

M. CECILIA LANSANG, MD, MPH

Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH
Director, Inpatient Diabetes Services
Department of Endocrinology, Diabetes and Metabolism
Cleveland Clinic

GUILLERMO E. UMPIERREZ, MD, CDE

Department of Medicine, Emory University School of Medicine, Atlanta, GA

Inpatient hyperglycemia management: A practical review for primary medical and surgical teams

■ ABSTRACT

Inpatient hyperglycemia is common and is associated with an increased risk of hospital complications, higher health-care resource utilization, and higher in-hospital mortality rates. Appropriate glycemic control strategies can reduce these risks, although hypoglycemia is a concern. In *critically ill* patients, intravenous (IV) insulin is most appropriate, with a starting threshold no higher than 180 mg/dL. Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL. In *noncritically ill* patients, basal-bolus regimens with basal, prandial, and correction components are preferred for those with good nutritional intake. In contrast, a single dose of long-acting insulin plus correction insulin is preferred for patients with poor or no oral intake. Measuring hemoglobin A1c at admission is important to assess glycemic control and to tailor the treatment regimen at discharge.

■ KEY POINTS

Hyperglycemia in hospitalized patients, with or without diabetes, is associated with adverse outcomes.

Measurement of hemoglobin A1c is recommended in all patients at hospital admission.

Insulin administration is the preferred way to control hyperglycemia in hospitalized patients, with a starting threshold below 180 mg/dL then maintaining a level between 140 and 180 mg/dL.

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Hyperglycemia in hospitalized patients, with or without diabetes, is associated with adverse outcomes including increased rates of infection and mortality and longer hospital length of stay.¹⁻³ The rates of complications and mortality are even higher in hyperglycemic patients without a history of diabetes than in those with diabetes.^{1,2} Randomized clinical trials in critically ill and noncritically ill hyperglycemic patients demonstrate that improved glycemic control can reduce hospital complications, systemic infections, and hospitalization cost.⁴⁻⁶ However, intensive glycemic therapy is associated with increased risk of hypoglycemia, which is independently associated with increased morbidity and mortality in hospitalized patients. The concern about hypoglycemia has led to revised blood glucose target recommendations from professional organizations and a search for alternative treatment options.

This manuscript provides a review of updated recommendations for the management of inpatients with hyperglycemia in the critical care and general medical and surgical settings.

■ HYPERGLYCEMIA IN CRITICAL CARE SETTINGS

A substantial body of evidence links hyperglycemia in critically ill patients to higher rates of hospital complications, longer hospital stay, higher healthcare resource utilization, and greater hospital mortality.^{7,8} Although evidence from several cohort studies and randomized clinical trials suggests that tight glucose control can reduce hospital complications and mortality,^{9,10} this target has been difficult to achieve without increasing the risk of severe hypoglycemia. In addition, data from trials using intense glycemic control in patients in the intensive care unit (ICU) have failed to show a significant improvement in mortality and, in some instances, showed increased mortality risk associated with the therapy.^{11,12}

The recommended target glucose levels are 140 to 180 mg/dL for most ICU patients.¹³ In agreement with this, the recent GLUCO-CABG trial reported no significant differences in the composite end points of complications and death between an intensive glucose target of 100 to 140 mg/dL and a conservative target of 141 to 180 mg/dL after cardiac surgery.¹⁴

■ HYPERGLYCEMIA IN NONCRITICAL CARE SETTINGS

In general medical and surgical patients, a strong association has been reported between hyperglycemia and prolonged hospital stay, infection, and disability after hospital discharge.^{1,15,16} For example, the risk of postoperative infections in patients undergoing general surgery was estimated to increase by 30% for every 40 mg/dL rise in glucose over normoglycemia (< 110 mg/dL).¹⁶ In general, appropriate glycemic control to maintain recommended glycemic levels in noncritically ill patients can reduce the risks and improve outcomes.

