

PRACTICAL MANAGEMENT OF

Inpatient Hyperglycemia

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Introduction

In 2001, the standard of care for hospitalized patients with hyperglycemia was forever changed by a landmark study showing that continuous insulin infusion to maintain near-normal blood glucose levels among critically ill patients markedly improved clinical outcomes.¹ This prospective, randomized controlled trial by Van den Berghe et al demonstrated a 43% reduction of intensive care unit (ICU) mortality and a 34% decrease in overall hospital mortality in patients whose average blood glucose levels were maintained at 103 mg/dL, targeting a range of 80 to 110 mg/dL. Also, strict glycemic control was associated with fewer bloodstream infections, reduced frequency of neuropathy, lower incidence of dialysis-dependent renal failure, fewer blood transfusions, and less need for mechanical ventilation. Importantly, hypoglycemia was of minimal consequence in both the control and intervention groups—challenging the pervasive belief that aggressive treatment of hyperglycemia is too risky in hospitalized patients.

The revelation that a simple, safe, and inexpensive insulin infusion protocol could dramatically improve outcomes in critically ill patients prompted practitioners and medical organizations to seek uniform standards for managing inpatient hyperglycemia in both diabetic and nondiabetic patients. Lending further weight to this movement were studies relating poor glycemic control to adverse outcomes, particularly mortality, infectious complications, longer hospital stays, and more costly care.²⁻¹⁴

In response to the growing impetus for change, the American Diabetes Association (ADA) issued a comprehensive technical review evaluating the evidence relating to issues of glycemic control and its possible impact on hospital outcomes.¹⁵ Additionally, the American Association of Clinical Endocrinologists (AACE) organized a consensus conference, cosponsored by several medical organizations (including the American Association of Diabetes Educators, ADA, American Heart Association, American Society of Anesthesiologists, Endocrine Society, and Society of Critical Care Medicine), to further delineate the mechanisms by which control of hyperglycemia or the use of insulin per se might benefit inpatients and to clarify the best methods for implementing intensive insulin protocols in the hospital. The resulting recommendations were published in 2004.¹⁶

This monograph integrates these latest published recommendations with experience-based advice to offer realistic approaches for improving inpatient glycemic control that may be adapted to different hospital environments. It addresses longstanding barriers to controlling hyperglycemia in hospitalized patients, most notably fear of hypoglycemia, and describes specific strategies for implementing insulin-infusion protocols, standardizing insulin dosing algorithms, monitoring glycemia, and promoting patient self-management. Methods for educating clinicians and patients are also discussed with the aim of redefining treatment of hyperglycemia as a healthcare priority, rather than a threat to patient safety, both during and beyond the hospital stay.

CHAPTER 1**Why the Fuss?**

The number of hospital discharge forms with diabetes listed as a diagnosis increased more than 50% in the United States during the 1990s, signaling the rising epidemic of this costly chronic disease.¹⁷ By 2001, diabetes accounted for more than 4.6 million hospitalizations, costing \$40 billion—a figure that represents the single largest component of direct medical expenditures incurred by the disease.¹⁸ Yet in many hospitals, treatment of hyperglycemia remains haphazard at best, and is often viewed as secondary to the pressing demands of acute care.

One explanation for this arbitrary approach is that the preeminent goal of glycemic management in the hospital has been avoiding hypoglycemia rather than detecting and controlling hyperglycemia. In a study of 1034 adults consecutively admitted to an inner-city teaching hospital, for example, chart review showed that 13% had blood glucose levels >200 mg/dL.¹⁹ Of these, 36% remained undiagnosed at the time of discharge, despite frequent mention of hyperglycemia in progress notes.

Further, the common phenomenon of stress hyperglycemia—that is, high blood glucose levels associated with acute illness even in patients without diabetes—is often overlooked or misunderstood. In one study, retrospective chart review of 1886 patients admitted consecutively to a community hospital revealed that 12% of patients with no prior history of the disease had undiagnosed diabetes or stress hyperglycemia, with patients in this group exhibiting significantly higher in-hospital mortality and worse functional outcome than patients with known diabetes.⁵ Additionally, a Swedish study showed that 31% of 181 nondiabetic patients with acute myocardial infarction had hyperglycemia at the time of hospital discharge, and 25% upon follow-up at 3 months, illustrating the insidiousness of this maladaptive response to stress.²⁰

Glycemic evaluation is also routinely downplayed in the acute care setting, as implied in a recent survey at a large teaching

hospital, where, according to respondents, 20% of diabetic patients underwent lipid testing, while only 13% had glycosylated hemoglobin (A1C) analysis.²¹ This surprising result may reflect the fact that cardiovascular disease accounts for the vast majority of hospitalizations among people with diabetes, and that treating the underlying hyperglycemia is still perceived by many clinicians as unacceptably risky, overly demanding, or simply irrelevant to medical outcomes.

It is anticipated that such attitudes will soon become the exception rather than the rule, in light of ongoing research demonstrating that hyperglycemia has detrimental effects on inpatient morbidity and mortality and that near-normal blood glucose levels, or the use of insulin per se, might reduce these risks. Key studies are highlighted below.

INPATIENT HYPERGLYCEMIA IS ASSOCIATED WITH ADVERSE OUTCOMES

Evidence that inpatient morbidity and mortality are increased by hyperglycemia includes the following:

- In patients undergoing cardiac surgery, hyperglycemia was associated with increased incidence of deep sternal wound infections and more infectious complications overall.^{10,11} Subsequent analysis also revealed the lowest mortality in patients maintaining average postoperative blood glucose <150 mg/dL.⁶
- A meta-analysis of 15 studies of patients with or without diabetes hospitalized for acute myocardial infarction reported that blood glucose levels >110 mg/dL were associated with increases in both in-hospital mortality and congestive heart failure.³
- Patients on general medical and surgical wards with new and preexisting hyperglycemia had an 18- and 2.7-fold increase in inpatient mortality, respectively, compared with normoglycemic patients. Length of stay was also higher in the new hyperglycemia group compared with the other two groups, and hyperglycemic patients had a greater need for subsequent nursing home care and a higher incidence of infection than normoglycemic patients.⁵

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- Hyperglycemic patients in a surgical ICU who received conventional therapy to maintain blood glucose levels between 180 and 200 mg/dL exhibited increased overall mortality, as well as higher risk of sepsis, acute renal failure, and critical-illness-related neuropathy, compared with intensively treated patients whose blood glucose levels were in the range of 80 to 110 mg/dL.¹
- A review of 1826 patients admitted to a medical-surgical ICU showed that hospital mortality was strongly associated with glycemic control. Patients with mean blood glucose levels between 80 and 99 mg/dL during the ICU stay had 9.6% hospital mortality; between 100 and 119 mg/dL, 12.2% mortality; and >300 mg/dL, up to 42.5% mortality.²²
- A meta-analysis of 26 studies on stroke showed increased mortality in patients hospitalized with blood glucose levels of >110 to 126 mg/dL.²³ Moreover, stroke survivors without known diabetes whose blood glucose was >121 to 144 mg/dL had poor functional recovery. Additionally, a comparison of euglycemic patients, nondiabetic patients with stress hyperglycemia, patients with newly diagnosed diabetes, and patients with known diabetes reported higher mortality in all three groups of hyperglycemic patients.²⁴

Possible Mechanisms

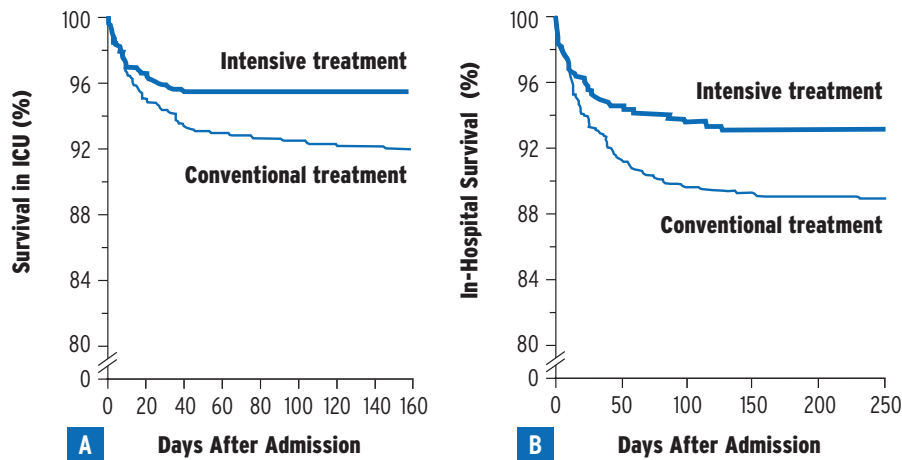
Adverse effects of hyperglycemia in severely ill intensive care patients are attributed to several interrelated mechanisms.²⁵ In the majority of critically ill patients, resistance to insulin, reduced secretion of insulin, and accelerated production of counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hormone) elevate blood glucose, free fatty acids (FFAs), ketones, and lactate, which in turn increase levels of inflammatory cytokines, such as interleukin 6 and tumor necrosis factor- $\kappa\beta$, and enhance damaging nitric oxide synthesis in a variety of cells. This "cytokine storm" also suppresses inhibitor $\kappa\beta$ (I- $\kappa\beta$) in the skeletal muscle, leading to unchecked production of nuclear factor- $\kappa\beta$ (NF- $\kappa\beta$), the proinflammatory transcription factor most responsible for generating reactive oxygen species (ROS) and oxidative stress. While initially adaptive, such acute activation of the immune system leads to deleterious changes in body metabolism, including neutrophil dysfunc-

tion, catabolism, cardiac reperfusion injury, abnormal activation of the inflammatory pathway, endothelial dysfunction, thrombotic tendency, and tissue injury.¹⁵

IMPROVED OUTCOMES WITH INSULIN

The beneficial effects of intensive insulin therapy on a number of outcome parameters in critically ill patients have been shown in two randomized controlled trials and several observational studies:

- In a landmark study by Van den Berghe et al, 1548 mechanically ventilated adults admitted to a surgical ICU were randomized to receive either continuous insulin infusion to keep blood glucose levels within the target range of 80 to 110 mg/dL or conventional therapy to maintain blood glucose between 180 and 200 mg/dL.¹ Compared with conventional therapy, the insulin infusion protocol reduced intensive care mortality by 43%, overall in-hospital mortality by 34%, newly developed kidney failure requiring dialysis by 41%, bacteremia by 46%, the number of red blood cell transfusions by 50%, and critical illness polyneuropathy by 44% (Figure 1). Interestingly, only 13% of patients in the study had a prior history of diabetes, and the benefits of intensive insulin therapy were achieved without significant consequences from hypoglycemia.
- In the Diabetes and Insulin-Glucose Infusion in Myocardial Infarction (DIGAMI) study, 620 patients with acute myocardial infarction and hyperglycemia, with or without a history of diabetes, were randomly assigned to an insulin infusion group or a control group. The infusion group received intravenous (IV) insulin for 24 hours, then multiple subcutaneous doses of insulin for 3 months or longer; the control group received standard therapy. After 1 year, mortality was reduced by 30% in the intensively treated group.²⁶ After an average of 3.4 years, absolute mortality was reduced by 11%.²⁷ A recent follow-up to this trial showed minimal difference in mortality between patients receiving insulin infusions followed by insulin-based long-term glucose control versus standard glucose control (ie, no insulin); however, this was possibly due to inconsistent adherence to the study protocol posthospitalization.²⁸

PRACTICAL MANAGEMENT OF **INPATIENT HYPERGLYCEMIA****Figure 1. Cumulative survival of critically ill patients who received intensive insulin treatment or conventional treatment in the ICU**

Patients discharged from the ICU (A) and the hospital (B) were considered to have survived. From Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359-1367. Copyright ©2001 Massachusetts Medical Society. All rights reserved.

- In the Portland Diabetic Project, mortality among patients with diabetes undergoing coronary artery bypass grafting (CABG) was reduced from 5.3% to 2.5% ($P < 0.0001$) by an intensive glycemic management protocol that called for IV insulin until the morning of postoperative Day 3.^{6,12} The Portland Protocol also reduced the risk of deep sternal wound infection by 66% ($P < 0.005$). Another recent study of diabetic patients undergoing CABG showed decreased perioperative morbidity, enhanced survival, and fewer recurrent ischemic events in patients treated with a glucose insulin potassium (GIK) solution versus intermittent subcutaneous insulin.²⁹
- Retrospective review of 800 patients admitted consecutively to a medical-surgical ward before and after implementation of a protocol advocating more stringent insulin-titrated glycemic control revealed that improved control was associated with a 29% reduction of in-hospital mortality, decreased new organ failure, fewer blood transfusions, and shorter ICU stay.³⁰
- A recent meta-analysis of 35 trials to determine the effect of insulin therapy on mortality in hospitalized adult patients with critical illness found that insulin therapy decreased short-term mortality by 15% in different clinical settings.³¹

Possible Mechanisms

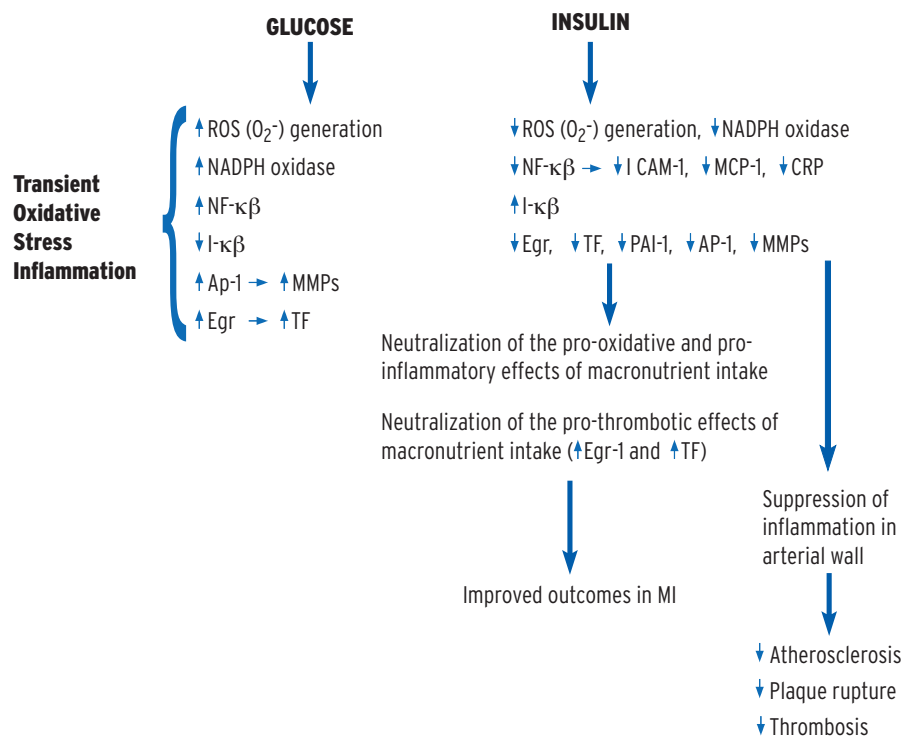
Emerging evidence suggests that early and aggressive control of blood glucose—or perhaps the independent action of insulin itself—attenuates the proinflammatory effects of stress hyperglycemia that may contribute to poor outcomes in hospitalized patients with or without diabetes (Figure 2).^{25,32,33} Insulin therapy improves homeostasis of glucose and lipids, both of which are harmful to tissues if elevated, especially during acute stress. Additionally, insulin stimulates I- κ B expression and inhibits NF- κ B binding activity, thereby reducing the transcription of proinflammatory genes, adhesion molecules, chemokines, and the enzymes responsible for generation of ROS. Insulin also increases energy delivery to the ischemic myocardium, and by reducing circulating FFAs, normalizes endothelium-dependent vasodilation, replenishes intracellular calcium, and prevents arrhythmias. Moreover, through its anabolic effects, insulin may promote tissue repair and prevent transfusions, dialysis, and critical illness polyneuropathy.³⁴

