Hyperglycemia Management in Non-critically Ill Hospitalized Patients

Lindsay M. Arnold and Darcie L. Keller

Journal of Pharmacy Practice 2009; 22; 467 originally published online Mar 2, 2009;
DOI: 10.1177/0897190008330198

Journal of Pharmacy Practice
Volume 22 Number 5
October 2009 467-477

10.1177/0897190008330198
http://jpp.sagepub.com
hosted at
http://online.sagepub.com

Hyperglycemia Management in Non-critically Ill Hospitalized Patients

Lindsay M. Arnold, PharmD, BCPS, and
Darcie L. Keller, PharmD, BCPS

There is increasing evidence demonstrating negative consequences and poor clinical outcomes associated with untreated hyperglycemia in hospitalized patients. Data in specific patient populations, primarily critically ill patients, demonstrate improved patient outcomes with tight glycemic control. To date, no clear evidence exists to determine optimal glycemic targets in non-critically ill patients; however, experts agree that better glycemic control in hospitalized patients is warranted. Glycemic control is complicated by numerous factors in hospitalized patients including increased circulating stress hormones, changing nutritional status, and administration of medication therapies that contribute to hyperglycemia. In addition, fear of hypoglycemia among health care providers, a commonly cited barrier, contributes to the failure to adopt more intensive insulin regimens. Current practice trends have proven ineffective and major changes are needed. Some of those trends include the use of sliding scale insulin, continuation of oral agents or combination insulins upon admission, and provider reluctance to initiate insulin in patients not receiving insulin prior to admission. With proper education, safe and effective use of insulin can be used during hospitalization to improve glycemic control. The following article reviews the benefits of glycemic control, identifies barriers to achieving glycemic control, and describes strategies for health care providers and institutions to realize glycemic control in medically ill hospitalized patients.

Keywords: glycemic control; basal-bolus insulin; medically ill patients; hyperglycemia; insulin therapy

Hyperglycemia, in diabetic and nondiabetic patients, has historically been seen as a benign condition of hospitalized patients, considered secondary to the primary illness or event causing hospitalization. However, growing evidence and expert opinion has brought increased attention to what can no longer be considered a secondary condition in the medically ill hospitalized patient.[1-3]

A variety of factors have been found to play a role in the complex relationship between hyperglycemia and acute illness. Increased circulating stress hormones, including cortisol, glucagon, and epinephrine, are major contributors to hyperglycemia in medically ill patients.[2] Hyperglycemia has been correlated to a number of negative outcomes at the cellular level including immunosuppression, endothelial dysfunction, inflammation, increased oxidative stress, and thrombosis.[1]

Poor clinical outcomes have been demonstrated in a number of retrospective studies. Postoperative hyperglycemia in patients undergoing coronary artery bypass surgery has been shown to be an independent predictor of infectious complications in patients with known diabetes and glucose levels $\geq$ 207 mg/dL ($P < .05$).[4] In another cohort study evaluating 100 diabetic patients undergoing elective surgery, hyperglycemia (defined as blood glucose > 220 mg/dL the first day following surgery) was associated with a 5.8-fold increase in the rate of nosocomial infections.[5] In patients with blood glucose levels $\leq$ 220 mg/dL, the rate of infection was 11.5% compared with 31.3% in

From the Department of Pharmacy, Boston, Boston Medical Center, Massachusetts (LMA); and Department of Pharmacy, Kansas City Veterans' Affairs Medical Center, Kansas City, Missouri (DLK).

Address correspondence to: Darcie L. Keller, PharmD, BCPS, Department of Pharmacy, Kansas City Veterans' Affairs Medical Center, Kansas City, MO 64154; e-mail: kellerdl@umkc.edu.

patients with elevated blood glucose ($P < .05$). In addition, mortality has been shown to increase progressively with rising glucose values in critically ill patients, reaching as high as 42.5% in patients found to have a mean blood glucose value > 300 mg/dL.[6]

A number of cardiovascular changes have been found with acute hyperglycemia including electrophysiologic changes (QTc prolongation), catecholamine elevations, platelet abnormalities, increased natriuretic peptide levels, reduced coronary collateral blood flow, and increased systolic and diastolic blood pressure.[1] Admission blood glucose and hemoglobin A1c (A1c) were shown to be independent predictors for increased mortality in diabetic patients with acute myocardial infarctions.[7] A systematic review looking at outcomes in patients with or without preexisting diabetes following myocardial infarction not only found an increase in mortality among diabetic patients but also demonstrated a significantly increased rate of death, congestive heart failure, or cardiogenic shock among hyperglycemic nondiabetic patients.[8]

Until recently, the majority of data examining the effects of hyperglycemia were limited to very specific patient populations, primarily in the intensive care unit (ICU). In 2002, Umpierrez et al evaluated the prevalence and impact of hyperglycemia in hospitalized patients.[3] Adult patients admitted to the hospital over a 4-month time period with 1 or more blood glucose measurements were included. Hyperglycemia was defined as a fasting or admission blood glucose > 126 mg/dL or a random blood glucose > 200 mg/dL. The primary endpoint was inpatient mortality. Of the 1886 patients included in the study, 38% were found to have hyperglycemia; 26% had a history of diabetes and 12% had new hyperglycemia (no prior diagnosis of diabetes). Inpatient mortality was significantly increased in patients with new hyperglycemia (16%) compared to those with known diabetes (3%) and normoglycemia (1.7%) ($P < .01$). This finding of higher mortality was seen in both ICU and non-ICU patients. Additionally, length of stay, need for ICU transfer, and discharge to a nursing home or transitional care were all seen at significantly higher rates in the new hyperglycemia patients than in the other 2 groups. This study has served as a foundation for the increased recognition of the role of hyperglycemia in affecting acute care outcomes in patients with and without a history of diabetes.