■ HYPOGLYCEMIA INCIDENCE

Hypoglycemia, defined as glucose less than 70 mg/dL, is a common complication of hyperglycemia treatment.¹⁷ Severe hypoglycemia is defined as glucose less than 40 mg/dL.¹⁸ The incidence of hypoglycemia in ICU trials ranged between 5% and 28%, depending on the intensity of glycemic control,¹⁹ and between 1% and 33% in non-ICU trials using subcutaneous (SC) insulin therapy.²⁰ The most important hypoglycemia risk factors include older age, kidney failure, change in nutritional intake, interruption of glucose monitoring, previous insulin therapy, and failure to adjust therapy when glucose is trending down or steroid therapy is being tapered.^{21,22}

In hospitalized patients with diabetes, hypoglycemia has been associated with poor outcomes, including a 66% increased risk of death within 1 year and 2.8 days longer hospital stay compared with patients without hypoglycemia.²³ Hypoglycemia also has been associated with prolonged QT interval, ischemic electrocardiogram changes, angina, arrhythmias, and sudden death in patients with type 1 diabetes.²⁴ Despite these observations, other studies have reported that the increased in-hospital mortality rate is limited to patients with spontaneous hypoglycemia rather than drug-associated hypoglycemia,²⁵ raising the possibility that hypoglycemia may represent a marker of disease burden rather than be a direct cause of death.

■ INPATIENT ASSESSMENT OF HYPERGLYCEMIA

Clinical guidelines recommend glucose measurement in all patients admitted to the hospital.^{13,26} Patients with hyperglycemia (glucose > 140 mg/dL) and patients with a history of diabetes should undergo bedside point-of-care glucose testing before meals and at bedtime. Premeal testing should be done close to the time of the meal tray delivery and no longer than 1 hour before meals. For patients taking nothing by mouth or receiving continuous enteral nutrition, point-of-care testing is recommended every 4 to 6 hours.

Hemoglobin A1c (HbA1c) should be measured in patients with hyperglycemia and in those with diabetes if it has not been performed in the preceding 2 to 3 months. In hyperglycemic patients without a history of diabetes, an HbA1c of 6.5% or greater suggests that diabetes preceded hospitalization. In patients with diabetes, the HbA1c can help assess glycemic control prior to admission and tailor the treatment regimen at discharge.^{13,26}

■ TARGET GLUCOSE LEVELS

Glycemic targets recommended by several organizations are shown in **Table 1**. For critically ill patients, most societies recommend glucose targets below 180 mg/dL, with the lower limit being anywhere from 110 to less than 150 mg/dL.

For patients in non-ICU settings, the Endocrine Society²⁶ and the American Diabetes Association/American Association of Endocrinologists¹³ practice guidelines recommend premeal glucose levels below 140 mg/dL, and below 180 mg/dL if checked randomly. Higher glucose ranges (< 200 mg/dL) may be acceptable in terminally ill patients or in patients with severe comorbidities.²⁶ Guidelines from the Joint British Diabetes Societies recommend targeting glucose levels between 108 and 180 mg/dL with an acceptable range of between 72 and 216 mg/dL.²⁷

■ INPATIENT MANAGEMENT OF HYPERGLYCEMIA AND DIABETES

Insulin regimens in critical care settings

Insulin administration is the preferred way to control hyperglycemia in hospitalized patients. In critically ill patients, such as those with hypotension requiring pressor support, hyperglycemic crises, sepsis, or shock, insulin is best given via continuous intravenous (IV) infusion. The short half-life of IV insulin (< 15 minutes) allows flexibility in adjusting the infusion rate in the event of unpredicted changes in nutrition or the patient's health. If the glucose level

TABLE 1
Major guidelines for treatment of hyperglycemia in a hospital setting

Organization	Intensive care unit	Non-intensive care unit
American Diabetes Association/ American Association of Endocrinologists ¹³	Initiate insulin therapy for persistent hyperglycemia (glucose > 180 mg/dL [10 mmol/L]). Treatment goal: For most patients, target a glucose level between 140 and 180 mg/dL. More stringent goals (110–140 mg/dL) may be appropriate for select patients, if achievable without significant risk of hypoglycemia.	No specific guidelines. If treated with insulin, premeal glucose targets should generally be < 140 mg/dL, with random glucose levels < 180 mg/dL.
American College of Physicians ⁴⁶	Recommends against intensive insulin therapy in patients with or without diabetes in surgical or medical intensive care. Treatment goal: Target glucose level is between 140 and 200 mg/dL in patients with or without diabetes in surgical or medical intensive care.	
Critical Care Society ²⁹	Glucose level > 150 mg/dL should trigger insulin therapy. Treatment goal: Maintain glucose level < 150 mg/dL for most adult patients in intensive care. Maintain glucose level < 180 mg/dL while avoiding hypoglycemia.	
Endocrine Society ²⁶		Premal glucose target < 140 mg/dL. Random glucose < 180 mg/dL. A lower target range may be appropriate in patients able to achieve and maintain glycemic control without hypoglycemia. Glucose < 180–200 mg/dL is appropriate in patients with terminal illness or with limited life expectancy or at high risk for hypoglycemia. Adjust antidiabetic therapy when glucose falls < 100 mg/dL to avoid hypoglycemia.
Society of Thoracic Surgeons ²⁸	Guidelines specific to adult cardiac surgery. Continuous insulin infusion preferred over subcutaneous or intermittent intravenous boluses. Treatment goal: Recommend glucose < 180 mg/dL during surgery (≤ 110 mg/dL in fasting and premeal states).	
Joint British Diabetes Societies ²⁷		Target glucose levels in most patients are between 6 and 10 mmol/L (108–180 mg/dL) with an acceptable range of between 4 and 12 mmol/L (72–216 mg/dL).

