# Insulin in the Hospital Setting

**Irl B. Hirsch, MD**
**Professor of Medicine**
**University of Washington**
**Medical Director, Diabetes Care Center**
**University of Washington Medical Center**
**Seattle, Washington**

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# Introduction

*Diabetes typically is a lifelong illness affecting about 6% of the population in the United States. It is highly likely that the patient with diabetes will be hospitalized for a surgical or nonsurgical procedure, or for medical management. Hospital stays are often longer for patients with diabetes compared with those without; and for those with undiagnosed diabetes, hospitalization may provide the first opportunity for detection and treatment. Given these realities, it is fundamentally important that clinicians possess the skills for evaluating and treating diabetes in the inpatient setting.*

*However, diabetes management in the hospital setting has progressed very little over the past 30 years, despite dramatic advances in outpatient care. Indeed, lessons gleaned from the 1993 Diabetes Control and Complications Trial (DCCT) and the subsequent United Kingdom Prospective Diabetes Study (UKPDS) regarding the value of meticulous glycemic control are only marginally reflected in current hospital protocols. Reasons for this lack of progress include a dearth of studies focusing on inpatient management, difficulty carrying out individualized care regimens in the hospital, and widespread misperception about the appropriate use of insulin.*

*The focus of this monograph is application of the latest knowledge about the benefits of controlling hyperglycemia to the special situations of inpatient management. It offers evidence-based alternatives to outmoded protocols and provides practical information about using insulin in specific circumstances during each phase of the hospital stay. Additionally, factors complicating treatment of inpatients with diabetes, such as the erratic nature of insulin absorption in critically ill patients and potential delays in meals, are discussed with the aim of preventing metabolic crises and improving outcomes in the heretofore largely overlooked, but essential, therapeutic milieu of the hospital.*

## Chapter 1: Epidemiology of Diabetes

According to the American Diabetes Association (ADA), diabetes mellitus affects 17 million people in the United States—about 6.2% of the population.[1] Although an estimated 11 million people with diabetes have been diagnosed, the disease may remain undetected in as many as 6 million more. Type 1 diabetes, an autoimmune disorder in which the body fails to produce any insulin, accounts for 5% to 10% of cases, whereas type 2 diabetes, a metabolic disorder caused by the body's inability to sufficiently produce or properly use insulin, accounts for 90% to 95%. The cause of diabetes remains unknown, although genetics and environmental factors such as obesity and lack of exercise appear to play a role.

The prevalence of diabetes in the United States is increasing,[2,3] in tandem with that of obesity, which often presages diabetes.[4] The implications for public health are significant, given the high mortality, morbidity, and economic costs associated with the disease. According to the most recent data from the ADA, the total cost of diabetes care in 1997 was $98.2 billion.[5] Direct costs of diabetes are estimated to be about $50 billion annually in the US.[6]

In 1996, more than 3.8 million hospitalizations were associated with diabetes, accounting for 25 million hospital days with an average length of stay of 6.5 days.[7] The absolute number of diabetes-related hospitalizations increased by more than 70% from 1980 to 1996, although the average length of stay declined from 11 to 6.5 days. The most common reason for hospitalization among patients with diabetes is disease involving the circulatory system, which in 1996 accounted for 36% of hospitalizations in this group, followed by diseases of the respiratory system (19%) and infection (2.8%).[7]

In a recent report, of 4245 hospital admissions of patients with diabetes, 1.2% had a primary diagnosis of peripheral vascular disease, infection, neuropathy, or ulceration; when subsidiary diagnoses were included, these categories accounted for 7379 (2.1%) of all hospital admissions (Figure 1).[8]

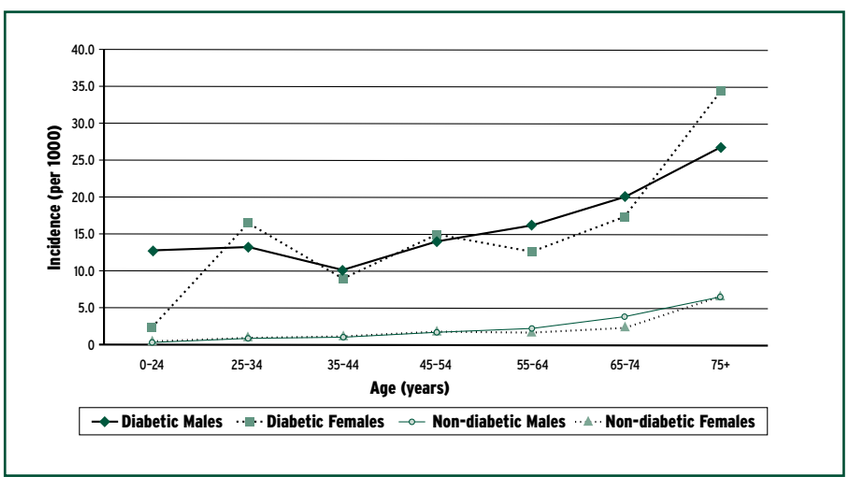


**Figure 1.** Rate of hospital admission for peripheral vascular disease, infection, neuropathy, and ulceration by age, sex, and diabetic status. (From Currie et al. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. *Diabetes Care.* 1998;21:42-48. Copyright ©1998 American Diabetes Association. Reprinted with permission from the American Diabetes Association.)

Moreover, patients with diabetes comprised 15.4% of primary admissions, a crude annual admission incidence of 18.8 per 1000. The length of stay for these patients was almost double that of patients without diabetes—15.5 vs 8.7 days.

Diabetes often remains undiagnosed until the onset of another medical problem, when hyperglycemia may be found incidentally. In a study of 1034 consecutively hospitalized adult patients at an inner-city teaching hospital, after excluding patients who were admitted for a primary diagnosis of diabetes, 38% of all hyperglycemic medical patients and 33% of hyperglycemic surgical patients had undiagnosed diabetes at the time of admission (Table 1).[9] Mean blood glucose concentration in these patients was 299 mg/dL and 66% had 2 or more elevated blood glucose values during their hospitalization. Despite marked hyperglycemia, most medical records did not mention the possibility of unrecognized diabetes.

**Table 1. Distribution of Hyperglycemic Patients by Medical Service**

| Service | Glucose >200 mg/dL, n | Diabetes Recognized Before or at Admission, n | Diabetes Unrecognized at Admission, n (%) |
|---|---|---|---|
| **Medicine** | 64 | 40 | 24 (37.5) |
| **Surgery** | 48 | 32 | 16 (33) |
| **Gynecology** | 2 | 1 | 1 (50) |
| **Podiatry** | 1 | 1 | 0 |
| **Total** | 115 | 74 | 41 (36) |

Adapted from Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. *Diabetes Care.* 1998;21:246-249.

## Chapter 2: Reasons for Hospitalization in Patients with Diabetes

Patients with diabetes may require hospitalization for a variety of reasons (Table 2),[10] including acute metabolic complications of diabetes, uncontrolled diabetes, or chronic cardiovascular, neurologic, renal, and other complications of the disease. Children and adolescents with newly diagnosed diabetes, and pregnant women with uncontrolled or newly discovered insulin-requiring diabetes, are often best managed in the inpatient setting. Patients with significant and chronic poor metabolic control may also require inpatient management in order to identify the underlying problem and discern the most appropriate therapeutic intervention.[10]

Surgical patients with diabetes are especially susceptible to adverse outcomes, and even more so if they have preexisting complications such as atherosclerotic vascular disease, nephropathy, retinopathy, or peripheral or autonomic neuropathy. This is because surgery and general anesthesia stimulate a neuroendocrine stress response resulting in release of corticotropin (ACTH), growth hormone, catecholamines, and glucagon.[11] The extent of the response is related to the severity of the surgery and the development of any complications such as sepsis.[12] If glycemia is not well controlled during the perioperative period, acute metabolic complications such as hypoglycemia, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemic nonketotic syndrome may occur. Even patients with mild blood glucose intolerance must be monitored to avoid other, less severe, complications such as electrolyte abnormalities, immune suppression, infection, impaired wound healing, and neurologic difficulties.[13] Patients with long-standing diabetes are at risk for silent myocardial ischemia although the mechanisms are controversial.[14]

**Table 2. Diabetes-Related Reasons for Hospitalization**

1. **Life-threatening acute metabolic complications of diabetes (diabetic ketoacidosis, hyperglycemic hyperosmolar state, hypoglycemia with neuroglycopenia)**
2. **Substantial and chronic poor metabolic control that necessitates close monitoring to determine etiology of the problem, with subsequent modification of therapy**
3. **Severe chronic complications of diabetes that require intensive treatment, or other severe conditions unrelated to diabetes that significantly affect its control or are complicated by diabetes**
4. **Newly diagnosed diabetes in children and adolescents**
5. **Uncontrolled or newly discovered insulin-requiring diabetes during pregnancy**

Adapted from American Diabetes Association. Hospital admission guidelines for diabetes mellitus. *Diabetes Care.* 2002;25(suppl 1):S109.

## Chapter 3: Barriers to Insulin Therapy in the Hospitalized Patient

Intravenous (IV) insulin, with its rapidity of action, safety profile, and predictable glucose-lowering effects, is the most reliable means of controlling blood glucose levels in the hospitalized patient.[15] Yet, for a variety of reasons many physicians are uncomfortable using insulin in the hospital setting. Often they lack experience, stemming in part from a dearth of formal training in medical school and residency programs.[16] Also, many physicians subscribe to the erroneous notion that insulin therapy signals worsening disease. Even those who appreciate the value of insulin may be deterred by the lack of standardized protocols for therapy, as well as the substantial time required to educate patients about its use.

Another factor complicating insulin therapy in the hospitalized patient with diabetes is the erratic nature of insulin absorption, which can result in inexplicable levels of glycemia, especially in patients with type 1 diabetes.[17,18] Issues affecting the variability of insulin absorption (Table 3) include the day-to-day intra-individual variation in the time required to absorb 50% of an injected dose (about 25% in controlled settings), and the day-to-day variation between patients (possibly as high as 50%).[19] In the acutely ill hospitalized patient, these fluctuations may be even more pronounced because of fluid shifts and changes in blood flow to the subcutaneous tissue.[20] Additionally, circumstances such as pain, trauma, surgery, sepsis, burns, hypoxia, cardiovascular disease, and mental stress may increase the requirement for insulin due to the counterregulatory stress response.[12,20,21]

**Table 3. Factors Affecting Variability in Insulin Absorption**

| |
|---|
| **Insulin type** |
| • Basal: glargine < NPH < Ultralente |
| • Prandial: lispro = aspart < regular |
| **Volume** |
| • Synergistic with duration of action (? analogues) |
| **Site of injection** |
| • Rate of absorption: abdomen > arm > thigh > buttock |
| • May not be an issue for analogues |
| **Depth of injection** |
| • Rate of absorption: IV > IM > SC |
| **Regional blood flow, which is affected by** |
| • Exercise |
| • Skin temperature |
| • Hydration status |
| • Local factors (heat, friction) |

Adapted from Burge MR, Schade DS. Insulins. *Endocrinol Metab Clin North Am.* 1997;26:575-598.

