day to reduce risk of nocturnal hypoglycemia.[4]

Patients with insulin deficiency, such as those with type 1 diabetes, require basal insulin replacement at all times to prevent iatrogenic DKA. Other clinical features that tend to characterize patients with insulin deficiency include history of pancreatectomy or pancreatic dysfunction, wide fluctuations in blood glucose levels, DKA, and insulin use for more than 5 years and/or a history of diabetes for more than 10 years.[4] Withholding basal insulin from these patients causes blood glucose levels to rapidly rise by approximately 45 mg/dL per hour and leads to ketoacidosis.[4,35,36]

The Case Against Sliding-Scale Insulin Regimens

Sliding-scale insulin regimens are commonly used to administer insulin to hospital patients with elevated blood glucose levels. For a number of reasons, they are often ineffective for controlling hyperglycemia when used as a sole modality of insulin therapy.[4,37,38] Sliding-scale insulin regimens prescribed at the time of admission tend to be used throughout a patient's hospital stay without any modification relative to subsequent blood glucose levels.[38] Another difficulty is that sliding-scale insulin is administered without regard to timing of food intake, previous insulin administration, or individualization of a patient's sensitivity to insulin.[4,37] Finally, sliding-scale insulin is essentially a reactive approach, focusing on treatment of hyperglycemia only after it has already occurred rather than on proactive preventive treatment.[4,37,38] As a result, rapid changes in blood glucose levels may occur, tending to exacerbate both hyperglycemia and hypoglycemia. Hospital patients with diabetes who are treated with sliding-scale insulin alone have been shown to have an increased incidence of hypoglycemia and three-fold higher rates of hyperglycemia compared with those who receive no pharmacologic therapy.[38]

Subcutaneous Insulin Therapy Regimens

Patients who require insulin for control of hyperglycemia and are able to eat are given SC basal insulin, either as a SC injection of intermediate-acting insulin twice daily (eg, neutral protamine Hagedorn [NPH]) or long-acting insulin analog once daily (eg, insulin glargine). Basal insulin therapy is administered as a core component of SC insulin therapy for all types of diabetes and/or hyperglycemia in the hospital.[4,35,36] Basal insulin controls blood glucose between meals, overnight, and in the fasting state. Because insulin glargine is given once daily and may be administered at any time during the day, it may be particularly well-suited for hospital use as a basal insulin.[39] It has a consistent pharmacokinetic profile with no pronounced peak with respect to insulin delivery over 24 hours, mimicking continuous SC insulin infusion.[40] Insulin glargine also exhibits lower intersubject variability than NPH insulin.[40]

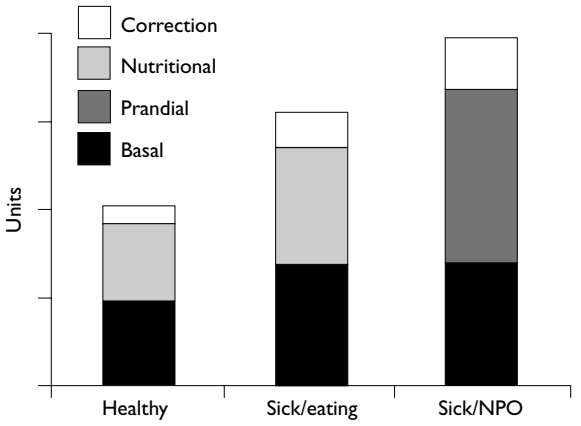

Figure 3. Insulin requirements in health versus illness. NPO = nothing by mouth. (Adapted with permission from Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. American Diabetes Association Diabetes in Hospitals Writing Committee [published errata appear in Diabetes Care 2004;27:856 and 2004;27:1255]. Diabetes Care 2004;27:553–91. Reprinted with permission from The American Diabetes Association.)

Prandial insulin (ie, insulin lispro, insulin aspart, regular insulin) is usually administered prior to meals; however, if one is not certain that the meal will be well-tolerated, rapid-acting insulin may be given after the meal either as a full dose or as a reduced dose if only a portion of the meal was eaten.

