

# In-patient management of diabetes: Controversies and guidelines

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### ABSTRACT

Hyperglycemia is associated with adverse outcomes in hospitalized patients with and without previously known diabetes. Some therapies that are used in the in-patient setting, including glucocorticoids, enteral and parenteral nutrition are associated with new onset hyperglycemia even in previously normoglycemic patients. Current guidelines advise that fasting and premeal blood glucose (BG) be maintained at < 140 mg/dl, with maximal random BG < 180 mg/dl in non-critically ill-patients. In critically ill-patients, intravenous (IV) insulin infusion therapy with BG targets of 140-180 effectively maintains glycemic control with a low risk for hypoglycemia. Protocols targeting "tight" glycemic control, defined as BG 80-110 mg/dl, are no longer recommended due to the high frequency of severe hypoglycemia. Rational use of basal bolus insulin (BBI) regimens in non-critical care and IV insulin infusions in critical care settings has been demonstrated to effectively achieve and maintain recommended BG targets with low risk for hypoglycemia. The safety of BBI relies upon provider awareness of prescribing recommendations for initiating and adjusting insulin regimens according to changes in overall clinical and nutritional status, as well as careful review of daily BG measurements. Smooth transition of care to the out-patient setting is facilitated by providing oral and written instructions regarding the timing and dosing of insulin as well as education in basic skills for home management.

**Key words:** Diabetes mellitus, hospitals, hyperglycemia, in-patients, insulin

## INTRODUCTION

In-patient hyperglycemia has been demonstrated to adversely affect clinical outcomes in patients with and without diabetes. blood glucose (BG) levels > 200 mg/dl are associated with an increase in complications, length of stay and mortality in patients admitted with infections, congestive heart failure, myocardial infarction and stroke.<sup>[1,2]</sup>

Approximately, 25-40% of hospitalized patients have underlying diagnosis of diabetes. Another 12-20% of

patients experience hyperglycemia as a manifestation of the acute illness. In critically ill-patient populations, approximately 50% of patients experience hyperglycemia.<sup>[2]</sup>

Despite the well-documented negative impact of uncontrolled hyperglycemia on both early and late morbidity and mortality, controversy remains regarding appropriate glycemic targets as well as the methods for achieving these targets.<sup>[3]</sup> Much of this controversy stems from the observation of a higher incidence of severe hypoglycemia, defined as BG levels <40 mg/dl that were observed with intensive protocols using intravenous (IV) insulin infusions to achieve what has been defined as "tight" glycemic targets of 80-110 mg/dl.<sup>[4]</sup> Despite modifications of recommendations for glycemic targets in both critically ill- and non-critically ill-patient populations, concern for hypoglycemia has resulted in variability in in-patient glycemic management strategies. In one recent review, hyperglycemia (defined as BG >180 mg/dl) accounted for >30% of all recorded glucose values in over 500 hospitals reporting their results.<sup>[5]</sup>

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Because a program of rational glycemic management that targets BG 100-180 mg/dl has the potential to favorably influence both short and long-term patient outcomes, it is important to define the glycemic targets and strategies that are both efficacious and safe for the in-patient population hypoglycemia. Some hospitals have implemented programs that target the early detection and prompt management of hyperglycemia in patients with and without known diabetes as this allows prompt intervention for achieving and maintaining desired levels of BG that are associated with improved patient outcomes.

## BARRIERS TO OPTIMAL PRACTICE

Fear of hypoglycemia represents the most significant barrier to the rational use of insulin therapy in the hospital setting.<sup>[6]</sup> Other obstacles include a lack of familiarity on the part of many physicians and health-care providers regarding the appropriate dosing and adjustment of multicomponent insulin regimens that require both long (basal) and short or rapid acting insulin preparations administered as pre-specified time points throughout the day.<sup>[7]</sup> Due to this complexity, there is a continued over dependence on the use of “sliding scale insulin” regimens, which has been demonstrated to be both ineffective and fraught with hazards when used as the sole insulin approach in patients who have a documented insulin requirement.<sup>[8]</sup> In the hospital setting, there is often poor coordination of processes of care that ensure safety of a glycemic management program.<sup>[9,10]</sup>

## IDENTIFYING PATIENTS WHO ARE AT RISK FOR HYPERGLYCEMIA IN THE HOSPITAL

Given the high prevalence of both diagnosed and undiagnosed diabetes in the general population, and the known frequency of illness associated hyperglycemia, all patients require measurement of a random BG at the time of hospital admission.<sup>[2]</sup> Patients with known diabetes should have this documented in the medical record at the time of admission. An A1C should be obtained if a result is not available within the prior 2-3 months as a way of determining pre-admission glycemic control.