The timing of food consumption also affects inpatient insulin therapy.[22] Hypoglycemia may result when meals and snacks arrive late or are interrupted by diagnostic and therapeutic procedures. Moreover, the prescribed "diabetic diet" does not necessarily include a bedtime snack even though it may have been part of the patient's usual regimen; this is particularly important with NPH and regular insulin-based regimens.

Another challenge is monitoring the interval between administration of regular insulin and eating, commonly known as the lag time.[23] Patients who practice intensive insulin therapy strive to keep the lag time consistent when premeal glycemia is in the target range—increasing or decreasing it only when blood glucose concentrations fall above or below the target level.[24] Yet, because of the many variables in the hospital environment, maintaining this degree of coordination requires a concerted effort by both patients and staff.[22]

Additionally, even when the timing is right, the product may be wrong. Although a wide array of insulin products is now commercially available (see Chapter 5), hospital formularies do not always stock the needed preparations. The best way to correct this problem is to check the formulary before admission. If the patient's usual products are not included, he or she should be told to bring them to the hospital.[22]

A final limitation associated with inpatient management of diabetes is the fact that commonly used narcotic agents may impair transit time in the gut, resulting in deleterious effects on glycemic control because of a mismatch between calories and insulin, similar to that seen with gastroparesis.[25] This potential problem may be resolved by limiting narcotic use as much as possible and avoiding other medications with potential to retard gut motility, such as anticholinergic agents.

## Chapter 4: Rationale for Using Insulin to Control Inpatient Hyperglycemia

Inpatient insulin therapy has many established benefits. It minimizes the adverse consequences of acute perioperative metabolic complications, such as hypoglycemia, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycemic nonketotic syndrome, and may ward off less severe complications, such as electrolyte abnormalities and volume depletion from osmotic diuresis, even in individuals with mild glucose intolerance.[26,27] Moreover, the studies described below suggest that treatment of hyperglycemia with insulin confers advantages in a variety of hospitalized patients, with and without diabetes. They support the tenet that using insulin to maintain glucose levels at <200 mg/dL leads to improved morbidity and mortality, fewer infections, and more rapid wound healing.

The explanation may lie with the intrinsic anti-inflammatory properties of insulin: Severely ill intensive care patients experience a "cytokine storm" as acute illness increases the production of inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α)[28] and macrophage migration inhibitory factor (MIF).[29] TNF-α causes endothelial dysfunction, triggers procoagulant activity and fibrin deposition,[30] and enhances damaging nitric oxide synthesis in many different cells.[31] TNF-α expression also increases insulin resistance in the liver and skeletal muscle of obese patients with type 2 diabetes, most likely through the modification of signaling properties of insulin receptor substrates.[32] Insulin suppresses both production of TNF-α (as demonstrated in an animal model) and antagonizes the detrimental effects of TNF-α [33,34] and MIF.[35] Additionally, insulin increases the production of nitric oxide, a potent vasodilator and platelet antiaggregator, which typically is low in patients with diabetes.[36] Future studies are needed to assess the relations among serum insulin levels, cytokine levels, and clinical outcomes.

### Morbidity and Mortality

In a prospective, randomized, controlled study, 1548 critically ill hospitalized adults receiving mechanical ventilation were admitted to a surgical intensive care unit and randomly assigned to receive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dL) or conventional treatment (insulin infusion if blood glucose exceeded 215 mg/dL and maintenance of glucose between 180 and 200 mg/dL).[37] At time of admission, only 13% of the patients in the intensive treatment group had a history of diabetes and 5% were receiving treatment with insulin. At 12 months, 35 patients (4.6%) in the insulin treatment group had died during intensive care, compared with 63 patients (8%) in the standard treatment group—a risk reduction of 42% (Figure 2). About 20% of patients receiving conventional treatment remained in the intensive care unit for more than 5 days, compared with 10.6% in the insulin group ($P = 0.005$). Insulin therapy also reduced

- overall in-hospital mortality by 34%
- bloodstream infections by 46%
- acute renal failure requiring dialysis or hemofiltration by 41%
- the median number of red-cell transfusions by 50%
- critical-illness polyneuropathy by 44%

Furthermore, patients receiving insulin therapy had less need for mechanical ventilation and intensive care.

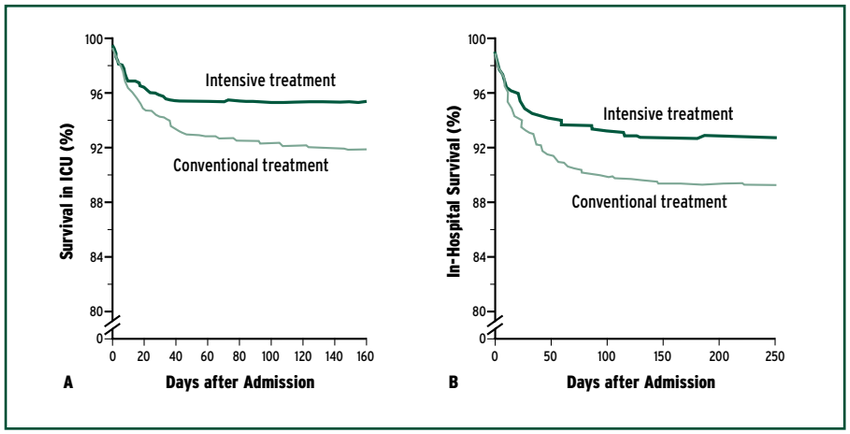


**Figure 2.** **Cumulative survival of critically ill patients who received intensive insulin treatment or conventional treatment in the intensive care unit. Patients discharged from the ICU (A) and the hospital (B) were considered to have survived. (Reprinted from Van den Berghe et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359-1367. Copyright ©2001 Massachusetts Medical Society. All rights reserved.)**

In the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study—the only large, randomized, placebo-controlled clinical trial of insulin–glucose infusion therapy in patients with acute MI in the era of thrombolytic therapy—620 patients with diabetes mellitus and acute MI were randomized to receive either standard treatment for MI plus insulin–glucose infusion for at least 24 hours followed by multidose insulin treatment, or standard treatment alone.[38] In these patients, insulin–glucose infusion followed by SC insulin treatment improved long-term survival by nearly one third, and the effect persisted for at least 3.5 years, with 11% absolute reduction in mortality. The reduction in mortality was most apparent in patients with low cardiovascular risk and no previous insulin treatment.

Also suggesting the potential benefits of insulin is a study in which adult patients with newly discovered hyperglycemia (defined as an admission or in-hospital fasting glucose level of 126 mg/dL or more or a random blood glucose level of 200 mg/dL or more on 2 or more occasions) had a higher in-hospital mortality rate (16%) compared with patients with a history of diabetes (3%) and persons with normoglycemia (1.7%; both $P < 0.01$), even though the new-hyperglycemia group had a lower mean blood glucose level than those with preexisting diabetes.[39] An intriguing consideration is that in contrast to those with established diabetes, few patients with new hyperglycemia received insulin.

Finally, results of a meta-analysis of 9 randomized, placebo-controlled trials with a total of 1932 patients without diabetes who received glucose–insulin–potassium (GIK) therapy for treatment of acute MI showed that hospital mortality was reduced from 21% in patients who received a placebo to 16.1% ($P = 0.004$) in those given GIK therapy. The proportional reduction in mortality was 28%, and 49 lives were saved per 1000 patients treated.[40]

### Infection Control and Wound Healing

Although there are no prospective studies comparing different levels of perioperative glycemia with rates of wound infection, it has been reported that plasma glucose levels above 200 mg/dL and high

levels of serum ketones increase the risk for developing infectious complications.[41] Further, postoperative hyperglycemia is an independent predictor of short-term infectious complications in patients with diabetes who undergo coronary artery surgery[42] and is also associated with surgical-site infections (SSI), as shown in a study of 1000 patients undergoing cardiothoracic surgery at a large university-affiliated hospital.[43] Nearly half of patients with diabetes in this study had hyperglycemia in the first 48 postoperative hours, compared with 12% of those without, and each group of hyperglycemic patients (with and without diabetes) had an approximately twofold higher rate of SSI than the comparable normoglycemic group. (Interestingly, among patients known to have diabetes, elevated levels of A1c did not significantly increase risk of infection.) The study also found that 42 (6%) of 700 patients who showed evidence of undiagnosed diabetes had an infection rate comparable to that of patients with a history of diabetes (6% to 7%), suggesting that the level of glycemia (specifically a blood glucose level below 200 mg/dL), not the preexisting level of blood glucose control, is a critical determinant of SSI.

In a study comparing patients with diabetes who underwent cardiac surgery to historical controls, a protocol of postoperative continuous IV insulin infusion to maintain blood glucose levels below 200 mg/dL was found to decrease levels for the first 2 postoperative days and lower the incidence of deep wound infections from 2.8% before the protocol was implemented to 0.74% the third year after implementation.[44] Moreover, elevated blood glucose levels at 48 hours were associated with a significantly increased risk of deep wound infections ($P = 0.002$) (Figure 3).