risers above 180 mg/dL, IV insulin infusion should be started to maintain levels below 180 mg/dL.^{13,26,28,29}

A variety of infusion protocols have been shown to be effective in achieving glycemic control with a low rate of hypoglycemia. The ideal protocol should allow flexible rate adjustment taking into account current and previous glucose values as well as changes in infusion rate. Hourly glucose measurements until stable glycemic control is established, followed by point-of-care testing every 1 to 2 hours, is needed to assess response to therapy and prevent hypoglycemia.

Insulin regimens in noncritical care settings

For most patients in a general, non-ICU setting, SC insulin therapy with basal insulin administered once or twice daily, alone or in combination with prandial insulin, is effective and safe.¹³ Inhaled insulin is approved by the US Food and Drug Administration, but its use in the hospital has not been studied. The use of sliding-scale insulin is not acceptable as the single regimen in patients with diabetes, as it results in undesirable hypoglycemia and hyperglycemia.³⁰ **Figure 1** presents an algorithm for selecting initial insulin treatment for patients with type 2 diabetes in the non-ICU setting.

Several SC insulin products are available, each with a different pharmacokinetic profile, as outlined in **Table 2**.³¹

Basal insulin prevents hyperglycemia during fasting states. Basal insulin is usually given as a once- or twice-daily long-acting insulin, such as glargine and detemir insulin. On occasion, twice-daily intermediate-acting insulin (neutral protamine Hagedorn; NPH) is used as a basal insulin.

Prandial insulin, also referred to as *nutritional* or *bolus* insulin, is given before meals as rapid-acting insulin (aspart, lispro, or glulisine) or short-acting insulin (regular) to prevent postmeal hyperglycemia. Rapid-acting insulin is preferred to regular insulin because of the faster onset and shorter duration of action, which may reduce the risk of hypoglycemia.

Correction or supplemental insulin is given to correct hyperglycemia when the glucose is above the goal. The same formulation is given together with prandial insulin.

Total daily dose of insulin is a measure that comprises basal and prandial insulin **Figure 1** lists the

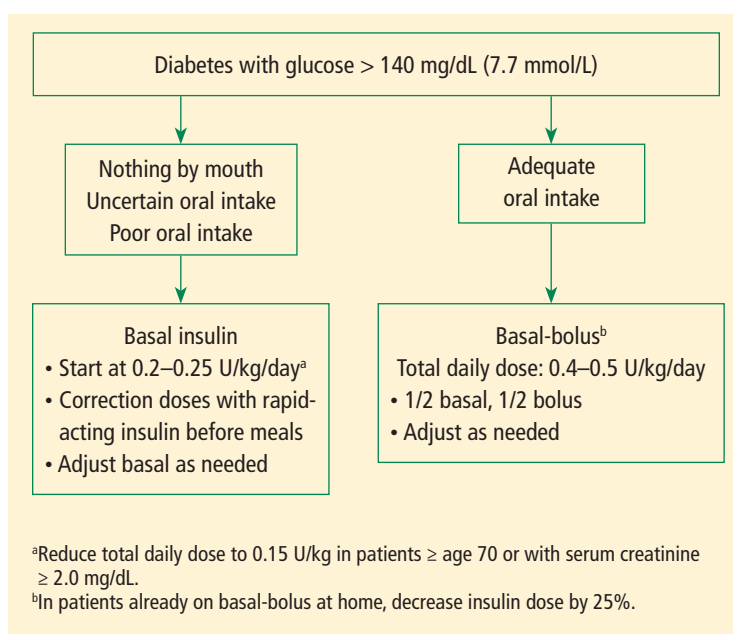


FIGURE 1. Initial insulin treatment for patients with type 2 diabetes in the non-intensive care setting.

recommended total daily dose for different clinical situations and patient populations.

