Management of Inpatient Hyperglycemia

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INTRODUCTION

Over the past decade, hyperglycemia in the hospitalized patient has gained tremendous attention due to its association with increased mortality and inpatient complications as well as its negative economic impact. Likewise, hypoglycemia is associated with poor outcomes and remains the limiting factor in controlling hyperglycemia. Even the experienced clinician is challenged every day at achieving the glycemic target, and a multitude of variables besides food intake and insulin dosing exist. Improvements in glycemic control throughout the hospital stay are associated with decreases in short- and long-term risk of mortality, inpatient complications, and hospital lengths of stay. Financial benefits of glycemic control are significant, not just in reducing direct hospital costs by reducing length of stay, but also in decreasing hospital readmission rates. Hospital care accounts for half of the health care costs for patients with diabetes.

Conservative estimates of the incidence of diabetes in adult hospitalized patients range from 12% to 26%. The incidence of hyperglycemia in non-diabetic patients at the time of hospital admission is estimated to be 12%, which translates into 1 out of every 8 hospital admissions. Stress hyperglycemia (in the nondiabetic patient) historically was felt to be part of the natural course of acute illness and not treated unless glucose levels exceeded 200 mg/dL or the patient was symptomatic. However, we now know that stress hyperglycemia has been associated with longer hospital stays, higher rates of intensive care unit (ICU) admission, greater need for rehabilitation services at the time of discharge, and higher mortality rates.

In the largest review of hospital glycemic control, which included 576 hospitals and over 49 million blood glucose readings from 3.5 million patients, the average ICU glucose level was 166 mg/dL and the average non-ICU glucose level was 167 mg/dL. The analysis further revealed that one-third of both ICU and non-ICU patient-days were characterized by hyperglycemia (> 180 mg/dL) and 6% of patient-days in each group met criteria for hypoglycemia (< 70 mg/dL). The need to improve the treatment of hyperglycemia in hospitals is increasingly being recognized, but still has yet to be universally accepted.

The link between hyperglycemia and adverse hospital outcomes is multifactorial. Elevated blood glucose concentrations produce a proinflammatory cytokine predominance, leading to a multitude of
downstream effects, including capillary basement membrane thickening, impaired phagocytosis and immunity, oxidative stress, abnormal lipid metabolism, decreased vascular contractility, increased platelet adhesiveness, increased concentrations of coagulation factors, and increased C-reactive protein levels.\(^8\) Contributing factors to hyperglycemia include elevations in stress-related hormones (growth hormone, catecholamines, cortisol, glucagon), pharmacologic agents,\(^11\) enteral and total parenteral nutrition,\(^12,13\) and glucocorticoid therapy.\(^14\) As a result, a glycemic control plan should be in place for all hospitalized patients with hyperglycemia.

**HYPERGLYCEMIA AND PATIENT OUTCOMES**

Historically, diabetes is associated with higher perioperative mortality,\(^15\) deep sternal wound infections,\(^16\) postoperative strokes, and longer length of hospital stays.\(^17\) Tighter glucose control has been beneficial in a variety of patient settings including acute myocardial infarction,\(^18\) strokes,\(^19\) community-acquired pneumonia,\(^20\) and chronic obstructive pulmonary disease exacerbations, and in non-ICU postsurgical settings such as renal transplantation,\(^21\) total joint arthroplasty,\(^22\) and colorectal surgery.\(^23\) Morbidity and mortality are correlated with the presence and degree of hyperglycemia in the postoperative period\(^24\) and are independent of a prior diagnosis of diabetes.

Interventional outcomes studies have shown benefits in inpatient morbidity and mortality from intensive inpatient hyperglycemia management, especially in individuals without a prior history of diabetes.\(^25–31\) In Van den Berghe’s landmark study in a single Belgian surgical ICU, tight glycemic control was associated with a 34% reduction in hospital mortality, 46% reduction in sepsis, 41% reduction in renal impairment requiring dialysis, 50% reduction in blood transfusions, and 44% reduction in the incidence of ICU polyneuropathy, as compared with standard hyperglycemia management.\(^25\) Based on these results, the standard of care in the glucose management of ICU patients began to change, but the optimal glycemic target remained controversial in different patient populations because the results of van den Berghe’s study were not reproducible.