Benefits of Glycemic Control

Studies using intensive insulin therapy, typically with continuous intravenous insulin infusions, have established a foundation for tight glycemic control in critically ill hospitalized patients. However, these studies consist of a variety of designs, methodologies, and patient populations. Prospective randomized studies conducted in critically ill populations have demonstrated decreased in-hospital mortality and including ICU mortality in patients treated with intensive insulin therapy. Some of these populations were postsurgical, post–myocardial infarction and post–coronary artery bypass graft surgery.[9-12] Additional benefits demonstrated include decreased rates of bacteremia, multiorgan failure, surgical site infections, and recurrent ischemia. A shorter duration of ventilatory support and a lower incidence of renal failure, or need for renal replacement therapy, was also demonstrated.[9,13]

Despite the growing evidence in the critically ill patients, data showing improved clinical outcomes using tight glycemic control in non-ICU patients have been lacking. To date, there has been only 1 randomized controlled trial in non-critically ill hospitalized patients. The RABBIT-2 trial was a prospective, multicenter, randomized trial conducted in patients admitted to a general medicine service with blood glucose values >140 mg/dL but <400 mg/dL.[14] Inclusion criteria consisted of a diagnosis of type II diabetes for greater than 3 months, lack of prior insulin use, and age >18 years. Exclusion criteria included corticosteroid use, admission to the ICU, serum creatinine > 3.0 mg/dL, pregnancy, expectation of surgery during admission, relevant hepatic disease, and significant mental illness.

Patients were randomly assigned to either sliding scale insulin (SSI) or a basal-bolus weight-based regimen. All oral hypoglycemics were discontinued on admission. Basal-bolus regimens were initiated based on admission blood glucose using glargine and glulisine insulins. For patients with blood glucose of 140 to 200 mg/dL, insulin therapy was started at 0.4 units/kg. For patients with blood glucose of 201 to 400 mg/dL, insulin was started at 0.5 units/kg. The glargine dose consisted of one-half of the total daily dose (TDD) of insulin; glulisine accounted for the other one-half and was given in 3 equally divided doses before meals. If patients were not eating

Table 1. Glycemic Goals[15,16]

	ADA	AACE
Intensive care setting	Goal: 110 mg/dL; Maximum: <140 mg/dL	80-110 mg/dL
Non-critical care setting	Preprandial: <126 mg/dL; Postprandial: <180-200 mg/dL	Preprandial: <110 mg/dL; Postprandial: <180 mg/dL

Abbreviations: ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists.

discrete meals, glargine was administered and glulisine was held. Patients randomized to receive SSI were treated with regular insulin 4 times a day when blood glucose values were >140 mg/dL. Patients in the SSI group were switched to basal-bolus therapy if 3 consecutive values were >240 mg/dL. Differences in mean daily blood glucose between treatment groups served as the primary outcome. Hypoglycemic events, episodes of severe hyperglycemia, length of hospital stay, and mortality were included as secondary outcome measures.

A total of 65 patients were randomized to each treatment arm, with similar baseline characteristics seen between the 2 groups. Basal-bolus therapy was associated with significantly lower mean blood glucose when compared with SSI, 166 mg/dL vs. 193 mg/dL, respectively ($P < .001$). The mean glucose target of <140 mg/dL was seen in 66% of basal-bolus–treated patients compared with only 38% of patients treated with SSI. On the last day of therapy, mean glucose concentrations were significantly higher in the SSI group compared with the basal-bolus group, 187 mg/dL vs. 140 mg/dL, respectively ($P < .001$). Nine patients (14%) in the SSI group had to be switched to basal-bolus therapy for consistently elevated blood glucose values. There was no difference between the treatment groups in terms of hypoglycemia, length of stay, or mortality.