Basal-bolus insulin usually refers to a regimen of long-acting basal insulin plus prandial insulin. In patients with adequate oral intake, the basal-bolus approach is preferred. The RABBIT 2 trial reported that basal-bolus regimens resulted in greater improvement in glucose control than sliding-scale regimens (correction insulin alone without basal or prandial components) in general medicine patients with type 2 diabetes.³² In general surgery patients, basal-bolus regimens significantly improved glucose control and reduced the numbers of postoperative complications, primarily wound infections compared with sliding-scale regimens.⁴

Multiple doses of NPH and regular insulin were compared with basal-bolus treatment with long-acting and rapid-acting insulin in two controlled trials in medical patients with type 2 diabetes.^{20,33} Both studies reported that treatment with NPH and regular insulin resulted in similar improvements in glycemic control and no difference in the rate of hypoglycemic events or in hospital length of stay, compared with basal-bolus insulin. Because NPH has a peak of action approximately 8 to 12 hours after injection, there is a risk of hypoglycemia in patients with poor oral intake.

In hospitalized patients who have reduced total caloric intake due to lack of appetite, acute illness,

TABLE 2
Insulin classes: Onset-of-action profiles

Insulin class	Generic (brand)	Onset	Peak	Duration
Fast- or rapid-acting	Aspart (Novolog)	10–15 min	~60 min	3–4 hrs
	Lispro (Humalog)	10–15 min	~60 min	3–4 hrs
	Glulisine (Apidra)	10–15 min	~60 min	3–4 hrs
Short-acting	Regular insulin (Humulin R, Novolin R/ReliOn R)	30–60 min	2–4 hrs	6–8 hrs
Intermediate-acting	NPH insulin (Humulin N, Novolin N/ReliOn N)	1–2 hrs	3–8 hrs	12–15 hrs
Long-acting	Glargine (Lantus)	2 hrs	No real peak	22–24 hrs
	Glargine (Toujeo)	6 hrs	No real peak	22–24 hrs
	Glargine (Basaglar) ^a	2 hrs	No real peak	24 hrs
	Detemir (Levemir)	3–8 hrs	No real peak	17–24 hrs
	Degludec (Tresiba)	1 hr	No real peak	42 hrs
Premixed	75% Insulin lispro protamine/25% insulin lispro (Humalog mix 75/25)	5–15 min	Dual	10–16 hrs
	50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)	5–15 min	Dual	10–16 hrs
	70% Insulin lispro protamine/30% insulin aspart (Novolog mix 70/30)	5–15 min	Dual	10–16 hrs
	70% NPH insulin/30% regular insulin (Humulin, Novolin/ReliOn)	30–60 min	Dual	10–16 hrs

^aApproved by the US Food and Drug Administration; scheduled to be marketed December 2016.

NPH = neutral protamine Hagedorn.

medical procedures, or surgical interventions, the Basal Plus trial³⁴ reported that a single daily dose of glargine plus correction doses of rapid-acting insulin resulted in similar improvement in glycemic control and no difference in the frequency of hypoglycemia compared with a standard basal-bolus regimen. These results indicate that the basal-plus-correction regimen may be preferred for patients with poor or no oral intake, whereas an insulin regimen with basal, nutritional (basal-bolus), and correction components is preferred for patients with good nutritional intake.³⁵

SC insulin dosing refers to insulin doses administered subcutaneously calculated based either on weight or on home insulin doses. For insulin-naïve patients, the starting total daily dose of insulin can usually be computed as 0.4 to 0.5 U/kg/day. Higher starting doses are associated with greater odds of hypoglycemia than doses lower than 0.2 U/kg/day.³⁶ In elderly patients and those with impaired renal function, lower initial daily doses (≤ 0.3 U/kg) may reduce the risk of hypoglycemia.²⁶

In patients treated with insulin prior to admission, the total daily insulin dose at home can be given as half long-acting basal insulin and half prandial insu-

lin. The dose can be reduced by 20% to 25% to prevent hypoglycemia, particularly in those with poor or uncertain caloric intake.³¹

Noninsulin therapies

The use of oral antidiabetic agents is generally not recommended in hospitalized patients due to the limited data available on their safety and efficacy, frequent contraindications, risk of hypoglycemia, and slow onset of action that may preclude achieving rapid glycemic control and daily dose adjustments. **Table 3** lists the pros and cons of these agents in hospitalized patients.