The largest randomized ICU trial assessing intensive glycemic control, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, reported higher mortality and hypoglycemia rates in ICU patients treated with intensive glycemic control (80–110 mg/dL) compared to less tight glycemic control (glucose <180 mg/dL).\(^32\) The conventional group in NICE-SUGAR, however, required insulin 69% of the time in order to achieve the target glucose below 180 mg/dL, indicating a continued need for insulin therapy in the majority of critically ill patients, just with a less intensive glucose target range. The goal target range for all critically ill patients remains controversial, but likely is population specific and should be individualized based on the clinical situation, training of ICU personnel with insulin protocols, and risk of hypoglycemia.

Glycemic variability has emerged as an additional component affecting hyperglycemia outcomes. In the outpatient setting, wider glucose fluctuations (defined as the amplitude from peak to trough in glucose) corresponds to an increased risk of diabetic microvascular complications in patients with diabetes.\(^33\) Krinsley previously identified the near-linear relationship between ICU mortality and mean glucose.\(^34\) Further data from his mixed medical, cardiac, and surgical ICU shows glucose variability within each subset of mean glucose (even within the euglycemic range) is also an indicator
of ICU mortality. In patients with the best glycemic control (mean glucose 70–99 mg/dL), those with the largest glycemic variability had a fivefold increase in mortality compared to patients with the least glycemic variability.\textsuperscript{34} A larger European ICU study had similar results.\textsuperscript{35} Outside the ICU, glycemic variability is also a predictor of mortality in patients on parenteral nutrition,\textsuperscript{36} but not in the general medical ward population. In non-ICU surgical patients, glycemic variability is associated with postoperative mortality and hospital complications in hyperglycemic patients without known diabetes, but not in patients with diabetes undergoing general surgery.\textsuperscript{37}

### AACE/ADA GUIDELINES FOR OPTIMAL GLYCEMIC CONTROL

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) have developed guidelines for optimal glycemic control in the hospital setting.\textsuperscript{38,39} These recommendations can be summarized as follows: 1) identify elevated blood glucose in all hospitalized patients, 2) establish a multidisciplinary team approach to diabetes management in all hospitals, 3) implement structured protocols for aggressive control of blood glucose in ICUs and other hospital settings, 4) create educational programs for all hospital personnel caring for people with diabetes, and 5) plan for a smooth transition to outpatient care with appropriate diabetes management.\textsuperscript{40,41} The AACE/ADA guidelines provide structure around which institutions can develop protocols that achieve blood glucose goals yet allow for individualization of algorithms and policies to fit with the hospital’s culture and environment. In May 2009, AACE/ADA revised their inpatient glycemic targets to 140 to 180 mg/dL for ICU patients, to below 140 mg/dL for preprandial glucose levels in non-ICU patients, and to below 180 mg/dL for all random glucose levels (Table 1).

### HYPERGLYCEMIA TREATMENT OPTIONS IN THE HOSPITAL SETTING

#### CASE PATIENT

A 68-year-old Caucasian man with a past medical history significant for type 2 diabetes, hypertension, and hypercholesterolemia is admitted with an acute myocardial infarction. Blood glucose on admission is 254 mg/dL. His home dia-

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**Table 1. Glycemic Goals in the Hospital**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Glycemic Goals</th>
<th>Preferred Method of Insulin Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically ill patients</td>
<td>140–180 mg/dL</td>
<td>Intravenous insulin infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiate insulin at glucose &gt;180 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain glucose 140–180 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose &lt;110 or &gt;180 mg/dL not recommended</td>
</tr>
<tr>
<td>Non-critically ill patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preprandial blood glucose</td>
<td>&lt;140 mg/dL</td>
<td>Subcutaneous insulin</td>
</tr>
<tr>
<td>Maximum blood glucose</td>
<td>&lt;180 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

The optimal diabetes regimen to use during this patient’s hospital stay?