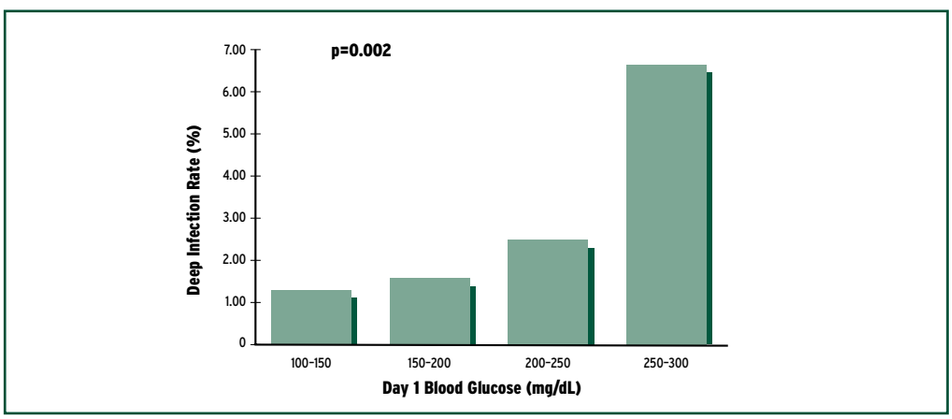


**Figure 3.** **Relation between postoperative (day 1) blood glucose levels and deep infection rates. (From Zerr et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg.* 1997;63:356-361. Reprinted with permission from the Society of Thoracic Surgeons.)**

In patients who have infection at the time of hospital admission or who are undergoing surgery, insulin therapy can alleviate compromised leukocyte function associated with hyperglycemia.[45] Moreover, continuous treatment with insulin may improve white blood cell function in patients with diabetes, thereby increasing resistance to postoperative infection.[46]

Control of hyperglycemia also ameliorates delayed wound healing, common in people with diabetes who have peripheral vascular disease. Recent speculation on the underlying mechanism has focused on high glucose–induced activation of nuclear factor kappa B–inhibited endothelial cell migration.[47] In addition to hyperglycemia, conditions that may impede wound healing include malnutrition, vasoconstriction, and use of corticosteroids.[48]

## Chapter 5: Key Concepts in Insulin Therapy

Intravenous insulin is the most effective means of controlling blood glucose levels in the hospitalized patient with type 1 or type 2 diabetes.[15] Patients with type 1 diabetes always require insulin and thus will continue to need it during hospitalization, even in the absence of any nutrient intake. Type 2 patients whose blood glucose levels are well controlled with the use of an established oral glucose-lowering regimen may be able to continue their usual oral therapy during hospitalization, provided certain agents are discontinued in the event of surgery. However, because acute illness typically amplifies insulin resistance and thus hyperglycemia, it is often necessary to temporarily switch patients with type 2 diabetes to insulin therapy.[49]

### Glycemic Goals

An initial glycemic objective is to keep blood glucose levels sufficiently high to prevent hypoglycemia and low enough so that excess catabolism and deleterious effects such as DKA and hyperosmolarity do not occur.[22] As noted in the previous chapter, maintaining blood glucose at <200 mg/dL has been shown to benefit a variety of hospitalized patients with and without diabetes.[37]

### Physiologic Model of Diabetes Therapy

The physiologic model of diabetes therapy mimics natural insulin secretion by a healthy pancreas, approximating as closely as possible "basal" insulin secretion, the small amount of insulin the pancreas secretes continually, as well as the "prandial" insulin surge secreted in response to meals. To address both types of insulin secretion, manufacturers offer longer-acting or "basal" insulins to cover basal secretion and shorter-acting "prandial" insulins to cover mealtime secretion. Insulin products currently available in the United States are listed in Table 4.

#### *Basal Insulin*

The intermediate-acting insulins, NPH and Lente, and the long-acting insulin, Ultralente, have long served as the standard basal insulins. NPH, the most commonly used basal insulin preparation, begins to work within 1 to 3 hours, peaks at 4 to 8 hours, and has a duration of action of 12 to 14 hours when 0.1 to 0.2 U/kg are injected into the abdomen. However, because NPH has a pronounced peak and its duration of action is <24 hours, glycemic control can be difficult with this formulation. Lente insulin has a 13- to 20-hour duration of action, which is slightly longer than that of NPH. It has a pronounced peak at 4 to 8 hours and its effects are very variable. Ultralente insulin has an onset of action at 2 to 4 hours, peak activity at 8 to 14 hours, and a 16- to 20-hour duration of action when 0.1 to 0.2 U/kg are injected into the abdomen. However, Ultralente is the most erratically absorbed of all available insulin products.

The traditional approach to diabetes management is to use an older basal insulin, such as NPH or regular insulin, to serve as the prandial insulin as well. With traditional twice-daily NPH and regular

**Table 4. Insulin Products Currently Available in the United States***

| Insulin | Manufacturer | Onset of Action | Peak Action | Duration of Action |
|---|---|---|---|---|
| **Rapid-acting** | | | | |
| Humalog (insulin lispro) | Eli Lilly | 5-15 minutes | 1-2 hours | 4-6 hours |
| Novolog (insulin aspart) | Novo-Nordisk | 5-15 minutes | 1-2 hours | 4-6 hours |
| **Short-acting** | | | | |
| Humulin R (insulin, human regular) | Eli Lilly | 30-60 minutes | 2-3 hours | 6-8 hours |
| Novolin R (insulin, human regular) | Novo-Nordisk | 30-60 minutes | 2-3 hours | 6-8 hours |
| Velosulin BR (insulin, human regular) | Novo-Nordisk | 30-60 minutes | 2-3 hours | 6-8 hours |
| **Intermediate-acting** | | | | |
| Humulin N (insulin, NPH, human isophane suspension) | Eli Lilly | 1-3 hours | 4-8 hours | 12-14 hours |
| Novolin N (insulin, NPH, human isophane suspension) | Novo-Nordisk | 1-3 hours | 4-8 hours | 12-14 hours |
| Humulin L (insulin, Lente, human zinc suspension) | Eli Lilly | 1-3 hours | 4-8 hours | 13-20 hours |
| Novolin L (insulin, Lente, human zinc suspension) | Novo-Nordisk | 1-3 hours | 4-8 hours | 13-20 hours |
| **Long-acting** | | | | |
| Humulin U (insulin, Ultralente, human extended zinc suspension) | Eli Lilly | 2-4 hours | 8-14 hours | 16-20 hours |
| Lantus (insulin glargine) | Aventis | 2 hours | None | ~24 hours |

**Table 4. Insulin Products Currently Available in the United States* (continued)**

| Insulin | Manufacturer | Onset of Action | Peak Action | Duration of Action |
|---|---|---|---|---|
| **Mixtures** | | | | |
| Humulin 70/30 (insulin, 70% NPH, human isophane suspension, 30% human insulin injection) | Eli Lilly | 1-3 hours<br>30-60 minutes | 4-8 hours<br>2-3 hours | 12-14 hours<br>6-8 hours |
| Novolin 70/30 (insulin, 70% NPH, human isophane suspension, 30% human regular) | Novo-Nordisk | 1-3 hours<br>30-60 minutes | 4-8 hours<br>2-3 hours | 12-14 hours<br>6-8 hours |
| Humalog Mix 75/25 (75% insulin lispro protamine suspension, 25% insulin lispro injection) | Eli Lilly | 15 minutes<br>5-15 minutes | 4-8 hours<br>1-2 hours | 12-14 hours<br>4-6 hours |
| Novolog Mix 70/30 (70% NPH human isophane suspension, 30% insulin aspart) | Novo-Nordisk | 15 minutes<br>5-15 minutes | 4-8 hours<br>1-2 hours | 12-14 hours<br>4-6 hours |

*Time activity profiles for these products vary considerably and may not be valid for all patients.

insulin regimens, the morning NPH is used as both the basal and lunchtime prandial insulin. In fact, the morning regular insulin is a prandial insulin for breakfast but, because of its relatively long duration, also serves as both a basal insulin once breakfast is absorbed and a prandial insulin for lunch. Even with long-acting Ultralente insulin, unpredictable absorption requires the patient to snack, or unexpected hypoglycemia may occur.

Insulin glargine (Lantus), a once-daily basal insulin approved by the FDA in the spring of 2001, features a smoother release profile over 24 hours, allowing for less complicated regimens and decreased risk of hypoglycemia. It is released slowly and evenly into the bloodstream from the SC injection site, approximating basal insulin secretion more closely than NPH, Lente, or Ultralente insulins. Clinical studies have shown that when insulin glargine is used in place of once-daily or twice-daily NPH in a variety of insulin regimens, it controls blood glucose levels at least as well as NPH but with fewer episodes of nocturnal hypoglycemia.[50-52] Moreover, use of insulin glargine, with its once-daily administration, has the potential to simplify the current haphazard approach to managing inpatient hyperglycemia.

### *Prandial Insulin*

Regular insulin (with onset of action at approximately 30 to 60 minutes, peak at 2 to 3 hours, and duration of action of 6 to 8 hours) has been the primary prandial insulin; this is changing, however, with the growing popularity of two relatively new rapid-acting analogues—insulin lispro (Humalog)

and insulin aspart (Novolog). Each of these prandial insulins can be administered immediately before eating, or 10 minutes before a meal if premeal glucose is within the target range of 120 to 180 mg/dL (although the patient with diabetes will not be in that range all of the time); this range well mimics the physiologic insulin profile, allows improved postprandial glycemic control, and lowers risk of late hypoglycemia. Insulin lispro has onset of action at 5 to 15 minutes, peaks at 1 to 2 hours, and has a duration of action of 4 to 6 hours. It lowers the mealtime surge in blood glucose more efficiently than does regular insulin,[53] and its effect subsides more quickly. Insulin aspart has a profile of activity similar to that of insulin lispro.[54]

### Premixed Insulin Combinations

In the outpatient setting, premixed insulin combinations such as 70% NPH and 30% regular, 75% insulin lispro protamine suspension and 25% insulin lispro, and, most recently, 70% NPH and 30% insulin aspart, may help simplify the insulin regimen and reduce the number of injections. However, use of premixed insulin regimens is problematic for hospitalized patients. With stress of illness, change in timing of meals, and alteration in amount of calories (even if the patient is eating), giving a fixed mixture of basal and prandial insulin often results in unstable glycemia. Modern-day insulin regimens, for both out- and inpatients, emphasize flexibility as much as possible, and it is difficult to maintain any degree of flexibility with a premixed regimen.

### Insulin Supplements

Whatever the patient's insulin regimen, if blood glucose falls outside the acceptable range of 120 to 180 mg/dL, adjustments may be needed. In some cases, elevations of blood glucose can be treated with supplemental insulin—an ad hoc dose of rapid-acting insulin (ie, insulin lispro or insulin aspart).[55] Insulin supplements are typically administered before a meal or snack. In the event of a recurring problem with blood glucose concentrations outside the target range, a change in treatment regimen is warranted, rather than continual supplemental insulin doses.

When using a supplement, it is important to consider the lag time of the insulin. Insulin lispro and aspart, which are preferable to regular insulin because of their shorter duration of action and therefore with less theoretical risk of later hypoglycemia (especially during the night), are ideally given 5 to 10 minutes before a meal provided premeal glucose is within target range; if premeal hyperglycemia is present, a longer lag time (up to 30 minutes) is desirable. Supplements of regular insulin are best given 20 to 30 minutes before eating if glucose levels are in target range, or up to an hour before eating in the event of premeal hyperglycemia. Realistically, however, a range of 0 to 10 minutes for insulin lispro/aspart or 10 to 20 minutes for regular insulin is acceptable.