COST CONSIDERATIONS

More stringent control of inpatient hyperglycemia could yield substantial cost savings as the result of improved hospital outcomes, lowered mortality, and shortened length of stay (LOS). In a nonrandomized retrospective review, consultation with a diabetes team reduced LOS by 56%, with an estimated

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Figure 2. Insulin may improve vascular wall structure and function by direct or indirect mechanisms



Excessive macronutrients, including glucose, have negative effects on vascular endothelial and smooth muscle cells by generating ROS and proinflammatory proteins, including early growth response (Egr) transcription factor and activator protein-1 (AP-1), that lead to increased production of matrix metalloproteinases (MMPs) and tissue factor (TF). Insulin potentially reverses these effects by reducing circulating glucose and inhibiting ROS, cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), and other proteins involved in the inflammatory process such as C-reactive protein (CRP) and plasminogen activator inhibitor (PAI-1). MCP-1 = monocyte chemoattractant protein-1; MI = myocardial infarction; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; NF-κβ = nuclear factor-κβ. From Le Roith D. Molecular mechanisms by which metabolic control may improve outcomes. *Endocr Pract.* 2004;10(suppl 2):57-62. Copyright ©2004 American Association of Clinical Endocrinologists.

cost savings of \$2,353 per patient.³⁵ Similarly, the use of continuous IV insulin in diabetic patients after cardiac surgery was associated with a net savings of \$5,580 per patient attributable to decreased LOS and lower rates of deep sternal wound infection.¹²

Three published studies have directly assessed the cost-effectiveness of intensified inpatient glucose management. In the DIGAMI study, the estimated cost per life-year gained in the setting of acute myocardial infarction was 16,900 euros.¹⁴ In a retrospective analysis of patients undergoing CABG directly, each increase of 50 mg/dL in blood glucose directly correlated with a mean increase of \$2,824 (range, \$1,599 to \$4,049) in hospitalization charges and a mean

increase of \$1,769 (range, \$928 to \$2,610) in hospitalization costs for patients with or without a prior history of diabetes.¹³ Finally, a study of diabetic patients undergoing CABG found that implementing an insulin infusion protocol with routine endocrinology consultation was a revenue-neutral intervention that improved glycemic control, tended to shorten LOS, and reduced the rate of deep sternal wound infection.³⁶

Additional cost-effectiveness studies are needed to compare the risks and benefits of these insulin strategies with more expensive therapeutic innovations (eg, activated protein C for sepsis) used routinely in the intensive care setting.³⁷

CHAPTER 2**Demystifying Inpatient Insulin Therapy**

Insulin is the most powerful and effective pharmacologic tool available to treat hyperglycemia and diabetes. Although all patients with type 1 diabetes need insulin to survive, the use of insulin in outpatients with type 2 diabetes is often delayed because of lingering stigmas associated with older formulations. During hospitalization, however, patients with newly diagnosed type 2 diabetes, or those formerly treated with oral antihyperglycemic agents, are best served by conversion to insulin therapy, which is more versatile and easily titrated than oral therapy, and less likely to cause adverse effects. While subcutaneous insulin is appropriate for the majority of hospitalized patients with type 1 or type 2 diabetes, IV insulin infusion, with its unparalleled rapidity of action and short duration, predictable glucose-lowering effect, and potential nonglycemic benefits, is often preferable in the rapidly changing environment of acute illness or surgery.³⁸ The following review of the physiologic principles of insulin therapy addresses common misperceptions about insulin that often impede its successful use in the hospital.

“SLIDING SCALES” AND OTHER BARRIERS

A major obstacle to effective treatment of inpatient hyperglycemia has been widespread use of one-size-fits-all “sliding scale” regimens that call for insulin only when blood glucose

levels are elevated.³⁹ This popular approach to inpatient glycemic management, which alternates too much insulin with too little, actually promotes a roller coaster pattern of blood glucose fluctuation (Table 1). Unfortunately, it also reinforces the assumption that preventing and treating hyperglycemia is too risky, complex, and labor-intensive for routine hospital practice.

A preferable alternative to sliding scales is correction-dose therapy. Correction-dose therapy differs from sliding scale monotherapy in that the doses are proportionate to daily insulin requirements and are offered as a supplement to, not a replacement for, the basic insulin regimen.

Other real and perceived barriers contributing to poor management of hyperglycemia in the hospital include:

- **Risk of hypoglycemia.** The risk of mild to severe hypoglycemia is generally increased with intensive insulin therapy, depending on age, weight, duration of disease, degree of insulin resistance, the presence or absence of diabetic neuropathy, glycemic goals, endogenous insulin secretion, and history of hypoglycemia. Overall, patients using insulin analogues (lispro, aspart, glulisine, glargine) in regimens more closely resembling physiologic insulin release are less susceptible to hypoglycemia than patients using traditional insulins (regular and NPH).⁴⁰⁻⁴⁶
- **Erratic insulin absorption.** The onset and duration of action of insulin varies greatly depending on the type of insulin used, the site of injection, and the particular

Table 1. Disadvantages of “sliding scale” insulin protocols

- Dosing scale is determined on the basis of one blood glucose reading and rarely changed
- No basal insulin is provided
- No insulin is given for normal blood glucose values
- Hyperglycemia is treated only after it occurs, causing a roller coaster pattern of glycemia
- Variables, such as mealtime caloric intake, or the patient’s weight and illness, are not considered
- Insulin administration is based on when the nurse measures a blood glucose value versus when the patient eats
- Creates the false impression that diabetes is being managed

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patient.⁴⁷ For example, large doses of human insulins form an insulin depot, unpredictably prolonging the duration of action. Further, in acutely ill hospitalized patients, glycemic fluctuation may be more pronounced because of fluid shifts, changes in blood flow to the subcutaneous tissue, and the counterregulatory stress response.⁴⁸ Any strategy that increases the consistency of delivery, such as the use of IV insulin infusion or insulin analogues, should decrease glucose fluctuations.

- *Timing of food consumption.* Coordinating meal delivery with the timing and dosing of insulin is an obvious means of preventing inpatient hypoglycemia, yet meals and snacks commonly arrive late in the hospital. The bedtime snack may be omitted altogether, predisposing patients on some regimens to nocturnal hypoglycemia. Also, failure to monitor the lag time between administration of regular or rapid-acting insulin and eating may likewise lead to glycemic fluctuations.⁴⁷ The prescribed interval (15 minutes for insulin aspart, lispro, or glulisine; 30 minutes for regular) should be increased or decreased only when premeal blood glucose levels are above or below target.
- *Myth that exogenous insulin promotes atherogenesis.* This misperception evolved from evidence that insulin resistance increases rates of cardiovascular disease.⁴⁹ Yet, in reality, elevated endogenous insulin levels are most likely a marker for the constellation of cardiovascular risk factors typical of the metabolic syndrome. Indeed, the landmark United Kingdom Prospective Diabetes Study (UKPDS) showed a nearly significant reduction ($P=0.052$) of myocardial infarction in association with randomization to intensive therapy.^{50,51} In the original DIGAMI trial, moreover, initiation of insulin therapy during the immediate postinfarction period reduced cardiovascular mortality at 1 and 3 years.²⁷ While the mechanisms behind these improved clinical outcomes are not fully understood, the role of insulin in suppressing FFA and inflammatory cytokine production is considered a key factor (see Chapter 1).
- *Fluctuating insulin demands related to stress or concomitantly used medications.* Circumstances such as pain and trauma, surgery, sepsis, burns, hypoxia, cardiovascular disease, and emotional stress may increase the demand for insulin in hospitalized patients,

whether they have diabetes or not. Additionally, several commonly employed clinical interventions, such as vasopressors, corticosteroids, and narcotics can affect insulin needs.⁵²

- *Hospital formularies.* When insulin products used in the outpatient setting are not on the hospital formulary, patients with diabetes should be instructed, within hospital regulatory guidelines, to bring their own insulins to the hospital to ensure continuity of treatment.

The potential of any or all of these factors to confound inpatient insulin therapy may be minimized with appropriate education and protocols that encourage communication between services and floors. Additionally, routine use of standardized order sets, with blanks for specific patient variables, serves to familiarize hospital staff with the action of insulin and commonly used treatment strategies (see Chapters 4 and 5).⁵³

INPATIENT GLYCEMIC GOALS

Van den Berghe et al demonstrated that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL improved clinical outcomes among critically ill patients in the surgical ICU.¹ Similarly, the DIGAMI study found that strict glycemic control improved long-term prognosis in diabetic patients following acute myocardial infarction.²⁷ On the basis of these two randomized prospective studies, and a number of observational studies demonstrating that decreasing hyperglycemia reduces morbidity and mortality in different clinical situations, recommended targets for blood glucose in the hospital are as follows (Table 2):⁵⁴

- Critically ill patients: Blood glucose levels should be kept as close to 110 mg/dL as possible and generally <180 mg/dL.
- Noncritically ill patients: Premeal blood glucose should be kept as close to 90 to 130 mg/dL as possible (mid-point of range: 110 mg/dL) given the clinical situation, with postprandial blood glucose levels <180 mg/dL.

Significant hyperglycemia warrants reevaluation of the preadmission diabetes care plan (in the case of patients with previously diagnosed diabetes), or close follow-up to distinguish hospital-related stress hyperglycemia from undiagnosed diabetes.

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Table 2. ADA-suggested inpatient glycemic goals in nonpregnant adults

Intensive care unit	Noncritical care units	
	Preprandial	Postprandial
<180 mg/dL (target, 110 mg/dL)	90 to 130 mg/dL (target, 110 mg/dL)	<180 mg/dL

Data from American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28:S4-S36.

THE COMPONENTS OF INSULIN THERAPY

When writing insulin orders, the basal and prandial/nutritional insulin doses are written as *scheduled* (or programmed) insulin, constituting the standard insulin regimen, while *correction doses* of insulin are written as an algorithm for prn (as needed) insulin to be given in response to temporary elevations of blood glucose levels. Because acute illness in itself generally increases insulin requirements, *illness-related* insulin is a component of total insulin need that can be apportioned among the basal, nutritional, and correction insulin doses. Importantly, illness-related insulin requirements decline as the patient’s condition improves and therefore may be difficult to assess (Figure 3). Rapid changes in illness-related insulin requirements call for frequent blood glucose monitoring and daily changes in scheduled insulin doses, as determined by blood glucose levels.

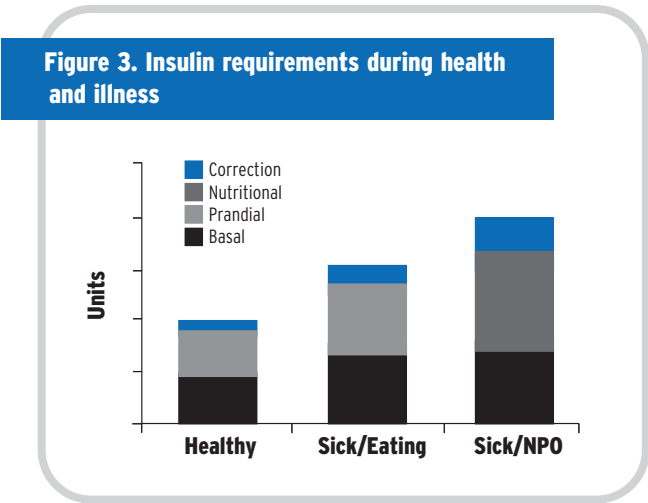
Defining the Components of Scheduled (or Programmed) Insulin Therapy

In normal physiology, pancreatic insulin secretion is divided almost equally between *basal* and *prandial* components.

- The basal component is the amount of insulin required when food is not being absorbed (ie, during the normal fasting or postabsorptive state) to regulate endogenous glucose output primarily from the liver.
- The prandial component is the amount needed in relation to normal meals to promote conversion of digested nutrients into storage forms of energy.

In the outpatient setting, strategies for insulin replacement are governed largely by the pharmacokinetic and pharmacodynamic profiles of available insulin products (Table 3). *Physiologic regimens* using insulin analogues that closely mimic normal basal or prandial insulin secretion (eg, basal insulin glargine with rapid-acting insulin aspart, lispro, or glulisine) generally allow for more rational and flexible insulin administration, with simpler dose adjustments.

In the hospital, where nutritional intake is not necessarily provided as discrete meals (eg, patients may “graze” on transitional meal plans, receive between-meal nutritional



Insulin components in an unstressed condition of health consist of basal, prandial/nutritional, and correction-dose therapy; illness-related changes of dose requirement are apportioned between these components. Actual requirements may vary widely. NPO = nothing by mouth. Adapted from Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004; 27:553-591. Copyright ©2004 American Diabetes Association.

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Table 3. Action of standard insulins and insulin analogues*

Insulin preparation	Onset of action	Peak action	Effective duration of action
Standard			
• Regular (soluble)	30-60 min	2-3 hr	8-10 hr
• NPH (isophane)	2-4 hr	4-10 hr	12-18 hr
• Zinc insulin (Lente)	2-4 hr	4-12 hr	12-20 hr
• Extended zinc insulin (Ultralente)	6-10 hr	10-16 hr	18-24 hr
Analogues			
• Lispro	5-15 min	30-90 min	4-6 hr
• Aspart	5-15 min	30-90 min	4-6 hr
• Glulisine	5-15 min	30-90 min	4-6 hr
• Glargine	2-4 hr	no pronounced peak	20-24 hr

*Serum insulin profiles are based on a subcutaneous injection of 0.1 to 0.2 units per kilogram of body weight; large variation between and within persons may be noted.

supplements, IV dextrose, enteral feedings, or total parenteral nutrition [TPN]), the insulin dose components for inpatients are referred to as the *basal insulin requirement* or the *nutritional insulin requirement*:

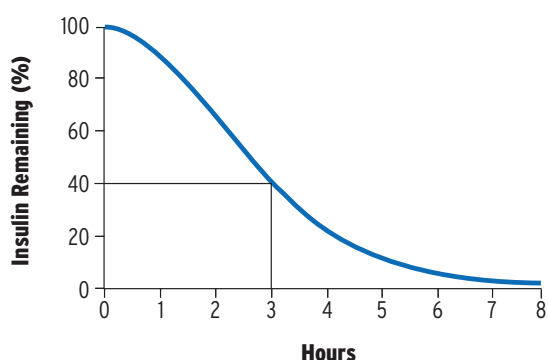
- The basal insulin requirement constitutes the amount of exogenous insulin per unit of time necessary to prevent unchecked postprandial or fasting gluconeogenesis (production of glucose) and ketogenesis (build-up of ketone bodies).
- The nutritional insulin requirement covers caloric exposure of all types, including IV dextrose, TPN, enteral feedings, nutritional supplements, or discrete meals. (In the case of discrete meals, nutritional and prandial insulin requirements are one and the same.)