Upon admission to the hospital, hyperglycemic patients should be managed using either intravenous (IV) or subcutaneous (SC) insulin algorithms. Insulin therapy should be effective (reach acceptable glucose targets in the shortest duration of time) and safe (with minimal incidence of hypoglycemia). Patients with hyperglycemia should be on a carbohydrate consistent diet (if eating), and glucose monitoring should be ordered before each meal and at bedtime. Alternatively, glucose monitoring should be ordered every 4 to 6 hours in patients who are NPO, on tube feeding, or on total parenteral nutrition (TPN). All patients with hyperglycemia should have their glycosylated hemoglobin (A1C) checked on admission to help differentiate between long-term or relatively new-onset hyperglycemia. The Joint Commission recommends obtaining an A1C level during the hospital stay if one is not documented in the past 60 days to identify previously unrecognized diabetes or to help guide optimization of the outpatient diabetes regimen if the A1C is elevated. Recently, an international expert committee recommended that an A1C of 6.5% or higher indicates a diagnosis of diabetes.42

Most inpatient diabetes algorithms recommend discontinuing oral antidiabetic drugs (OADs) and initiating insulin analog therapy. OADs should be discontinued on admission for various reasons. Insulin secretagogues, such as sulfonylureas and glitinides (nateglinide, repaglinide), are associated with an increased risk of hypoglycemia. Metformin should not be used for inpatients because of the increased risk in changes in renal function and impairment (due to volume shifts, medications, or contrast-induced nephropathy). Thiazolidinediones (rosiglitazone, pioglitazone) are insulin sensitizers that can increase circulating plasma volume by 6% to 7%, and therefore should not be used in patients with edema or heart failure. Incretin-based agents (sitagliptin, saxagliptin, linaglaptin, exenatide, liraglutide, and pramlintide) may increase the risk of gastrointestinal adverse effects, which may slow the recovery of a hospitalized patient, although they have not been frequently studied in the inpatient setting. IV infusion of a glucagon-like peptide 1 agonist was recently compared to IV insulin infusions in non-critically ill patients and controlled blood sugars with less hypoglycemia.43 This proof of concept study raises the hope for non–insulin-based mechanisms of glycemic control to be further investigated.

**INSULIN**

Insulin is the preferred agent for glycemic control in hospitalized patients. The pharmacodynamic properties of insulin allow it to be adapted to the changing physiology of the sick patient, it can be easily titrated, and it does not have a dosage threshold. Furthermore, insulin has a rapid onset of action, minimal side effects except for hypoglycemia, and minimal drug interactions. Unfortunately, insulin also is considered a high-risk drug with regards to medication safety and administration errors.
Table 2. Insulins Used in Hospitalized Patients

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Onset/Duration</th>
<th>IV/SC Use</th>
<th>Recommended Use in Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro (Humalog)</td>
<td>5–15 min/3–5 hr</td>
<td>SC</td>
<td>15 min before or immediately after meal</td>
</tr>
<tr>
<td>Insulin aspart (NovoLog)</td>
<td>5–15 min/3–5 hr</td>
<td>SC, IV*</td>
<td>5–10 min before meal</td>
</tr>
<tr>
<td>Insulin glulisine (Apidra)</td>
<td>5–15 min/3–5 hr</td>
<td>SC, IV*</td>
<td>15 min before or 20 min after starting meal</td>
</tr>
<tr>
<td>Short-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin</td>
<td>30–60 min/6–8 hr</td>
<td>SC, IV</td>
<td>Preferred for insulin drips; avoid for post-prandial use; do not use sliding scale</td>
</tr>
<tr>
<td>(Humulin R, Novolin R)</td>
<td>(longer with U-500 or renal insufficiency)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting insulins</td>
<td>2–4 hr/8–12 hr</td>
<td>SC</td>
<td>Can be used as a twice-daily substitute for basal insulin regimen</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>(Novolin N, Humulin N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(longer with renal insufficiency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>3–8 hr/16–24 hr</td>
<td>SC</td>
<td>Preferred for basal insulin use</td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>2–4 hr/24 hr</td>
<td>SC</td>
<td>Preferred for basal insulin use</td>
</tr>
</tbody>
</table>

IV = intravenous; SC = subcutaneous.

*Insulin analogs have no benefit over regular insulin for IV infusions.


The Society of Hospital Medicine has developed a workbook to guide hospitals in creating safe and effective glycemic control plans. The workbook includes multiple successful, published inpatient insulin protocols. Common themes in these protocols are the utilization of regular insulin for continuous insulin infusion and a basal/bolus SC insulin regimen including a long-acting insulin given once daily (insulin glargine or detemir) and prandial doses of a rapid-acting insulin (insulin aspart, glulisine, or lispro).44–47 The ideal insulin protocol will help attain the glucose target range in a timely manner, effectively treat all degrees of hyperglycemia and do so with minimal glycemic variation, and minimize the risk of hypoglycemia; it should also be easy for nurses to carry out in a timely fashion.48