Despite the study's limitations, the RABBIT-2 trial clearly established that weight-based basal-bolus insulin is more effective than SSI in controlling hyperglycemia in non-critically ill hospitalized patients. This investigation did not demonstrate a difference in key clinical outcomes shown in ICU studies, namely length of stay and mortality. The authors recognized that the study was not adequately powered to assess these differences. A low rate of hypoglycemia was observed, with only 2 patients in each treatment arm reporting a blood glucose < 60 mg/dL. This may be due to the strict selection criteria by the investigators, particularly the exclusion of patients with renal dysfunction and corticosteroid use. The most significant limitation of this study is the exclusion of patients with hyperglycemia without a previous diagnosis of diabetes. As was shown previously by Umpierrez et al, this population was shown to have a much higher rate of morality and would therefore likely benefit from improved glycemic control.[3]

Although the RABBIT-2 trial designated <140 mg/dL as the appropriate blood glucose goal, optimal glycemic targets identified through well designed randomized controlled trials have yet to be determined in non-critically ill hospitalized patients. However, both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have established recommendations for glycemic control in hospitalized patients (Table 1).[15,16] Establishing appropriate glycemic targets is the first step toward improving glycemic control in hospitalized patients, as unidentified goals are rarely met. The Society of Hospital Medicine calls for each institution to determine an institution-wide glycemic target.[17] When determining the glycemic target, consideration should be given to the needs of the population being served and the ability of the health care providers within the institution to successfully reach the proposed target. Although intravenous insulin is the most effective way to rapidly control blood glucose, this may not be feasible in the majority of patients located outside of an ICU setting. When subcutaneous insulin is used, it is recommended that insulin is provided to cover both basal and prandial needs. Additionally, correction insulin should be available to account for hyperglycemia not controlled by scheduled insulin therapy.[1,15,16] Furthermore, patients' glycemic control should be evaluated on a daily basis with insulin adjusted accordingly to achieve glycemic goals.

Challenges to Obtaining Glycemic Control

A number of barriers exist to obtaining glycemic control in hospitalized patients. One typically cited

reason is that hyperglycemia is not usually the primary reason for admission and therefore does not receive the utmost concern.[18] Insulin resistance and secretion are also affected by numerous factors, including type and severity of illness, activity level, medication therapy, and nutritional status. For instance, glucocorticoids and vasopressors have been shown to increase insulin resistance, and intravenous medications are often provided in dextrose-based solutions that may contribute to hyperglycemia. Furthermore, nutritional status and route of administration is often variable in hospitalized patients. Glucose provided enterally leads to a very different physiological response than that seen with intravenous dextrose provided with parenteral nutrition, which affects how those patients will need to be managed.[19] Nutritional intake may be inconsistent when patients are ill and may be withheld temporarily for procedures, both requiring adjustments in insulin regimens to avoid hypoglycemia. In addition, diets provided in the hospital may be different from what the patient eats at home, and quantity of food may vary considerably with acutely ill patients consuming less than usual and those with limited access to food at home potentially consuming more. It is important to realize that medications used to control a patient's blood glucose at home may not be appropriate for control during hospitalization, and regimens will need to be adjusted to optimize glycemic control. Interpretation of blood glucose levels may be further complicated by mistiming of assessment, omitted insulin doses, missed meals, or grazing patients who consume carbohydrates between scheduled meals.

In addition to the commonly encountered barriers related to hospitalization cited above, multiple reports cite fear of hypoglycemia as another major contributor to hyperglycemia in hospitalized patients, which contributes to failure to adopt more intensive insulin regimens.[1,20-22] Hypoglycemia is associated, albeit rarely, with several catastrophic consequences such as seizures, coma, and death. A number of factors in the hospital can increase the potential for hypoglycemia. Identifying these factors proactively and creating institutional systems to address them should help minimize the risk and incidence of hypoglycemia.[1] High-risk conditions include unexpected cessation of nutrition (including oral, parenteral, or enteral), reduction in corticosteroid dose, and unexpected transfer from one care area to another shortly after the administration of rapid-acting insulin.

Response to insulin therapy should be monitored closely and regimens adjusted empirically when persistently decreasing blood glucose values are observed.[15] All patients receiving insulin therapy should have additional orders for the treatment of potential hypoglycemia.[1,16] Treatment of hypoglycemia should be based on symptoms, not a blood glucose value. For patients who have a blood glucose $\leq$ 70 mg/dL without any changes in mental status, they should be provided 12 to 15 g of simple sugar via juice or similar oral agents. For patients with a blood glucose $\leq$ 70 mg/dL with mental status changes, 12.5 to 25 g of intravenous dextrose should be administered. Blood glucose should be rechecked 15 to 30 minutes following treatment to ensure the patient is responding appropriately.

Current practice trends present challenges to reaching glycemic goals. These trends include the use of SSI, stagnant insulin orders, continuation of oral agents or combination insulin agents upon admission, and provider reluctance to initiate insulin in patients not on insulin prior to admission. Despite expanding evidence for weight-based basal-bolus insulin, many clinicians continue to prescribe SSI alone or in combination with patient's outpatient diabetes regimen upon admission to the hospital. Providing only SSI is a reactive rather than proactive response to hyperglycemia, and data to support the efficacy of this method for achieving glycemic control are lacking. In a large, prospective cohort study conducted to examine the effectiveness of SSI in improving glycemic control in medically ill patients outside the ICU, patients who received only SSI were 3 times more likely to have a hyperglycemic episode than patients who did not receive glycemic control therapy.[23] Additionally, SSI was found to have no effect on the incidence of hypoglycemia.