Patients with no prior history of diabetes who have an admission BG > 140 mg/dl may have undiagnosed diabetes or stress-related hyperglycemia associated with the presenting illness. Measurement of an A1C with initiation of BG monitoring for 24-48 h is recommended in these patients to determine the presence of undiagnosed diabetes and need for scheduled in-patient insulin therapy, which is defined as the administration of long or intermediate acting insulin in combination with rapid or short acting

insulin preparations. A laboratory measure of A1C  $\geq$  6.5% is consistent with a diagnosis of diabetes.<sup>[11]</sup>

Patients who are normoglycemic at admission may develop hyperglycemia in response to one of several therapies initiated in the hospital setting, including use of glucocorticoids, immunosuppressants, octreotide or enteral and parenteral nutrition. Bedside BG monitoring for a period of 24-48 h allows early identification of glycemic excursions that require initiation of scheduled insulin therapy.

## GLYCEMIC GOALS

### Non-critical illness

Premeal and fasting glycemic targets are defined as BG values <140 mg/dL with maximal random BG <180 mg/dl for the majority of non-critically ill-patients.<sup>[1,2]</sup> Patients with multiple co-morbidities, who are at high risk for hypoglycemia or who have limited life expectancy can have these glycemic goals modified to allow maximal BG values of 200 mg/dl as a way of minimizing risk for hypoglycemia and symptomatic hyperglycemia.

### Critical illness

Glycemic goals of 140-180 mg/dl are recommended for the majority of patients with critical illness. Lower goals of 110-140 mg/dl may be reasonable for surgical patients, particularly those undergoing cardiac procedures.

## THERAPEUTIC STRATEGIES

### Admission

Patients who are admitted to the hospital can have previously diagnosed type 1 or type 2 diabetes or newly recognized hyperglycemia. Patients with type 1 or insulin treated type 2 diabetes require continuation of at least some component of their insulin regimen when they are hospitalized. Modifications to the home regimen can be made following an assessment of their home insulin doses, their A1C and current nutritional status.

Patients who used insulin therapy at home and who are expected to have regular meals while hospitalized can usually continue their usual doses of basal and nutritional insulin with added correction insulin for BG above desired goal range. Exceptions to this are those patients who were on monotherapy with high doses of basal insulin prior to admission (i.e., >0.5-0.7 units/kg/day). These patients will usually require a redistribution of their insulin doses into basal and bolus insulin components with an overall dose reduction of 10-20% in the total daily dose of insulin. Patients who have a poor appetite or who have changes in their diet will often require modification of their premeal insulin doses to avoid both hyperglycemia and hypoglycemia.

Patients who used insulin therapy at home who will not be eating regular meals can usually continue their basal insulin with discontinuation of their usual doses of premeal scheduled short or rapid-acting insulin preparations until nutrition is resumed. Use correction or supplemental insulin at 4-6 h intervals to treat glycemic excursions above 140-150 mg/dl can help avoid hyperglycemia.<sup>[1,2]</sup> The use of basal insulin in combination with correction insulin has been referred to as a basal plus regimen.

There is very limited data available regarding the efficacy or safety of other oral or non-insulin injectable agents such as alpha-glucosidase inhibitors, dipeptidyl peptidase IV inhibitors or glucagon-like peptide analogs in the hospital setting. Patients with type 2 diabetes treated with oral diabetes agents (ODA) or non-insulin injectable therapy prior to admission require some consideration of changing to insulin therapy when hospitalized. Many hospitalized patients have contraindications to the use of non-insulin agents, such as renal or hepatic impairment or decompensated heart failure. Sulfonylureas can cause severe and prolonged hypoglycemia in patients with poor nutritional intake or who are >65 years of age, or who have estimated glomerular filtration rate (i.e. <30 ml/min/1.73 m<sup>2</sup>).<sup>[12]</sup>

Patients with newly recognized hyperglycemia, defined as persistent BG > 140-150 mg/dl, may require an observation period of 24-48 h with bedside BG monitoring in combination with correction insulin to determine if there will be a need for scheduled insulin therapy. Measurement of an A1C in these patients can help differentiate between previously undiagnosed diabetes and hyperglycemia related to the underlying illness. Patients who are unable to maintain bedside BG levels between 100 and 180 mg/dl without exogenous insulin require conversion to scheduled insulin therapy.