Insulin analogs are preferred for basal, meal-time, and correction doses instead of human insulins (regular and NPH), because analogs have a more predictable absorption and action profile and less pharmacokinetic fluctuation in patients with renal insufficiency. High doses of regular insulin not only have a greater peak effect than lower doses, but also have a longer duration of action that can lead to overlap of insulin doses (known as insulin stacking) and increase the risk of a hypoglycemic event. The duration of action of rapid-acting insulin analogs is predictable at both low and high doses, thereby decreasing the risk of insulin stacking. Insulin analogs have a more consistent pharmacokinetic and pharmacodynamic profile (less interindividual and intraindividual variability),49,50 so it is easier to predict the effect the dose will have on an individual’s blood glucose concentration. Table 2 describes the types of insulin recommended for hospital use.51,52
Continuous infusion of regular insulin is suggested for critically ill ICU patients, pre- and post-operative patients, peripartum women with hyperglycemia, patients with severe hyperglycemia with metabolic decompensation (diabetic ketoacidosis and hyperosmolar non-ketotic states), and any patient in whom tight glycemic control is clinically indicated. Insulin given intravenously has a half-life of 7 to 8 minutes, and therefore reaches a new steady state in less than 1 hour after any titration. Most insulin infusion algorithms suggest glucose monitoring every 1 to 2 hours until reaching the target glucose range. Some insulin protocols include a bolus dose of IV insulin when the drip rate is increased to help reach steady state more quickly.\(^4^4\) A review of IV insulin infusion protocols that adjusted the insulin drip rate based on the rate of change of glucose (not just the current glucose level) showed that such protocols were more effective.\(^5^3\) Paper-based and computer-based insulin infusion algorithms are available to guide clinicians to achieve optimal glycemic control.\(^4^4,5^4,5^5\)

**CASE CONTINUED**

In the ICU, the patient is placed on a continuous insulin infusion with a drip rate averaging 2 units/hr. He is stable after his cardiac intervention. In the past 24 hours, his glucose has ranged from 100 to 150 mg/dL without hypoglycemia. He is tolerating an oral diet. He is ready for transfer from the ICU to the general medical ward for further monitoring.

- **What is the optimal diabetes regimen for this patient upon leaving the ICU?**

**DOSING OF INSULIN**

Many clinicians struggle with the appropriate dosing of insulin when admitting patients to the hospital or transferring patients out of the ICU. The key concept in dosing of SC insulin is estimating the patient’s total daily dose of insulin (TDD). The TDD can be derived in many ways such as measurement of 24-hour insulin requirements on an insulin drip, review of the patient’s pre-hospital insulin regimen (if they were on insulin prior to admission), or using a weight-based calculation.

**Converting from IV to SC Insulin**

Conversion from IV to SC insulin commonly occurs when the critical illness resolves and the patient is extubated, off vasopressors, and ready to start eating or has achieved a stable tube-feed rate. When the patient is being converted from an IV insulin drip, the drip rate is used as a guide to determine total daily insulin requirements. The insulin drip rate over the preceding 6 hours is averaged to obtain a stable hourly rate. The average hourly rate is multiplied by 24 hours to calculate TDD required. The basal insulin dose ordered is 60% to 80% of the TDD and the prandial insulin dose for each meal is 10% of the TDD. The prandial insulin dose is adjusted accordingly as the patient’s appetite improves. The proportion of insulin given for prandial dosing is substantially less because these patients are generally consuming only a clear liquid diet initially with a reduced caloric content. The insulin infusion should be continued for 4 hours after the first injection of basal insulin is given (if insulin glargine or detemir; 2 hours if NPH insulin). Practical necessities sometimes outweigh physiologic reasoning in that conversion from IV to SC insulin often coincides in time with transfer of the patient out of the ICU, with the result that the insulin infusion is simply stopped without an overlap period. In this scenario, a conversion dose of a rapid-acting insulin (10% of TDD) can be given simultaneously
with the basal insulin and the insulin infusion can be discontinued without an overlap period.\textsuperscript{56}

**Basal-Bolus Insulin Regimens**

For all non-critically ill patients, a basal/bolus insulin regimen is the preferred method of glycemic control (Table 3). Basal insulin suppresses hepatic gluconeogenesis between meals and overnight. During illness, basal insulin requirements rise with any physical stress including surgery, infection, infarction, or fever. For patients who are eating, a scheduled mealtime insulin dose with a rapid-acting insulin analog helps prevent the glucose from rising from carbohydrate intake. Whether eating or not, when blood sugars are outside the glycemic target range, a correctional dose of rapid-acting insulin can be given to lower the glucose.

