Chapter 35
Guidelines on Inpatient Management of Hyperglycemia

Sukhminderjit Singh Bajwa, Manash P Baruah, Sanjay Kalra, Mukul Chandra Kapoor

ABSTRACT
Hospitalized diabetic patients pose numerous clinical challenges. Socio-behavioral, economic, nutritional, racial, ethnic, and other factors make it difficult for application of hitherto published western guidelines in India. The present chapter is an effort to bring forth the various clinical challenges encountered during management of different diabetic hospitalized populations and to formulate a set of patient and physician friendly guidelines to control hyperglycemia in such patients. Keywords: Diabetes; hyperglycemia; inpatients; insulin therapy; insulin analogs

INTRODUCTION
Prolonged hospitalization and poorer outcome is a common phenomenon amongst patients with diabetes mellitus (DM). There are inconsistent data regarding outcome of intensive control of hyperglycemia amongst hospitalized patients. Such inconsistencies create doubts regarding the adoption of precise therapeutic interventions in indoor patients with hyperglycemia.

A large number of DM cases are diagnosed for the first time when they get admitted for various indications, which may or may not be related to DM. Although Indian data reveal that every sixth patient admitted to hospital has diabetes, in reality the number may be higher.

NEED FOR INDIAN/ASIAN GUIDELINES
Although a number of guidelines on inpatient hyperglycemia management have been published, they are not without confounding biases involving nutritional status, level of awareness, socio-behavioral, cultural and economic factors. Moreover, racial, ethnic and genetic differences in insulin resistance and glucose and lipid metabolism may limit the extrapolation of western guidelines to an Indian population. There is an acute need for formulation of user-friendly guidelines relevant in India and other developing nations as well.

The guidelines delineated in this chapter are based upon evidences derived from available literature. Initial core writing group consisted of the authors of this article. Review of the draft and grading of recommendations were done by a panel of experts consisting of four endocrinologists, one internist, one pediatrician and one obstetrician, each having at least a decade of experience. Grading was based on a method suggested by Frid et al. (2010), which includes an ABC scale of recommendation and 123 scale for supporting scientific evidence (Table 1). For each recommendation, the postfixed capital letter in bold indicates how much weight a recommendation should carry in daily practice, while the number defines its degree of support in medical literature.

GUIDELINES FOR GLYCEMIC CONTROL
Hyperglycemia can have detrimental effects in both medical and surgical hospitalized patients. So far as the management of hyperglycemia is concerned, the hospitalized patients can be categorized into two broad categories: (1) non-critically ill, and (2) critically ill.

Non-critically Ill Patients
Compared to ICU patients, non-critical patients are less likely to receive adequate attention for hyperglycemia per se. Physicians’ concerns for the management of primary pathology, lack of proper monitoring facility and dedicated paramedical staff in general wards, unsupervised dietary intake and fear of inducing hypoglycemia are amongst the factors responsible. These factors are also responsible for avoidance/delay in usage of insulin even in inpatients. Hyperglycemia may lead to longer hospitalization, impaired wound healing, and occasional risk of polyneuropathy, higher incidence of systemic infections, urinary tract infections, acute renal failure and increased cardiac morbidity.

The targets proposed by American Diabetic Association (ADA) for premeal blood glucose (BG) (< 140 mg/dL) and usual (random) BG (< 180 mg/dL) are generally acceptable. Target can be lower than this threshold in the following situations: (1) stable patients with optimal glycemic control prior to admission, (2) postoperative ward and gestational DM patients in a background of available adequately trained staff for monitoring and treating hypoglycemia. Patients who are able to eat adequately at regular intervals are right candidates for subcutaneous (SC) insulin, because intravenous (IV) insulin regimen is less flexible.