Correction-Dose or Supplemental Insulin Dose Therapy

Hyperglycemia correction is an adjunct to scheduled insulin therapy. Correction-dose insulin (also called supplemental insulin) is usually administered as a predetermined dose of rapid- or short-acting insulin to treat hyperglycemia before or between meals. In the hospital, correction-dose insulin is used both as a dose-finding measure and as a supplement when rapidly changing insulin demands lead to hyperglycemia. Guidelines for correction-dose therapy

are presented in Chapter 5. If frequent correction doses are required, scheduled insulin doses should be increased the following day to accommodate increased insulin needs. Repeated blood glucose excursions above target range should be addressed by a change in the scheduled insulin regimen rather than by continued administration of correction doses.

Finally, if patients are using insulin supplements between meals, they must be aware of “insulin stacking,” which refers to the practice of providing correction-dose insulin before the prior dose of prandial or correction insulin (or the peak action of neutral protamine Hagedorn [NPH] insulin) has had its full effect.⁴⁶ Without an understanding of how much of the previous insulin has yet to be absorbed, hypoglycemia may occur as a result of insulin stacking (Figure 4). For example, injecting additional short- or rapid-acting insulin 1 hour after a dose of regular and NPH insulin potentially would result in hypoglycemia within several hours because the first dose of insulin would not have been fully absorbed upon administration of the second.^{46,47} Among patients with hypoalbuminemia, edema, hypotension, or concurrent pressor therapy, there may be increased risk of delayed effect and late snowballing from repeated doses of rapid-acting analogue or other insulin preparations.

PRACTICAL MANAGEMENT OF **INPATIENT HYPERGLYCEMIA****Figure 4. Timing of insulin aspart absorption**

The use of this graph showing delivery of insulin aspart (0.2 units per kilogram of body weight, delivered into the abdomen) helps patients avoid “insulin stacking.” For example, 3 hours after the administration of 10 units of insulin aspart, there is still approximately 40% times 10 units, or 4 units, of insulin remaining. From Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-183. Copyright ©2005 Massachusetts Medical Society. All rights reserved.

Insulin Products and Pointers

Selecting the appropriate insulin depends largely on the desired time course of insulin action. Table 3 shows the pharmacokinetic characteristics—time to onset of action, time of peak action, and effective duration of action—of currently available insulins. Yet, clinically, insulin pharmacodynamics may influence blood glucose levels more than pharmacokinetics because absorption rates vary among and within individual patients.⁴⁶ This is especially true in the hospital setting, where the action of insulin may be prolonged in the presence of renal failure, or after subcutaneous injection in patients having edema, hypotension, or a requirement for blood pressure support.

Human insulin preparations may be categorized as follows:

- **Rapid-acting:** insulin lispro, aspart, glulisine (genetically engineered insulin analogues)
- **Short-acting:** regular (soluble) insulin
- **Intermediate-acting:** NPH (isophane); Lente (insulin-zinc suspension)
- **Long-acting:** Ultralente (extended insulin-zinc suspension); insulin glargine, insulin detemir (genetically engineered insulin analogues) (*Note: Insulin detemir is not approved for use in the United States at the time of this writing.*)

Rapid-Acting Insulin. The genetically engineered insulin analogues lispro, aspart, and glulisine have a rapid onset of 15 to 30 minutes, peak in 30 to 90 minutes, and have an effective duration of 4 to 6 hours when injected subcutaneously because they do not self-aggregate in solution as does human (regular) insulin. Glulisine, a new rapid-acting insulin analogue, is associated with more accurate insulin coverage and less weight gain than regular insulin.⁵⁵ Use of these rapid-acting analogues results in less variable absorption at the injection site and possibly between and within patients.⁴⁶ They are commonly used for continuous subcutaneous insulin infusion in insulin pumps.

Prandial-Correction Usage of Rapid-Acting Insulin Analogues:

In subcutaneous injection therapy, rapid-acting insulins are most suitably used at mealtime as prandial insulin and as correction-dose therapy.^{46,47} Ideally, this type of insulin should be administered 15 minutes before a meal; yet, realistically, the interval between insulin administration and mealtime is often shorter. In general, more severe hyperglycemia warrants a longer lag time. Rapid-acting insulin is preferred for prandial coverage when patients are eating discrete meals; it is not appropriate for coverage of continuous feedings or IV dextrose infusions.

Short-Acting Insulin (Regular). Regular insulin has a delay to onset of action of 30 to 60 minutes, a peak of 2 to 3 hours, and an effective duration of 8 to 10 hours. Proper use

Table 4. Common causes of inaccurate blood glucose results

Sources of analytical error	Sources of user error
Low hematocrit*	Inadequate meter calibration
High hematocrit†	Using a test strip that does not match the meter code or that has passed the expiration date
Shock and dehydration‡	Inadequate quality-control testing
Hypoxia‡	Poor meter maintenance
Hyperbilirubinemia, severe lipemia*	Poor technique in performing finger prick
Specimen additives: sodium fluoride†	Poor technique of applying drop of blood to test strip
Drugs—acetaminophen overdose, ascorbic acid, dopamine, fluorescein, mannitol, salicylate‡	Failure to record results in patient's chart or to take action if blood glucose is out of target range

*Falsely elevates result; †Falsely lowers result; ‡Can either falsely lower or elevate result, depending on device used. Adapted from Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553-591. Copyright ©2004 American Diabetes Association.

requires injection 20 to 30 minutes prior to meals to match insulin availability and carbohydrate absorption.⁴⁷ Although blood levels peak at 2 to 5 minutes after IV injection, it is only after interstitial equilibration and initiation of cellular action that the hypoglycemic effect of regular insulin peaks, often within 30 to 45 minutes after injection.

Intermediate-Acting Insulin. Neutral protamine Hagedorn (isophane insulin; NPH) insulin is slowly absorbed due to the addition of protamine to regular insulin. Its onset of action occurs 2 to 4 hours from the time of injection, with a peak effect lasting 4 to 10 hours, and an effective duration of 12 to 18 hours. Lente insulin, which is regular insulin bound to zinc, has a slightly longer effective duration than NPH. (*Note: Regular insulin may bind with Lente or Ultralente, which blunts its effect. Therefore, whenever regular insulin is mixed with these agents, it should be injected immediately. The mix should not be left in the syringe for any length of time.*) Lente and NPH are commonly used as twice-daily basal insulins.⁴⁷

Long-Acting Insulin. Ultralente insulin (insulin zinc extended) is absorbed slowly in its zinc crystalline form, with an onset of action occurring 6 to 10 hours from the time of injection,

a peak effect of 10 to 16 hours, and an effective duration of 18 to 24 hours. When mixed with regular insulin, it must be injected immediately. Once-daily insulin glargine, a modified human insulin that forms a microprecipitate in the subcutaneous tissue, is released slowly with no pronounced peak over the course of about 20 to 24 hours in most patients.^{46,47} Insulin detemir, a long-acting analogue of neutral pH (pending US Food and Drug Administration approval as of this writing), has a shorter time-action profile than glargine, necessitating twice-daily injections in patients with type 1 diabetes.⁴⁶ (*Note: Insulin glargine cannot be mixed with other insulin preparations because the higher pH of other insulins may cause acidic glargine to precipitate when it is used in a syringe.*)

Basal Insulin Analogues: The basal insulin analogues glargine and detemir are designed to provide basal insulin coverage. Whereas prandial needs of ambulatory patients are met either by endogenous insulin secretion during use of oral antihyperglycemic therapy, or by the prandial use of shorter-acting insulin, between-meal and overnight glycemic control are achieved with basal insulin analogue therapy. *Important: When using long-acting insulin or insulin analogues in the hospital, doses should not be titrated to levels that exceed*

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*estimated basal requirements, even when energy needs are being consistently met by enteral feedings or infusions of dextrose. This precaution minimizes risk in the event of abrupt interruption of caloric intake.*¹⁵

Insulin Mixtures. Premixed preparations of regular and NPH insulins, insulin lispro protamine suspension (NPL) and insulin lispro, and insulin aspart protamine suspension and insulin aspart are commercially available. Although these products may be helpful for elderly patients, blind patients, or others who cannot easily mix insulin in a syringe, they limit flexibility, especially with respect to prandial insulin replacement, and are not useful for patients involved in intensive insulin programs. (*Note: Premixed fixed-ratio insulins are not appropriate for patients with type 1 diabetes, who are highly dependent on a relatively precise match between carbohydrate intake and insulin activity profiles.*)

SELECTION OF INSULINS AND SCHEDULING COMPONENTS OF THERAPY IN THE HOSPITAL

Among patients who are eating, subcutaneous basal insulin can be provided by any one of several strategies. These include continuous subcutaneous insulin infusion (CSII) or subcutaneous injection of intermediate-acting insulin or a long-acting insulin analogue.

For patients with type 1 or type 2 diabetes who require both basal and nutritional coverage, if caloric intake is continuous, then one type of insulin or a mixture of insulins in a consistent ratio may be appropriate to cover both basal and nutritional requirements. However, for patients eating discrete meals, the easiest and most effective means of insulin therapy, with the lowest risk of hypoglycemia, incorporates long-acting insulin analogue glargine for coverage of basal insulin needs, and a rapid-acting insulin analogue (lispro, aspart, or glulisine) for prandial coverage.^{46,47} (Possible exceptions are oncology patients receiving chemotherapy, who tend to graze their meals, or patients with gastroparesis, whose prandial coverage might better be met with premeal injections of regular insulin.) Correction doses are then given as small doses of rapid-acting analogue when hyperglycemia occurs. The shorter duration of action of these analogues compared with regular insulin avoids the problem of insulin

stacking (see Chapters 2 and 5). Such a treatment plan requires understanding of the timing of onset, peak action, and duration of the selected insulins (Table 3).

INPATIENT BLOOD GLUCOSE MONITORING

Intensive diabetes therapy in the hospital setting must be guided by frequent and accurate blood glucose data. Bedside blood glucose monitoring is preferred over laboratory testing because rapid results obtained at the point of care can expedite therapeutic decision-making. When setting and monitoring glycemic goals, it is important to remember that most currently available glucose meters report plasma rather than whole blood glucose. Also, a system should be in place to ensure good monitoring technique and to confirm the accuracy of each meter on a daily basis. Table 4 lists conditions that commonly contribute to erroneous readings in the hospital.

A chart of blood glucose values and insulin doses in an easy-to-interpret, time-based format posted at the bedside can facilitate adjustment of insulin dosages based on glycemic patterns. Further, systematic downloading of blood glucose data from patients' meters onto a centralized computer database can expedite access to serial data and enhance quality control.

Frequency of Monitoring

For patients with known or newly diagnosed diabetes who are eating, glucose monitoring should be performed before meals and at bedtime. Also, it is useful to test between 2:00 AM and 3:00 AM to assess for nocturnal hypoglycemia, particularly if the patient has just increased the basal insulin dose, has a history of hypoglycemia unawareness, uses regular insulin as the prandial insulin, or used a correction dose at bedtime. For patients not eating, testing every 4 to 6 hours is usually sufficient for determining correction insulin doses. Patients receiving continuous IV insulin typically require hourly blood glucose testing until blood glucose levels are stable, at which time the interval can be increased to 2 hours.¹⁵ Hospitalized patients with diabetes who are well enough to continue their regular diabetes therapy and wish to test their own blood glucose should be allowed to do so under the supervision of hospital staff.

CHAPTER 3

Inpatient Insulin Dose Requirements: General Principles

To determine the requirement for exogenous insulin in hospitalized patients, it is necessary to distinguish between patients who are insulin deficient and those with some capacity for endogenous insulin secretion. Patients with type 1 diabetes are, by definition, insulin deficient and thus must receive 24-hour insulin coverage. For practical purposes, a patient treated with insulin monotherapy prior to admission might be assumed to have type 1 diabetes. Realistically, this simple criterion will also encompass many patients with type 2 diabetes. (Additional criteria have been recommended for classification on clinical grounds.¹⁵) Failure to give insulin having action during the night to insulin-deficient patients guarantees development of nighttime and morning hyperglycemia, and may result in ketoacidosis. Because many diabetic patients are not correctly classified at the time of hospital admission, and insulin needs are often increased by the conditions of acute illness, a useful principle in the hospital is to provide 24-hour coverage for *all* patients receiving insulin.⁵⁶ Oral agents used for outpatient treatment of type 2 diabetes are not recommended in the hospital setting, as they require prolonged observation between dose adjustments and provide little flexibility or opportunity for titration under rapidly changing circumstances. Thus, the challenge for the caregiver is to decide how much insulin to prescribe, what insulin preparations to use, and in what pattern to deliver the components of the insulin therapy.

MEETING BASAL REQUIREMENTS WITH SUBCUTANEOUS INSULIN THERAPY

In the hospital, the caregiver often must modify the preadmission insulin regimen of those patients already receiving insulin therapy. Some preadmission regimens result in peaks of insulin action that would normally cover both basal and prandial insulin needs. (Premixed insulins and intermediate-acting insulin frequently are used in the

ambulatory setting to cover both needs.) Because the pattern of exposure to meals might change in the hospital, the amount of long-acting insulin should be restricted to the estimated basal requirement, thus reducing the risk of hypoglycemia.¹⁵

In type 1 diabetes, a reasonable minimum starting dose for basal coverage generally accounts for 40% to 50% of the preadmission daily insulin requirement (see Chapter 6). Patients with type 1 diabetes who are not insulin resistant usually require total insulin doses of 0.4 to 0.8 units/kg/day. The basal component is the amount necessary to prevent unchecked gluconeogenesis and ketogenesis, and remains remarkably stable over time.⁵³ Yet, in the event of ward or service transfers, many hospitals cancel medication orders and require rewriting of all orders. The responsibility for rewriting transfer orders often falls upon physicians who are not acquainted with the patient and who sometimes give verbal orders without reassessing the patient's condition. With this in mind, the admitting physician should strive to establish a subcutaneous basal insulin program that will be appropriate for renewal throughout the hospital stay, regardless of changes in nutritional coverage, and that will be retrievable from the record during sign-out procedures by the cross-covering teams. The basal regimen can be suspended *only* during intervals of continuous IV insulin infusion, and must be resumed before interruption of the infusion.