As mentioned previously, current practice usually leads to continuation of oral hypoglycemic agents when patients are admitted to the hospital. In patients who are hyperglycemic on admission, oral agents are not rapidly titratable and are generally not recommended for use in hospitalized patients.[1,15,16] The majority of oral agents take days to weeks to see their full impact on glycemic control. Agents such as sulfonylureas and meglitinides work by increasing insulin secretion. Although these agents should work in a glucose-dependent fashion, the effect time is not rapid or sensitive enough in patients with rapidly fluctuating serum glucose values. This results in a high potential for causing

Table 2. Action of Various Insulin Preparations and Nutrition-specific Recommendations

	Name	Onset	Peak	Duration	Nutritional Status
Rapid and short-acting insulins: used for prandial and correction therapy	Lispro Aspart Glulisine Regular	5-15 minutes 5-15 minutes 5-15 minutes 30-60 minutes	1-2 hours 1-2 hours 1-2 hours 2-4 hours	4-6 hours 4-6 hours 4-6 hours 6-10 hours	Standing, meal-time doses should be held while NPO or for low blood glucose values. Correction insulin should be given if NPO or a meal is omitted. Correction insulin is given *in addition* to prandial insulin when hyperglycemic before meals.
Intermediate and long-acting insulins: used for basal therapy	NPH Glargine Detemir	2-4 hours 2-4 hours 2-4 hours	6-12 hours None None	12-18 hours 24 hours 24 hours	The usual dose of NPH should be reduced by 1/3 when patients are NPO. The dose should not be held or adjusted for those receiving detemir or glargine insulins.

Abbreviation: NPO, nothing by mouth.

hypoglycemia, particularly when given to patients in whom nutrition is being withheld. Another oral agent, metformin, is contraindicated in patients with a serum creatinine $\geq$1.4 mg/dL in women and $\geq$1.5 mg/dL in men, metabolic acidosis or with concomitant use of iodinated contrast dye, all of which are common in hospitalized patients.[24] Thiazolidinediones are not recommended for use in patients with New York Heart Association (NYHA) class III-IV heart failure.[25] The role of agents involved with the incretin system has yet to be defined; however, their role is likely to be small, given their delayed onset and marginal glucose reductions in comparison to insulin.

Combination insulin preparations (mixtures of intermediate and rapid or short-acting insulins) are difficult to titrate in patients with changing nutritional status and should not be used in hospitalized patients. These formulations are designed for patients in their usual state of health, eating their typical diet, and maintaining normal activities. When patients come into the hospital, each of these factors is altered. Diets are typically modified by providing consistent carbohydrates with each meal, or meals may be withheld. As referenced earlier, the stress response of illness will affect insulin requirements. By using the fixed ratios of intermediate and short or rapid-acting insulins found in combination preparations, titration of the individual components of the insulin regimen cannot occur. Given the limitations of oral hypoglycemic agents and premixed combination insulins in hospitalized patients, a more practical method for safe and effective insulin administration in these patients is needed to achieve glycemic goals and improve patient outcomes.

Strategies for Achieving Glycemic Control

The concept behind providing basal-bolus therapy is to mimic normal physiology. The advent of newer insulin analogs helps provide a more predictable pharmacodynamic response than was seen previously with older agents. Agents such as glulisine, lispro, and aspart provide better postprandial control than regular insulin (Table 2).[26] To obtain results that mimic normal physiologic response, therapy should involve basal, prandial, and correction insulin. Basal insulin is provided with a long-acting agent such as glargine or detemir, or an intermediate-acting agent such as NPH. Basal insulin should be provided to all type I diabetic patients to prevent ketoacidosis and to all hyperglycemic patients who are consistently requiring correction therapy. Prandial insulin is used prior to meals to help minimize elevations in blood glucose secondary to dietary carbohydrate intake. Correction insulin is provided in addition to scheduled insulin to account for preexisting hyperglycemia before meals and at bedtime.

Prior to initiating insulin therapy, factors that will affect insulin sensitivity should be recognized. The usual range for total daily insulin requirements is 0.3 to 1.5 units/kg/d. Patients who have type I diabetes, lean body weight, renal dysfunction, significant hepatic dysfunction, are elderly, or requiring <30 units/d are likely to be more insulin "sensitive" and

