

# Management of Hyperglycemia in Critical Care- A Comprehensive Review

Mohd. Rafi Mir, Mohammed Sharfraz Ahamed, Sidharth Arora, Ankit Chhabra, Raiz Ahmad Misgar

Department of Endocrinology, SKIMS

## ABSTRACT

Hyperglycemia is a common occurrence in critically ill patients and is associated with prolonged hospital stays, higher rates of infection, and increased mortality. Effective management of hyperglycemia in critical care settings is paramount. Several studies and meta-analyses consistently highlight hyperglycemia as an indicator of illness severity in these patients. Studies recommend intensive insulin therapy for managing hyperglycemia in critically ill patients, irrespective of their diabetes status. Given that glycemic variability and hypoglycemia can exacerbate the patient's condition, monitoring tools for these parameters are essential in critical care settings. Insulin therapy should strive to minimize glycemic variability and avoid hypoglycemia. Adequate nutritional support is crucial, with evidence supporting enteral nutrition over parenteral nutrition due to its lower infection and mortality risks. Some patients may transition from intravenous to subcutaneous insulin, preferring a basal-bolus insulin regimen over a sliding-scale insulin regimen. Establishing appropriate glycemic targets and thresholds for initiating insulin therapy is essential for managing hyperglycemia in these patients. Continuous blood glucose monitoring and appropriate medical nutrition therapy can significantly enhance patient outcomes.

Keywords: Hyperglycemia, Critical Care, ICU, Insulin.

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## INTRODUCTION

Over the last few decades, diabetes has emerged as a global health emergency becoming the 9th leading cause of death as per WHO. Once considered a disease of affluent societies, recent epidemiologic studies have reported its spread to the developing world too. India is among the top 3 countries bearing the major burden of this disease along with China and the United States<sup>1</sup>. The improving socioeconomic status leading to changing eating patterns with the adoption of a sedentary lifestyle along with population growth and ageing are a few reasons causing this shift. Presently, India ranks second only to China in terms of diabetes prevalence, with an estimated 77 million individuals affected<sup>2</sup>. A pressing concern is that over 50 per cent of cases in developing countries remain undiagnosed, warranting focused attention<sup>1</sup>. In congruence with the increasing burden, the standards of diabetes care have evolved to encompass more comprehensive approaches, resulting in a decline in the incidence of both microvascular and macrovascular complications. However, this

improvement has also led to a growing population of elderly individuals living with diabetes<sup>3</sup>, contributing to an increased proportion of adult hospitalizations associated with the condition<sup>4</sup>. Patients diagnosed with diabetes are commonly perceived to exhibit heightened susceptibility to specific infections compared to non-diabetic individuals. As per the data provided by the American Diabetes Association in 2012, approximately 25% of hospital admissions are attributed to individuals diagnosed with diabetes<sup>5</sup>. Another important consideration is stress-induced hyperglycemia, first described by Claude Bernard in 1877, which denotes transient hyperglycemia following an acute illness that resolves spontaneously<sup>6</sup>. This phenomenon typically manifests in individuals previously undiagnosed with diabetes but may also serve as an exacerbating factor in those with known diabetes (7). It is reported in 22% to 46% of non-critically ill hospitalized patients. Hyperglycemia is a common issue in critically ill

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### Correspondence:

Dr. Raiz Ahmad Misgar, DM  
Additional Professor, Department of Endocrinology, SKIMS  
Email: [drreyaz07@rediffmail.com](mailto:drreyaz07@rediffmail.com)

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patients, even in the absence of pre-existing DM, and is associated with increased morbidity and mortality. The diverse array of pathophysiological mechanisms associated with this phenomenon encompasses heightened levels of catecholamines, elevated insulin resistance, and the administration of specific pharmaceutical agents (beta blockers, lithium, vasopressors, glucocorticoids) alongside parenteral nutrition<sup>8</sup>. Multiple investigations conducted among both intensive care unit (ICU) and non-ICU hospitalized patients have revealed a robust correlation between stress-induced hyperglycemia and unfavourable clinical outcomes. These outcomes encompass mortality, morbidity, prolonged hospitalization, susceptibility to infections, and overall complication rates (9). The focus on glycemic control extends beyond hyperglycemia; prevailing evidence indicates adverse outcomes associated with hypoglycemia<sup>10,11,12</sup> and glycemic variability<sup>13</sup>. Acknowledging the diverse patient population in the intensive care unit (ICU), it is conceivable that a standardized method for establishing glycemic targets and anticipating outcomes may lack universal applicability. Extensive research endeavours have focused on delineating optimal glycemic targets within this demographic. However, ongoing discourse surrounds the most effective strategy for managing glycemia among critically ill patients, with persisting obstacles arising from less-than-optimal approaches in clinical practice.