In type 2 diabetes, requirements for exogenous basal insulin in the hospital will depend on the nutritional and metabolic status of individual patients. For patients with type 2 diabetes who will be eating and were treated previously with insulin monotherapy, the total daily minimum basal requirement is either all or a part of the preadmission total insulin dose requirement. It should be noted that maintenance of a high dose established in the ambulatory setting may not be appropriate. This is because some outpatients receive excessive basal insulin, titrated to achieve first-morning normoglycemia, without prescription of additional therapy to control prandial elevations of blood glucose. In other words, the therapy envisioned as basal insulin coverage in the ambulatory setting was in fact used to play nighttime catch-up for inadequacies of daytime prandial coverage.⁵⁷

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If basal insulin is continued in the hospital at a dosage greater than the actual basal requirement, restriction of oral nutrition intake may then lead to hypoglycemia. A red flag for this circumstance would be a dose of insulin glargine exceeding 60% of the patient's total daily dose (TDD) of insulin when both basal and prandial insulin are administered. Also, the index of suspicion should be high when a patient using basal insulin alone (or glargine with one injection of prandial insulin per day) has an A1C >6.5%. In these situations, lowering the preadmission dose of glargine is a valid precautionary measure. Furthermore, declining insulin resistance resulting from changing caloric intake (or from the development of organ dysfunction) in patients with type 2 diabetes who are not eating and who produce endogenous insulin may obviate the need for basal insulin replacement altogether. However, even during prolonged fasting, the need for basal insulin replacement is absolute in type 1 diabetes. *Important: Withholding basal insulin in insulin-deficient patients results in rapidly escalating blood glucose levels, eventually leading to ketoacidosis if unchecked. This is especially likely when sliding scale insulin therapy is the sole method of coverage.*

For patients with type 2 diabetes whose previous dose requirement is unknown, and who have no complicating factors that might exacerbate hyperglycemia, a reasonable assumption is that the TDD of insulin would be approximately 0.3 to 0.4 units/kg/day (with about half providing basal

coverage) (see Chapter 6); however, many patients require a higher dose, owing to the effects of preexisting insulin resistance combined with intercurrent stress.⁵⁸

NUTRITIONAL STATUS AND CALORIC NEEDS

The demand for insulin is determined largely by patients' nutritional status and caloric needs. In healthy individuals, caloric requirements are approximately 25 to 30 kcal/kg body weight. With illness or after surgery, caloric needs often rise—a rule of thumb is to add 25% to the above estimate if the illness is moderate and 50% to 100% if it is severe.⁵⁶ Patients on IV dextrose solutions (5%) often receive far fewer calories than their estimated nutritional needs; after 72 hours of IV fluids, those unable to eat should receive enteral or parenteral nutrition. Because all these routes of nutrient delivery are relatively constant over 24 hours, continuous insulin coverage must be provided to sustain glycemic targets.

Patients with diabetes who are able to eat commonly receive a consistent carbohydrate diet consisting of three meals and a bedtime snack. Since meals are often skipped when a procedure or diagnostic test is planned, nurses and other caregivers must be aware of the patient's schedule and plan accordingly. If there are unanticipated changes in the time of eating, the staff should withhold the prandial insulin (rapid-acting analogue or short-acting insulin) until the appropriate time.

CHAPTER 4

Intravenous Insulin Therapy

Intravenous insulin is the best method for achieving glycemic control quickly. It is recommended over subcutaneously administered insulin for treatment of hyperglycemic emergencies (ketoacidosis and nonketotic hyperosmolar state), critical care illness, myocardial infarction and cardiogenic shock, and postoperative care related to cardiac surgical procedures.⁵⁹ Intravenous insulin infusion is also warranted in the case of NPO (nothing by mouth) status; general perioperative care, including organ transplantation; TPN; corticosteroid-related hyperglycemia; stroke; labor and delivery; and other acute illness having volatile effects on glycemia. Intravenous insulin infusion sometimes is used without concomitant dextrose to control unchecked gluconeogenesis. Caveats to bear in mind are:

- For prolonged NPO status, enough glucose must be provided to avoid starvation ketosis. Although not required to cover the insulin infusion itself, for prevention of ketosis, 5 to 10 g/hour of glucose is generally recommended, and overfeeding should be avoided.^{60,61}
- The blood glucose level must be checked frequently at the bedside to ensure safety. Most authorities recommend testing every hour until results are stable, at which point every 2 hours is sufficient.
- The protocol should include some mechanism for changing the infusion rate to reach glucose targets and to avoid hypoglycemia.

WHEN TO INITIATE

Recommended thresholds for initiation of IV insulin infusion therapy in select patients appear in Table 5.⁵⁹ Intravenous insulin should be considered when patients fail to reach target blood glucose levels with scheduled and correction-dose subcutaneous insulin therapy (see Chapter 5). Preoperative insulin infusion in patients with diabetes allows easy correction of out-of-target blood glucose levels. For patients on subcutaneous basal insulin anticipating

Table 5. Thresholds for initiation of intravenous insulin infusion therapy

Situation	Glucose threshold (mg/dL)
Perioperative care	>180
Surgical ICU care	>110-180
Nonsurgical illness	>140-180*
Pregnancy	>100

* The patient who will start IV insulin infusion therapy because of failure of subcutaneous management might have a higher threshold for initiation of the infusion than the patient who requires IV insulin infusion because of medical conditions, such as myocardial infarction or type 1 diabetes with NPO status. ICU = intensive-care unit; IV = intravenous. Adapted from Bode BW, Braithwaite SS, Steed RD, Davidson PC. Intravenous insulin infusion therapy: indications, methods, and transition to subcutaneous insulin therapy. *Endocr Pract.* 2004;10:71-80.

elective surgery, an alternative approach is to monitor blood glucose levels frequently preoperatively and intraoperatively, introducing IV insulin infusion as soon as the level exceeds 140 mg/dL. *Important: Continuous subcutaneous insulin infusion is not appropriate for delivery of basal insulin in critical care patients and should be replaced with IV insulin infusion from the outset because of concerns about perfusion of subcutaneous sites.*

During TPN, enteral nutrition, or corticosteroid therapy, sustained blood glucose readings >180 mg/dL are reason to initiate IV insulin therapy. Further, in the surgical ICU, among patients who do not have known diabetes, persistent levels >140 mg/dL over the short-term portend ongoing hyperglycemia and thus may warrant IV insulin therapy.⁶²

METHODS

Hospitals should maintain well-designed standardized protocols for the use of insulin infusions. Because frequent blood glucose monitoring and close nursing supervision are necessary for safe, effective administration of IV insulin, formal training is essential. With in-service teaching of pharmacy, nursing, and physician staff, proper administration of insulin infusions should be possible in any well-staffed general or medical surgical ward.

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Caloric Support

Regardless of the insulin titration formula, if carbohydrate is given at all, IV insulin requires a steady-state carbohydrate source. Not all short-term recipients of IV insulin infusion therapy receive or require carbohydrate. For example, post-operative heart surgery patients often require treatment with insulin despite negligible carbohydrate exposure. Carbohydrate may be given as a simultaneous infusion of dextrose, a parenteral nutrition mixture, or continuous enteral feeding. While most infusion algorithms can accommodate a slow increase or decrease in glucose intake, none can accommodate a drastic change without destabilization of blood glucose levels. Attempts at oral feeding should be accompanied by a subcutaneous bolus of rapid-acting insulin analogue (1 unit for every 10-15 g of carbohydrate consumed). A sudden discontinuation of glucose intake necessitates immediate discontinuation, reset, or decrease of the insulin drip to avoid hypoglycemia.

Mixing the Insulin Infusion

Depending on availability of infusion pumps that accurately deliver very low hourly volumes, IV therapy is prepared by mixing regular insulin with 0.9% saline in a solution of 1 unit per 1 mL saline (100 units of regular insulin in 100 mL of 0.9% saline [or 1 unit in 1 mL]). The drip is then piggybacked into an IV fluid line, and the infusion rate is controlled by an infusion pump that the nurse can adjust as directed by the algorithm. Importantly, the infusion pump must be able to deliver accurately 0.1 unit/hr increments in insulin infusion rate; the concentration of insulin in the IV drip can be adjusted if necessary, but it is strongly recommended that one insulin concentration be used consistently in a given hospital. It is also prudent to flush the drip to avoid non-specific binding of the insulin and to ensure more uniform concentration throughout the entire bag. The use of a “priming bolus” to initiate IV insulin infusion is controversial. Because repeated IV bolus insulin therapy does not maintain adequate blood insulin levels or target tissue action of insulin, the initial priming bolus of IV insulin, if used, must be followed by maintenance insulin infusion therapy.¹⁵

Algorithms

There are numerous approaches to IV insulin infusion therapy.^{12,59,63-65} The ideal method should effectively maintain blood glucose targets with minimal risk of hypoglycemia; be adaptable to all hospital units; integrate stability and responsiveness to avoid overshooting or falling short of blood glucose targets; and allow easy prescription and implementation. In particular, well-designed protocols strike a careful balance between the need for individualized care and the practical demand for standardized procedures that can be readily executed, monitored, and communicated in the hospital setting. The best protocols can be ordered with a single signature, and do not rely on mathematical calculations or analysis of sequential events by the nursing staff.⁵³ Direct order entry through a centralized database may further reduce error.

To date, no large studies have compared the effectiveness and safety of different algorithms for IV insulin therapy. Tables 6-8 show insulin infusion protocols that have been used successfully in medical and surgical ICUs—although it is up to each institution to address where and when an IV insulin infusion can be administered based on staffing experience and other resource considerations. Note that each protocol takes into account not only the current blood glucose level, but also the rate of glycemic change and the current insulin infusion rate. Ideally, insulin infusion therapy should produce progressively smaller oscillations of the hourly insulin infusion rate and more narrow excursions of blood glucose, as the clinician discovers the hourly rate that will maintain normoglycemia for a given patient.¹⁵

Correcting Hypoglycemia

A policy for correcting hypoglycemia should be the standard of care at all hospitals (see Chapter 7). For patients who cannot swallow or who are NPO, the preferred treatment is IV administration of dextrose when IV access is available. Although methods vary, one approach is to administer repeated small amounts of 50% dextrose IV until stability is assured.

Table 6. Portland Protocol: continuous intravenous insulin

Target blood glucose (BG) level, 100 to 150 mg/dL

1. Start "Portland Protocol" during surgical procedure and continue through 7 AM of the third postoperative day (POD). Patients who are not taking enteral nutrition on POD 3 should remain on this protocol until taking at least 50% of a full liquid or soft ADA diet.
2. For patients with no previous diagnosis of diabetes mellitus (DM) who present with hyperglycemia: start Portland Protocol if BG level >200 mg/dL. Consult endocrinologist on POD 2 for DM workup and follow-up orders.
3. Start insulin infusion through pump "piggybacked" to maintenance intravenous line, as follows:

Blood glucose (mg/dL)	Intravenous insulin bolus (U)	Initial insulin rate (U/h) (circle one)	
		Type 2 DM preoperatively	Type 1 DM preoperatively
80-119	0	0.5	1.0
120-179	0	1.0	2.0
180-239	0	2.0	3.5
240-299	4	3.5	5.0
300-359	8	5.0	6.5
≥360	12	6.5	8.0

4. Test BG level by finger-stick method or arterial line drop sample. The frequency of BG testing should be as follows:
 - a. If BG ≥200 mg/dL, check BG every 30 minutes.
 - b. If BG <200 mg/dL, check BG every hour.
 - c. When titrating vasopressors (such as epinephrine), check BG every 30 minutes.
 - d. If BG is 100 to 150 mg/dL with <15 mg/dL change *and* insulin rate has remained unchanged for 4 hours (stable infusion rate), then may test BG every 2 hours.
 - e. May stop every-2-hour testing on POD 3 (see items 5 and 8 below).
 - f. At night on telemetry unit:
 - If BG is 150 to 200 mg/dL, test every 2 hours.
 - If BG <150 mg/dL and stable insulin infusion rate exists, test every 4 hours.
5. Insulin titration guidelines:

Blood glucose (mg/dL)	Action
<50	Stop insulin; give 25 mL of 50% dextrose; recheck BG in 30 minutes. When BG >75 mg/dL, restart with rate 50% of previous rate.
50-75	Stop insulin; if previous BG >100 mg/dL, then give 25 mL of 50% dextrose; recheck BG in 30 minutes. When BG >75 mg/dL, restart with rate 50% of previous rate.
76-100	If <10 mg/dL lower than last test, decrease rate by 0.5 U/h. If >10 mg/dL lower than last test, decrease rate by 50%. If ≥last test result, maintain same rate.
101-150	Use same rate.
151-200	If 20 mg/dL lower than last test, use same rate. Otherwise, increase rate by 0.5 U/h.
>200	If ≥30 mg/dL lower than last test, use same rate. If <30 mg/dL lower than last test (OR if higher than last test), increase rate by 1 U/h. AND if >240 mg/dL, give intravenous bolus of regular insulin per "intravenous insulin bolus" dosage scale (see item 3 above). Recheck BG in 30 minutes.

If BG >200 mg/dL and has not decreased after 3 consecutive increases in insulin, give intravenous bolus per item 3 and double the insulin rate.

If BG >300 mg/dL for 4 consecutive readings, call physician for additional intravenous bolus orders.

6. Begin use of 1,800-calorie ADA diabetic diet with any oral intake.
7. Postmeal subcutaneous insulin lispro (Humalog) supplement in addition to insulin infusion when oral intake advances beyond clear liquids:
 - a. If patient eats 50% or less of servings on breakfast, lunch, or supper tray, then give 3 U of insulin lispro subcutaneously immediately after that meal.
 - b. If patient eats more than 50% of serving on breakfast, lunch, or supper tray, then give 6 U of insulin lispro subcutaneously immediately after that meal.
8. On POD 3: Restart preadmission glycemic control medication, unless patient is not tolerating enteral nutrition— then maintain insulin drip per protocol.

From Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract.* 2004;10(suppl 2):21-33. Copyright ©2004 American Association of Clinical Endocrinologists.

Table 7. Example of a standardized IV insulin infusion

General guidelines: **Goal blood glucose (BG) = _____** (usually 80-180 mg/dL)

- **Standard drip:** 100 Units/100 mL 0.9% NaCl via an infusion device.
- Surgical patients who have received an oral diabetes medication within 24 hrs should start when BG >120 mg/dL. All other patients can start when BG ≥70 mg/dL.
- Insulin infusions should be discontinued when a patient is eating AND has received 1st dose of subcutaneous insulin.