### Sliding-Scale Insulin Regimens

Sliding-scale insulin regimens—ie, those determined retrospectively based on a single blood glucose level—are commonly used in hospitalized patients with diabetes who have been taking insulin prior to admission, despite criticism of this method in the literature. A typical sliding-scale insulin regimen

would provide no insulin if the blood glucose concentration is <180 mg/dL, 2 U of regular insulin if the blood glucose concentration is in the range of 180 to 250 mg/dL, and 4 U if blood glucose is 251 to 300 mg/dL, with increasing doses of insulin specified as blood glucose concentrations increase further. Sliding-scale insulin regimens provide no basal insulin; they institute dysfunctional supplemental insulin replacement only when hyperglycemia occurs before a meal, and do not consider mealtime caloric intake. An important limitation of sliding-scale insulin regimens is their nonphysiologic dosing schedule, which calls for administration of short-acting insulin only after hyperglycemia has already occurred. No insulin is given when the blood glucose concentration is normal, so blood glucose rises significantly by the time of the next blood glucose measurement. Then a large dose of regular insulin is given, increasing the patient's risk for hypoglycemia and producing a "roller coaster" pattern of glycemic control. Sliding-scale insulin regimens do not take into consideration the timing of meals and differences in insulin requirements at different times of the day.[22]

Sliding-scale regimens are prescribed for most hospitalized patients with diabetes; however, data suggest that the nonphysiologic dosing schedule of these regimens provides no benefit and in fact may place patients at risk for unnecessary hyperglycemia when used alone. In a study of 171 adults with diabetes as a comorbid condition who were admitted to an urban university hospital, 130 (76%) began a sliding-scale insulin regimen.[56] These regimens differed according to the starting capillary blood glucose level and were categorized as aggressive (<175 mg/dL, 36% of patients) or conservative (>175 mg/dL, 64% of patients). When used alone, these regimens were associated with a threefold higher risk of hyperglycemic episodes compared with patients following a nonpharmacologic regimen.[56] Moreover, the use of a sliding-scale insulin regimen in combination with a standing glycemic control regimen did not appear to provide any additional benefit to the standing regimen alone.

### Blood Glucose Monitoring

Any intensive insulin regimen requires frequent bedside blood glucose monitoring.[13] However, the optimal frequency for blood glucose measurement has not been studied. If the patient is receiving IV insulin, monitoring every hour or, at most, every 2 hours is usually adequate. If insulin is administered subcutaneously, monitoring should occur at least once before each meal and at bedtime.

Hospital personnel must be adequately trained to perform bedside blood glucose determinations and to interpret them appropriately.[57] Some hospitalized patients with diabetes are well enough to continue their regular diabetes therapy and should be encouraged to continue self-monitoring of blood glucose and administration of SC insulin under the supervision of hospital staff. However, many hospitalized patients are too ill to play a role in their diabetes treatment.

## Chapter 6: Inpatient Intravenous Insulin Strategies

Intravenous insulin is generally administered in hospitalized patients with shock, DKA, pregnancy, high-dosage corticosteroid therapy, sepsis, transplantation surgery, or cardiopulmonary bypass surgery. Continuous IV insulin infusion is usually the best approach for the inpatient with diabetes who cannot eat because, when used in conjunction with frequent blood glucose monitoring, it provides predictable insulin delivery and permits the dose to be altered quite rapidly when necessary.

For the hospitalized patient with type 1 diabetes who is not permitted to eat for at least 24 hours, IV glucose as a calorie source and IV insulin to control hyperglycemia are essential. If insulin is withheld, these patients are at risk for DKA. Pumps that deliver small quantities of insulin are useful to administer accurate insulin doses, which vary with the patient. Highly insulin-sensitive patients may require lower infusion rates, whereas critically ill patients or those treated with corticosteroids may need higher rates.

Early studies with animal insulins suggested that delivery of insulin in saline or dextrose solution could be uneven because the insulin might adhere to the infusion bottle or tubing.[58] Because of this concern, it may be prudent to flush the infusion apparatus with insulin–saline solution before use. For a 250-mL or 500-mL infusion bag, 50 mL of the insulin–saline solution is recommended. This practice results in subsequent stable insulin delivery and eliminates the need for protein additives.[59]

Glucose is needed to provide calories and to prevent hypoglycemia and starvation ketosis. Although the most commonly recommended glucose dosage is 5 g/hour, most patients require a minimum of 10 g/hour. If the 5g/hour recommendation is adopted, urinary ketones should be measured if food will be withheld for 24 hours or more. A larger dosage of glucose should be considered if ketonuria develops because of caloric restriction. Most patients who receive an insulin infusion also require IV potassium; the current recommendation is 20 mEq added to each liter of IV fluid.[22]

### IV Insulin Infusion Protocols

A variety of fixed-rate insulin infusion rate protocols have been developed for hospitalized patients; other protocols provide for individualization of the rate of insulin infusion. One individualized protocol that proved successful in patients with diabetes undergoing surgery is based on a simple bedside algorithm for insulin adjustment suitable for use by general ward nurses; it regulates insulin according to a "glucose feedback" formula to maintain plasma glucose between 120 and 180 mg/dL.[60] When this protocol was utilized immediately following a surgical procedure, in spite of elevated initial mean glucose levels, the mean glucose level was in the target range after 8 hours and remained stable for the remainder of the study period. Another, more recent, approach to postoperative glycemic management in a community hospital included use of a standardized protocol for nurse-implemented IV infusion therapy in patients with diabetes undergoing cardiac surgery (Tables 5 and 6).[61] A comparison (from postoperative days 0 through 4) of 29 patients managed with this protocol and 29 patients managed without it showed

**Table 5 . Nurse-Implemented Glycemic Management Protocol Developed in a Community Hospital***

**The protocol for glycemic management in the treatment of postoperative cardiac patients with diabetes includes**

- Definition of the target blood glucose level (120 to 199 mg/dL)
- Blood glucose monitoring guidelines for patients who do and do not require IV insulin therapy
- Thresholds for initiation of IV insulin therapy (glucose levels >200 mg/dL for patients without diabetes and >140 mg/dL for all patients with diabetes or for any patient without diabetes receiving norepinephrine, epinephrine, or phenylephrine infusion)
- Priming bolus insulin doses based on blood glucose level
- Table containing 5 scales, or columns (see Table 6), each for a different severity of insulin resistance and a series of rows each showing insulin infusion rates appropriate for a specific blood glucose level; a default column for initiation of IV insulin therapy by nursing staff; and guidelines for nursing staff to move between columns without a physician order
- Instructions to interrupt IV insulin therapy for low blood glucose level; instructions on when to discontinue IV insulin therapy and how often to monitor blood glucose after discontinuation; and instructions for contacting the endocrine department before discontinuation of the IV insulin infusion or in the event of hyperglycemia >200 mg/dL after discontinuation
- To achieve glycemic control more rapidly, physicians may order a column other than the default column when IV insulin therapy is initiated. Similarly, after insulin treatment is started, physicians may order movement to higher columns more quickly than specified in the protocol.
- Patients are not transferred from the critical-care unit until the IV insulin infusion has been stopped (often coinciding with the introduction of a meal plan).
- Therapy implemented approximately 2 hours before discontinuation of the IV insulin infusion generally consists of twice-daily injections of split-mix NPH and regular insulin, in conjunction with daily dosage revision and premeal supplementation with regular insulin as needed.
- For patients able to take oral glucose-lowering agents, the choice of an orally administered agent is made or preadmission orally administered agents are resumed near the time of dismissal from the hospital.

*Devised in consultation with a staff endocrinologist and critical-care unit nurses

From Markovitz LJ, Wiechmann RJ, Harris N, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract.* 2002;8:10-18.

- a greater number of blood glucose determinations
- a trend toward greater utilization of IV insulin therapy without a significant increase in the number of patients treated with this approach
- no change in the frequency of hypoglycemia

During the same interval, 27.5% of patients not managed using the protocol had at least 1 blood glucose determination ≥250 mg/dL, compared with 16.8% in the protocol group ($P = 0.0318$). The key finding of the study was a reduction in the percentage of postoperative days during which mean blood glucose values were ≥200 mg/dL by more than half—from 38.4% in patients not subject to the protocol to 16.8% with the protocol ($P = 0.0001$). This protocol has proven effective in the author's clinical practice.[62]

**Table 6. Insulin Infusion Rates for Postoperative Glycemic Management in Patients Undergoing Cardiac Surgery***

| Column 1 | | Column 2 | | Column 3 | | Column 4 | | Column 5 | |
|---|---|---|---|---|---|---|---|---|---|
| BG | U/h | BG | U/h | BG | U/h | BG | U/h | BG | U/h |
| | | <100 | 0ff | <100 | 0ff | <100 | 0ff | <100 | 0ff |
| <120 | 0ff | 100-119 | 0.5 | 100-119 | 1.0 | 100-119 | 1.0 | 100-119 | 1.0 |
| 120-149 | 0.5 | 120-149 | 1.0 | 120-149 | 1.5 | 120-149 | 2.0 | 120-149 | 2.0 |
| 150-179 | 1.0 | 150-179 | 1.5 | 150-179 | 2.0 | 150-179 | 3.0 | 150-179 | 4.0 |
| 180-239 | 1.5 | 180-239 | 2.0 | 180-209 | 3.0 | 180-209 | 4.0 | 180-209 | 8.0 |
| | | | | 210-239 | 4.0 | 210-239 | 6.0 | 210-239 | 12.0 |
| 240-299 | 2.0 | 240-299 | 3.0 | 240-269 | 5.0 | 240-269 | 8.0 | 240-269 | 16.0 |
| | | | | 270-299 | 6.0 | 270-299 | 10.0 | ≥270 | 20.0 |
| 300-359 | 2.5 | 300-359 | 4.0 | 300-329 | 7.0 | 300-329 | 12.0 | | |
| | | | | 330-359 | 8.0 | 330-359 | 14.0 | | |
| ≥360 | 3.0 | ≥360 | 6.0 | ≥360 | 12.0 | ≥360 | 16.0 | | |

BG = blood glucose (mg/dL).

*Column 1 is for patients whose estimated insulin rate is ≤1.0 U/h for maintenance; column 2 is for patients whose estimated rate is 1.1-1.5 U/h for maintenance (the starting point for most patients); column 3 is for patients whose estimated rate is 1.6-2.0 U/h for maintenance and for patients for whom column 2 has failed (some postcardiac surgery patients, insulin-requiring patients who use more than 80 U/d, and corticosteroid-treated patients start here); column 4 is for patients whose estimated rate is >2 U/h for maintenance and for whom column 3 has failed (no patient starts here); column 5 is for patients whose estimated rate is 4 U/h for maintenance and for whom column 4 has failed: candidates include patients receiving high-dosage corticosteroids or patients with intra-aortic balloon pumps (no patient starts here).