Hospitalized patients have unpredictable eating and diagnostic testing schedules and thus are more susceptible to an insulin-food dyssynchrony—the risk of hypoglycemia increases if insulin peaks before the patient has eaten or consumed enough carbohydrates; hyperglycemia results if the insulin peak is insufficient to meet glucose intake or metabolic stress needs. Rapid-acting insulin analogs can be given immediately before or up to 20 minutes following food consumption and thus are more flexible and less likely to cause hypoglycemia.\textsuperscript{57} Furthermore, if the patient is not eating reliably, mealtime insulin doses can be adjusted based on actual carbohydrate intake (such as reducing the dose 50\% if half the food is consumed).

For patients who are on insulin at home, continuing their home insulin dosing is not always the appropriate inpatient regimen. Many patients eat a significantly different diet at home compared to the carbohydrate-consistent diet given in the hospital. Also, medications and acute physical stress from their illness often increase their insulin requirements. The key is to anticipate the change in insulin requirements based on what is known about their home glucose control, which requires a brief assessment of their diabetic behaviors prior to admission and an understanding the physiologic changes that medication, surgery, or illness will have on their insulin requirements.

Premixed insulins are generally not recommended for use in the hospital setting, as there is an increased risk of hypoglycemia in patients with variable oral intake. Some hospitals have pharmacy personnel perform a simple conversion from premixed insulin to separate long-acting and rapid-acting insulin Analogs upon admission to the hospital by multiplying the total daily home dose of premixed insulin by the basal/bolus ratio (either 70/30 or 75/25). This allows basal and premeal insulins to be ordered separately; thus, mealtime insulin can be administered in a timely manner with the patient’s meal or held if the patient is not eating. Subsequently, at the time of discharge, these patients can be converted back to their premixed insulin if appropriate.

For patients on OADs at home and who are insulin naive, TDD insulin requirements can be estimated with a weight-based algorithm (Table 4).\textsuperscript{58–60}

### Table 3. Summary of Recommendations for Insulin Regimens in Different Patient Situations

<table>
<thead>
<tr>
<th>Situation</th>
<th>Insulin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU or severe hyperglycemia</td>
<td>Insulin drip while critically ill</td>
</tr>
<tr>
<td>Eating</td>
<td>Basal + Prandial + Correction scale</td>
</tr>
<tr>
<td>NPO/Tube feeds</td>
<td>Basal + Correction scale</td>
</tr>
<tr>
<td>TPN (if insulin in TPN)</td>
<td>Correction scale only</td>
</tr>
<tr>
<td>TPN (if insulin not in TPN)</td>
<td>Basal + Correction scale</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; TPN = total parenteral nutrition.
ing basal-bolus insulin to regular insulin sliding scales, 0.5 units/kg daily appears to be a safe and effective dosing estimate.\textsuperscript{58,59} In patients with renal dysfunction (creatinine above 2.0 mg/dL) or age greater than 70 years, 0.3 units/kg/day is recommended (patients with a creatinine > 3 mg/dL were excluded from these trials). Using the TDD estimate, 50% of the insulin requirement is ordered as basal insulin (long-acting insulin analog such as glargine or detemir) with the other 50% divided into 3 mealtime or prandial doses using a rapid-acting insulin (such as lispro, aspart, or glulisine).

Subsequently, blood sugar values should be reviewed on a daily basis, with a 10% increase in the basal insulin doses for morning glucose ranging between 140 and 180 mg/dL, and a 20% increase in basal insulin doses for glucose over 180 mg/dL consistently. Alternatively, if the glucose levels are below the target range, a decrease in the basal insulin dose by 10% is appropriate for glucose levels between 80 and 100 mg/dL, and a 20% decrease in the basal insulin dose is appropriate for glucose values below 80 mg/dL or in the hypoglycemic range. Pre-lunch and pre-dinner glucose values will be heavily dependent on the mealtime insulin dose at the prior meal and the amount of food eaten. Appropriate adjustments to mealtime insulin doses should be made as well.