The objective of the present review is to analyze various aspects related to glucose control in critically ill patients including the prevailing guidelines to manage in-patient hyperglycemia, and to define the optimal management of hyperglycemia in these patients with a reference to our institutional protocol.

### Prevalence of Diabetes and Hyperglycemia in Hospitalized Patients.

Observational studies have indicated that hyperglycemia and diabetes are prevalent among hospitalized patients, ranging from 38% to 40% in general and 70-80% in those with diabetes who experience critical illnesses or undergo cardiac surgery. A 2017 report based on point-of-care bedside glucose test data from nearly 3.5 million individuals (653,359 ICU and 2,831,436 non-ICU patients) across 575 hospitals in the United States found a prevalence of hyperglycemia (defined as a glucose level >180 mg/dl [10.0 mmol/l]) in 32.2% of ICU patients and 32.0% of non-

ICU patients. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) consensus on inpatient hyperglycemia defines stress or hospital-related hyperglycemia as any blood glucose concentration >140 mg/dl (>7.8 mmol/l) in patients without a prior history of diabetes. While stress hyperglycemia typically resolves as the acute illness or surgical stress diminishes, a significant proportion (up to 60% in some reports) of individuals had confirmed diabetes 6-12 months after discharge. Measurement of HbA1c is recommended in individuals with hyperglycemia without a history of diabetes to differentiate between stress-induced hyperglycemia and previously undiagnosed diabetes. Recommendations from the Endocrine Society and the UK Joint British Diabetes Societies for Inpatient Care suggest that individuals hospitalized with both an elevated blood glucose >140 mg/dl (7.8 mmol/l) and an HbA1c of 6.5% (48 mmol/mol) or higher can be identified as having diabetes<sup>14</sup>.

### Pathophysiology:

Hyperglycemia in critically ill patients may either independently influence prognosis or simply serve as an indicator of disease severity. The development of hyperglycemia in critical illness is attributed to various factors, including the release of stress hormones (such as corticosteroids and catecholamines) and proinflammatory mediators, as well as the administration of exogenous corticosteroids, vasopressors, and dextrose-containing parenteral solutions. Gluconeogenesis, primarily mediated by glucagon (but also influenced by cortisol and epinephrine), appears to be the main contributor to stress-induced hyperglycemia. Critical illness disrupts the immune system and the inflammatory response, leading to a nonspecific immune response that results in oxidative stress, mitochondrial dysfunction, cell death, tissue damage, and ultimately organ failure.

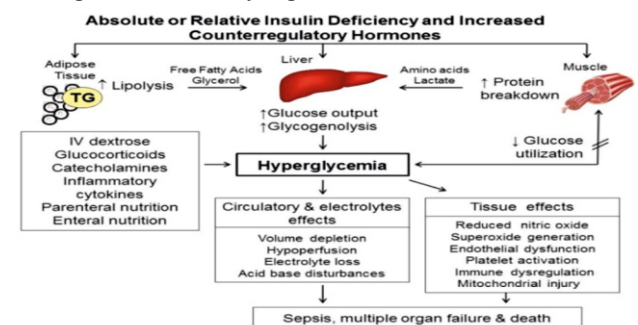


Figure 1. Adapted from Hulkower RD, Pollack RM, Zonszein J. Understanding hypoglycemia in hospitalized patients. Diabetes Management (Lond). 2014;4:165–176.