The safety and efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the management of inpatient hyperglycemia was evaluated in a randomized pilot study in patients with type 2 diabetes treated at home with diet, oral antidiabetic agents, or a low daily insulin dose (≤ 0.4 U/kg/day).³⁷ Patients were randomized to one of two treatments:

- Sitagliptin alone or with low-dose glargine insulin
- Basal-bolus insulin regimen plus supplemental doses of insulin lispro.

TABLE 3**Comparison of medications for the management of hyperglycemia in the hospital setting**

Medication	Advantages	Disadvantages
Insulin	Extensive experience with glycemic control Protocols widely available Easy to adjust in the event of hypoglycemia, changes in nutrition, diagnostic procedures, or reduced kidney function	Hypoglycemia Common source of hospital errors Requires injection
GLP-1-based therapy	Good glucose-lowering effect Low risk for hypoglycemia Nonglycemic beneficial effects	Limited data on safety and efficacy Gastrointestinal side effects Injectable
Metformin	Good glucose-lowering effect Low risk for hypoglycemia Inexpensive Oral route	Limited experience Risk of lactic acidosis in patients with impaired kidney function, heart failure, hypoxemia, alcoholism, cirrhosis, contrast exposure, surgery, and shock Gastrointestinal side effects
Sulfonylureas	Good glucose-lowering effect Inexpensive Oral route	Risk for hypoglycemia especially in patients with reduced oral intake or impaired renal function.
Thiazolidinediones	Good glucose-lowering effect Low risk of hypoglycemia Oral route	Slow onset of action Contraindicated in patients with heart failure and hepatic dysfunction Fluid retention
Bromocriptine-quick release	Low risk of hypoglycemia Oral route	No studies in the hospital Risk of hypotension, dizziness
Colesevelam	Low risk of hypoglycemia Oral route	No studies in the hospital Constipation
DPP-4-inhibitors	Modest glucose-lowering effect Low risk of hypoglycemia No major side effects reported in pilot trial Oral route	Limited experience Contraindicated in patients with history of pancreatitis
SGLT-2-inhibitors	Good glucose-lowering effect Low risk of hypoglycemia Oral route	Limited experience Increase risk of urinary and genital tract infections Risk of dehydration, hypotension

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

Both treatment regimens resulted in similar improvement in mean daily glucose concentrations. However, patients admitted to the hospital with glu-

cose levels above 180 mg/dL in the sitagliptin group had higher mean daily glucose levels than patients treated with basal-bolus or sitagliptin plus glargine.

Transitioning from IV to SC insulin

When patients in critical care units are ready to be transferred to a general medical floor, appropriate transition from IV insulin to scheduled SC insulin is needed to prevent rebound hyperglycemia. This is imperative in patients with type 1 diabetes in whom just a few hours without insulin can result in diabetic ketoacidosis.

There are three general ways to calculate the SC insulin dose during the transition period. The first two methods are weight-based and based on the home dose, as previously discussed. The third method is to extrapolate from the IV insulin. A common way is to sum up the total IV insulin dose in the past 6 or 8 hours and multiply by 3 or 4, and then reduce by 20% to achieve the basal insulin dose, presuming the patient had no oral intake on the IV insulin infusion. This last method is preferred in hemodynamically stable patients with stable insulin requirements.

If long-acting insulin is chosen as basal insulin, it should be given 2 to 4 hours before discontinuation of the IV insulin infusion. Intermediate-acting insulin should be given 1 to 2 hours before IV insulin discontinuation.

SPECIFIC SITUATIONS AND POPULATIONS

Type 1 diabetes

Patients with type 1 diabetes have minimal to absent pancreatic beta cell function and rely on the exogenous administration of insulin to maintain glucose homeostasis. They have worse glycemic control and higher rates of acute kidney injury than patients with type 2 diabetes; however, the impact of inpatient glycemic control on clinical outcomes has not been determined in patients with type 1 diabetes. Insulin therapy must provide both basal and nutritional components to achieve the target goals. It is important to ask the patient directly to determine the times and doses of prescribed insulin, medication adherence, recent dietary habits (including changes in appetite), and level of physical activity. This information will be used to guide insulin therapy.