Patients who receive nutrition intermittently, such as those being transitioned from NPO status to a regular diet or those receiving bolus tube feedings, are generally best managed with basal insulin therapy combined with a rapid-acting insulin analog timed to match the intermittent nutritional intake.[4,35,36] Practical guidelines for initiating SC therapy in hospital patients and essential components of the insulin order are provided in **Table 3**.

Table 3. Insulin Therapy in the Hospital: Essential Components of Insulin Orders

Programmed/Scheduled Insulin		
Basal	**Nutritional**	**Correction/Supplemental Insulin**
Intermediate (NPH) twice daily (or bedtime)	Regular or rapid (aspart, lispro) before meals	Regular or rapid *when fingerstick blood glucose above target value*
Long-acting (glargine) at bedtime or in morning		
Insulin drip (regular or rapid)		
Analog mixes		
• Fingerstick blood glucose monitoring: before meals and at bedtime ± 3 AM if eating; every 4 to 6 hr if not eating		
• Rapid insulin given *with* nutrition: regular insulin 30 to 45 min *pre*-nutrition		

NPH = neutral protamine Hagedorn.

DISCHARGE MANAGEMENT

For effective discharge planning, collaboration among the treating physician, nurses, and the diabetes educator is essential for providing continuity of care back to the outpatient setting. Prior to discharging patients with preexisting diabetes requiring insulin, the SC insulin regimen should be reestablished with adjustments as needed to enable stable glycemic control. In newly diagnosed or recognized diabetes or type 2 diabetes that did not previously require insulin therapy, transition to oral agents may be made prior to discharge if blood glucose levels are controlled on low doses of insulin as the clinical condition improves.

Diabetes Education and Glucose Tolerance Reevaluation

Patients who are being newly treated with insulin should be taught survival skills prior to discharge, including specifics of insulin administration; self-glucose monitoring; hypoglycemia recognition, prevention, and treatment; and when to call their physician. It is also important to schedule a postdischarge follow-up visit in timely fashion to review blood glucose readings and to adjust insulin and/or oral agent doses as appropriate once the patient has returned to the outpatient setting to assure safety and optimal glycemic control.

Finally, glucose tolerance should always be reevaluated in the outpatient setting after patients are fully recovered following hospitalization to rule out an underlying diagnosis of prediabetes or diabetes if stress or illness was the suspected cause of hyperglycemia. Indeed, individuals who have no prior history of diabetes but who are at high risk may be identified during their hospital stay. A correlation between impaired glucose tolerance or hyperglycemia at discharge and the presence of impaired glucose tolerance and outright diabetes at 3-month postdischarge follow-up has been demonstrated.[41] The ADA, therefore, recommends that patients with in-hospital hyperglycemia and no prior diagnosis of diabetes should be followed up at 1 month after discharge for assessment of glucose tolerance status.[4]

Future Directions for Subcutaneous Insulin Therapy in the Hospital

The AACE/ACE expert panel and the ADA writing group suggest that well-designed studies are needed in the acute care setting to provide evidence to support use of specific strategies for SC insulin delivery.[4,32,33] Particular areas of need include optimization of methods for delivering basal insulin in various clinical situations, including the operating room and in the perioperative period, and simple, safe, and effective algorithms for SC delivery of scheduled basal, prandial/nutritional, and correction doses of insulin.[4]

CONCLUSION

Numerous observational studies and a small but accumulating number of randomized clinical trials provide evidence that achieving and maintaining tight glycemic control can improve clinical outcomes in the hospital. Insulin is used as the treatment of choice for aggressive management of hyperglycemia in the hospital. IV insulin therapy is usually preferred for the management of hyperglycemia in critical care patients and severely decompensated diabetes. SC insulin is used to manage hyperglycemia in most hospital patients outside the ICU setting. The SC insulin regimen is tailored to the clinical circumstances and the individual insulin requirement. The insulin regimen will meet basal, nutritional, and correction-dose needs. Aggressive treatment of hyperglycemia in the hospital using insulin will enable attainment of blood glucose targets of 80 to 110 mg/dL in the ICU setting and 110 to 180 mg/dL for general medicine and surgery patients. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 28.

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