**Guidelines for managing hyperglycemia in ICU.****Glycemic targets:**

In most critically ill adult patients, target blood glucose has been a matter of debate previously with Certain trials showing benefits with intensive insulin therapy (IIT), whereas other trials show no benefits with IIT. A landmark clinical trial was conducted in a surgical intensive care unit (ICU) by Van den Berghe et al.<sup>15</sup> in which they demonstrated that an intensive intravenous insulin protocol with a glycemic goal of 80–110 mg/dL reduced mortality by 40% compared with a standard approach of a glycemic goal of 180–215 mg/dL. This was a single-centre Belgian trial that included 1548 surgical ICU patients. However, the largest randomized trial was the multicenter NICE-SUGAR trial. In this trial, 6104 medical and surgical ICU patients were randomized to either IIT (target blood glucose level of 81 to 108 mg/dL) or conventional glucose control (target blood glucose of <180 mg/dL) using an insulin infusion<sup>16</sup>. In patients treated with IIT, 90-day mortality was higher than in patients treated with the conventional strategy and also resulted in an increased number of severe hypoglycemia episodes. Several Meta-analyses have been performed to consolidate the data from numerous randomized trials. Meta-analysis of 26 randomized trials including the NICE SUGAR trial (13,567 patients) that compared IIT with conventional glycemic control in mixed medical and surgical ICU patients reported no difference in mortality between the groups<sup>17</sup>.

Based on these studies various organizations have proposed the glycemic targets in critically ill patients as shown in Table 1.

**Glucose monitoring in critical care:**

It is crucial to achieve target glucose levels but care is to be taken to reduce the risk of hypoglycemia. This can be achieved through regular monitoring of BG levels. In patients receiving intravenous (IV) insulin, initial blood sugar should be estimated every hour till the blood sugar level is stable. Once stable, testing can then follow every 2 hours. BG levels in patients on oral feed are measured four times a day, before meals and at bedtime. In some patients, the change of medication such as the use of corticosteroid necessities changes the frequency of monitoring glucose levels<sup>18</sup>. More frequent and intense monitoring may be required if the patient is older, has a comorbidity or has a previous episode of hypoglycemia. Capillary glucose monitoring has been the routine clinical practice and evidence suggests it is both safe and efficient in providing information on fluctuations and trends in glucose control.

**Initiating Insulin:**

There is no universally accepted insulin regimen for glycemic control in critically ill patients. However, short-acting preparations as either an intermittent subcutaneous regimen or continuous infusion to achieve the optimal target value are used in most centres. Longer-acting insulin preparations are avoided during the early phases of illness to mitigate the risk of hypoglycemia given acute changes in insulin requirement. There are several IV insulin protocols available for critically ill patients in ICU settings<sup>15,19,20</sup>. However, these protocols have a complex set of instructions and are thus confusing. A new algorithm suggested by Chawla, et.al<sup>21</sup> which is easy to implement and easily comprehensible and includes an algorithm for making temporary corrective increments or decrements in infusion rate is shown in Table 2.

**Table 1: Global Glycemic targets in ICU as per different associations<sup>21</sup>.**

| ORGANIZATION                                      | TREATMENT THRESHOLD (MG/DL) | TARGET GLUCOSE (MG/DL) |
|---------------------------------------------------|-----------------------------|------------------------|
| American Diabetes Association                     | 180                         | 140-180                |
| Canadian Diabetes Association                     | 180                         | 108-180                |
| RSSDI                                             | 180                         | 140-180                |
| Society of Critical Care Medicine                 | 180                         | 150                    |
| American Association of Clinical Endocrinologists | 180                         | 140-180                |

**Table 2:** Insulin infusion and titration algorithm<sup>21</sup>:

| Glucose value (mg/dl) | Infusion rate (scale 1)                                                                        | Infusion rate (scale 2)                                              | Infusion rate (scale 3)                                              |
|-----------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| <70                   | Stop infusion.<br>Give 25%dextrose 100ml and check capillary blood glucose (CBG) in 15 minutes | Stop infusion.<br>Give 25%dextrose 100ml and check CBG in 15 minutes | Stop infusion.<br>Give 25%dextrose 100ml and check CBG in 15 minutes |
| 70-110                | Stop infusion and check CBG in 30 minutes                                                      | Stop infusion and check CBG in 30 minutes                            | Stop infusion and check CBG in 30 minutes                            |
| 110-149               | 1.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 150-199               | 2.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 200-249               | 2.5 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 250-299               | 3.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 300-349               | 3.5 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 350-399               | 4.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 400-449               | 4.5 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 450-499               | 5.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 500-549               | 5.5 unit/hr                                                                                    | +1                                                                   | +2                                                                   |
| 550-599               | 6.0 unit/hr                                                                                    | +1                                                                   | +2                                                                   |

The starting insulin infusion rate is arrived at by dividing the capillary glucose value (mg/dL) by 100 and rounding it off to the nearest decimal. If glucose levels are above the target for >6 h, shift to scale 2/3 but first ensure that the cannula is patent, the infusion pump is working appropriately and ensure that the infusion is running at the correct rate. If any glucose level <70 mg/dL and/or persistently <140 mg/dL, shift to a lower scale.