Regular insulin should be avoided for SC post-prandial blood glucose correction and should not be used as a sliding-scale regimen. Numerous studies over the past 50 years show that sliding-scale insulin (SSI) alone is not effective for inpatient glycemic control (Figure) and more recently has been associated with increased inpatient mortality.\textsuperscript{61} SSI does not allow for basal or mealtime insulin requirements, grossly underestimating total daily insulin requirements. Admittedly, SSI may be appropriate when used for a short duration (less than 24 to 48 hours) as a measurement of total daily insulin requirement. Appropriate clinical situations include elevated admission glucose in nondiabetic patients, individuals beginning corticosteroid therapy, or with initiation of enteral or parenteral nutrition.\textsuperscript{62} Measuring insulin requirements for 24 hours allows for an assessment of the TDD that can then be converted to a basal-bolus insulin regimen.

### Steroids

Steroid-induced hyperglycemia affects all patients, and not just those with preexisting diabetes. Glucose monitoring is recommended for the first 48 hours of high-dose glucocorticoid therapy to identify those individuals in which insulin therapy will be necessary to maintain near-normal glycemia.\textsuperscript{63} Although optimal insulin dosing for patients on steroids is unknown, increasing insulin doses approximately 20% is generally safe.\textsuperscript{64} Blood sugar values should be reviewed on a daily basis, with adjustment of the insulin regimen as needed. As steroid doses are tapered, it is critically important to anticipate the decrease in insulin requirements rather than wait for a hypoglycemic episode to occur to prompt a reduction in insulin doses.

<table>
<thead>
<tr>
<th>Weight-Based Estimation of the Total Daily Insulin Requirement</th>
<th>Age &gt; 70 years</th>
<th>Creatinine &gt; 2.0 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 units/kg [Umpierrez\textsuperscript{58}]</td>
<td>Patient with diabetes + glucose &lt; 200 mg/dL on admission</td>
<td></td>
</tr>
<tr>
<td>0.6 units/kg [Magaji and Johnston\textsuperscript{60}]</td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin resistant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td></td>
</tr>
</tbody>
</table>
Patients on enteral or parenteral nutrition often have hyperglycemia induced by the constant carbohydrate administration. For patients on enteral feeds, reduced carbohydrate and modified fat content formulas result in lower glucose levels and these formulas should be used.\(^6\) In TPN patients, hyperglycemia is associated with significant adverse outcomes.\(^6\) Insulin dosing in TPN (usually with regular insulin) can be initiated at 0.1 units for every gram of carbohydrates in the TPN solution. Insulin dosing for enteral feeding can use the weight-based estimation of TDD, administering basal insulin at 50% of the TDD. The optimal glycemic range should be slightly higher (in the 140–180 mg/dL range) in these groups, as measured blood sugars are not fasting in nature. Since discrete meals are not being consumed, using basal insulin with correction dose insulin every 4 to 6 hours is the optimal insulin regimen (every 4 hours if using a rapid-acting insulin for correction doses, and
every 6 hours if using regular insulin for correction doses). Unanticipated discontinuation of the carbohydrates can occur if the tube feed is accidentally removed or if the TPN is discontinued. Adding a 10% dextrose solution at the same rate as the tube feeding or TPN infusion can prevent hypoglycemia in these situations. Insulin is usually administered in the TPN solution, so discontinuation of the TPN includes discontinuation of insulin therapy and a dextrose replacement solution is only needed if SQ basal insulin is being used.

Understanding insulin physiology allows the clinician to tailor an appropriate insulin regimen in a variety of clinical scenarios. Table 5 reviews the initiation of insulin regimens in a variety of different patient situations.

MINIMIZING HYPOGLYCEMIA

Hypoglycemia is the limiting factor to aggressively normalizing blood glucose levels in all patients. Hypoglycemia is an independent predictor of hospital mortality. Spontaneous hypoglycemic events (not induced by insulin) are associated with significantly higher mortality rates when compared to iatrogenic or insulin-induced hypoglycemic events. In the review of 576 hospitals, 6.3% of ICU patient-days had a hypoglycemic event (defined as a glucose < 70 mg/dL) and 5.7% of non-ICU patient-days had a hypoglycemic event. In a study of over 100,000 inpatient admissions in patients with diabetes, patients who experienced hypoglycemic episodes had longer hospital stays, a 7% higher risk of inpatient mortality, a 39% increase in hospital costs, and a 58% increased likelihood of discharge to a skilled nursing facility.