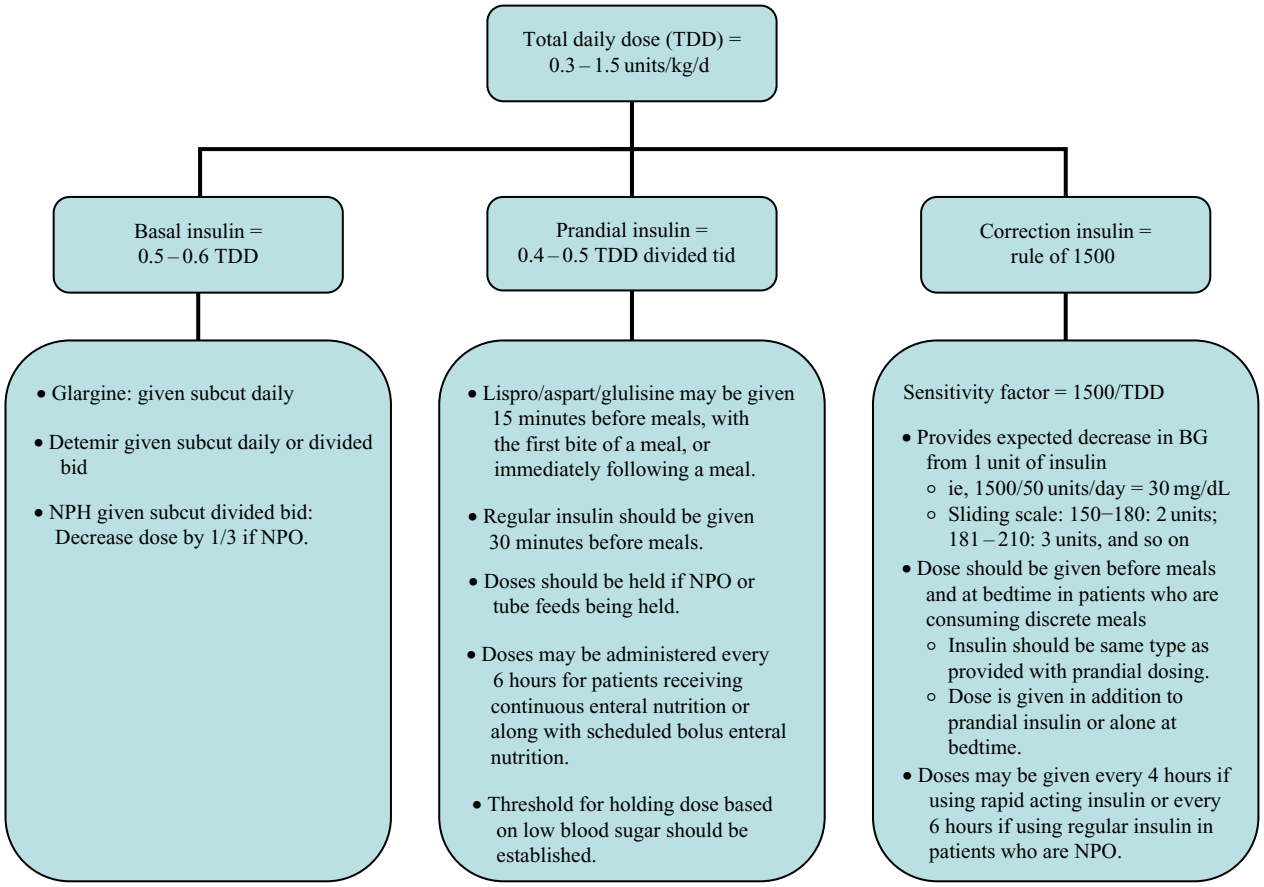

Figure 1. Weight-based subcutaneous insulin dosing algorithm. Abbreviations: bid, twice a day; BG, blood glucose; NPO, nothing by mouth; subcut, subcutaneously; tid, three times a day.

typically require a lower TDD (approximately 0.3-0.5 units/kg/d). Patients with type II diabetes, obesity or those who are infected, receiving corticosteroids, postoperative, post–myocardial infarction, or requiring >50 units/d will have lower sensitivity to insulin, therefore requiring a higher TDD (approximately 0.5-1.5 units/kg/d). Most patients will fall into the range of 0.5 to 0.7 units/kg/d.[27] In patients who are receiving insulin prior to admission, it is reasonable to resume their home insulin regimen in addition to correction insulin if it includes both basal and prandial insulins if they were previously well controlled on this regimen. If their blood glucose level is markedly elevated on admission or if it was poorly controlled on their home insulin regimen, it is reasonable to either increase their insulin by 10% to 20% or use the patient's weight and expected insulin sensitivity to determine the appropriate TDD. In patients who are receiving combination insulin preparations (mixtures of intermediate and rapid or short-acting insulin), it is recommended to convert these patients to long-acting basal insulin plus short or rapid-acting prandial insulin during hospitalization to allow ease in dose titration. Correction insulin should be provided to all patients on insulin to correct preexisting mealtime and bedtime hyperglycemia and to serve as a foundation for daily dose adjustment (ie, adding 50% of correction insulin administered in previous 24 hours to basal and 50% to prandial insulin doses).

Basal insulin is provided using 50% of the calculated TDD (Figure 1). This can be provided using daily injections of glargine or detemir insulin or by splitting the dose of NPH into morning and evening meal/bedtime. In some patients, detemir may need to be given twice daily to obtain optimal glycemic control. Because glargine and detemir provide a fairly consistent level throughout the day, it is not recommended to decrease or withhold the dose if nutrition is suspended. For patients receiving NPH insulin, it is recommended to decrease the usual dose by 1/3 (ie, give 2/3 of the usual dose) when nutrition is withheld.

This is because NPH has a peak concentration 6 to 12 hours following administration.

The remaining 50% of the TDD is supplied with prandial insulin. For patients eating 3 discrete meals, this should be provided equally with each meal. For patients receiving enteral nutrition, they should receive prandial dosing prior to bolus feedings or every 6 hours if receiving continuous enteral nutrition. Rapid-acting insulins, lispro, glulisine, and aspart should be given 15 minutes before or after the start of a meal. Regular insulin should be given 30 minutes prior to eating, which may not be practical in most clinical settings. Allowing rapid-acting insulins to be given after the start of a meal allows for adjustment based on a patient's intake, or lack of, in some circumstances. Meal time insulin should be withheld in patients who are not eating. Patients receiving enteral nutrition often require temporary discontinuation for procedures or due to high residual. Standing short- or rapid-acting insulin should also be withheld under such circumstances.