A systematic review of 16 clinical studies reported that patients who possess excellent self-management skills can be suitable for successful inpatient diabetes self-management.³⁸ The American Diabetes Association supports patient self-management of diabetes in the hospital.³⁹ However, the competence and readiness of each patient with type 1 diabetes need to be carefully determined in an individualized manner. Potential candidates for inpatient self-management

are those with unaltered mental status, proven proficient outpatient skills (eg, carbohydrate counting, frequent glucose monitoring, strong knowledge related to the management of insulin pump or injection techniques), and who are tolerating oral intake.

Enteral nutrition and tube feeding

Accidental dislodgement of feeding tubes, temporary discontinuation of nutrition due to nausea or for diagnostic testing, and cycling of enteral nutrition with oral intake in patients with an inconsistent appetite pose unique challenges in the hospital. Although it may be tempting to give basal and nutritional requirements to these patients as a single dose of long-acting insulin, this is not recommended. Low-dose basal insulin plus scheduled doses of short-acting (regular) insulin (every 6 hours) or rapid-acting insulin (every 4 hours) with correction insulin is often used. Some providers prefer giving intermediate-acting (NPH) plus short-acting (regular) insulin every 8 hours or every 12 hours.

It is generally accepted that diabetic enteral formulas that are low in carbohydrate and high in monounsaturated fatty acids are preferable to standard high-carbohydrate formulas in hospitalized patients with diabetes. In a meta-analysis, the postprandial rise in glucose was reduced by 20 to 30 mg/dL with the low-carbohydrate high-fat formulations compared with standard formulations.⁴⁰

Parenteral nutrition

The use of parenteral nutrition has been linked to aggravation of hyperglycemia independent of a history of diabetes as well as a higher risk of complications, infections, sepsis, and death.⁴¹ Regular insulin can be added to the parenteral solution at a starting dose of 0.1 U/g of dextrose in nondiabetic patients and at 0.15 U/g of dextrose in patients with diabetes.⁴²

Alternatively, insulin can be given as a continuous IV infusion. Hemodynamically stable patients with mild to moderate hyperglycemia can be managed with basal insulin plus scheduled or as-needed doses of short-acting (regular) insulin every 6 hours. To prevent waste, it is better to underestimate the insulin added to parenteral nutrition so as to avoid having to discontinue it prematurely or add additional glucose.

Glucocorticoids

Glucocorticoids typically raise glucose starting 4 to 6 hours after administration. Low doses of glucocorticoids given in the morning tend to raise the late morning to evening glucose levels without affecting the fasting glucose. In this situation, the patient may

be managed on prandial insulin without long-acting basal insulin or with intermediate-acting insulin given in the morning. Higher glucocorticoid doses may raise fasting glucose levels, in which case basal-bolus insulin would be appropriate, with the basal component comprising about 30% and the bolus about 70% of the daily dose.²⁶

Insulin pump

Approximately 400,000 US patients with diabetes use an insulin pump.⁴³ Successful management of inpatient diabetes with the continuation of insulin pump therapy has been previously demonstrated in select patients. Clear hospital policies, procedures, and physicians' orders with specifics on the type of diet, frequency of point-of-care glucose testing, and insulin doses (ie, basal rates, carbohydrate ratios, and correction formulas) should be in place. An inpatient diabetes specialist should assist with the assessment and management of a patient with an insulin pump.

If pump use is contraindicated (**Table 4**)⁴⁴ or if inpatient diabetes resources are not available, discontinuation of insulin pump and transition to a basal-bolus insulin regimen ("pump holiday") may be the safest and most appropriate step. Most patients knowledgeable in insulin pump therapy are able to display in their pump screen the average total daily insulin used for the past few days. Based on this, safe estimations of basal, bolus, and supplemental insulin can be calculated. To avoid severe hyperglycemia or ketoacidosis from lack of basal insulin, it is important to administer the basal insulin component at least 2 hours before disconnecting the insulin pump.

Concentrated insulins

U-500 regular insulin is concentrated insulin that delivers the same amount of units in one-fifth the volume of conventional insulins, which are U-100. Whereas there are 100 units of insulin in 1 mL for conventional insulins, there are 500 units of U-500 regular insulin in 1 mL. Its onset of action is similar to that of regular insulin, and the peak and duration are similar to that of NPH insulin. Concentrated insulin is often administered in the outpatient setting to patients who are insulin resistant and require close to 200 units a day. The U-500 pen device was approved in January 2016 and was projected to be available in April 2016. For now, it can only be procured in the vial form. This causes confusion in its dosing since it is given either with the usual insulin syringes, which are designed for U-100 insulin administration, or a tuberculin syringe, which is not marked in units but in milliliters.