Reprinted from Markovitz LJ, Wiechmann RJ, Harris N, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract.* 2002;8:10-18, with permission from *Endocrine Practice*.

It should be noted that when insulin-treated patients with type 2 diabetes are hospitalized for an acute illness where little or no food is likely to be eaten for at least 24 hours or for surgery during which general anesthesia will be administered for longer than 1 to 2 hours, a continuous IV infusion is the best approach because IV insulin has more predictable bioavailability than SC insulin, is easier to titrate, and may afford a higher level of safety. Patients with type 2 diabetes typically have insulin resistance and are thus likely to require higher insulin infusion rates to control hyperglycemia, particularly if their usual insulin regimen included more than 100 U/day (see columns 3 and 4 in Table 6). For such individuals, the initial rate when hospitalized may be 2 U/hour. Intravenous glucose at a rate of 5 or 10 g/hour must be administered to prevent hypoglycemia and starvation ketosis.

Further, for type 2 diabetes patients treated with one or any combination of a sulfonylurea, metformin, thiazolidinedione, or diet alone who will not be permitted food for 24 hours or more, a continuous IV infusion of insulin should be considered if blood glucose concentrations are >200 mg/dL, with concomitant administration of 5 or 10 g/hour of IV glucose. Because glucose is delivered at a constant rate, the patient should receive insulin in the same manner.[22]

**Table 7. IV Insulin Algorithm Accounting for Rate of Change in Blood Glucose***

| Blood Glucose (mg/dL) | Change in Blood Glucose | |
|---|---|---|
| | Increase >60 mg/dL/h | Decrease >60 mg/dL/h |
| <70 | N/A | Stop infusion† |
| 71-120 | No change | Decrease rate by 0.6 U/h |
| 121-180 | Increase rate by 0.3 U/h | Decrease rate by 0.3 U/h |
| 181-240 | Increase rate by 0.6 U/h | No change |
| 241-300 | Increase rate by 1.0 U/h | No change |
| >300 | Increase rate by 1.5 U/h | No change |

* When blood glucose is no longer fluctuating by 60 mg/dL/h, a standard IV insulin algorithm can be used.

† Stop the infusion for 30 min; administer 10 g glucose. Recheck blood glucose in 20 min and restart when blood glucose is >100 mg/dL. Restart infusion at 3 mL/h (0.3 U/h) after the blood glucose level is >100 mg/dL (should be remeasured 15 min after turning off insulin infusion); if blood glucose is still <100 mg/dL, may wait another 15 min.

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Another protocol for IV insulin use in hospitalized patients with diabetes takes into account the rate of change in blood glucose, ie, an increase or decline of 60 mg/dL per hour or more (Table 7).[63] If IV glucose is discontinued to enable administration of antibiotic or blood products, for example, the blood glucose level may drop sharply. A decline of >60 mg/dL per hour requires a decrease in insulin infusion dosage—even if capillary blood glucose is not yet within the target range—to avoid development of hypoglycemia before the next blood glucose measurement. The protocol in Table 6 also allows change in insulin rate if there is a significant change in blood glucose: simply move up or down to a different column.

## Chapter 7: Inpatient Subcutaneous Insulin Strategies

The effects of SC insulin are unpredictable in the inpatient population even under optimal circumstances.[20] Because blood pressure changes and fluid shifts occur during surgery, for example, significant alterations in peripheral blood flow may ensue, heightening the usual variability of SC insulin. Additionally, problems often arise related to SC administration of insulin because basal insulins such as NPH and Ultralente, which have been used traditionally, are absorbed unevenly,[64] and thus do not accommodate the fluctuating meal schedules typical of inpatient care. This situation can be addressed by using treatment regimens that clearly separate basal from prandial insulin.

### When the Patient Is Taking Insulin Glargine or NPH Before Hospitalization

For many hospitalized patients, basal insulin glargine is an easier and more convenient approach to therapy than IV insulin infusion.[50,52,65] Approved by the FDA in the spring of 2001, insulin glargine is released slowly and evenly into the bloodstream from the SC injection site, approximating basal insulin secretion more closely than NPH, Lente, or Ultralente insulins. Clinical studies have shown that when insulin glargine is substituted for once- or twice-daily NPH in various outpatient insulin regimens, it controls blood glucose levels at least as well as NPH, but with fewer episodes of nocturnal hypoglycemia. It must be remembered, however, that any basal insulin, if not carefully dosed, can lead to next-day hypoglycemia. Nevertheless, using prandial (usually 3 injections per day) plus basal insulin is the only effective means of maintaining meticulous glycemic control in patients with severe insulin deficiency.

For the patient who has been taking an NPH-based regimen before being admitted to the hospital, options include adjusting the dose of NPH and continuing with the complicated NPH regimen (see below), or switching to insulin glargine. The latter option is preferable, provided the patient is willing to administer 3 daily injections of prandial insulin in addition to the once-daily insulin glargine.

The strategy for switching from an NPH-based regimen typically entails taking 50% of the total daily insulin dosage as insulin glargine, and then decreasing *this* dosage by 20%. Fasting blood glucose levels are the initial main outcome; at least 3 days are required to determine if the dosage is correct. Clinical observation shows that with this method, one third of patients will have the correct dosage, one third will require more of the basal insulin, and one third will require less.[66]

For patients who are already taking a regimen of insulin glargine before hospitalization, no change in the dosage is required. Theoretically, even if the patient is not eating, insulin glargine may be easier to use and more convenient than IV insulin therapy. Patients with either type 1 or type 2 diabetes receiving insulin glargine before hospitalization require at a minimum the same basal dosage of insulin. Except for certain situations as described elsewhere (notably surgery, hypotension from any etiology, high-dosage corticosteroids), continuing on the insulin glargine at the same dosage should be effective in maintaining basal insulin requirements. Prandial insulin may be withheld, or small supplements may be given to treat hyperglycemia.

Management is more difficult for the hospitalized patient whose outpatient insulin regimen is NPH-based. One approach is to continue the NPH regimen, although this may be problematic because NPH often covers both basal and prandial insulin requirements, which are unpredictable for many inpatients. Traditionally, the morning dose of NPH is decreased by 50%, but this may result in erratic glycemic control, depending on how much, if any, food is allowed.

For patients taking NPH as a bedtime basal insulin, dosing decisions are easier because there are fewer variables. Another option is to switch the patient from NPH to a regimen comprising one injection of basal insulin glargine per day, plus three daily injections of prandial insulin. Many patients are more comfortable with the clear distinction between the basal and prandial components of this regimen than with the more complex and ambiguous release profiles of NPH.

### Switching from IV to SC Insulin

Patients on IV insulin must be switched to SC insulin before discharge. For patients with type 1 diabetes, administration of IV glucose and insulin should continue through the time of the first light meal in case the food is not tolerated. If the food cannot be eaten for whatever reason, glycemic control is not sacrificed. If it becomes clear that more substantial amounts of food can be tolerated, the IV infusion will need to be discontinued. For patients with type 1 diabetes on non–glargine-based basal insulin regimens, this would present a good opportunity to change the basal insulin to insulin glargine. For those who will continue on NPH, Lente, or Ultralente, the timing of both basal and prandial insulin must be considered before discontinuing the insulin infusion. The majority of patients with type 1 diabetes receive one or a combination of these older basal insulins twice daily.

Choosing a strategy for discontinuing IV glucose depends on the type of basal insulin administered. For patients using insulin glargine, the IV infusion should serve as the basal insulin until the specified time for the once-daily bedtime injection. If dinner is planned, a prandial insulin, preferably lispro or aspart, should be administered 10 to 15 minutes before the meal; this also applies if the first scheduled meal is lunch.

If the patient will be discharged from the hospital during the day and insulin glargine was not given the night before, there are two options for satisfying the basal insulin requirement until the evening dose of insulin glargine can be administered at home. One entails administering regular insulin as the usual basal/prandial insulin, supplementing with insulin lispro/aspart if pre-meal hyperglycemia is present. Alternatively, a small dose of NPH (0.1-0.2 U/kg) may be given at lunch and dinner, followed by the usual bedtime injection of insulin glargine. For patients using twice-daily NPH, Lente, or Ultralente as their basal insulin, discontinuation of the infusion should coincide with the next scheduled injection of the basal and prandial insulins.

When patients are switched from IV to SC insulin, adjustments to their usual insulin dosage are common (Table 8).[13] If stress of illness has substantially increased the daily insulin requirement during administration of IV insulin, a small increase in the basal insulin dosage might be warranted. Significant hyperglycemia before meals should be treated with supplemental insulin (Table 9). For patients consuming less food than prior to hospitalization, and in whom the insulin requirement has been lower than usual during IV insulin therapy, baseline insulin dosages should be lowered.

**Table 8. Guidelines for Switching Hospitalized Patients With Diabetes From IV to SC Insulin**

1. Continue the insulin and glucose infusion through the first liquid and even solid food to ensure that food is tolerated.
2. Once tolerance of solid foods seems likely, the insulin infusion should be discontinued at the time insulin is normally administered (usually prior to meals). Subcutaneous insulin may be administered during this interval.
3. The usual dosage of SC insulin can be used when the IV insulin is discontinued.
4. Insulin lispro/aspart may be given 10–15 minutes prior to the arrival of food.
5. For patients using insulin glargine, the IV infusion should serve as the basal insulin until time for the once-daily bedtime injection.*
6. For patients using a non–insulin-glargine basal insulin (NPH, Lente, Ultralente), discontinuation of the infusion should coincide with the next scheduled injection of the basal and prandial insulins.

*If discharge from the hospital is during the day and insulin glargine was not given the night before, regular insulin may be used as the basal/prandial insulin, supplementing with insulin lispro/aspart as needed; or NPH (0.1–0.2 U/kg) may be used as the prandial insulin, followed by the usual bedtime injection of insulin glargine.

**Table 9. Guidelines for Supplemental Insulin**

1. Supplemental insulin lispro or aspart should be administered only before meals to prevent or correct a blood glucose level outside the target range of 120–180 mg/dL.
2. Normal lag time is 0–15 min; it should be increased when appropriate for greater degrees of hyperglycemia.
3. For patients with type 1 diabetes, the initial approach is to add 1 U of insulin lispro or insulin aspart for every 50 mg/dL increment over blood glucose level 180 mg/dL.
4. For patients with type 2 diabetes, the initial approach is to add 1 U of insulin lispro or insulin aspart for every 30 mg/dL increment over blood glucose level 180 mg/dL. A more conservative approach is to add 1 U of insulin lispro or insulin aspart for every 50 mg/dL increment over blood glucose level 180 mg/dL.
5. For the more insulin-resistant patient, the initial approach is to add 1 U of insulin lispro or insulin aspart for every 20 mg/dL increment over blood glucose level 180 mg/dL.
6. Patients should test their blood glucose level 2 hours after eating; the supplemental insulin dose should be adjusted until the postmeal glucose level is <180 mg/dL.
7. Urinary ketones should be measured for any premeal blood glucose level >300 mg/dL.