High-dose corticosteroids are known to increase insulin requirements and present a unique challenge to obtaining glycemic control in hospitalized patients. Hyperglycemia is typically seen in these patients 8 to 12 hours after a daily dose is given. Due to this late in the day predictable hyperglycemia, treatment regimens can be adjusted in anticipation. For a patient who is able to eat, rather than dividing a prandial regimen evenly between meals, gradually increasing the mealtime dose, progressing from breakfast to dinner may help in obtaining control. Some authors have even suggested altering meal time doses daily for patients receiving corticosteroids on alternate days.[1]

Correction, or supplemental, insulin in addition to scheduled prandial and basal insulin should be made available in an adjustable fashion to correct preexisting mealtime and bedtime hyperglycemia. This is provided in addition to meal time insulin or alone at bedtime or if a patient is not receiving nutrition. The same type of insulin should be used for both prandial and correction dosing. To create a dosing regimen, it is recommended to first take into account a patient's sensitivity to insulin. A sensitivity factor (SF) is a marker of how much a patient's glucose level will decrease, given 1 unit of insulin. One way to calculate this is by using the rule of 1500, although some have proposed using 1800 in the age of more rapid-acting agents. The SF is determined by dividing 1500 by the TDD. For example, a patient with a TDD of 50 would have SF of 30 (1500/50 = 30), meaning that 1 unit of insulin would be expected to decrease the blood glucose by 30 mg/dL. Correction orders should start at a threshold that is safe for the patient to receive when they are not receiving nutrition. Typically, correction orders begin when the blood glucose is above the identified glycemic target (ie, >150 mg/dL). Correction orders should start at 2 units and increase by 1 unit for every increment of the SF. Using the example mentioned earlier, a meal time blood glucose correction scale would include the following: 150 to 180 mg/dL give 2 units, 181 to 210 mg/dL give 3 units; 211 to 240 mg/dL give 4 units, and so on. Some practitioners recommend using a less-aggressive scale, or starting at a higher threshold, at bedtime for more sensitive patients.

Once regimens are initiated, glycemic control should be reassessed daily. For patients receiving basal therapy with glargine or detemir, doses should be adjusted based on morning fasting glucose values. If twice daily NPH is used, morning doses are adjusted based on evening glucose values and evening doses are adjusted based on morning glucose values. In general, if reasonable starting doses were used, daily increases should not be more than 20% to 30% of the current regimen. Some authors have also recommended adjusting the basal dose by adding half of the correction dose required to the basal regimen.[2] Prandial insulin doses are adjusted based on the level of postprandial glucose (ie, glucose readings before lunch and dinner). Correction insulin can be adjusted based on a patient's response to prior doses administered.

Implementing Glycemic Control Programs

Institutions must use a multidisciplinary approach when striving to improve glycemic control for their patients.[1,15,16,27] These groups should consist of a variety of disciplines including physicians, pharmacists, nursing educators, staff nurses, dieticians, diabetic educators, and technical support. Each of these disciplines can bring a distinct perspective to optimizing glucose control. By having representatives from different disciplines involved in these decisions, they can serve as champions among their colleagues for improving glycemic control.

Several authors have noted that glycemic control is not the primary reason for admission and is

therefore often cited as a reason why it is not addressed.[2,20,27] However, given the plethora of data now showing that hyperglycemia is not a benign condition, it can no longer be ignored. Education on the consequences of hyperglycemia and how to safely dose and administer insulin should be supported at an institutional level. Once attention to glycemic control becomes the standard of care around the institution, health care providers can begin to overcome the barriers to achieving optimal glycemic control and can develop systems for safe and effective administration of insulin.

Focused educational sessions should be provided to all those involved in the direct care of patients. This includes medical, nursing, nutrition, and pharmacy personnel. Education of new practitioners is imperative as they will inevitably become the trainers of the next group of practitioners. Most teaching institutions provide structured, routine educational sessions for their residents in training. Optimization of glycemic control should be included during those times. The support of nursing staff for this type of initiative cannot be over emphasized. The bedside nurse is likely to spend the most time with the patient. If they do not see hyperglycemia management as a necessity, it will not be effectively managed. Nursing input into order set development is also imperative. Nursing staff can provide feedback on the clarity of administration instructions (ie, when to hold an insulin dose) or provide valuable information regarding system issues. For example, increased awareness of the need for improved glycemic control translates into an increase in the amount of point-of-care blood glucose monitoring. Typically, nursing units may only have 1 or 2 glucometers for an entire floor. Having nursing staff involved in order set and protocol development early on can help bring issues such as this to light and help avoid any delay in care.