Intravenous fluids:

- Most patients will need 5-10 g of glucose per hour.
 - D₅W or D₅W1\2NS at 100-200 mL/hr or equivalent (TPN, enteral feeds, etc)

Initiating the infusion:

- **Algorithm 1:** Start here for most patients.
- **Algorithm 2:** For patients not controlled with Algorithm 1, or start here if s/p CABG, s/p solid organ transplant or islet cell transplant, receiving glucocorticoids, or patient with diabetes receiving >80 units/day of insulin as an outpatient.
- **Algorithm 3:** For patients not controlled on Algorithm 2. NO PATIENTS START HERE without authorization from the endocrine service.
- **Algorithm 4:** For patients not controlled on Algorithm 3. NO PATIENTS START HERE.
- Patients not controlled with the above algorithms need an endocrine consult.

Algorithm 1		Algorithm 2		Algorithm 3		Algorithm 4	
BG	Units/hr	BG	Units/hr	BG	Units/hr	BG	Units/hr
<60 = Hypoglycemia (See below for treatment)							
<70	Off	<70	Off	<70	Off	<70	Off
70-109	0.2	70-109	0.5	70-109	1	70-109	1.5
110-119	0.5	110-119	1	110-119	2	110-119	3
120-149	1	120-149	1.5	120-149	3	120-149	5
150-179	1.5	150-179	2	150-179	4	150-179	7
180-209	2	180-209	3	180-209	5	180-209	9
210-239	2	210-239	4	210-239	6	210-239	12
240-269	3	240-269	5	240-269	8	240-269	16
270-299	3	270-299	6	270-299	10	270-299	20
300-329	4	300-329	7	300-329	12	300-329	24
330-359	4	330-359	8	330-359	14	>330	28
>360	6	>360	12	>360	16		

Moving from algorithm to algorithm:

- Moving up: An algorithm failure is defined as BG outside the goal range (see above goal), and the BG does not change by at least 60 mg/dL within 1 hour.
- Moving down: When BG is <70 mg/dL X 2.

Patient monitoring:

- Check capillary BG every hour until it is within goal range for 4 hours, then decrease to every 2 hours for 4 hours, and if remains stable may decrease to every 4 hours.
- Hourly monitoring may be indicated for critically ill patients even if they have stable BG.

Treatment of hypoglycemia (BG <60 mg/dL):

- Discontinue insulin drip AND
- Give D₅₀W IV
 - Patient awake: 25 mL (1/2 amp)
 - Patient not awake: 50 mL (1 amp)
- Recheck BG every 20 minutes and repeat 25 mL of D₅₀W IV if <60 mg/dL. Restart drip once BG is >70 mg/dL X2 checks. Restart drip with lower algorithm (see Moving down).

Notify the physician:

- For any BG change greater than 100 mg/dL in 1 hour
- For BG >360 mg/dL
- For hypoglycemia that has not resolved within 20 min of administering 50 mL of D₅₀W IV and discontinuing the insulin drip

From Trence DL, Kelly JL, Hirsch IB. The rationale and management of hyperglycemia for in-patients with cardiovascular disease: time for a change. *J Clin Endocrinol Metab.* 2003;88:2430-2437. Copyright 2003, The Endocrine Society.

Table 8. Yale insulin infusion protocol

The following insulin infusion 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 blood glucose (BG) ≥ 500 mg/dL, a physician should be consulted for specific orders. Also, please notify a physician if the response to the insulin infusion is unusual or unexpected or if any situation arises that is not adequately addressed in these guidelines.

Initiating an insulin infusion

- 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 infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing).
- 3) **TARGET BG LEVELS:** 100-139 mg/dL.
- 4) **BOLUS & INITIAL INSULIN INFUSION RATE:** Divide initial BG level by 100, then round to nearest 0.5 U for bolus AND initial infusion rate.
 Examples: 1) Initial BG = 325 mg/dL: $325 \div 100 = 3.25$, round \uparrow to 3.5: IV bolus 3.5 U + start infusion @ 3.5 U/hr.
 2) Initial BG = 174 mg/dL; $174 \div 100 = 1.74$, round \downarrow to 1.5: IV bolus 1.5 U + start infusion @ 1.5 U/hr.

Blood glucose monitoring

- 1) Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary BG (ie, finger sticks) may be inaccurate and obtaining the blood sample from an indwelling vascular catheter is acceptable.
- 2) Then check BG q 2 hours; once stable, x 12-24 hours. BG checks can then 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 BG monitoring, until BG is again stable (2-3 consecutive BG values within target range):
 - a) any change in insulin infusion rate (ie, BG out of target range)
 - b) significant changes in clinical condition
 - c) initiation or cessation of pressor or steroid therapy
 - d) initiation or cessation of renal replacement therapy (hemodialysis, CVVH, etc)
 - e) initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feeding, etc)

Changing the insulin infusion rate

- If BG <50 mg/dL: Give 1 amp (25 g) D₅₀ IV; recheck BG q 15 minutes.
- D/C INSULIN INFUSION** → When BG ≥ 100 mg/dL, wait 1 hour, then restart insulin infusion at 50% of original rate.
- If BG 50-74 mg/dL: 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 infusion 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 2 PM was 150 mg/dL and the BG at 4 PM is now 120 mg/dL, the hourly change over 2 hours is $-30 \text{ mg/dL} \div 2 \text{ hours} = -15 \text{ mg/dL/hr}$.]

BG 75-99 mg/dL	BG 100-139 mg/dL	BG 140-199 mg/dL	BG ≥ 200 mg/dL	Instructions*
		BG \uparrow by >50 mg/dL/hr	BG \uparrow	\uparrow INFUSION by 2Δ
	BG \uparrow by >25 mg/dL/hr	BG \uparrow by 1-50 mg/dL/hr OR BG UNCHANGED	BG UNCHANGED OR BG \downarrow by 1-25 mg/dL/hr	\uparrow INFUSION by Δ
BG \uparrow	BG \uparrow by 1-25 mg/dL/hr BG UNCHANGED OR BG \downarrow by 1-25 mg/dL/hr	BG \downarrow by 1-50 mg/dL/hr	BG \downarrow by 26-75 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED OR BG \downarrow by 1-25 mg/dL/hr	BG \downarrow by 26-50 mg/dL/hr	BG \downarrow by 51-75 mg/dL/hr	BG \downarrow by 76-100 mg/dL/hr	\downarrow INFUSION by Δ
BG \downarrow by >25 mg/dL/hr see below†	BG \downarrow by >50 mg/dL/hr	BG \downarrow by >75 mg/dL/hr	BG \downarrow by >100 mg/dL/hr	HOLD x 30 min, then \downarrow INFUSION by 2Δ

†D/C INSULIN INFUSION; \sqrt{BG} q 30 min; when BG is ≥ 100 mg/dL, restart infusion at 75% of most recent rate.

(continued on next page)

Table 8. Yale insulin infusion protocol (continued)

*CHANGES IN INFUSION RATE (Δ) are determined by the current rate:

Current rate (U/hr)	Δ = Rate change (U/hr)	2Δ = 2 \times 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 physician)

From Goldberg PA, Siegel MD, Sherwin RS, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care*. 2004;27:461-467. Copyright ©2004 American Diabetes Association.

CHAPTER 5

Switching From Intravenous to Subcutaneous Insulin

After insulin infusion therapy, patients with diabetes previously on insulin must resume subcutaneous insulin therapy. Review of preadmission control is helpful in deciding whether a new regimen should be initiated to achieve glycemic targets. A crucial consideration is the anticipated pattern of carbohydrate exposure.⁶⁶

RECONSIDER PREADMISSION REGIMEN

A common pattern is to move directly from NPO status to eating discrete small meals. For the patient previously on an NPH-based regimen, options include adjusting the dose of NPH and continuing with the nonphysiologic NPH regimen, or switching to a basal-prandial regimen consisting of once-daily basal insulin glargine and a rapid-acting insulin at mealtimes. Insulin glargine is released slowly and evenly into the bloodstream from the subcutaneous injection site, replicating physiologic basal insulin secretion more closely than NPH, Lente, or Ultralente insulin.⁶⁷ When substituted for once- or twice-daily NPH in various outpatient insulin regimens, insulin glargine controls blood glucose levels at least as well as NPH, but with fewer episodes of hypoglycemia.^{40,41,44,68,69} Patients using mixed NPH and regular insulin prior to hospitalization often welcome the opportunity to go home on a regimen that offers the potential for hypoglycemia reduction, as well as more freedom in the timing and composition of meals. However, others, such as blind or elderly patients who have difficulty drawing up insulin in a syringe, may prefer a less intensive regimen with fewer injections.

No Fixed Rule

Patients not on insulin prior to hospitalization, but whose A1C levels exceed the target range of $\leq 7.0\%$, should be started on a revised treatment plan. For patients whose recovery is not likely to be jeopardized by a period of dose titration, the addition of a new class of oral agents at discharge may be helpful. For others, the addition of insulin therapy is desirable to achieve and maintain glycemic

control. Testing A1C when patients are first admitted to the hospital helps to determine whether hyperglycemia on discharge is due to unrecognized diabetes or hospital-related stress.⁷⁰ Patients with type 2 diabetes (or who have no prior history of diabetes) whose blood glucose levels are well controlled with ≤ 0.5 units of IV insulin therapy per hour may not require transition to subcutaneous insulin therapy. However, there is no fixed rule. A patient newly diagnosed with type 2 diabetes exhibiting a high A1C, for example, may do well with oral agents alone once the cycle of glucotoxicity and insulin resistance is disrupted; or, in the case of a patient with longstanding type 2 diabetes and a high A1C, transition to subcutaneous insulin may be required at discharge despite effective glucose control with relatively low doses of IV insulin under the conditions of hospitalization. In all cases, regular blood glucose monitoring should continue throughout the hospital stay, with correction-dose insulin administered as needed.

PREPARING PATIENTS AND CAREGIVERS

Intravenous insulin infusion should be continued until at least 2 hours after the first doses of subcutaneous basal insulin to guard against any gaps in coverage that could lead to ketoacidosis in insulin-deficient patients. However, if both basal and prandial insulin are given, empirical evidence suggests that IV insulin may be discontinued after 15 minutes. A program of glucose monitoring to discern falling insulin requirements before and after discharge is vital. Patients and subsequent caregivers should receive careful instruction about methods for blood glucose monitoring as well as administration and adjustment of basal, prandial, and correction doses of insulin. Arrangements must be made for timely follow-up with the physician and the diabetes team, and for home health care services, if needed (see Chapter 8).

MAKING THE SWITCH

Conversion from IV to subcutaneous insulin can begin only upon discontinuation of volume resuscitation or pressor support. Scheduled subcutaneous insulin therapy should meet basal and nutritional insulin needs and include correction doses for hyperglycemia. Basal insulin glargine, with its even release profile over approximately 20 to 24 hours,

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is commonly used to facilitate the transition to subcutaneous therapy, sometimes starting hours or days before the insulin infusion finally is terminated. If no rapid-acting analogue is administered concurrently, the insulin drip should continue for at least 2 hours after initiation of basal subcutaneous insulin therapy.

The 24-hour basal insulin requirement can be estimated from the average amount of insulin infused during a recent previous 6- to 8-hour interval when carbohydrate exposure was negligible. This process should begin after the patient is taken off pressor agents and the blood glucose is stable and in target range. In the observation of some users, if a column protocol is employed, an indicator of short-term stability of insulin requirement during insulin infusion therapy (for patients who are not eating) might be maintenance of the same column assignment for at least the preceding 8 to 24 hours.

PREDICTING INSULIN REQUIREMENTS

The ability of the insulin infusion to predict insulin requirements has been shown most convincingly in nonsurgical settings.⁷¹ Experience of some practitioners in the postoperative setting also has suggested that, during sharply curtailed caloric intake and the absence of other insulin administration, requirements for IV insulin infusion can approximate the daily basal insulin requirement, at least for initial dosing, under the ambient conditions of stress. Thus, for patients not receiving IV dextrose, unless downward dose modification is required based on analysis of other patient attributes (renal failure, steroid taper, etc), about 80% of the projected 24-hour basal insulin requirement is administered subcutaneously as the first daily injection of long-acting insulin glargine; the mean overnight insulin drip rate in units per hour can be multiplied by 20 hours to calculate the initial loading dose of glargine.⁵⁹ The dose should be adjusted each evening, most likely downward, based on the patient's response, and the order then should be renewed as appropriate. After the first dosing of glargine and each upward adjustment, it is wise to order a glucose test for the mid-sleep period and to administer IV dextrose or give a 15 to 30 g carbohydrate snack if the result is <80 mg/dL. Although many patients start out by eating poorly, patients who have started to eat will need more insulin during the day

than at night. The amount of prandial coverage gradually is increased until approximately equal amounts of basal and bolus insulin are administered.

Discovering the Daily Dose

In patients whose status is rapidly changing, or when stability is uncertain, it may be advisable to discover the daily dose requirements for subcutaneous insulin before introducing or reintroducing the use of long-acting insulin or insulin analogues. Dose-finding is achievable by use of shorter-acting insulin for one day, or perhaps several days if necessary, after which approved guidelines can be used for transition from a shorter-acting insulin to a long-acting insulin analogue. *Important: When two injections of NPH are used daily, at the time of discontinuation of NPH, the first dose of glargine is determined to be 80% of the NPH dose requirement.*

For prandial coverage, use of rapid-acting insulin analogues (lispro, aspart, or glulisine) or oral agents must be postponed until the patient has demonstrated ability to eat discrete meals. It must be stressed that no guidelines for transition to subcutaneous insulin have been validated in published trials.

The foregoing discussion pertains to patients who will be eating. However, different transitioning regimens are used for patients who will not resume discrete meals but rather will have alternative exposure to carbohydrate, often in a fairly continuous manner (see Chapter 6). Rapid-acting insulin analogues are inappropriate for these patients; and, as yet, no particular method of nutritional coverage has been validated for this situation. One approach, based on anecdotal evidence, might be the use of longer-acting insulins, in combination or singly, given at 6- to 12-hour intervals.

DAILY DOSE REVISION

In addition to making an initial dose assignment for subcutaneous insulin, one important challenge facing the physician is to make ongoing revisions of scheduled insulin until true needs are discovered or, as the patient's condition changes, rediscovered. Therefore, a dose-finding strategy that will minimize hyperglycemia and prevent hypoglycemia is necessary for making daily revisions in scheduled therapy. Following is an example of such an approach for a patient

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whose upper target might be a blood glucose level of 180 mg/dL, as, for example, during continuous enteral feedings, which calculates increments or decrements of scheduled insulin dose based on the effect of the insulin regimen given the day before:

- Determine the total insulin dose administered the previous day
- Review the corresponding glycemic control for that day
- Then calculate today's scheduled insulin dose as follows:
 - If some glucoses were <80 mg/dL, use 80% of the previous day's total
 - If glucoses were 80 to 179 mg/dL, use 100% of the previous day's total
 - If some glucoses were ≥180 mg/dL, and none were <80 mg/dL, use 110% of the previous day's total

Because food intake is often erratic in the hospital, prandial insulin can be estimated as 1 to 2 units of rapid-acting analogue per 15-g serving of carbohydrate at meals, starting with 1 unit per 15-g serving or 3 to 5 units at each meal and increasing as needed.⁵³ For the first light meals, if food intake is not known, it is best to use little lag time and be especially

conservative with the first doses of insulin, taking care to use correction doses appropriately and as a dose-finding strategy for the next day. During recovery, the basal requirement often falls, and the prandial requirement rises.