### Patients With Type 2 Diabetes Who Cannot Eat

The management of patients with type 2 diabetes who cannot eat differs according to whether their prehospitalization glycemic regimen consisted of insulin or oral glucose-lowering agents. Recommendations for patients with type 2 diabetes may be difficult because of variability in metabolic defects and glycemic regimens.

## Insulin in the Hospital Setting

### Insulin-Treated Patients With Type 2 Diabetes

When it is anticipated that the insulin-treated patient with type 2 diabetes will be able to eat within 24 hours, SC insulin may be given, although glycemia may be difficult to control. In the event of an early morning procedure, it may be advisable to withhold all insulin until after the procedure, because food will be delayed for only a short period of time. However, supplemental insulin (preferably lispro or aspart) may be given before the procedure if there is significant premeal hyperglycemia (>180 mg/dL). Although the appropriate doses of insulin for this situation are dictated by the patient's individual characteristics, for the typical patient with type 2 diabetes, 1 U of insulin lispro or aspart will lower blood glucose by approximately 30 mg/dL. Patients on insulin glargine are likely to exhibit greater glycemic stability in this situation because they will have received an injection the previous evening. For patients who do not consume food for more than 12 hours, IV glucose (5 or 10 g/hour) is recommended.[22]

### Noninsulin-Treated Patients With Type 2 Diabetes

Patients with type 2 diabetes who are normally treated with diet or oral glucose-lowering agents may not require insulin if they are not eating and are not under severe stress due to illness or surgical procedure.

If the patient is on metformin, alpha-glucosidase inhibitor, or thiazolidinedione monotherapy, continuing use of the oral agent will not alter blood glucose. However, metformin should be discontinued for procedures in which IV contrast agents will be administered (eg, cardiac catheterization) or when hospitalization is related to hypoxia (CHF, COPD, or hypotension from any etiology). Additionally, use of any thiazolidinedione should be discontinued if fluid overload of any etiology is present.

When food will be withheld for only a short period of time, such as for a morning procedure, insulin secretagogues (sulfonylurea or meglitinide) should not be given until after the procedure, but can then be administered before the next meal. If fasting hyperglycemia (>180 mg/dL) occurred before the procedure, use of the insulin secretagogue in all or part of the usual dosage may be considered. Many patients with fasting hyperglycemia, especially those with Alc levels >8%, may no longer respond to the agent, in which case long-term insulin therapy should be considered.[67] Determining whether hyperglycemia is due to oral agent failure or stress of illness could be difficult in some patients. Therefore, in many cases, the most prudent course is to administer small doses of supplemental insulin (lispro or aspart) for glucose levels above the target range. As mentioned above, a typical starting dose for most patients with type 2 diabetes is 1 U per 30 mg/dL above target, but one could be more conservative and initiate a supplemental dose at 1 U per 50 mg/dL above target.

### Patients With Type 1 Diabetes Who Can Eat

For the hospitalized 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. Yet, recent data indicate that for 41% of patients with type 1 diabetes, the usual regimen is only 1 or 2 injections of insulin per day,[68] which is less than optimal. With this in mind, the hospital period should be viewed as an 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.

***Choosing an Insulin Regimen***

The choice of insulin regimen depends on the individual patient's needs. In general, once- and twice-daily regimens are not suitable for type 1 diabetes patients, who require complete replacement of physiologic insulin. In many cases, the best glycemic control is provided by a multiple daily injection (MDI) regimen or continuous subcutaneous insulin infusion (CSII) with an insulin pump.

The MDI regimen best suited to inpatients because of its excellent glycemic control and flexibility in the timing of meals uses Ultralente or insulin glargine as the basal insulin. When using Ultralente, it is easiest to start with half the dosage at breakfast and the rest with dinner. Either regular insulin or insulin lispro/aspart may be used as the prandial insulin. *(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. Avoid leaving the mix in the syringe for any length of time.)*

Alternatively, one bedtime injection of insulin glargine may be used as the basal insulin and regular insulin or insulin lispro/aspart as the prandial insulin. *(Note: Insulin glargine cannot be mixed with other insulin preparations because the higher pH of other insulins may cause acidic insulin glargine to precipitate within the syringe.)* Again, this regimen affords greater flexibility in the timing of meals, an important consideration in hospitalized patients. Furthermore, studies of outpatients have suggested that insulin glargine can provide glycemic control at least as well as NPH, but with fewer episodes of nocturnal hypoglycemia.[50,52,65]

CSII via an insulin pump can be an especially precise way to deliver insulin. Pumps deliver either regular insulin or insulin lispro/aspart at a preprogrammed basal rate. Most pumps allow patients to program variable basal rates throughout the day to correspond to the body's diurnal changes in insulin sensitivity, which would otherwise result in nighttime hypoglycemia and morning hyperglycemia. In fact, the pump can be suspended altogether, or the basal insulin dose decreased, prior to intense physical activity to avoid hypoglycemia. Further, prandial insulin can be administered by activating the pump prior to a meal, based on the amount of carbohydrate intake anticipated as well as the preprandial blood glucose level.

***Starting Insulin in the Newly Diagnosed Patient***

If the patient is newly diagnosed in the hospital, 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 may have higher insulin requirements.

Following is a general procedure for establishing an initial insulin regimen in the newly diagnosed patient. It is intended only as a rough guideline and must be tailored to the patient's individual needs. *(Note: Pre-mixed fixed-ratio insulins are rarely appropriate for type 1 patients, who are highly dependent on a relatively precise match between carbohydrate intake and insulin activity profiles.)*

- *Calculate the patient's total daily dosage (TDD) of insulin, ie, 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 U/kg; range, 0.3 U/kg to 1.0 U/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 x 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.* If the patient's insulin sensitivity is unknown, it is wise to start with a conservative dose, eg, 1 U per 50 mg/dL, and titrate upward based on the results of blood glucose testing.

### Patients With Type 2 Diabetes Who Can Eat

Although patients may achieve excellent control of diabetes without insulin outside the hospital, insulin is often indicated during a hospital stay. For example, the patient with pre-dinner blood glucose in the range of 280 mg/dL will require supplemental insulin, such as rapid-acting insulin lispro or aspart, which quickly reduces blood glucose and has a rapid offset to minimize the risk of hypoglycemia.[55] It should be noted that repeated need for pre-meal supplemental insulin is often a signal of secondary failure of an oral agent. Measuring A1c can usually determine whether this is the case.[22]

#### *Supplementing Insulin*

When blood glucose levels are outside the normal range (pre-prandial, 90 mg/dL to 130 mg/dL; bedtime, 100 mg/dL to 140 mg/dL, A1c <7%), supplements with short-acting insulin analogues may be warranted. However, if hyperglycemia occurs persistently at the same time each day, the underlying problem in the insulin regimen should be addressed.

When administering supplemental insulin in patients with type 2 diabetes, it is important to design an algorithm based on pre-meal blood glucose levels. A good starting point is adding 1 U of shorter-acting insulin for every 30 mg/dL increment over blood glucose level 150 mg/dL. Patients should test their blood glucose level after meals, and the supplemental insulin dose should be adjusted until the level is <180 mg/dL.[69]

#### *Starting Insulin*

Since many patients with type 2 diabetes are insulin-resistant, they may require large amounts of insulin, on the order of 100 to 200 units, to control blood glucose levels. However, it is best to start basal insulin conservatively and then increase the dosage according to blood glucose response.

A dosage of about 10 U at bedtime is likely to improve glycemic control without causing hypoglycemia. The patient should monitor blood glucose levels at least twice daily to determine the effect of this dosage. The insulin dosage may be increased 5 to 10 U weekly until the fasting blood glucose level falls within the 90 mg/dL to 130 mg/dL range, with a target of 100 mg/dL.

***Once-Daily Insulin Regimens***

These regimens may be appropriate for patients in the early stages of type 2 diabetes. The most commonly used once-daily regimen is one injection of NPH or insulin glargine at bedtime. Although some type 2 diabetes patients on a once-daily regimen successfully maintain blood glucose levels within the target range, others require at least two daily injections to achieve significant long-term control. These two injections may be basal insulin alone or, more commonly, basal mixed with prandial insulin.

***A Twice-Daily "Split-Mix" Regimen***

These regimens offer better glycemic control than single-injection regimens and are appropriate for type 2 diabetes patients who have adequate endogenous insulin secretion. A "split-mix" regimen is a mixture of intermediate-acting insulin (NPH or Lente) and a shorter-acting insulin (regular insulin or insulin lispro/aspart) given twice daily, before breakfast and dinner.

***MDI (or "Basal/Prandial") Regimens***

These regimens are warranted in severely insulin-deficient type 2 diabetes patients who have not had success with once- or twice-daily injection regimens. Detailed descriptions of these regimens may be found in the previous section (Patients With Type 1 Diabetes Who Can Eat).

## Chapter 8: Oral Agents

In the inpatient setting, oral glucose-lowering agents (Table 10) are limited to patients who have been taking them prior to admission, have only mild elevations of blood glucose, are able to ingest oral medications, and do not have comorbid conditions or risk for such conditions that may contraindicate their use.[70] Sulfonylureas[71] and other insulin secretagogues such as the meglitinides repaglinide[72]

**Table 10. Oral Glucose-Lowering Agents in Hospitalized Patients With Diabetes**

| Drug Class | Mechanism of Action | Considerations in Hospitalized Patients |
|---|---|---|
| **Sulfonylureas**<br>• Glimepiride (Amaryl)<br>• Glipizide (Glucotrol, Glucotrol XL)<br>• Glyburide (Micronase, DiaBeta, Glynase) | Stimulate insulin secretion | Glucose-lowering effects occur within hours to days; limited dosing flexibility; risk of hypoglycemia increased with limited oral intake; avoid in patients with compromised hepatic function |
| **Meglitinides**<br>• Repaglinide (Prandin)<br>• Nateglinide (Starlix) | Stimulate insulin secretion | Effects are primarily on postprandial glucose, with limited effects on fasting glucose; hypoglycemia rare |
| **Alpha-glucosidase inhibitors**<br>• Acarbose (Precose)<br>• Miglitol (Glyset) | Slow the absorption of carbohydrate from the small intestine | Effects are mainly on post-prandial glucose, with limited effects on fasting glucose; effective only with enteral nutrition; commonly cause gas and flatulence |
| **Biguanides**<br>• Metformin (Generic, Glucophage Glucophage XR, Glucovance) | Decrease hepatic glucose production and increase insulin sensitivity | Onset of action too slow for most hospitalized patients; contra-indicated in patients with renal dysfunction, liver disease, and hypoxic states because of increased risk for lactic acidosis; should not be administered con-comitantly with IV contrast agents |
| **Thiazolidinediones**<br>• Pioglitazone (Actos)<br>• Rosiglitazone (Avandia) | Decrease peripheral insulin resistance | Onset of action too slow for most hospitalized patients; limited efficacy in patients with inade-quate endogenous production of insulin; contraindicated in patients with hepatic disease and heart failure; contraindicated in the presence of fluid overload of any etiology |

Adapted from Hoogwerf B. Postoperative management of the diabetic patient. *Med Clin North Am.* 2001;85:1213-1228.