Clinicians need to work collaboratively with support personnel, such as information technology staff, to devise a system for insulin administration that is both safe and effective. Providing clinicians with preformed order sets that provide dosing recommendations and administration guidance can be extremely helpful to those involved in caring for the patient. Preformed order sets should specify the institution's glycemic goal, standardize frequency of glucose assessment, prompt orders for basal, prandial, and correction insulin, and provide guidance for patients with changing nutritional status. These order sets will serve to standardize the approach to glycemic control among providers and simplify the process of ordering safe and effective insulin regimens for hyperglycemic patients.

A computerized order entry system will provide a number of advantages, yet also bring a different set of challenges, when compared with hospital systems still using a handwritten, paper order system. Using computerized order entry programs, including an electronic medication administration record (EMAR), allows for customized timing of insulin administration and allows detailed nursing instructions to be included with each insulin dose. These instructions are then reviewed by the nursing staff prior to administration of all insulin. Prandial insulin orders can be preset to populate the EMAR at times consistent with when meals are delivered to patient care areas. Instructions for dose reductions in the setting of a patient being NPO or having a decrease blood sugar can be included in the order. This allows for a more timely response by the nursing staff by not having to contact another clinician for each event. Use of computerized order entry systems is expected to decrease transcription and interpretation errors.

Discharge Planning

Decisions regarding discharge diabetes regimens should begin early on during hospitalization. It is important to let patients know that simply because they were receiving insulin while in the hospital, it does not mean they will necessarily have to go home continuing to use insulin. For patients who were generally well controlled prior to admission, they can often be discharged on their same regimen. The best way to ascertain this is to evaluate a patient's A1c. If an A1c has not been measured within the past 3 months, it should be done while they are in the hospital. Modification of a home regimen may be warranted for patients found to have A1c values >7% but <10%. Patients will need to go home receiving insulin if they were previously receiving insulin or are found to have an A1c > 10%.[16] These factors demonstrate that the need for insulin was not due solely to the acute illness. Additionally, some patients may benefit from short-term insulin therapy upon discharge if continued hyperglycemia is expected (ie, using oral steroids). For patients who have been very tightly controlled while in the hospital, it may be safest to send them out on a slightly lower insulin dose to ensure safety at home.

Decreasing doses by 10% to 20% is recommended. For patients who have been found to have a new diagnosis of diabetes or hyperglycemia during their hospitalization, education should begin during admission. Education should include topics such as medication administration, self-monitoring of blood glucose, signs, symptoms, and correction of hypoglycemia, and an explanation of conditions in which a healthcare provider should be contacted.[15] Newly diagnosed patients should also have follow-up with a primary care clinician or a multidisciplinary diabetes group established prior to discharge.

Table 3. Fundamental Principles of Achieving Glycemic Control

1. Determine glycemic target; goals cannot be met if they have not been established
2. The same regimen that controls a patient's blood glucose as outpatient may not control their glucose as an inpatient
3. No evidence exists to support the use of SSI
4. Insulin is the agent of choice for easy titration and rapid achievement of glycemic control
5. Glycemic control requires frequent evaluation of glucose readings and adjustment to therapy
6. Correction insulin should not be confused with SSI, it is given in addition to scheduled insulin, not as a replacement

Abbreviation: SSI, sliding scale insulin.

Discussion

Currently no data exist to identify optimal glycemic targets in non-critically ill hospitalized patients. However, considerable data have demonstrated harmful effects and worse outcomes in patients with untreated hyperglycemia, most notably the increased risk of mortality seen in patients with and without a history of diabetes. Until data from well-designed, randomized, controlled trials (including patients representative of those hospitalized outside of the critical care setting) are available, each institution will need to establish feasible glycemic targets based on available data in critically ill patients, and guidance from the ADA and AACE.

Major changes in current practice trends are needed to realize proposed glycemic targets. Fundamental principles of achieving glycemic control in hospitalized patients should be taught to all health care providers that will have a role in prescribing, administering, or monitoring patients' glycemic control (Table 3). The first principle to achieving glycemic control is to realize that it is impossible to achieve goals that have yet to be determined. Each institution needs to set a glycemic target and educate all health care personnel on how to safely and effectively reach that target. Second, health care providers must be willing to adjust home regimens to meet the changing needs of hospitalized patients. Providers are often reluctant to change patient's diabetes regimens (insulin or oral hypoglycemic agents) or to initiate insulin in patients not previously on insulin prior to admission; however, insulin is the agent of choice for easy titration and rapid achievement of glycemic control in hospitalized patients. As discussed previously, use of oral hypoglycemic agents and premixed insulin combinations are often contraindicated in acutely ill patients or unfeasible for use. Patients who were previously controlled without insulin may use insulin during hospitalization and resume their previous medication upon discharge when their acute illness or cause of hyperglycemia is resolved. Patients with poor glycemic control prior to admission and those failing oral therapies may need to continue insulin therapy upon hospital discharge.

Another fundamental principle to achieving glycemic control is to avoid the "one size fits all" mentality. No evidence exists to support the use of SSI for effective glycemic control. Sliding scale insulin has been around for decades; however, little benefit has been derived from its use. Patients placed on SSI alone are more likely to experience hyperglycemic episodes and fluctuating glucose levels than patients not on SSI. In addition, current practice trends result in patients being started on SSI for admission hyperglycemia without further adjustment of insulin regimens throughout their hospital stay. The RABBIT-2 trial provides clear evidence in support of weight-based basal-bolus insulin to more effectively achieve glycemic control in medically ill hospitalized patients. Future research should be done to evaluate this method of insulin administration in patients excluded in the RABBIT-2 trial (ie, patients without a history of diabetes, patients with renal dysfunction, and patients receiving corticosteroid therapy).