Sliding scale insulin (SSI), although quite popular, has been found to be inferior to basal bolus (BB) regimen using rapid-acting analog to fulfill prandial requirement and once daily long-acting analog to fulfill the basal and supplemental need. Apart from achieving better

| TABLE 1 | Criteria for grading and rating recommendations
<table>
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<tr>
<td><strong>Strength of recommendation</strong></td>
<td><strong>Rating</strong></td>
</tr>
<tr>
<td>A</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Recommended</td>
</tr>
<tr>
<td>C</td>
<td>Unresolved issue</td>
</tr>
<tr>
<td><strong>Scale of scientific support</strong></td>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>1</td>
<td>At least one randomized controlled study</td>
</tr>
<tr>
<td>2</td>
<td>At least one non-randomized or non-controlled epidemiologic study</td>
</tr>
<tr>
<td>3</td>
<td>Consensus expert opinion based on extensive patient experience</td>
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BG control, the incidence of various infections, respiratory failure and acute renal failure is much lower in patients treated with insulin analogs. Similarly, basal insulin analogs imparts better glycemic control in diabetic patients receiving enteral nutrition as compared to SSI.\textsuperscript{13,14}

**Recommendations**

- Premeal BG target should be 110–130 mg/dL, and postmeal target should be 140–180 mg/dL. Targets should be less stringent for the elderly and patients with significant medical comorbidity. Non-critically ill inpatients on enteral nutrition should be preferably managed with insulin [A1].
- Basal insulin to cover the basal and correctional need, and prandial rapid-acting insulin to cover the nutritional need are preferred choice. SSI is not recommended [A1].
- Insulin analogs should be preferred in indoor patients as they are associated with less hypoglycemia, better therapeutic outcomes, and are more flexible to use [A2].

**Critically Ill Patients**

Glycemic control in critically ill patients is a unique challenge for both intensivist and endocrinologist, as these patients invariably have multigorgan dysfunction. In spite of extensive data indicating a relation between uncontrolled hyperglycemia and poor outcome in critically ill, optimal glycemic targets are not precisely defined. While evidence favors a tighter control in the range of 110–140 mg/dL in surgical patients, a less aggressive target may suit medically ill patients.\textsuperscript{5,11} Such stringent targets can lead to severe hypoglycemia (<40 mg/dL), which is a cause of increase mortality in the critically ill. A goal range of 140–180 mg/dL has been recently recommended and has been approved by most, if not all.\textsuperscript{5,16}

The only acceptable modality of treatment is continuous IV insulin infusion, which should be initiated when BG levels are greater than 180 mg/dL ([Tables 2 to 4]). There are many IV insulin infusion regimens available, but those regimens are preferred, which contain orders that take into account both current BG values and rate of change of BG.\textsuperscript{5,17}

For basal, mealtime and correction doses, insulin analogs are preferred over regular and neutral protamine hagedorn (NPH) insulin as they have a predictable absorption mechanism and exhibit minimal pharmacokinetic variability. The incidence of hypoglycemia is significantly minimized if pre- and postprandial regular insulin is replaced by rapid-acting insulin analogs. Predictable duration of action with minimal stacking effect enables the analogs to achieve euglycemia with minimal hypoglycemia.\textsuperscript{18}

**Recommendations**

- Maintain BG level at a range of 140–180 mg/dL for majority of patients with medical morbidity, and 110–140 mg/dL for those with surgical morbidity [A1].
- Only IV insulin is recommended. Subcutaneous regimens with premixed insulin, intermediate-acting or long-acting insulin and SSI are not recommended [A1].
- Regular insulin or rapid-acting insulin analogs (aspart, lispro, glulisine) can be used as IV infusion. Glulisine should be used only with normal saline [A2].

**TABLE 2** Estimated initial dose of insulin in non-critically ill hospitalized patients

<table>
<thead>
<tr>
<th>Total daily dose of insulin (units/kg body wt)</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>• Geriatric patients</td>
</tr>
<tr>
<td></td>
<td>• Renal or hepatic impairment</td>
</tr>
<tr>
<td></td>
<td>• On hemodialysis</td>
</tr>
<tr>
<td>0.5</td>
<td>• Ordinary patients</td>
</tr>
<tr>
<td>1.0</td>
<td>• Obesity and other insulin resistance state</td>
</tr>
<tr>
<td></td>
<td>• Glucocorticoid treatment</td>
</tr>
<tr>
<td></td>
<td>• Severe infections</td>
</tr>
<tr>
<td></td>
<td>• Coronary artery bypass graft (CABG)</td>
</tr>
<tr>
<td></td>
<td>• Total parenteral nutrition (TPN)</td>
</tr>
</tbody>
</table>

Calculation of subcutaneous dose of insulin in a 60 kg adult male with body mass index (BMI) of 25 having moderate hyperglycemia:

- Total daily dose (TDD) = 0.5 units/kg body wt × 60 = 30 units
- Basal insulin dose = 50% of TDD = 50% of 30 units = 15 units basal insulin
- Bolus insulin dose per meal = (50% of TDD)/3 = (50% of 30 units)/3 = 15/3
  = 5 units of rapid-acting insulin before each meal
- Assessment of correctional scale insulin is based on TDD. For a patient with a TDD of 40 units, the low correctional scale should be ordered.