**Table 11. Conditions for Use of Metformin in Hospitalized Patients**

| Absolute Contraindications | Relative Contraindications |
|---|---|
| Renal disease or renal dysfunction (specifically, serum creatinine concentration ≥1.5 mg/dL [≥133 µmol/L] in males and ≥1.4 mg/dL [≥124 µmol/L] in females) | Age ≥80 y (unless creatinine clearance level indicates renal function is not reduced) |
| CHF requiring drug therapy | Clinical or laboratory evidence of hepatic disease |
| Acute or chronic metabolic acidosis | Concomitant use of cationic drug |
| Metformin should be discontinued at time of a procedure requiring intravascular iodinated contrast material, for at least 48 hours after the procedure, and until renal function is considered normal | Presence of any condition associated with hypoxemia (eg, COPD and acute MI), dehydration, or sepsis |
| | Excessive alcohol use |
| | After any surgery, until patient's oral intake is resumed and renal function is considered normal |

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction.

Adapted from Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao H. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med.* 2002;162:434-437, with permission from the American Medical Association.

and nateglinide[73] acutely lower glucose, with a risk for hypoglycemia. For patients with diabetes who are undergoing surgery, sulfonylureas should be discontinued on the morning of surgery and then withheld after surgery until the patient resumes eating. The risk for hypoglycemia is minimal with insulin sensitizers as monotherapy. The glucose-lowering effects of biguanide agents such as metformin[74] and thiazolidinediones such as pioglitazone and rosiglitazone[75] typically are not sufficiently rapid for patients who have not taken these drugs for diabetes management prior to hospitalization. In addition, metformin is contraindicated for patients with risk factors for lactic acidosis, hypotension from any cause, sepsis, MI, congestive heart failure, and hypoxia from any cause (Table 11).[76] Patients undergoing a procedure with a contrast agent or surgery should be taken off metformin for 48 hours subsequent to the procedure. Fluid retention may be of concern in patients taking thiazolidinediones. For patients on a biguanide or thiazolidinedione before hospital admission, these agents can be discontinued temporarily at time of surgery and restarted in the postoperative period when oral therapy is again possible and hepatic and renal function is stable. The use of alpha-glucosidase inhibitors is limited in hospitalized patients because of potential side effects.[77]

In the hospitalized patient with newly diagnosed type 2 diabetes, insulin therapy is often preferable to the use of oral agents because it acts more rapidly. If the patient is not severely hyperglycemic, however, the oral agent glimepiride is a reasonable alternative to insulin. Unlike other sulfonylureas, it does not block the beneficial effects of ischemic preconditioning, possibly due to its lower affinity for mitochondrial K (ATP) channels.[78] The effects of the short-acting insulin secretagogues repaglinide and nateglinide on ischemic preconditioning are not as well studied.

## Chapter 9: Special Issues

The management of hospitalized patients with diabetes may be complicated by several factors including use of corticosteroid therapy and total parenteral nutrition (TPN). Patients receiving both corticosteroids and TPN are especially challenging.

### Corticosteroid Therapy

Corticosteroids, commonly used in the treatment of asthma, neurosurgical emergencies, transplant rejection, and connective tissue diseases (eg, rheumatoid arthritis and lupus), are well known for effects on carbohydrate metabolism that may exacerbate existing diabetes or precipitate "steroid diabetes." Higher dosages of corticosteroids may increase severity of insulin resistance and hyperglycemia.

The hyperglycemia induced by corticosteroids typically is characterized by

- minimal elevation of fasting blood glucose
- exaggeration of postprandial hyperglycemia
- lack of sensitivity to exogenous insulin

The degree of hyperglycemia correlates with the preexisting level of glucose tolerance. Patients with diabetes may develop profound hyperglycemia. Ketosis is rare, but most patients have a negative nitrogen balance due to the catabolic effects of corticosteroids on nitrogen metabolism.

In patients with corticosteroid-induced diabetes and those with well-controlled type 2 diabetes, the overall effect of corticosteroid therapy is minimally elevated fasting blood glucose and a marked increase in postprandial blood glucose concentrations. If fasting blood glucose exceeds 180 mg/dL, oral sulfonylureas are unlikely to be effective and variable-rate insulin infusion may be the most appropriate therapeutic choice.[13] This approach is particularly useful for patients who receive IV pulse corticosteroids (ie, a very large bolus given over a short period). In such patients, the insulin infusion rate can be titrated rapidly to control capillary blood glucose and tapered rapidly when the corticosteroid therapy is discontinued. In hospitalized patients receiving a constant dose of corticosteroid who have fasting blood glucose concentrations >180 mg/dL and who are not already receiving insulin, oral agents are unlikely to control hyperglycemia. Metformin and the thiazolidinediones, in particular, work too slowly to be of benefit. In cases of severe hyperglycemia (>300 mg/dL), insulin is the only effective therapy.

Because postprandial hyperglycemia is the primary abnormality in corticosteroid-induced diabetes, patients who have not been previously diagnosed with diabetes can often be treated with prandial insulin alone, although small amounts of basal insulin are sometimes warranted. Patients with an established diagnosis of type 2 diabetes receiving corticosteroids will require basal insulin, but not at the usual dosage (ie, approximately 50% basal, 50% prandial). In the author's experience, 70% prandial, 30% basal usually yields better results.

Self-monitoring of blood glucose is especially important in patients with diabetes who receive corticosteroid therapy, and patients should be advised to initiate this practice if they are not already doing so, or to increase frequency of monitoring while taking corticosteroids. Because corticosteroid-induced diabetes manifests primarily as postprandial hyperglycemia, blood glucose results taken 1 or 2 hours after mealtime are particularly useful.

### Total Parenteral Nutrition

Malnourished or severely ill hospitalized patients often receive TPN, which commonly leads to hyperglycemia. Patients with no history of diabetes therefore should be screened for diabetes by obtaining a fasting blood glucose or A1c determination before initiation of TPN. In patients with type 2 diabetes who require TPN, the insulin requirement is likely to be increased. According to a study in patients with diabetes who required nutritional support, 77% of patients with type 2 diabetes who did not receive insulin regularly required insulin for the control of glycemia while receiving TPN, with mean insulin dosages of 100 ± 8 U/d, and 67% of patients with type 1 diabetes taking insulin regularly required a mean increase in their insulin dosage of 22 ± 8 U/d.[79]

Several methods are commonly used to deliver insulin to the patient receiving TPN. Insulin can be added to the TPN bag, although several days may be required to determine the correct insulin dosages, because the TPN solution is changed infrequently. Another approach is the use of separate, variable-rate insulin infusion, which permits minute-by-minute control of blood glucose level.[80] With this method, most patients quickly achieve stabilization of blood glucose concentration when the TPN infusion rate is constant. Insulin delivery can then be transferred via the TPN solution. Sliding-scale insulin regimens should not be used if a variable-rate insulin infusion is employed because glucose control may be more erratic and the risk for hypoglycemia may be higher. With frequent blood glucose monitoring, excellent glycemic control can be achieved with little risk of hypoglycemia in the patient with diabetes who is receiving TPN.

#### *Nocturnal TPN*

Nocturnal TPN has become increasingly more common in the treatment of hospitalized patients receiving insulin; this requires additional coordination and judgment on the part of the clinician. In the author's experience, NPH insulin offers the best glycemic control in nocturnal TPN; however, if it is administered when TPN is initiated, a common practice, short-acting insulin must be added during the first 1 to 3 hours when severe insulin deficiency is likely to be present. Dosing is determined by frequent monitoring of blood glucose levels (every 2 to 3 hours the first few nights).

## Summary

Numerous factors are involved in managing hyperglycemia during hospitalization in patients with diabetes, including whether they have type 1 or type 2 disease, how well their diabetes was managed prior to hospitalization, the presence of comorbid conditions, whether or not they are able to eat, and their ability to participate in diabetes management while hospitalized. The large number of insulin products and oral glucose-lowering agents available today allows the physician to tailor therapy to the individual patient with diabetes. Continuous IV insulin therapy plays an important role in hospital management because it affords predictable insulin delivery and permits the insulin dosage to be adjusted rapidly to accommodate variability in blood glucose levels.

Hospitalization should be seen as an opportunity to improve long-term outcomes. Management goals related to the control of diabetes and prevention of complications can be reviewed; the importance of glycemic control, nutrition, and exercise reemphasized; and prehospitalization insulin and/or oral drug regimens adjusted. For the newly diagnosed patient, the hospital stay is an opportune time to introduce general diabetes education and initiate therapy.

Because there are few studies focusing on the metabolic requirements of hospitalized patients, many of the recommendations in this monograph are based on clinical experience or extrapolated from other situations. Future research is necessary to refine the treatment guidelines presented here and to develop informed protocols for inpatient glycemic control that could close the gap between inpatient and outpatient care.