If the patient receives IV dextrose or continuous nutritional support, about 1 unit of insulin for every 10 g of carbohydrate is a reasonable estimate of the initial daily requirement for nutritional insulin coverage. (For example, D₅-containing fluids administered at 83 cc/hr would deliver 2 liters or 100 g of dextrose daily and might initially be covered by approximately 10 units of scheduled subcutaneous insulin above basal requirements delivered in a continuous manner.) The initial dose may substantially underestimate the need that will eventually be demonstrated during nutritional support.

CORRECTION DOSES

Correction doses for hyperglycemia are given preferably as rapid-acting insulin analogue. The correction dose is administered before meals, at bedtime, and at 3:00 AM in patients who are eating, or every 4 to 6 hours in patients receiving continuous feeding or NPO. To determine the correction dose, it is necessary to estimate how much the blood glucose level is lowered by 1 unit of rapid-acting insulin. This factor is

Table 9. ADA glycemic goals for adults with diabetes

Index	Goal
A1C	<7.0%*
Preprandial plasma glucose	90-130 mg/dL (5.0-7.2 mmol/L)
Peak postprandial plasma glucose†	<180 mg/dL (10.0 mmol/L)

Key concepts in setting goals:

- A1C is the primary target for glycemic control
- Goals should be individualized
- Certain populations (children, pregnant women, and elderly) require special considerations
- Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia
- More stringent glycemic goals (ie, a normal A1C, <6%) may further reduce complications at the cost of increasing the risk for hypoglycemia (particularly in patients with type 1 diabetes)
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial goals

*Referenced to a nondiabetic range of 4.0% to 6.0% using a DCCT-based assay.

†Postprandial glucose measurements should be made 1 to 2 h after the beginning of the meal.

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called the *correction factor* or insulin sensitivity factor and is calculated by dividing the TDD into 1700. For most patients, 1 unit of rapid-acting insulin lowers the blood glucose level, on average, by 30 to 50 mg/dL. The formula for the correction dose is the actual blood glucose level minus the target blood glucose (usually a value between 100 and 150 mg/dL) divided by the correction factor.

In calculating the correction dose, it is important to remember that postprandial blood glucose targets differ from preprandial targets (Table 9). The preprandial standard

should not be applied until 3 to 5 hours after a meal. It is also necessary to keep in mind that overlapping of effect, or insulin stacking, will occur if a correction dose is repeated within the action timeframe of the previous dose (Figure 4). The use of a rapid-acting analogue every 2 hours has not been validated outside the context of treatment of metabolic emergency.⁷² Thus, administration of correction doses of rapid-acting insulin analogue or of regular insulin generally should not be repeated more often than every 4 hours or every 6 hours, respectively.

CHAPTER 6

Subcutaneous Insulin Strategies

Many patients are satisfactorily managed with subcutaneous insulin therapy throughout their hospital stay. In the hospital, the ambulatory concept of basal-prandial-correction therapy is replaced by the concept of scheduled and correction therapy. Thus, the estimated daily requirement for exogenous insulin should be ordered as scheduled therapy. Any increase of insulin requirement manifests as an elevated blood glucose level and necessitates the use of correction-dose therapy (see Chapter 5). If correction doses are frequently required, the scheduled insulin dose should be increased to accommodate the higher demand for insulin.¹⁶ Establishing clear, consistent protocols for prevention of hypoglycemia is likely to increase the level of comfort among hospital staff with respect to providing or augmenting scheduled insulin therapy (see Chapter 7).⁵³

WRITING INSULIN ORDERS

Declining blood glucose levels may signify a reversal of medical stress, requiring reduction of insulin dosages. Such downward trends can be anticipated by writing a “withhold” order for short-acting components of scheduled therapy under certain conditions, thus providing a buffer against hypoglycemia. Additionally, incorporating “alert” or “call” parameters into insulin orders is an effective means of alerting physicians, nurses, and other staff to the potential need for revising a standing order. Table 10 presents a sample standardized order form that addresses the basal, prandial, and correction components of subcutaneous insulin therapy.

PERIOPERATIVE REQUIREMENTS

The safety and effectiveness of perioperative protocols using subcutaneous insulin analogues have not been well studied in the context of specific procedures, NPO status, or surgery. In patients with diabetes (free of hypoglycemia), prandial insulin is often withheld but basal insulin maintained on the night before a scheduled procedure, during brief NPO status, or for anesthesia <1 to 2 hours. If it is suspected that the

patient is normally overtreated, the dose can be reduced by 20%. For patients with type 1 diabetes using NPH, half the normal dose is given on the morning of the procedure, and if the patient returns to the floor before lunch, the other half is administered. For patients with type 2 diabetes, NPH can be withheld entirely on the morning of the procedure, but if the patient returns to the floor before lunch, two thirds of the normal dose can be given. In diabetic patients scheduled for brief surgical procedures, glargine can be administered the night before the operation without interruption. Correction doses of rapid-acting or regular insulin can be used on the morning of the procedure if the blood glucose level is >180 mg/dL.

REQUIREMENTS IN PATIENTS NOT EATING

When NPO status persists, or when continuous IV dextrose therapy or enteral feeding lasts for a prolonged period, subcutaneous insulin therapy is often used. Administered dextrose or enteral feedings are likely to necessitate upward revision of the initially assigned doses of scheduled subcutaneous insulin, as determined by the requirement for supplementation. For many patients, a ratio of regular to NPH insulin can be discovered such that when the needed doses are administered at 6- to 12-hour intervals, they will deliver fairly constant effect.

In the experience of one author, a reasonable starting place for coverage of continuous carbohydrate exposure is to calculate the basal insulin as 0.15 units/kg/day, and the nutritional as 1 unit/10 g/day, to split the daily total into four equal portions, and to mix each dose as two-thirds NPH and one-third regular insulin. *For example:*

- Patient: Melinda (female)
- Weight: 80 kilos
- History: type 2 diabetes
- Treatment: previously on metformin
- Current problem: ovarian carcinoma
- Status: postop, NPO, D₅ in 0.45 at 100 cc/hr

Table 10. Example of standardized subcutaneous insulin orders for patients who are eating

Blood glucose (BG) monitoring: Before meals and at bedtime ___ Hrs after meals 2-3 AM
Goal premeal BG = (90-130 mg/dL for most patients)

	<i>Breakfast</i>	<i>Lunch</i>	<i>Dinner</i>	<i>Bedtime</i>
Prandial insulin orders	Give ___ units of: <input type="checkbox"/> Lispro <input type="checkbox"/> Aspart <input type="checkbox"/> Glulisine <input type="checkbox"/> Regular	Give ___ units of: <input type="checkbox"/> Lispro <input type="checkbox"/> Aspart <input type="checkbox"/> Glulisine <input type="checkbox"/> Regular	Give ___ units of: <input type="checkbox"/> Lispro <input type="checkbox"/> Aspart <input type="checkbox"/> Glulisine <input type="checkbox"/> Regular	
Basal insulin orders	Give ___ units of: <input type="checkbox"/> NPH <input type="checkbox"/> Lente <input type="checkbox"/> Ultralente <input type="checkbox"/> Glargine	Give ___ units of: <input type="checkbox"/> NPH <input type="checkbox"/> Lente <input type="checkbox"/> Ultralente <input type="checkbox"/> Glargine	Give ___ units of: <input type="checkbox"/> NPH <input type="checkbox"/> Lente <input type="checkbox"/> Ultralente <input type="checkbox"/> Glargine	Give ___ units of: <input type="checkbox"/> NPH <input type="checkbox"/> Lente <input type="checkbox"/> Ultralente <input type="checkbox"/> Glargine

Suggested lag times for prandial insulin:*

Aspart/Lispro/Glulisine: 0-15 minutes before eating Regular: 30 minutes before eating

For BG <60 mg/dL

- A. If patient can take PO, give 15 g of fast-acting carbohydrate (4-oz fruit juice/nondiet soda, 8-oz nonfat milk, or 3-4 glucose tablets).
- B. If patient cannot take PO, give 25 mL of D₅₀ as IV push.
- C. Check finger capillary glucose q 15 minutes and repeat above if BG <80 mg/dL.

Premeal correction-dose algorithm for hyperglycemia: To be administered in addition to scheduled insulin dose to correct premeal hyperglycemia.

Lispro Glulisine Aspart

Low-dose algorithm

(For pts requiring ≤40 units of insulin/day)

Premeal BG (mg/dL)	Additional insulin (units)
150-199	1
200-249	2
250-299	3
300-349	4
>349	5

Medium-dose algorithm

(For pts requiring 40-80 units of insulin/day)

Premeal BG (mg/dL)	Additional insulin (units)
150-199	1
200-249	3
250-299	5
300-349	7
>349	8

High-dose algorithm

(For pts requiring >80 units of insulin/day)

Premeal BG (mg/dL)	Additional insulin (units)
150-199	2
200-249	4
250-299	7
300-349	10
>349	12

Individualized algorithm

Premeal BG (mg/dL)	Additional insulin (units)
150-199	
200-249	
250-299	
300-349	
>349	

General insulin dosing recommendations:

A. Patients with type 1 diabetes

This patient must have insulin to prevent ketosis. Even if the patient is not eating, he/she will need at least basal insulin (NPH/Lente/Ultralente/glargine) to prevent ketosis.

1. When admitting a patient with type 1 diabetes, continue the basal insulin that he/she was taking at home at the same dose. If the patient will be NPO, use an insulin drip rather than subcutaneous insulin. The prandial insulin (regular/lispro/aspart/glulisine) may require adjustment depending on the patient's situation. If the patient is eating much less, the prandial insulin will need to be reduced. Many hospitalized patients are under significant metabolic stress (infection, glucocorticoids, etc) and may require larger doses of prandial insulin despite eating less.
2. If a patient is newly diagnosed, the usual daily insulin requirement is 0.3 to 0.4 units/kg/day. Half, or 50%, should be given as basal insulin and the remainder as prandial insulin.

B. Patients with type 2 diabetes

1. If patient is using insulin at home, continue the outpatient regimen and adjust as needed.
2. If patient has not been using insulin previously, the usual total daily insulin requirement is 0.4 to 1.0 units/kg/day.

Note: Individual insulin doses vary widely and adjustments should be based on the bedside and laboratory glucose levels.
 *Lag time = interval of time between injecting and eating.

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- Basal insulin: $80 \text{ kg} \times 0.15 \text{ unit/kg} \rightarrow 12 \text{ units per 24 hr}$
- Insulin to cover D_5 : $2400 \text{ cc} \times 5 \text{ g/100 cc} = 120 \text{ g} \rightarrow 12 \text{ units per 24 hr}$
- Total insulin dose: 24 units per 24 hr
- Sample subcutaneous insulin orders:
 - 4 units NPH and 2 units regular insulin every 6 hr
 - Capillary BG every 6 hr
 - Withhold regular insulin for glucose $<90 \text{ mg/dL}$
 - Withhold scheduled insulin if D_5 is interrupted
 - Correction-dose algorithm for highs

Note: The sample orders appearing in this chapter are for illustration only. All treatment decisions must be based on the needs of individual patients.

Although methods for administering insulin to patients receiving TPN have not been formally studied, observational evidence suggests that 67% to 80% of the daily insulin requirement may be administered in the TPN bag; the balance may be given subcutaneously, as small doses of regular insulin or mixtures of NPH and regular insulin, or intravenously by continuous infusion apart from TPN.⁷³

For example: A patient has had an IV insulin infusion to cover TPN, with an increasing part of the insulin requirement added to the TPN each day. After several days, 40 units of insulin are in the 24-hour bag of TPN, and to maintain normoglycemia over the most recent 24-hour period, an additional 34 units of insulin were administered through the IV insulin infusion. The patient is hemodynamically stable. The TPN formula for the next day is not changed except for the insulin, which is increased to 54 units (approximately 75% of the daily requirement). Additionally, the IV infusion of insulin is discontinued and replaced with the following orders:

- 3 units NPH every 6 hr (withhold x 12 hr before TPN stops)
- 2 units regular insulin every 6 hr (withhold x 6 hr before TPN stops, withhold if BG $<100 \text{ mg/dL}$)

- Correction-dose regular insulin algorithm

This *sample* regimen enables the patient to be treated without the use of IV insulin infusion. Because the subcutaneous insulin can be interrupted, wastage of TPN is minimized should a downward trend due to resolution of insulin resistance occur.

Nocturnal enteral feedings require additional coordination and judgment on the part of the physician. Observational evidence indicates that NPH offers the best glycemic control in nocturnal enteral feedings; however, because the peak action of NPH is delayed if it is administered when enteral feedings are initiated (a common practice), short-acting insulin must be added at the start of tube feeds to cover the carbohydrate exposure during the first several hours. Dosing is determined by frequent monitoring of blood glucose (every 2 to 3 hours the first few nights).⁷⁴

Although experience is limited, the use of glargine to cover enteral feedings has been published.⁷⁵ The main concern about long-acting insulin in this setting is its inflexibility, which could potentially lead to hypoglycemia in the event of abrupt disruption of nutritional intake or a downward trend in insulin resistance. The safest course is to ensure the glargine dose meets only part of the daily insulin requirement (the true basal requirement), with the balance consisting of shorter-acting insulin.

For example: A patient with type 1 diabetes may have been placed on an 18-unit daily dose of glargine appropriate for true basal requirements at home. At a time when continuous enteral feedings are required, the caregiver may wish to “lock in” that basal dose. The requirement for nutritional coverage is gradually discovered over several days, starting with an assumption of 1 unit per 10 g, reading the labels of the cans to determine the 24-hour carbohydrate allotment. Each day, if hyperglycemia persists, 10% more insulin is added above the amount given the day before. If the patient finally is shown to require an additional 48 units of insulin daily for coverage, a *sample* order to maintain normoglycemia might be as follows:

- Capillary BG at 0400, 1000, 1600, 2200

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- Glargine: 18 units at 2200
- Regular insulin: 4 units at 0400, 1000, 1600, 2200 (withhold for BG <120 mg/dL or for interruption of tube feeds)
- NPH insulin: 8 units at 0400, 1000, 1600, 2200 (withhold for interruption of tube feeds)
- Correction-dose algorithm using rapid-acting or regular insulin

Note: The sample orders appearing in this chapter are for illustration only. All treatment decisions must be based on the needs of individual patients.