**TABLE 3** Suggested protocol for insulin infusion in ICU

<table>
<thead>
<tr>
<th>A. Preparation</th>
<th>50 units of regular insulin dissolved in 50 mL normal saline (NS) in a 50 mL disposable syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Mode of administration</td>
<td>IV infusion with an electronic syringe pump/infusion pumps</td>
</tr>
<tr>
<td>C. Primary target</td>
<td>To maintain blood sugar level within a predefined target 140 mg/dL</td>
</tr>
<tr>
<td>D. Control methodology</td>
<td>Blood sugar to be controlled gradually in case of severe hyperglycemia by titrating the dose of IV insulin</td>
</tr>
<tr>
<td>E. Pre-requisites</td>
<td>Initially 15–20 mL of solution should be flushed through plastic tubing to saturate the insulin binding sites in the tubing</td>
</tr>
<tr>
<td>F. Targets</td>
<td>Dose should be adjusted as per the levels of blood sugar</td>
</tr>
<tr>
<td>G. Monitoring</td>
<td>Either by capillary blood glucose or from the venous site/central line</td>
</tr>
</tbody>
</table>

**TABLE 4** Titration of insulin dose according to blood glucose (BG) levels

<table>
<thead>
<tr>
<th>Blood glucose levels (mg/dL)</th>
<th>Dosage of insulin infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>No insulin to be given</td>
</tr>
<tr>
<td>100–149</td>
<td>1–1.5 units/hour</td>
</tr>
<tr>
<td>150–199</td>
<td>2 units/hour</td>
</tr>
<tr>
<td>200–249</td>
<td>2.5 units/hour</td>
</tr>
<tr>
<td>250–299</td>
<td>3 units/hour</td>
</tr>
<tr>
<td>300–349</td>
<td>3.5 units/hour</td>
</tr>
<tr>
<td>350–399</td>
<td>4 units/hour</td>
</tr>
</tbody>
</table>

For any further increase in BG, consulting endocrinologist/physician/intensivist needs to decide the rate subjectively. If BG does not fall more than 10%, insulin can be increased to 1.5 times the normal dose. If BG is <50 mg/dL, administer 50 mL of dextrose (25 g), check blood sugar at 15 minutes and if blood glucose increases to more than 100 mg/dL, start insulin infusion after 1 hour.

If BG between 50 mg/dL and 75 mg/dL, infuse 50 mL dextrose (25 g) if hypoglycemia manifests clinically. If asymptomatic, give half dose of the above solution. Check blood sugar after 15 minutes and start insulin 1 hour after BG reaches >100 mg/dL.
Diabetology

- Transition to subcutaneous insulin from IV insulin should have an overlapping period of 1–2 hour. The overlap can be reduced to 15–30 min if rapid analogs are used [A2].

MOONITING OF BLOOD GLUCOSE

Technologies enabling bedside capillary blood glucose monitoring with agility, rapidity and reasonable safety have revolutionized inpatient management of hyperglycemia.20

Different approaches, such as venous, capillary blood and/or plasma or whole blood have been used for precise measurement of blood glucose.21 The question of accuracy of capillary vis-à-vis venous measurement has become redundant with the advent of newer glucometer, which allows samples from either source to be measured. The resulting advantages are minimal needle pricks (less injury, less contamination, cost cutting) and elimination of factitious reporting.22,23 However, to minimize errors, the glucometer readings should always be tested and compared intermittently with laboratory glucose values (internal quality control). A structured protocol-based approach is of utmost importance (Flow chart 1). Continuous glucose monitoring system (CGMS), which can monitor glucose levels continuously up to 72 hours, may be useful in emergency and intensive care units as it exhibits various glycemic trends and patterns, help in timely detection of hypoglycemia and assesses efficacy of ongoing therapy. However, the high cost, delay in obtaining the results (after 72 hours) and limitation of real time display are a few disadvantages.24