## References


1. American Diabetes Association. The impact of diabetes. Accessed June 20, 2002 at www.diabetes.org.
2. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med.* 1999;159:1450-1456.
3. Mokdad AH, Engelgau MM, Ford ES, et al. Diabetes Trends in the U.S.: 1990-1998. *Diabetes Care.* 2000;23:1278-1283.
4. Mokdad A, Serdula M, Dietz W, Bowman B, Marks J, Koplan J. The spread of the obesity epidemic in the United States, 1991 to 1998. *JAMA.* 1999;282:1519-1522.
5. American Diabetes Association. Economic consequences of diabetes mellitus in the United States in 1997. *Diabetes Care.* 1998;21:296-309.
6. Songer TJ, Ettaro L, and the Economics of Diabetes Project Panel. Studies on the cost of diabetes. Accessed June 26, 2002 at www.cdc.gov/diabetes/pubs/costs/intro.htm.
7. *Diabetes 2001 Vital Statistics.* Alexandria, Va: American Diabetes Association; 2001:111-123.
8. Currie CJ, Morgan CL, Peters JR. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. *Diabetes Care.* 1998;21:42-48.
9. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. *Diabetes Care.* 1998;21:246-249.
10. American Diabetes Association. Hospital admission guidelines for diabetes mellitus. *Diabetes Care.* 2002;25(suppl 1):S109.
11. Conill AM, Horowitz DA, Braunstein S. The surgical patient with diabetes mellitus. In: Goldman DR, Brown FH, Guarnieri DM, eds. *Perioperative Medicine.* New York: McGraw-Hill, 1994:243-250.
12. Porte D Jr, Woods SC. Neural regulation of islet hormones and its role in energy balance and stress hyperglycemia. In: Rifkin H, Porte D Jr, eds. *Diabetes Mellitus: Theory and Practice.* 4th Ed. New York: Elsevier; 1990:175-197.
13. Hirsch IB, Paauw DS. Diabetes management in special situations. *Endocrinol Metab Clin North Am.* 1997;26:631-645.
14. Airaksinen KE. Silent coronary artery disease in diabetes—a feature of autonomic neuropathy or accelerated atherosclerosis? *Diabetologia.* 2001;44:259-266.
15. Levetan CS, Magee MF. Hospital management of diabetes. *Endocrinol Metab Clin N Am.* 2000;29:745-770.
16. Hirsch IB. Insulin therapy for diabetes: Is the future now? *Clin Diabetes.* 2001;19:146-147.
17. Burge MR, Schade DS. Insulins. *Endocrinol Metab Clin North Am.* 1997;26:575-598.
18. Bantle JP, Laine DC. Day-to-day variation in glycemic control in type I and type II diabetes mellitus. *Diabetes Res.* 1988;8: 147-149.
19. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. *Diabetes Care.* 1984;7:188-199.
20. Hirsch IB, McGill JB. Role of insulin in management of surgical patients with diabetes mellitus. *Diabetes Care.* 1990;13: 980-991.
21. Surwit RS, Schneider MS, Feinglos MN. Stress and diabetes. *Diabetes Care.* 1992;15:1413-1421.
22. Hirsch IB, Paauw DS, Brunzell J. Inpatient management of adults with diabetes. *Diabetes Care.* 1995;18:870-878.
23. Hirsch IB, Farkas-Hirsch R. Type 1 diabetes and insulin therapy. *Nurs Clin North Am.* 1993; 28:9-23.
24. Hirsch IB. Implementation of intensive diabetes therapy for IDDM. *Diabetes Rev.* 1995;3:288-307.
25. Greiff JM, Rowbotham D. Pharmacokinetic drug interactions with gastrointestinal motility modifying drugs. *Pharmacokinetics.* 1994;27:447-461.
26. Ockert DM, Hugo JM. Diabetic complications with special anaesthetic risk. *S Afr J Surg.* 1992;30:90.
27. Seki S. Clinical features of hyperosmolar hyperglycemic nonketotic coma associated with cardiac operations. *J Thoracic Cardiovasc Surg.* 1986;91:867.
28. Li YP, Reid MB. Effect of tumor necrosis factor α on skeletal muscle metabolism. *Curr Opin Rheumatol.* 2001;13:483-487.

29. Yabunaka N, Nishihira J, Mizue Y, et al. Elevated serum content of macrophage migration inhibitory factor in patients with type 2 diabetes. *Diabetes Care.* 2000;23:256-258.

30. Meldrom DR, Donnahoo KK. Role of TNF in mediating renal insufficiency following cardiac surgery: evidence of a postbypass cardiorenal syndrome. *J Surg Res.* 1999;85:185-199.

31. Ferrari R. The role of TNF in cardiovascular disease. *Pharmacol Res.* 1999;40:97-105.

32. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor α: a key component of the obesity-diabetes link. *Diabetes.* 1994;43:1271-1278.

33. Satomi N, Sakurai A, Haranaka K. Relationship of hypoglycemia to tumor necrosis factor production and antitumor activity: role of glucose, insulin and macrophages. *J Natl Cancer Inst.* 1985;74:1255-1260.

34. Fraker DL, Merino MJ, Norton JA. Reversal of the toxic effects of cachectin by concurrent insulin administration. *Am J Physiol.* 1989;256:E725-E731.

35. Das UN. Is insulin an antiinflammatory molecule? *Nutrition.* 2001;17:409-413.

36. Mohan IK, Das UN. Oxidant stress, anti-oxidants and nitric oxide in non-insulin-dependent diabetes mellitus. *Med Sci Res.* 1997;25:55.

37. 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.

38. Malmberg K, for the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ.* 1997;1512-1515.

39. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab.* 2002;87:978-982.

40. Ordoubadi FF, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute mycardial infarction: an overview of randomized placebo-controlled trials. *Circulation.* 1997;96:1152-1156.

41. Hostetter MK. Handicaps to host defense: effects of hyperglycemia on C3 and *Candida albicans*. *Diabetes.* 1990;39: 271-275.

42. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care.* 1999; 22:1408-1414.

43. Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS Jr. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol.* 2001;22:607-612.

44. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg.* 1997;63:356-361.

45. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear clear leukocyte function and metabolic control of diabetes. *Diabetes Care.* 1992;15:256-260.

46. Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. *Anesth Analg.* 1999;88:1011-1016.

47. Hamuro M, Polan J, Natarajan M, Mohan S. High glucose induced nuclear factor kappa B mediated inhibition of endothelial cell migration. *Atherosclerosis.* 2002;162:277-287.

48. Hunt TK, Hopf HW. Wound healing and wound infection. What surgeons and anesthesiologists can do. *Surg Clin North Am.* 1997;77:587-606.

49. McCowen KC, Malhotra A, Bistrian BR. Endocrine and metabolic dysfunction syndromes in the critically ill. *Critical Care Clinics.* 2001;17:107-124.

50. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care.* 2000;23:1666-1671.

51. Matthews DR, Pfeiffer C, for the multicentre HOE901 research group. Comparative clinical trial of a new long-acting insulin (HOE901) vs. protamine insulin demonstrates less nocturnal hypoglycemia. *Diabetes.* 1998;47(suppl 1):A101.

52. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA, for the US Study Group of Insulin Glargine in Type 1 Diabetes. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care.* 2000;23:639-643.

53. DiMarchi RD, Chance RE, Long HB, Shields JE, Slieker LJ. Preparation of an insulin with improved pharmacokinetics relative to human insulin through consideration of structural homology with insulin-like growth factor I. *Horm Res.* 1994;41:93-96.

54. Home PD, Lindholm A, Hylleberg B, Round P, for the U.K. Insulin Aspart Study Group. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. *Diabetes Care.* 1998;21:1904-1909.

55. Holleman F, van den Brand JJ, Hoven RA, et al. Comparison of Lys B28, Pro B29-human insulin analog and regular human insulin in the correction of incidental hyperglycemia. *Diabetes Care.* 1996;19:1426-1429.

56. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med.* 1997;157:545-552.

57. American Diabetes Association. Bedside blood glucose monitoring in hospitals. *Diabetes Care.* 2002;25(suppl 1):S110.

58. Wisenfeld S, Podofsky S, Goldsmith L, Ziff L. Adsorption of insulin to infusion bottles and tubing. *Diabetes.* 1968;17: 766-771.

59. Peterson L, Caldwell J, Hoffman J. Insulin adsorbance to polyvinylchloride surfaces with implications for constant-infusion therapy. *Diabetes.* 1976;25:72-74.

60. Watts NB, Gebhart SSP, Clark RV, Phillips LS. Postoperative management of diabetes mellitus: steady-state glucose control with bedside algorithm for insulin adjustment. *Diabetes Care.* 1987;10:722-728.

61. Markovitz LJ, Wiechmann RJ, Harris N, et al. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract.* 2002;8:10-18.

62. Van den Berghe G, Bouillon R, Lauwers P. Intensive insulin therapy in critically ill patients [response to letter]. *N Engl J Med.* 2002;346:1587-1588.

63. Carr MC, Hirsch IB. Medical management of diabetic patients during the perioperative period. In: Bowker JH, Pfeifer MA, eds. *The Diabetic Foot.* 6th Ed. New York: Raven Press; 2000:513-523.

64. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes.* 2000;49:2142-2148.

65. Rosenstock J, Park G, Zimmerman J, for the U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. *Diabetes Care.* 2000;23:1137-1142.

66. Kelly JL, Trence DL, Hirsch IB. Rapid decrease in clinically significant hypoglycemia with insulin glargine. *Diabetes.* 2002;51(suppl 2):A123.

67. Groop LC, Pelkonen R, Koskimtes S, Botazzo GF, Donisch D. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes mellitus. *Diabetes Care.* 1986;9:129-133.

68. Roper Global Diabetes Program, Market Measures/Cozint. 2002 Survey of the U.S. Diabetes Market.

69. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2001; 24(suppl 1):33S-43S.

70. Hoogwerf BJ. Postoperative management of the diabetic patient. *Med Clin North Am.* 2001;85:1213-1228.

71. Kramer W, Muller G. Girbig F, et al. Differential interaction of glimeperide and glibenclamide with the B cell sulfonylurea receptor II. Photoaffinity labeling of a 65 Kd protein by (3H)glimeperide. *Biochim Biophys Acta.* 1994;119:278-290.

72. Jovanovic L, Dailey G III, Huang W-C, Strange P, Goldstein BJ. Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. *J Clin Pharmacol.* 2000;40:49-57.

73. Gribble FM, Manley SE, Levy JC. Randomized dose ranging study of the reduction of fasting and postprandial glucose in type 2 diabetes by nateglinide (A-4166). *Diabetes Care.* 2001; 24:1221-1225.

74. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997;103:491-497.

75. Whitcomb RW, Saltiel AR. Thiazolidinediones. *Exp Opin Invest Drugs.* 1995;4:1299-1309.

76. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao H. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med.* 2002;162:434-437.

77. Hollander P, Pi-Sunyer X, Coniff RF. Acarbose in the treatment of type 1 diabetes. *Diabetes Care.* 1997;20:248-253.

78. Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation.* 2001;103: 3111-3116.

79. Park HR, Hansell DT, Davidson LE, Henderson G, Legge V, Gray GR. Management of diabetic patients requiring nutritional support. *Nutrition.* 1992;8:316-320.

80. Woolfson AMJ. An improved method for blood glucose control during nutritional support. *J Parenter Enter Nutr.* 1981;5: 436-440.