During initiation of subcutaneous insulin therapy, scheduled doses should be revised daily, based on the patient's response. A system for preventing hypoglycemia should be in place (see Chapter 7).

REQUIREMENTS FOR PATIENTS EATING INTERMITTENTLY

Hospitalized patients may receive nutrition intermittently. This is common in patients who are being transitioned from NPO to a regular diet, who have anorexia or nausea, or who are receiving overnight cycling of enteral feedings. Appropriate insulins, used either alone or in combination, might include regular, intermediate, and long-acting insulins or insulin analogues. The selected regimen should cover basal needs and be timed to match intermittent nutritional intake. Following is a *sample* written order for a transitional meal plan:

- Capillary BG qid at 0800, 1200, 1800, 2200
- Estimate daily insulin requirement and split two thirds in AM (mixed), one third in PM (divided between supper and bedtime)
- Two thirds of AM dose as NPH, one third as regular insulin

- One half of PM dose as regular insulin at 1800
- One half of PM dose as NPH at 2200
- Reduce scheduled regular insulin by 50% for capillary BG 80 to 120 mg/dL, withhold for <80 mg/dL
- Correction-dose algorithm using rapid-acting analogue or regular insulin

An example of an order for overnight enteral feedings might be:

- Start enteral overnight feedings at 1800 daily
- Transitional daytime meal plan
- Capillary BG at 0800, 1200, 1800, 2400
- Regular insulin (~20-33%) and NPH (~67-80%) scheduled for 1800
- Possibly smaller doses of regular and NPH insulin scheduled for 0800
- Correction-dose algorithm using rapid-acting analogue or regular insulin

RESUMPTION OF DISCRETE MEALS

Once patients have begun to eat discrete meals, scheduled insulin can be replaced by the model of basal-prandial-correction therapy. This phase affords an ideal opportunity to devise and initiate a treatment plan appropriate for the ambulatory setting. The carbohydrate content of each meal can be prescribed; the initiation dose of premeal rapid-acting analogue and basal insulin glargine can be administered; the doses can be adjusted during consistent carbohydrate intake until target glucose results are achieved; and correction doses can be established and applied as needed. Patients can learn the purpose of each component of therapy, and come to understand how and why multiple daily injection (MDI) regimens provide better glycemic control, lower risk of hypoglycemia, and a more flexible lifestyle than conventional twice-daily regimens.

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Following is a *sample* order for initiating MDI in a patient newly started on multiple daily injections of insulin:

- Capillary BG qid AC and HS
- Diet to include 60-g carbohydrate at breakfast, lunch, and supper
- Glulisine: 6 units before breakfast, lunch, and supper
- Correction-dose algorithm using glulisine
- Glargine: 18 units at bedtime

After hospital discharge, patients should meet with diabetes educators and nutritionists to learn how to identify meals in terms of their carbohydrate content and to use food- and glucose-monitoring records for the purpose of calculating and applying their insulin-to-carbohydrate ratio (see Chapter 8).⁷⁶

Patients With Type 1 Diabetes

For the patient with type 1 diabetes able to consume food, the simplest approach to glycemic control is continuation of the usual basal and prandial insulin regimen. However, considering that many people with type 1 diabetes still administer insulin only twice per day, the hospital stay presents an invaluable opportunity to teach patients about intensive therapy, including desired glycemic goals, the need for frequent self-monitoring of blood glucose, and recommendations for diet and exercise.

In newly diagnosed patients, doses of basal and mealtime insulin should be conservative at first and then increased according to blood glucose results. Blood glucose levels should be monitored at least once before each meal and at bedtime, keeping in mind that hospitalized patients often have higher insulin requirements. Following is a general procedure for establishing an initial insulin regimen:

- *Calculate the patient's TDD of insulin—that is, the sum of all units of all types of insulin taken.* To determine the TDD in a newly diagnosed patient, multiply the patient's body weight in kilograms by 0.3 units (average for full insulin replacement in type 1 patients, 0.7 units/kg; range, 0.4 units/kg to 0.8 units/kg). For example, if the patient weighs 100 kg, the TDD = 30 units.

- *Determine the basal insulin requirement.* This should be 40% to 50% of the TDD. The basal insulin requirement may be in the form of NPH, Lente, Ultralente, or insulin glargine. The dosage may be advanced every 2 to 3 days for NPH and weekly for Ultralente and insulin glargine.
- *Determine the mealtime insulin requirement.* The total mealtime insulin dosage is equal to the TDD minus the basal insulin dosage. For example, if the TDD were 30 units and the basal insulin requirement 12 units (30×0.4), the total mealtime dosage would be 18 units. The pre-breakfast, pre-lunch, and pre-dinner doses will depend on the number of calories consumed at each meal and the type of insulin used.
- *Determine the correction dose.* For most patients, 1 unit of rapid-acting insulin lowers the blood glucose level, on average, by 30 to 50 mg/dL. The formula for the correction dose is the actual blood glucose level minus the target blood glucose (usually 100 mg/dL) divided by the correction factor (see Chapter 5).

Important: These guidelines are intended only as a rough starting point and must be tailored to the individual needs of patients.⁷⁷

Patients With Type 2 Diabetes

Patients with type 2 diabetes who achieve excellent control of diabetes outside the hospital may require correction doses of short-acting insulin analogues during the hospital stay, when blood glucose targets often exceed target range. However, repeated need for supplemental insulin may signal secondary failure of an oral agent. Measuring A1C can usually determine whether this is the case.⁷⁸

The following insulin regimens are suitable for patients with type 2 diabetes, depending on disease progression and the desired level of glycemic control:

- *Once-daily insulin regimens.* These regimens may provide adequate glycemic control during the early stages of type 2 diabetes when endogenous insulin secretion is still substantial. The most common of this type is one injection of NPH or insulin glargine at bedtime.^{79,80}

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- *Twice-daily "split-mix" regimen.* Usually a mixture of intermediate-acting insulin (NPH) and a short- or rapid-acting insulin (regular or insulin lispro/aspart/glulisine), these regimens offer better glycemic control than single-injection regimens and are appropriate for patients who have endogenous insulin secretion adequate to compensate for gaps in coverage. However, a recent study reported that adding insulin glargine once daily to glimepiride plus metformin therapy was safer and more effective than beginning twice-daily injections of 70/30 and discontinuing oral antidiabetic agents in patients with type 2 diabetes for whom oral therapy had failed.⁷⁹ Commercially prepared mixtures of regular and NPH insulin, neutral protamine lispro and insulin lispro, and insulin aspart protamine suspension and insulin aspart may be helpful for patients who are blind or elderly, who may find mixing insulin in a syringe difficult, or who simply will not be successful with a more sophisticated regimen. Mixtures are not useful for most patients who wish to maintain flexible or intensive insulin programs.
- *MDI regimens.* These basal-prandial-correction dose regimens are warranted in severely insulin-deficient patients with type 2 diabetes who have not had success with once- or twice-daily injection regimens.

Some patients with type 2 diabetes will require continuation of exogenous prandial insulin coverage after discharge. As recovery progresses, however, evening or daytime/evening insulin may be combined successfully with daytime oral therapy consisting of insulin secretagogues, metformin, and/or thiazolidinediones. Use of flat-release 24-hour basal insulin glargine in these combination regimens is associated with a lower risk of nocturnal hypoglycemia compared with NPH, coupled with the potential for optimal glycemic control.^{40,44}

CORTICOSTEROID THERAPY

Corticosteroids, which are commonly used in the treatment of asthma, neurosurgical emergencies, transplant rejection, and connective tissue diseases, have effects on carbohydrate metabolism that either exacerbate existing diabetes or precipitate "steroid diabetes." Corticosteroid-induced hyperglycemia is characterized by exaggeration of postprandial hyperglycemia; minimal to severe elevation of fasting plasma glucose; and lack of sensitivity to exogenous insulin. Because the minimal or initially predominant abnormality is postprandial hyperglycemia, some patients may require only prandial insulin (ie, rapid-acting insulin lispro, aspart, or glulisine), although no studies have been published comparing the effects of regular versus rapid-acting analogues in this situation. If between-meal glycemia cannot be sufficiently controlled with prandial insulin alone, small to larger amounts of basal insulin may be added.

For patients with poorly controlled type 2 diabetes or those who are already on insulin, both basal and prandial insulin will be required. After insulin dose-finding and stabilization of the corticosteroid dose to a maintenance level, patients may be converted to insulin glargine and a rapid-acting analogue at a ratio of approximately 30% glargine and 70% lispro/aspart/glulisine, with prandial doses based initially on the carbohydrate content of each meal. The requirement for prandial insulin at breakfast may be lower due to the diminishing action of morning doses of relatively short-acting corticosteroids, such as oral prednisone.

CHAPTER 7

Treating and Preventing Hypoglycemia

Fear of hypoglycemia often undermines the willingness of caregivers to address a potentially more profound threat to inpatient safety—hyperglycemia.⁶¹ Yet hypoglycemia is almost always preventable by means other than undertreatment of hyperglycemia, especially given that its predisposing conditions and triggering events are readily observable (Table 11). Preventive strategies should include not only the use of physician orders responsive to predisposing conditions, but also of ward-based protocols or hospital policies that sensitize nurses to triggering events and empower them to intervene appropriately.

TREATMENT

Reactive treatment strategies, rather than proactive preventive strategies, have been the rule for addressing hypoglycemia in most hospitals. Because hypoglycemia may cause seizures, alteration of vital signs, permanent neurologic injury, or even death, prompt treatment of incipient hypoglycemia is essential. If the patient is conscious and able to eat, ingestion of 15 g of carbohydrate is less likely to lead to overshoot hyperglycemia than the alternative therapy of 25 to 50 mL of 50% dextrose administered intravenously. Treatment is followed by retesting the blood glucose level within approximately 15 to 20 minutes. For patients who are NPO or unconscious, and who lack IV access, initial treatment may consist of 1-mg glucagon injected intramuscularly, with appropriate follow-up testing, establishment of IV access if necessary, and administration of carbohydrate. Hypoglycemia treatment orders usually provide for administration of glucose at a threshold glucose level of 70 mg/dL.

PREVENTION

Strategies for preventing hypoglycemia depend on matching antihyperglycemic therapy to the patient's medical condition and nutritional intake, coupled with conventional monitoring

Table 11. Predisposing conditions and triggering events for occurrence of hospital hypoglycemia during antihyperglycemic therapy

Predisposing conditions

Renal insufficiency
 Malnutrition
 Liver disease
 Sepsis
 Shock
 Pregnancy
 Malignant lesion
 Hyperkalemia
 Total parenteral nutrition
 Burns
 Alimentary disease
 Dementia
 Congestive heart failure
 Stroke
 Alteration of ability to self-report symptoms
 Hypoglycemic unawareness or defective counterregulation
 Old age
 Recovery from metabolic emergency
 Alcoholism or known illegal drug use
 Concomitant drug interactions or polypharmacy
 Tapering of glucocorticoid dose
 Adrenal or pituitary insufficiency

Triggering events

Transportation off ward, causing meal delay
 New NPO status
 Interruption of IV dextrose therapy
 Interruption of total parenteral nutrition
 Interruption of enteral feedings
 Interruption of continuous venovenous hemodialysis

From Braithwaite SS, Buie MM, Thompson CL, et al. Hospital hypoglycemia: not only treatment but also prevention. *Endocr Pract.* 2004;10(suppl 2):89-99. Copyright ©2004 American Association of Clinical Endocrinologists.

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of blood glucose concentration and appropriate caregiver responses.^{78,81} Patient self-management of diabetes in the hospital should be encouraged when appropriate, and staff understanding of new therapeutic approaches must be reinforced through in-service training. *Important: Orally administered antihyperglycemic agents should be prescribed with caution, keeping in mind changing organ function, potential drug interactions, and contraindications that might arise in the hospital.*

Embedding protections against hypoglycemia in physician orders for scheduled insulin therapy and addressing predisposing conditions before hypoglycemia develops are key strategies for prevention. In the presence of predisposing conditions, scheduled antihyperglycemic therapy should be maintained, but with the following precautionary measures: 1) more frequent monitoring of blood glucose levels to detect downward trending that might emerge over a period of hours or several days; 2) establishing a higher threshold for withholding scheduled rapid-acting or regular insulin during downward trending of blood glucose values; and 3) reducing doses of scheduled insulin therapy in response to blood glucose levels below the target range of 90 to 130 mg/dL. The nursing staff should also have authority to respond with appropriate preventive actions. Moreover, any emergency actions taken by the nursing staff on behalf of a patient should be covered under hospital policy.

With respect to patients who have already received orders for antihyperglycemic therapy, protocol or policy should: 1) define triggering events for hypoglycemia; 2) require interruption of antihyperglycemic therapy after a triggering event until further physician orders are received (except for

basal insulin for type 1 diabetes and correction doses of insulin for hyperglycemia); 3) require frequent blood glucose monitoring for the duration of action of previously administered antihyperglycemic drugs; and 4) provide for IV administration of dextrose during the timeframe of action of previously administered antihyperglycemic drugs, before hypoglycemia actually occurs (this threshold glucose level should be relatively low [eg, 110 mg/dL], but not at the bottom end of the non-fasting target range).

In general, ward-based protocol or hospital-based policies are likely to ensure standardized quality care of patients with hyperglycemia. In relation to the prevention of hypoglycemia, specific goals should include: 1) identification of patients with type 1 diabetes; 2) advance determination and recording of alternative basal insulin therapy for patients with type 1 diabetes; 3) determination of the timeframe within which elements of the policy take effect after occurrence of a triggering event (including initiation of alternative basal insulin therapy in relation to previously scheduled insulin treatment); 4) calculation of the duration of action of previously administered antihyperglycemic therapy by the floor nurse, in consultation with the pharmacy; 5) determination of appropriate preventive dextrose therapy; 6) identifying inconsistencies in physician practice patterns and existing ward- and service-based protocols; 7) balancing physician adherence to protocol against the need for physician autonomy and authority to override protocol; and 8) assessment of the comfort level of professional and administrative staff. Formation of a quality improvement team to monitor progress toward the aforementioned goals and to respond to concerns may reinforce good practices throughout the hospital.

CHAPTER 8

Patient Self-Management During and After the Hospital Stay

Many patients with type 1 or type 2 diabetes who are treated with insulin use MDI regimens to maintain excellent glycemic control. Yet during hospitalization, such patients are often expected to relinquish authority over their care to providers less equipped to understand their immediate needs. Patients in this situation are apt to become fearful of adverse events and frustrated over the rigidity of hospital practices. Thus, self-management of diabetes in the hospital should be considered for adult patients who have a stable level of consciousness, reasonably stable insulin requirements, and a history of successfully managing their diabetes at home.¹⁵ Patients should be able to demonstrate ability to self-administer insulin, perform self-monitoring of blood glucose, practice carbohydrate counting, implement MDI therapy or insulin pump therapy, and carry out the rules of sick-day management.