Insulin therapy is the preferred strategy for glycemic management in the in-patient setting as there is no delay in the onset of action and doses can be readily titrated and modified according to results of bedside BG monitoring. Conversion from non-insulin therapies to a basal-bolus or basal plus insulin regimen has been demonstrated to be both safe and effective in patients with type 2 diabetes treated with ODA prior to admission.<sup>[13-15]</sup>

## IMPLEMENTING SCHEDULED INSULIN THERAPY IN THE HOSPITAL

### Non-critical illness

Scheduled subcutaneous insulin therapy consists of the following components: Basal insulin administered as glargine, detemir, or neutral protamine Hagedorn (NPH)

insulin once or twice a day; nutritional (prandial, bolus) insulin administered as short-acting (regular) or as a rapid acting insulin (lispro, aspart, apidra) prior to meals or scheduled according to administration of other nutritional supplements such as enteral or parenteral nutrition and correction (supplemental) insulin to cover glycemic excursions above the desired range in patients already on scheduled basal or basal bolus insulin [Table 1].

### Calculating the insulin dose

The starting dose of basal and nutritional insulin can be calculated based on body weight at 0.1-0.2 units/kg/day for each component, for a total daily dose of 0.2-0.4 units/kg/day. Patients who are lean, who have renal insufficiency, or are >70 years of age may be started on the lower dose, while those who are more obese or with more evidence of insulin resistance will require the higher dose. The nutritional component can be divided into 3 equivalent premeal insulin doses or 4 equivalent scheduled doses in patients receiving continuous enteral or parenteral nutrition (see section below). Co-ordination of care with dietary services can help in maintaining glycemic control as this calculation depends on equal amounts of carbohydrate being provided at each meal. Carbohydrate counting represents an alternative dosing strategy for calculating the dose of premeal insulin. With this strategy, doses of regular or rapid acting insulin are based on the total number of grams of carbohydrate in a meal. This can be initiated at 1 unit of nutritional insulin for each 10-15 g of planned carbohydrate intake.

### For patients receiving enteral nutrition

Several regimens have been demonstrated to be effective for maintaining glycemic control for patients receiving EN.<sup>[16-18]</sup> For patients receiving continuous EN, administration of a long (glargine) or intermediate acting NPH acting insulin twice daily in combination with regular insulin administered every 6 h can be effective at maintaining desired BG levels. Regular insulin is the preferred bolus insulin due to the longer duration of action with need for less frequent insulin dosing than would be required with a rapid acting preparation.

**Table 1: Example of a correction (supplemental) insulin scale**

BG	Low dose	Mod dose	High dose	Patient specific
<70				
70-140	0	0	0	
141-180	1	2	3	
181-220	2	4	6	
221-260	3	6	9	
261-300	4	8	12	
301-340	5	10	15	
>340	6	12	18	

BG: Blood glucose

Many patients receive EN over a period of 8-14 h (usually overnight) in combination with consumption of usual meals during the day. Insulin regimens can be more complex than with continuous EN, but the principles of focusing insulin dosing according to planned administration of nutrition remains. One suggested approach includes administration of NPH (or glargine or detemir) with regular (R) insulin at initiation of EN followed by regular insulin every 6 h for the duration of the tube feeding. Patients who are eating during the day can receive scheduled or correction doses of rapid acting insulin according to BG results.

### Modifying and adjusting insulin therapy

All insulin treated patients require daily review of their bedside BG data to allow timely modification of insulin therapy. It is recommended that the dose of insulin provoking the high or low BG be the dose that is adjusted [Table 2]. Hospitalization is a dynamic period associated with changes in clinical status, insulin sensitivity and severity of illness, caloric intake, physical activity and administration of some medications, all which impact glycemic control. The Endocrine Society Clinical Guideline on Management of Hyperglycemia in the non-critical care setting recommends that consideration be given to modifying insulin doses for BG < 100 mg/dl and definitely for BG < 70 mg/dl<sup>2</sup>. This recommendation is supported by a recent report describing a greater frequency of BG values < 100 mg/dl in hospitalized patients who eventually experienced severe hypoglycemic events, described as BG values < 40 mg/dl.<sup>[19]</sup>

### Critical illness

Continuous IV insulin infusions are recommended for critically ill-patients with persistent hyperglycemia, starting at a threshold of no greater than 180 mg/dl.<sup>[1]</sup> There are several publications demonstrating the safety and efficacy of protocols targeting the recommended goal ranges.<sup>[20,21]</sup> Frequent glycemic monitoring performed every 1-2 h guides glycemic management and minimizes risk for hypoglycemia.

### Transitioning patients from IV to SQ insulin

As critically ill-patients begin to eat regular meals or are transferred to regular nursing units, they require transition

from IV to SQ insulin to maintain desired glycemic targets. Several transition protocols have been published.<sup>[22,23]</sup> The majority of these protocols recommend that 60-80% of the insulin administered IV over the preceding 24 h be administered as basal insulin in either a single or divided dose. Factors that influence this dosing strategy include the administration of EN or total parenteral nutrition (TPN), whether or not the patient was eating or use of vasopressors or other medications that can influence glycemic control. One protocol implemented daily SQ basal insulin with glargine (dose 0.25 units/kg) within 12 h of initiation of an IV insulin infusion.<sup>[24]</sup> These patients experienced less rebound hyperglycemia following transition to SQ insulin than a control group transitioned according to usual care.