A root cause analysis of over 1000 hypoglycemic events at a large academic medical center found that 67% of the documented hypoglycemic episodes were associated with a change in diet or enteral or parenteral rate within the previous 24 hours (unpublished data, Northwestern Medical Center, Chicago, IL). Additional factors that increase the risk of hypoglycemia include a lack of coordination between feeding and insulin administration (which can lead to mistiming of insulin action), insufficient frequency of blood glucose testing, orders not clearly or uniformly written, and failure to adjust insulin requirements in patients with advanced age, renal failure, liver disease, or changing clinical status. With the addition of a nursing electronic medical record–based hypoglycemia event form to document each event, the incidence of hypoglycemia was decreased 50%.

Preventing and minimizing the incidence and severity of hypoglycemia is possible with the use of standardized insulin protocols, hypoglycemia protocols, and use of insulin analogs. Hypoglycemia protocols should be nurse-driven and supported by point-of-care testing (POCT). Organizations should have a method of tracking hypoglycemic events and assessing adverse reactions related to insulin use, and should also monitor the use of 50% dextrose and glucagon as triggers and perform ongoing quality monitoring of hypoglycemic events. Ongoing review of insulin-related errors and near misses should be conducted at the hospital level.

THE ROLE OF POINT-OF-CARE TESTING

POCT is a convenient method of measuring glucose levels in a timely manner to allow for rapid insulin titration and clinical decision making. Glucometers, however, may not be the most accurate and reliable method to monitor glucose. An international standard is currently under development that recommends accuracy of ± 20 mg/dL for glucose values under 100
mg/dL and ± 20% for higher glucose values—quite a large variation for those aiming for a narrow therapeutic window. Common reasons for erroneous POCT blood glucose readings—such as improper handling of the test strips and equipment leading to analytic error—

**Table 5. Clinical Scenarios of Appropriate Insulin Regimens in Different Patient Situations**

**50-year-old male with type 2 diabetes mellitus (DM) admitted with pneumonia. Home diabetes regimen is insulin glargine 30 units daily, insulin aspart 10 units before each meal. He is ordered an American Diabetes Association (ADA) 1800kcal diet.**

- Capillary blood glucose monitoring: QAC (before meals) and QHS (at bedtime)
- Order hypoglycemia protocol for glucose < 70 mg/dL
- Order hemoglobin A1C
- Basal insulin: Order insulin glargine 30 units every 24 hr
- Mealtime insulin: Order insulin aspart 10 units before each meal
- Correction insulin scale: Moderate dose insulin aspart correction scale QAC (before meals) and QHS (at bedtime) if appropriate (use moderate scale since total daily insulin dose is 60 units)

**66-year-old female with type 2 DM admitted with a small bowel obstruction. Home diabetes regimen is insulin glargine 30 units daily, insulin aspart 10 units before each meal. She is made NPO on admission.**

- Capillary blood glucose monitoring: every 4 hr or every 6 hr
- Order hypoglycemia protocol for glucose < 70 mg/dL
- Order hemoglobin A1C
- Basal insulin: Order insulin glargine 30 units every 24 hr
- Mealtime insulin: Hold insulin aspart 10 units before meals as she will not be eating
- Correction insulin scale: Order moderate dose insulin aspart correction scale every 4 hr or every 6 hr (since total daily insulin dose is 60 units)

**72-year-old female with type 2 DM admitted with chest pain. Home diabetes regimen is insulin 70/30 25 units twice daily. She is made NPO on admission for a stress test.**

- Capillary blood glucose monitoring: every 4 hr or every 6 hr
- Order hypoglycemia protocol for glucose < 70 mg/dL
- Order hemoglobin A1C
- Calculate basal insulin requirements: 50 units per day x 70% basal component of insulin 70/30 = 35 units
- Basal insulin: Order insulin glargine 35 units every 24 hr
- Mealtime insulin: Hold mealtime insulin as she will not be eating
- Correction insulin scale: Order moderate dose insulin aspart correction scale every 4 hr or every 6 hr (since total daily insulin dose at home is 50 units)

**68-year-old male with type 2 DM admitted with a diabetic foot ulcer. Home diabetes regimen is metformin 1000 mg twice daily and glyburide 10 mg twice daily. He is ordered an ADA 1800kcal diet. He weighs 100 kg.**