Recommendations
- Mandatory BG testing for every patient on admission and at least two readings in the next 24 hours to rule out hyperglycemia [A2]
- Glycated hemoglobin should be obtained in patient with hyperglycemia without prior history of DM and with persistent hyperglycemia of uncertain etiology. This test is unreliable in patients receiving massive blood transfusions [B2].
- Point of care monitoring of blood glucose is to be done preferably with capillary method. In cases of hypotension, hypothermia, shock, use of vasoconstrictors and vasopressors, use venous sampling instead [A2].
- Initial monitoring should be done on an hourly basis. Interval of testing can be increased when three consecutive readings are consistently around the target [B2].
- If logistics permit, CGMS should be used while monitoring glycemic status in critically ill patients [B2].
- Postprandial testing should be included while monitoring glycemia in patients on oral feed [C3].

SPECIAL POPULATIONS

Perioperative Management

Insulin is the preferred therapy in majority of surgical patients. The most commonly used insulin regimens in India are GIK (glucose, insulin and potassium) and variable insulin infusion regimens. The cost associated with the pump infusion system prohibits the use of such regimens in low resource settings. Alternatively, the use of micro-drip set attached to dextrose solution containing therapeutic insulin and potassium is cost effective, and can be used in any setting where monitoring of BG is possible as and when required. Adequate control of hyperglycemia has shown to improve outcome in general as well as special surgery wards.25–27

Transplant surgery in diabetes is challenging as uncontrolled hyperglycemia is associated with increased cardiac morbidity, risk of organ failure, acute graft versus host disease (grade II-IV) and increased risk of non-relapse-related mortality.28 Each 10 mg/dL increase of BG is associated with 1–1.5 fold increase in odds ratio of bacteremia in neutropenic patients not on glucocorticoids.29 Administration of immunosuppressants in post-transplant period is associated with hyperglycemia. As such, insulin requirement is much higher in these patients. On the other hand, patient’s dietary changes may lead to sudden hypoglycemia. These factors warrant the use of insulin analogs due to their flexibility.30

Recommendations
- Tight glycemic control with insulin is advocated for a better surgical outcome, with targets of BG between 110 mg/dL and 140 mg/dL [A1].
- Glucose and insulin should be given through separate IV routes. Serum potassium should be monitored and maintained through supplementation [B2].
- Relatively minor procedure such as cataract surgery where patients need not remain nil per orally for prolonged periods may continue on oral hypoglycemic agents if they are well controlled [A2].
- The blood glucose target in post-transplant patients should be similar to that of surgical inpatients. Analogs should be preferred [A2].

PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Hyperglycemia has been found to be associated with poor clinical outcome in acute myocardial infarction (AMI) patients.31 Whether hyperglycemia is an indicator of the severity of AMI or it acts as a mediator in causation of various complications associated with AMI remains controversial. These controversies are further heightened by the fact that patients with hypoglycemia who suffer from acute MI also have an adverse outcome.32,33 Tight glycemic control may not contribute toward any increased mortality but it definitely reduces the risk of complications associated with MI such as congestive
cardiac failure and reinfarction. The efficacy of GIK regimen in patients with acute AMI has remained inconclusive.

**Recommendations**
- Hyperglycemia and hypoglycemia both should be avoided in patients with AMI to decrease morbidity and mortality [A1].
- Optimal glycemic control insulin, preferably analogs during and after the episode, decreases the risk of complications associated with AMI [A2].

**Patients on Glucocorticoid Therapy**
Due to sustained hyperglycemia especially during post-prandial period, susceptible glucocorticoid users can be treated with titration of meal-time insulin dose. The variable sensitivity and requirement of the insulin mandates monitoring of BG for 48 hours in patients receiving high-dose glucocorticoid therapy so as to prevent any episode of hyperglycemia or hypoglycemia. Basal bolus insulin in the patient can be adjusted on the basis of correctional insulin requirements. An increment of 20% of intermediate- or long-acting insulin doses is considered safe to control hyperglycemia. Due to inadequate quality evidence in medical literature, formulating the best approach to control hyperglycemia in patients on high-dose glucocorticoid therapy remains a difficult task.

**Recommendations**
- Regular and sustained monitoring of BG should be done in patients on high dose of glucocorticoid therapy [A1].
- Treatment naïve patients developing hyperglycemia after glucocorticoid initiation should be managed with insulin [A2].
- For patients already on insulin, 20% increment in total daily insulin dose at time of high-dose glucocorticoid initiation is a reasonable step [B2].