## SPECIAL SITUATIONS

### Peri-operative glycemic management

There are no studies that define the optimal BG range during the peri-operative period; however, it is reasonable to aim for glycemic targets of 140-180 mg/dl during the surgical procedures. This range minimizes risk for hypoglycemia in patients who are sedated or receiving general anesthesia and are thus not able to communicate the onset of hypoglycemic symptoms. Both pre- and postoperative glycemic control have been demonstrated to influence risk of postoperative complications and mortality.<sup>[15,25]</sup> It is therefore, important that diabetes regimens be continued in modified form for patients undergoing surgical or other procedures.

Treatment recommendations prior to surgery can be categorized according to type of diabetes, nature and extent of the surgical procedure, antecedent pharmacological therapy and metabolic control prior to surgery. Insulin treated patients require 50-70% of the usual dose of their basal insulin to maintain glycemic control.<sup>[26]</sup> Patients undergoing prolonged surgical procedures (e.g, coronary artery bypass grafting, transplantation) will usually require discontinuation of SQ insulin with start of an IV insulin infusion titrated to maintain BG 140-180 mg/dl. Patients treated with non-insulin therapies can be advised to take these agents as usual the day prior to surgery, but to withhold them on the day of surgery.<sup>[26]</sup> Frequent glucose monitoring during the peri-operative period is essential to allow early detection of hyperglycemia or hypoglycemia.

### Glucocorticoid therapy

The use of glucocorticoids in high doses is a major cause of hyperglycemia in the in-patient setting. Some of the patients receive "pulses" of steroids with doses of methylprednisolone up to 1000 mg a day, often provoking even more severe degrees of hyperglycemia. Although the

**Table 2: Suggested method for adjusting specific insulin doses**

If fasting BG is too high or too low	Adjust basal insulin dose or adjust insulin dose prior to evening meal
If pre-lunch BG is too high or too low	Adjust pre-breakfast insulin dose
If pre-dinner BG is too high or too low	Adjust pre-lunch insulin dose
If HS BG is too high or too low	Adjust pre-dinner insulin dose
If all BG are out of range	Adjust basal insulin dose Consider adjustment in premeal insulin doses

BG: Blood glucose, HS: Hour of sleep

majority of patients with and without diabetes will experience elevations in their BG during steroid therapy, some do not, making it difficult to make general recommendations for all patients who receive these therapies in the hospital.<sup>[27]</sup> There are several general principles that can guide therapy that helps to maintain reasonable glycemic control in these patients.<sup>[2]</sup> Bedside BG monitoring is recommended for 24-48 h together with correction insulin following initiation of glucocorticoid therapy helps to identify patients who will develop either new onset hyperglycemia or untoward glycemic excursions. Patients requiring multiple doses of correction insulin will require either initiation or augmentation of scheduled insulin therapy.

Patients with a prior history of glucocorticoid induced hyperglycemia are at high risk for recurrent hyperglycemia with initiation of steroid therapy. NPH insulin administered at the time of steroid administration and dosed according to dose of administered steroid (e.g, 0.1 unit/kg NPH insulin for each 10 mg Prednisone equivalent of administered glucocorticoid to maximum dose of 0.4 units/kg for doses  $\geq$  40 mg) has been demonstrated as being effective in maintaining glycemic control in one small study.<sup>[28,29]</sup> In patients who are already receiving scheduled insulin therapy, the NPH is added to their current insulin regimen, allowing immediate discontinuation if the steroids are stopped or tapered. Clinical judgment is always required in establishing a particular dose for an individual patient. Some patients may require IV insulin to achieve and maintain glycemic control following initiation of steroid therapy. For patients in critical care areas, this may not be an issue as they are often already on IV insulin that can be titrated to maintain glycemic control. However, outside critical care areas, it may be useful to use a 12-24 h period of IV insulin to calculate the insulin requirement for SQ insulin.

## TRANSITION FROM HOSPITAL TO HOME

Patients who are either newly started on diabetes medications or those with diabetes who have alterations in their regimen in the in-patient setting are at risk for hypoglycemia and hyperglycemia following discharge unless clear information is provided with attention needs to necessity for insulin adjustments as therapies started in the hospital are modified in the out-patient setting. This includes tapering of steroid doses, TPN or EN. It is therefore important that patients and their family members or caregivers receive clear discharge instructions including the timing and doses of insulin or other diabetes medications. It is essential that the physician or care provider who will be assuming ongoing out-patient care for these patients be informed as to the insulin regimen at time of discharge and expectations for what will need to occur over the ensuing weeks.

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