Additionally, the patient and physician, in consultation with the nursing staff, must agree that patient self-management is appropriate under the conditions of the hospital. Components of the program should include a physician order for self-management covering selection of food from a general diet, self-monitoring of blood glucose, self-determination and administration of insulin dose, and ranges of insulin to be taken. All blood glucose results and the details of insulin administration must be reported to the nursing staff for charting. If an insulin pump is used, provisions for trouble-shooting potential problems should be in place. Assistance might be needed if, for example, patients cannot reach an injection site because of their condition, or during unusual circumstances, such as temporary NPO status, or new corticosteroid therapy, when the patient may not know how to adjust insulin doses. Use of the patient's own equipment and drugs, if they are not on the formulary, should be allowed in compliance with institutional and external regulatory requirements. It is also important to reassure nurses and other providers that they are not expected to have an equivalent level of proficiency in

making intensive management decisions or using specialized equipment. A *sample* order for self-management might be:

- Patient to select diet from general menu
- Patient to perform capillary BG monitoring and report results to nursing once per shift
- Patient to administer rapid-acting insulin by continuous subcutaneous infusion:
 - 18 units as basal insulin daily,
 - 1 unit per 10 g of carbohydrate at meals,
 - plus correction doses at meals = (capillary BG - 120)/50;
 - report to nursing

It is the responsibility of the attending physician to assess patient candidacy for self-management, to determine additional blood glucose monitoring requirements, and to respond to nursing concerns about patient competency.

MOVING TOWARD DISCHARGE

Hospitalization is often an opportunity to refocus attention on the importance of health and strengthen patients' resolve to change behavior. Providers should use this "teachable moment" to impart skills and information that will improve glycemic control, reduce the risk of complications, minimize the potential for hypoglycemia, and overcome or avoid the burdens of poor disease management. With the healthcare team assembled, each member can provide beginning strategies in their specific area of expertise. For example, a registered dietician can introduce the basic idea of a 15-g carbohydrate serving and concepts of carbohydrate counting. Nurses, preferably certified diabetes educators (CDEs), are often enthusiastic about teaching "survival skills" as a first step in outlining the principles of diabetes management. Discussion should include: a description of the disease in terms of its treatment and complications; norms for blood glucose and individualized blood glucose targets; recognition, treatment, and prevention of hyper- and hypoglycemia; medical nutrition therapy (with guidance by a dietician or CDE); self-monitoring of blood glucose (if going home on insulin); sick-day management; and a review of community resources.¹⁵ The specific needs of patients previously diagnosed with diabetes must also be

PRACTICAL MANAGEMENT OF **INPATIENT HYPERGLYCEMIA****Table 12. Writing the DSME consult request**

Component of request	Example
Specific reason for consult and diagnosis	Insulin education for patient with new-onset type 2 diabetes
Discharge medication plan	Insulin glargine 30 units HS, aspart 6 units AC
Specific comments/instructions	Spanish-speaking patient; lives with daughter
Contact information	John Smith, MD, pager #

AC = before meals; HS = bedtime.

From Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553-591. Copyright ©2004 American Diabetes Association.

addressed with targeted instructions. Ideally, initial exposure to information in the hospital should inspire a lifelong process of continuing diabetes education.

DISCHARGE PLANNING

Documentation, reviewing chart notes/comments, and oral communication are essential components of successful discharge planning. Medical orders and the discharge plan of care need to be appropriate, achievable, and acceptable to the patient and family. To ensure continuity of care, the treating physician, nurses, and the CDE must work together to address the following questions related to discharge planning: Does the patient require outpatient diabetes self-management education (DSME)? Can the patient prepare his or her own meals? Can the patient perform self-monitoring of blood glucose frequently enough? Can the patient take his or her diabetes medications or insulin accurately? Is there a family member who can assist with tasks that the patient cannot perform? Is a visiting nurse needed to facilitate the

transition to home? Because recent hospital discharge is a strong predictor of subsequent serious outpatient hypoglycemia, antihyperglycemic therapy should be prescribed with care, especially for the elderly.⁸² Patients most likely in need of visiting nurses include those newly diagnosed with diabetes or new to insulin, the aged or infirm, and those for whom compliance concerns are an issue. Social workers and case managers should coordinate discharge planning and orders for home healthcare.

Writing DSME Consult Requests

When writing a request for consultation, specific reasons for the referral should be listed rather than just stating "diabetes education." Relevant details regarding patient status, the discharge plan, and contact information should be included (Table 12). Early referral is recommended, especially for patients newly diagnosed with diabetes. Patients who are in pain or sedated should not be referred for DSME until their condition improves, and caregivers must be identified and included in the teaching process.

CHAPTER 9

Institutional Change

Safe, effective systems for implementing glycemic control in the hospital should be driven by the primary goal of promoting organization, education, and communication to improve outcomes in hyperglycemic patients. A multidisciplinary approach, as well as institutional and physician commitment to quality control, are essential to this effort.⁸³ Introducing new strategies one unit at a time can ease the transition for hospital staff and keep outcomes assessment to a manageable scale. If possible, supporters or “champions” from each discipline should be appointed to provide continuous feedback.

The use of standardized order sets and computerized order entry helps physicians and staff gain familiarity with appropriate insulin treatment, and manage the necessary complexity effectively and safely. Indeed, the measure of a well-designed protocol or order set is that it should be complex enough to encompass individual variables, but also concise enough to be completed by entry of check marks and numbers, ordered with a single signature, and executed through a team approach to care. It must also be remembered that standardization of treatment algorithms or dose titration protocols, while desirable in many ways, can lead to oversimplification of hospital routines. Individualization is sometimes necessary and may require deviation from standardized protocols. This balance is especially important in the event that IV insulin therapy is administered outside of ICU wards.¹⁵ Another pitfall of standardization is proposing evidence-based targets that may be too ambitious for the

existing hospital staff or structure. Establishing standards gradually, with realistic parameters in mind, is essential to overcoming the natural resistance to change found in many large organizations.

Along with implementing well-designed and achievable protocols, hospitals should make every effort to minimize drug-dispensing and prescribing errors. Simple measures, such as prohibiting the use of trailing zeros after decimal points or establishing uniform abbreviations for insulin, prevent misinterpretation that may compromise patient safety. Barcoding of drugs and pharmacist participation in rounds and surveillance of prescribing patterns may also help to reduce error. Additionally, computerized order entry systems can reduce dependence on sliding scale protocols and identify patterns of failure by tracking transfers or readmission to the ICU.¹⁵

Although both hypoglycemia and hyperglycemia are considered patient safety issues, the risks associated with hypoglycemia have received greater emphasis with respect to continuous quality improvement evaluation (CQI). This is partly because hypoglycemic events are more easily identified and traceable through analysis of pharmacy records of 50% dextrose administration or adverse drug reactions.¹⁵ Yet hyperglycemia may be similarly tracked by scanning point-of-care blood glucose measurements into an electronic database, or monitoring the interval between presentation in the emergency room with hyperglycemic emergency and initiation of an insulin infusion. Such balanced emphasis on both hypoglycemia and hyperglycemia through quality-improvement programs would contribute substantially to creating a culture in which the potential benefits of inpatient glycemic control might be fully realized.

Summary

Although hypoglycemia has long been recognized as a patient safety factor in hospitals, the risks of hyperglycemia have been minimized. This is now changing in light of emerging evidence that stringent glycemic control improves outcomes in critical care. For critically ill patients, blood glucose levels should be kept as close to 110 mg/dL as possible and, generally, <180 mg/dL. This usually requires IV insulin therapy. In noncritically ill patients, the desired pre- and postmeal blood glucose levels are 90 to 130 mg/dL and <180 mg/dL, respectively, depending on the clinical situation. Optimal care involves determining the insulin dose, with ongoing monitoring and adjustment to replace correction therapy with scheduled insulin.

Fear of hypoglycemia is the primary barrier to normoglycemia. Hypoglycemia in the hospital is preventable by means other than undertreatment of hyperglycemia. Patients who are competent, eating, and experienced in self-management should be allowed to continue self-management in the hospital. Nationwide opportunities for improvement include facilitation of insulin infusion therapy, standardization of diabetes order sets and correction-dose algorithms, protocols for prevention of hypoglycemia, staff and patient education, appropriate discharge planning, and hospital policies on patient self-management.

Case Studies

1

Case 1: Estimating initial subcutaneous insulin dose in a postsurgical heart patient with type 2 diabetes previously on insulin drip. It is the morning of postoperative Day 3. The patient, who was on an insulin drip overnight without pressors, is well but eating poorly. Blood glucose is 110 mg/dL. He received 6 units of lispro at each of the previous day's meals, and the average hourly insulin requirement overnight was as follows:

12:00 AM	1.5 units/hr
1:00 AM	1.5 units/hr
2:00 AM	1.5 units/hr
3:00 AM	0.5 unit/hr
4:00 AM	2.0 units/hr
5:00 AM	1.5 units/hr
6:00 AM	2.0 units/hr
7:00 AM	1.5 units/hr

Based on the average hourly insulin requirement overnight, assuming no change, what is the patient's 24-hour basal insulin requirement?

For patients not receiving IV dextrose, about 80% of the projected 24-hour basal insulin requirement is administered subcutaneously as the first daily injection of long-acting insulin glargine; the mean overnight insulin drip rate in units per hour can be multiplied by 20 hours to calculate the initial loading dose of glargine. Since the average overnight insulin dose for this patient was 1.5 units/hr, the 24-hour basal requirement is 36 units, and the starting dose of insulin might be ~29 units.

Case 2: Determining the dose of basal insulin in an NPO patient with type 1 diabetes. You are the on-call physician. The nurse on duty calls at 10:00 PM about a patient previously unknown to you who is scheduled to receive 18 units of insulin glargine. The nurse is uncertain whether the patient should receive the full dose of glargine, considering a request by radiology for NPO after midnight in preparation for a computed tomography scan the next morning. The patient's blood glucose level is 170 mg/dL. What information might favor a decision to give the entire dose of insulin glargine?

1. The dose of insulin glargine is the same as the preadmission glargine dose
2. The dose of insulin glargine is about 50% of daily insulin therapy
3. The patient has type 1 diabetes without severe hypoglycemia
4. The duration of NPO status will be too brief to warrant IV insulin infusion
5. All of the above

The patient was not receiving a high dose of glargine and the amount was only 50% of the TDD of insulin; that is, there is no suspicion of insulin-resistant diabetes, and no suspicion that the glargine dose had been forced to a high amount to compensate for inadequate prandial coverage. The patient had type 1 diabetes, so that a correctly established basal dose should not be casually changed.⁸⁴ Although IV insulin infusion is preferred for prolonged NPO status, in this case the NPO status will be brief. (Answer: 5)

Case 3: Managing glycemia in a 55-year-old hypertensive man with type 2 diabetes receiving metformin, NPH, and regular insulin prior to hospital admission.

A 55-year-old man with a 10-year history of type 2 diabetes and a 20-year history of hypertension is admitted for pneumonia with an empyema. A chest tube is inserted and IV antibiotics started. His appetite is poor. At home, he takes 40 units of premixed 70% NPH/30% regular insulin both before breakfast and before dinner. His A1C, measured several weeks prior to admission, was 6.2%. His only other diabetes medication is metformin (1 g, twice daily). He has a temperature of 38.6° C, blood pressure of 90/60 mm/Hg, and right basilar rales. How would you manage his glucose in the hospital?

First, given the patient's long-standing hypertension and his relative hypotension now, his metformin should be discontinued, at least during hospitalization. For his insulin treatment, he will likely develop hypoglycemia, despite his increased insulin resistance in the hospital, due to the large dose of basal and prandial insulin and his near-normal A1C. One could simply decrease the 70/30 insulin to low levels and then increase the dose as his appetite improves. However, less guesswork would be required by switching him to a basal/bolus regimen in the hospital, since outpatient basal doses can be estimated (with the understanding that discontinuation of the metformin and the acute illness will change this somewhat). One way to make this conversion would be to calculate his total NPH dose (70% of 40 units = 28 units; since he is receiving 80 units/day of 70/30 insulin, this would amount to 28 units x 2 = 56 units). His initial basal insulin dose administered as insulin glargine would be 80% of this dose (80% x 56 units = 45 units). Consequently, he could receive 45 units of insulin glargine at bedtime, as well as mealtime insulin lispro, aspart, or glulisine based on his appetite. Considering the patient's preadmission dose, it is likely that large prandial doses (eg, 1 unit/5 to 7.5 g of carbohydrate) will be required in the hospital. One way of determining this would be to use the algorithm shown in Table 10 and, ideally, base the dosage of prandial insulin on

the patient's appetite and knowledge of how much carbohydrate will be delivered. In practice, however, these parameters are often impossible to judge, and for the first few meals at least, it may be necessary to administer insulin after eating, guided by the amount of food consumed. For example, if each meal contains approximately 50 g of carbohydrate, the patient could have 10 units of glulisine ordered per meal. If no food is eaten, no insulin should be given; if half is eaten, then 5 units may suffice. Nevertheless, it is always problematic to administer insulin after eating, when lag times cannot be controlled. Additionally, the correction dose should be given before the meal, as guided by the medium-dose algorithm (Table 10) in the case of this patient (although the high-dose algorithm might be more effective in the hospital, depending on the clinical circumstances). The optimal balance between basal and prandial insulin usually becomes easier to determine after 24 hours of regular meal consumption.

Case 4: A 62-year-old woman with uncontrolled type 2 diabetes hospitalized for cardiac arrhythmia. A 62-year-old woman with type 2 diabetes is admitted to the telemetry unit for a cardiac arrhythmia. She weighs 100 kg. She is eating and her premeal glucose levels in the hospital are generally >200 mg/dL. Accordingly, her A1C is 8.5%. At home, she receives metformin and glipizide for her diabetes. How should her diabetes be managed now and at discharge?

To achieve an A1C level <7% (the target recommended by the ADA), this patient will require insulin therapy. The Treat-to-Target study showed that basal insulin by itself was effective at lowering A1C to target range, without appreciably increasing the risk of hypoglycemia in patients using insulin glargine compared with NPH.⁴⁴ Yet this patient will likely need prandial as well as basal insulin replacement in the hospital, since the glargine dose will not be able to be increased quickly enough to correct her premeal blood glucose levels. One option is to start NPH and regular insulin (or NPH and a rapid-acting insulin analogue), perhaps as a premixed commercial insulin preparation, before breakfast and dinner; another is to use glargine at bedtime with a premeal rapid-acting insulin analogue. Using the protocol in Table 10, it is reasonable to start at 0.3 units/kg/day. This would be 30 units/day, with half as basal insulin glargine. Usually, one can use 80% of this dose of glargine to determine the bedtime dose (80% x 15 units = 12 units). The remaining 15 units can be divided based on the distribution of calories, guided by the low-dose algorithm in Table 10. Once the patient's glucose levels are controlled, she may do well with basal insulin alone.

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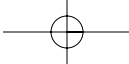
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Notes