TABLE 4

General contraindications to pump use in the hospital

Altered state of consciousness
Suicidal ideation
Prolonged instability of glucose levels
Diabetic ketoacidosis
Patient or family inability or refusal to participate in own care
Insulin pump malfunction
Lack of appropriate supplies for the insulin pump
Other circumstances as identified by the healthcare provider

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Because of its unique nature and providers' lack of familiarity with U-500, certain institutions have a policy for its use. In many institutions, the doses are confirmed by pharmacy staff and delivered by pharmacy to the patient's medication bin predrawn in a tuberculin syringe.⁴⁵ In addition, a study reported that many patients on U-500 at home required significantly lower doses of insulin (average dose of 100 U/day) while hospitalized patients could be managed with conventional insulin formulations.⁴⁵

There are newer concentrated insulins in the market, such as insulin glargine 300 U/mL (Toujeo) and insulin lispro 200 U/mL (Humalog). These insulins, so far, come only in the pen device form and not in vials, obviating the need for dose calculations using a U-100 insulin syringe or tuberculin syringe. The efficacy and safety of these insulin formulations have not been determined in the hospital setting.

Transitioning from home to hospital

Transition to an outpatient setting requires planning and coordination. Although insulin is used in the hospital for most patients with diabetes, many patients do not require insulin after discharge. On the other hand, diabetes regimens sometimes need intensification in other patients. One study showed that patients with acceptable diabetes control (HbA1c < 7.5%) near or on admission could be discharged on their prehospitalization treatment regimen, while those with HbA1c between 7.5% and 9% could be discharged on oral agents plus basal insulin at 50% of the hospital basal dose.⁴⁶ Additionally, patients with an HbA1c of 9% to 10% should be discharged

on a basal-bolus regimen or on a combination of oral agents plus basal insulin at 80% of hospital dose, with a reduction in HbA1c seen 12 weeks after discharge.

SUMMARY

Inpatient hyperglycemia is common and is associated with increased risk of hospital complications, higher healthcare resource utilization, and higher rates of in-hospital mortality. In the critically ill, IV insulin is most appropriate, with a starting threshold no higher than 180 mg/dL. Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL.

In noncritically ill patients, a basal-bolus regimen with basal, prandial, and correction components is preferred for patients with good nutritional intake. In contrast, a single dose of long-acting insulin plus correction insulin is preferred for patients with poor or no oral intake. Preliminary data indicate that incretin therapy has the potential to improve glycemic control in patients with mild to moderate hyperglycemia and a low risk of hypoglycemia.

Transition to an outpatient setting requires planning and coordination. Measuring HbA1c at admission is important to assess preadmission glycemic control and to tailor the treatment regimen at discharge. Patients with acceptable diabetes control could be discharged on their prehospitalization treatment regimen. Patients with suboptimal control should have more intensified therapy.