All health care providers should be educated on the concept of basal-bolus insulin therapy for use in patients with uncontrolled hyperglycemia upon admission and for those in whom oral hypoglycemic agents are contraindicated during hospitalization. This approach is used to mimic the normal

physiologic response to elevated glucose levels. All insulin-dependent patients, and those with consistently elevated fasting glucose levels, should be given basal insulin that is determined with a weight-based approach and accounts for the patient's level of insulin sensitivity. Patients with type I diabetes, insulin-dependent patients with type II diabetes, and patients with uncontrolled hyperglycemia who are receiving nutrition should additionally receive prandial insulin. Initial prandial insulin doses should also be determined using a weight-based approach, which takes the patient's level of insulin sensitivity into account. All patients should receive correction insulin to address preexisting mealtime and bedtime hyperglycemia. Correction insulin should not be confused with SSI. Correction insulin is given in addition to scheduled insulin, not as a replacement. Finally, providers will need to assess patient's glycemic control and adjust regimens on a daily basis.

Institutional support is necessary to safely and effectively promote change within current practice trends. Fear of hypoglycemia has lead to years of uncontrolled hyperglycemia and detrimental effects in hospitalized patients. Educating health care providers on effective methods to implement and achieve glycemic goals includes identifying barriers to achieving glycemic control, developing systems to overcome these barriers, and implementing strategies for safe and effective use of insulin therapy. In addition, development of consistent institution-wide glycemic targets will minimize confusion of patients, as they transition from one level of care to another within the facility. Hospitalizations can be used as an opportunity to stress the importance of glycemic control and provide patients the education necessary for them to maintain glycemic control upon discharge from the hospital.

Conclusion

Optimal glycemic targets in patients hospitalized outside of the critical care setting remain an unanswered question. Future research should be directed toward assessing patient outcomes at varying levels of glycemic control and identifying these targets. Until further data become available, health care providers should be educated on the use of weight-based basal-bolus insulin regimens $\pm$ correction insulin in place of SSI to improve glycemic control provided to hospitalized patients.

References

1. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553-591.
2. Inzucchi SE. Management of hyperglycemia in the hospital setting. *N Engl J Med*. 2006;355:1903-1911.
3. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978-982.
4. Golden SH, Peart-Vigilance C, Kao WHL, et al. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care*. 1999;22:1408-1414.
5. Pomposelli JJ, Baxter JK, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *J Parenter Enter Nutr*. 1998;22: 77-81.
6. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78: 1471-1478.
7. Malmberg K, Norhammer A, Wedel H, et al. Glycometabolic state at admission: Important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation*. 1999;99:2626-2632.
8. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;355:773-778.
9. Van den Berghe G, Wouters PJ, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
10. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion follwed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57-65.
11. Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and dcreases recurrent ischemic events. *Circulation*. 2004;190: 1497-1502.
12. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients. *Arch Intern Med*. 2004;164: 2005-2011.
13. 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.
14. Umpierrez GE, Palacio A, Smiley D, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type II diabetes (RABBIT 2 trial). *Diabetes Care*. 2007;30:2181-2186.

15. American College of Endocrinology. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocrine Pract*. 2007;13(suppl 1):59-63.
16. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2008;31(suppl 1):S12-S54.
17. SHM Glycemic Control Task Force. *Workbook for Improvement: Improving glycemic control, preventing hypoglycemia, and optimizing care of the inpatient with hyperglycemia and diabetes. Society of Hospital Medicine website, Glycemic Control Quality Improvement Resource Room*. Available at http://www.hospitalmedicine.org. Accessed July 23, 2008.
18. Umpierrez G, Maynard G. Glycemic chaos (not glycemic control) still the rule for inpatient care: how do we stop the insanity? *J Hosp Med*. 2006;1:141-144.
19. Elrick H, Stimmler L, Hlad CJ, et al. Plasma insulin response to oral and intravenous glucose administration. *J Clin Endocrinol Metab*. 1964;24:1076-1082.
20. Trujillo JM, Barsky EE, Greenwood BC, et al. Improving glycemic control in medical inpatients: a pilot study. *J Hosp Med*. 2008;3:55-63.
21. Ben-Ami H, Nagachandran P, Mendelson A, et al. Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med*. 1999;159:281-284.
22. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia*. 2002;45:937-948.
23. 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.
24. Glucophage (metformin hcl) package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2006.
25. Nesto R, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: consensus statement from the American heart association and American diabetes association. *Circulation*. 2003;108:2941-2948.
26. Gómez-Pérez FJ, Rull JA. Insulin therapy: current alternatives. *Arch Med Res*. 2005;36:258-272.
27. Moghissi ES, Hirsch IB. Hospital management of diabetes. *Endocrinol Metab Clin North Am*. 2005;34:99-116.