- Capillary blood glucose monitoring: QAC (before meals) and QHS (at bedtime)
- Order hypoglycemia protocol for glucose < 70 mg/dL
- Order hemoglobin A1C.
- Stop all oral antihyperglycemic agents on admission
- Calculate insulin requirement = 100 kg x 0.5 units/kg/day = 50 units/day
- Basal insulin = 50% of total daily insulin requirement = insulin glargine 25 units every 24 hr
- Mealtime insulin = 50% of total daily insulin requirement divided into 3 equal mealtime doses = insulin aspart 8 units before each meal
- Correction insulin scale: Order moderate dose insulin aspart correction scale QAC (before meals) and QHS (at bedtime) if appropriate (use moderate scale since total daily insulin dose is 50 units)
underscore that care must be used in following the manufacturer’s instructions regarding appropriate quality-control measures. POCT blood glucose results may be inaccurate in patients with extremes in hematocrit, glucose, PO\textsubscript{2} values, and body temperature.\textsuperscript{79} Specimens from arterial blood have higher glucose concentrations than venous samples; glucose levels in plasma are generally 10% to 15% higher than glucose measurements in whole blood. Capillary specimens may not be representative of central blood glucose concentrations in patients with shock or diabetic ketoacidosis. Certain medications may interact with the POCT equipment and produce a faulty reading (eg, maltose- and fructose-containing medications can interfere with meters utilizing the dehydrogenase method). In these cases, POCT should be used with caution. In general, it is a good idea to confirm unexpected POCT blood glucose results with a specimen sent to a central laboratory for analysis.

Continuous glucose monitoring systems have been developed for the outpatient setting, but none has been shown to be effective in the hospital. Given the limitations of POCT, the need for more accurate and real-time glucose monitoring is apparent. Development of SQ, transdermal, and IV glucose monitoring is underway at various phases of study.\textsuperscript{80–82}

**CASE CONTINUED**

On the general medical ward, the patient is prescribed insulin glargine 25 units at bedtime and insulin glulisine 8 units before each meal with a correction insulin scale. His blood glucose levels have ranged from 88 to 164 mg/dL over the past 24 hours. The patient’s cardiac status has been optimized and he is ready for discharge. Overall, he is satisfied with his blood sugars during his hospital stay and he hopes to maintain this level of glucose control at home.

**DISCHARGE**

Effective discharge planning for patients with hyperglycemia should begin at the time of admission. During the hospitalization, one should assess any new physical limitations (eg, blindness, amputation, debilitation), the patient’s socioeconomic factors (insurance coverage, family support), access to follow-up care, and any learning barriers (changes in cognition or dexterity as well as language and culture).

The A1c measurement will help guide the clinician on recommendations for a home diabetes regimen. If the A1c is in an acceptable range, less than 7%, then returning to the previous home diabetes regimen may be appropriate assuming there are no new contraindications to the diabetes medications (eg, an elevated creatinine in a patient previously on metformin). If the A1c is elevated, then there is a chance to intervene and advance the patient’s diabetes therapy. It is important for the patient to understand the big picture of outpatient diabetes control, specifically the prevention of cardiovascular events including heart attack and stroke and the prevention of diabetic microvascular complications. If the patient is new to insulin, the clinician should explain the importance of timing of blood sugar monitoring and insulin administration, review hypoglycemia symptoms and treatment, review the criteria for calling their physician, and consider a referral to an outpatient diabetes educator for follow-up instruction. Involving family members in the insulin education may increase compliance and understanding of the new insulin regimen. Communicating the new regimen to the primary physician is critical in case problems arise after hospital discharge.

For nondiabetic patients who have steroid- or stress-induced hyperglycemia during their hospital
stay, no definite data exists to indicate an increased risk of developing diabetes in the future. These individuals should have a fasting glucose and A1c measured 6 to 12 weeks after the hospital stay to make sure their hyperglycemia does not persist.

**SUMMARY**

Insulin is preferred therapy for treating all hospitalized patients with hyperglycemia, independent of their diabetes status. With recent outcomes studies like NICE-SUGAR, we have transitioned from the era of “tight” glycemic control to one of “less-tight” glycemic control focusing intensely on the safety and efficacy of the glycemic control plan. Although optimal target glucose ranges remain controversial, the consensus is that glycemic control is important and hospitals should continue to manage blood sugars with insulin. Those hospitals that are successful with lower glycemic targets may choose to continue current practice; others may choose higher glycemic targets to balance the risk of hypoglycemic events and ensure patient safety.

**REFERENCES**