REFERENCES

- 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.
- Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; 37:3001–3009.
- Kotagal M, Symons RG, Hirsch IB, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg* 2015; 261:97–103.
- Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care* 2011; 34:256–261.
- Murad MH, Coburn JA, Coto-Yglesias F, et al. Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2012; 97:49–58.
- Schroeder JE, Liebergall M, Raz I, et al. Benefits of a simple glycaemic protocol in an orthopaedic surgery ward: a randomized prospective study. *Diabetes Metab Res Rev* 2012; 28:71–75.
- Clement S, Braithwaite SS, Magee MF, et al; American Diabetes Association in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 2004; 27:553–591.
- Inzucchi SE. Clinical practice: Management of hyperglycemia in the hospital setting. *N Engl J Med* 2006; 355:1903–1911.
- van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359–1367.
- van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461.
- NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360:1283–1297.
- Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; 180:821–827.
- Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32:1119–1131.
- Umpierrez G, Cardona S, Pasquel F, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG Trial. *Diabetes Care* 2015; 38:1665–1672.
- Montori VM, Bistrian BR, McMahon MM. Hyperglycemia in acutely ill patients. *JAMA* 2002; 288:2167–2169.
- Ramos M, Khalpey Z, Lipsitz S, et al. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg* 2008; 248:585–591.
- American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010; 33(suppl 1):S11–S61.
- Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94:709–728.
- Krikorian A, Ismail-Beigi F, Moghissi ES. Comparisons of different insulin infusion protocols: a review of recent literature. *Current Opin Clin Nutr Metab Care* 2010; 13:198–204.
- Umpierrez GE, Hor T, Smiley D, et al. Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with type 2 diabetes. *J Clin Endocrinol Metab* 2009; 94:564–569.
- Smith WD, Winterstein AG, Johns T, Rosenberg E, Sauer BC. Causes of hyperglycemia and hypoglycemia in adult inpatients. *Am J Health Syst Pharm* 2005; 62:714–719.
- Maynard G, Lee J, Phillips G, Fink E, Renvall M. Improved inpatient use of basal insulin, reduced hypoglycemia, and improved glycemic control: effect of structured subcutaneous insulin orders and an insulin management algorithm. *J Hosp Med* 2009; 4:3–15.
- Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. *Diabetes Care* 2009; 32:1153–1157.
- Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes—the ‘dead in bed’ syndrome revisited. *Diabetologia* 2009; 52:42–45.
- Boucai L, Southern WN, Zonszein J. Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. *Am J Med* 2011; 124:1028–1035.
- Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012; 97:16–38.
- Dhatariya K, Levy N, Kilvert A, et al; Joint British Diabetes Societies. NHS diabetes guideline for the perioperative management of the adult patient with diabetes. *Diabet Med* 2012; 29:420–433.
- Lazar HL, McDonnell M, Chipkin SR, et al; Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. *Ann Thorac Surg* 2009; 87:663–669.
- Jacobi J, Bircher N, Krinsley J, et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med* 2012; 40:3251–3276.
- Hirsch IB. Sliding scale insulin—time to stop sliding. *JAMA* 2009; 301:213–214.

31. Dobri GA, Lansang MC. How should we manage insulin therapy before surgery? *Cleve Clin J Med* 2013; 80:702–704.
32. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care* 2007; 30:2181–2186.
33. Bueno E, Benitez A, Rufinelli JV, et al. Basal-bolus regimen with insulin analogs versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. *Endocr Pract* 2015; 21:807–813.
34. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. *Diabetes Care* 2013; 36:2169–2174.
35. American Diabetes Association. Standards of medical care in diabetes-2015 abridged for primary care providers. *Clin Diabetes* 2015; 33:97–111.
36. Rubin DJ, Rybin D, Doros G, McDonnell ME. Weight-based, insulin dose-related hypoglycemia in hospitalized patients with diabetes. *Diabetes Care* 2011; 34:1723–1728.
37. Umpierrez GE, Gianchandani R, Smiley D, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. *Diabetes Care* 2013; 36:3430–3435.
38. Munt R, Hutton A. Type 1 diabetes mellitus (T1DM) self management in hospital; is it possible? A literature review. *Contemp Nurse* 2012; 40:179–193.
39. American Diabetes Association. Diabetes care in the hospital, nursing home, and skilled nursing facility. *Diabetes Care* 2015; 38(suppl):S80–S85.
40. Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2005; 28:2267–2279.
41. Pasquel FJ, Spiegelman R, McCauley M, et al. Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. *Diabetes Care* 2010; 33:739–741.
42. Umpierrez GE, Spiegelman R, Zhao V, et al. A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. *Crit Care Med* 2012; 40:1792–1798.
43. RNCOS Industry Research Solutions. US to dominate the global insulin pump market—April 28, 2011. www.rncos.com/Press_Releases/US-to-Dominate-the-Global-Insulin-Pump-Market.htm. Accessed March 16, 2016.
44. Lansang MC, Modic MB, Sauvey R, et al. Approach to the adult hospitalized patient on an insulin pump. *J Hosp Med* 2013; 8:721–727.
45. Tripathy PR, Lansang MC. U-500 regular insulin use in hospitalized patients. *Endocr Pract* 2015; 21:54–58.
45. Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. *Diabetes Care* 2014; 37:2934–2939.
46. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011; 154:260–267.

Correspondence: Guillermo E. Umpierrez, MD, CDE, Professor of Medicine, Director, Grady Hospital Research Unit, A-CTSI, Emory University, Section Head, Diabetes & Endocrinology, Grady Health System, 80 Jesse Hill Jr. Drive SE, Atlanta, Georgia 30303; geumpie@emory.edu