**Patients on Enteral Nutrition**
The control of hyperglycemia is challenging in patients receiving enteral nutrition as glycemic levels show marked variability with type and duration of enteral nutrition (i.e. Ryles tube or gastrostomy tube). Basal insulin may exert hypoglycemic effects on sudden discontinuation of enteral nutrition. Basal insulin analogs control hyperglycemia, in combination with SSI, without any higher incidence of hypoglycemia as compared to SSI alone, as the latter regimen is associated with additional requirement of intermediate-acting insulin in 48% cases.

**Recommendations**
- Insulin analogs should be preferred to control hyperglycemia in indoor patients on enteral nutrition [A2].
- Basal plus multiple SC prandial boluses are to be preferred over SSI [A1].

**Patients Receiving Parenteral Nutrition**
Parenteral nutrition can be extremely detrimental to critically ill diabetic patients as the large amount of glucose in these solutions results in severe hyperglycemia. The uncontrolled hyperglycemia is responsible for higher incidence of complications and mortality in this subset of population.

**Recommendations**
- Intravenous insulin is the preferred treatment for control of hyperglycemia in patients receiving parenteral nutrition [A1].
- Glucose targets should be based on the severity of underlying illness [A1].

**Peripartum Control of Hyperglycemia**
The effect of placental hormones, growth factors and cytokines increases insulin resistance during pregnancy, and this significantly enhances insulin requirements. Constant vigil for sudden onset of metabolic complications like maternal ketoacidosis during labor and neonatal hypoglycemia is essential and has to be managed appropriately. Insulin dose should be titrated on an individual basis as parturient shows wide variability in insulin resistance after 14 weeks of gestation.

**Recommendations**
- Insulin is the preferred therapy in pregnancy complicated by diabetes [A1].
- Rapid-acting insulin analogs—aspart and lispro are preferred for use in pregnancy. Detemir is a preferred choice as basal insulin [A2].
- Patients in active labor should be on glucose, IV insulin plus potassium infusion to prevent hypokalemia, hypoglycemia as well as ketosis [A1].
- Incremental insulin dose is required for pregnant ladies receiving long-acting glucocorticoid for fetal maturity [B2].

**Critically Ill Pediatric Patients**
Management of hyperglycemia in pediatric patients is challenging especially among critically sick patients. Factors such as longer duration of hyperglycemia and higher peak BG (> 180 mg/dL) can lead to prolonged hospitalization, increased nosocomial infections and 3.5 fold increase in sepsis-related mortality risks. Management of hyperglycemia in ICU with IV insulin infusion is definitely a safer option in pediatric patients. The target of BG (110–150 mg/dL) should be modest, and insulin should be used judiciously to avoid hypoglycemia and ketosis. The physiological insulin resistance during pubertal growth may be perceived as increased insulin requirement in this age group. To this end, the use of insulin analogs (both basal and rapid) looks quite promising.

**Recommendations**
- Insulin is the preferred therapy in pediatric ICU with optimal BG target of 110–150 mg/dL [A2].
- Insulin analogs are preferred over conventional insulin. Recommended age limit is greater than 2 years for aspart, greater than 3 years for lispro, greater than 4 years for glulisine, greater than 2 years for detemir, and greater than 6 years for glargine [A2].

**Transition to Outdoor Management**
Discharge and outdoor management of patients with diabetes should be done only after prior stabilization of blood glucose levels.

**Guidelines on Inpatient Management of Hyperglycemia**

**Chapter 35**
The management of diabetes in hospitalized patients is easier as compared to outpatients, provided that there is good coordination among various disciplines. Appropriate use of insulin and insulin analogs using IV or SC regimes as required to target euglycemia ensures better therapeutic outcomes. Along with this, training of health workers, education of support staff, use of simple protocols, auditing of mortality and morbidity statistics and a good feedback system are essential for the successful management of hyperglycemia in low resource health set-up.

**ACKNOWLEDGMENTS**

The authors are grateful to Dr Ganpathi Bantwal, Dr Mathew John, Dr Rakesh K Sahay, Dr AG Unnikrishnan, Dr Raman Setty, Dr Inderpreet Sohi, Dr Sukhinder Kaur Bajwa for their critical inputs while formulating and grading the evidences.

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Guidelines on Inpatient Management of Hyperglycemia