#### Transition to basal-bolus insulin regimen:

Once the acute illness has resolved insulin requirements are stabilized, and the patient is started on oral nutrition, a transition to a fixed insulin regimen should be done. Previous studies highlight the supremacy of basal-bolus regimens over sliding scale regimens. As far as the choice of

bolus insulins is concerned, rapid-acting analogues are preferred over regular insulin owing to the lesser risk of hypoglycemia. Similarly, basal analogues are preferred over NPH insulin for long-acting preparations. In patients who are parenterally fed, the same strategy can be used. Alternatively, short-acting insulin can be added to parenteral feeding, which has the advantage of avoiding insulin administration when parenteral feeding is stopped.

#### Management of hyperglycemia in ICU at SKIMS:

We follow the American Diabetes Association (ADA) guidelines<sup>22</sup> and Joint British Diabetes Society (JBDS) for Inpatient Care guidelines<sup>24</sup> for the management of hyperglycemia at SKIMS, Soura, Srinagar; which have been summarized in Table 3.

**Table 3:** Management of Hyperglycemia in ICU in SKIMS, Soura, Srinagar:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li><b>Tests to assess patient's glycemic status admitted to ICU:</b> <ol style="list-style-type: none"> <li>Point of care (POC) blood glucose assessment on admission in ICU using a glucometer to assess rapidly the glycemic status of the patient, accompanied by laboratory assessment of blood glucose.</li> <li>Performing HbA1c levels in all patients with diabetes or hyperglycemia (random blood glucose &gt;140 mg/dl) admitted to the hospital if no A1C test is available from the prior three months, with an admission A1C value =6.5% suggesting pre-hospitalization onset.</li> </ol> </li> </ul> |
| <ul style="list-style-type: none"> <li><b>Blood glucose levels should be used to initiate glucose lowering therapy:</b> <ol style="list-style-type: none"> <li>Insulin and/or therapies should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of =180 mg/dl (confirmed on two consecutive blood glucose monitoring).</li> </ol> </li> </ul>                                                                                                                                                                                                                                                             |

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• <b>Class of glucose lowering drugs to be used in an ICU setting:</b> <ol style="list-style-type: none"> <li>1. In a resource -constrained setup, we recommend the use of human regular insulin preferably as continuous insulin infusion to achieve the optimal target value.<br/>Avoid use of longer-acting insulin preparations during early phases of critical illness to minimize the risk of developing hypoglycemia.</li> <li>2. Sodium glucose transporters 2 inhibitor (SGLT2i) can be initiated, continued during hospitalization and upon discharge in patient with heart failure if there are no other contraindications and after recovery from acute illness.<br/>SGLT2i should be avoided in cases of severe illness, in patients with ketonemia and ketonuria, and during prolonged fasting and surgical procedures.</li> <li>3. Avoid metformin in a critically ill patient.</li> <li>4. Other classes of oral anti-diabetic drugs such as thiazolidinedione, dipeptidyl peptidase 4 inhibitors (DPP4i), sulfonylureas, meglitinides and GLP -1 analogues should not be used and stopped if patient is already on this drug during acute illness due to lack of evidence for their use in acute illness</li> </ol> </li> </ul> |
| <ul style="list-style-type: none"> <li>• <b>Initiation of insulin therapy:</b> <ol style="list-style-type: none"> <li>1. In a resource- constrained set up like ours, we recommend diluting 50 units of regular human insulin (RHI) in 50 ml of normal saline and infusing intravenously via infusion pump at 0.1 unit/kg/hour. This dilution is not based on any guideline but for ease of assessment and communication among medical personnel.</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• <b>Monitoring response to insulin infusion:</b> <ol style="list-style-type: none"> <li>1. We recommend monitoring blood glucose one hourly with POC measurement till the blood glucose levels are stabilized, then reducing the frequency to every 2 hours. Up-titrate or down-titrate insulin infusion by two units if blood glucose readings are out of target range.</li> <li>2. Serum potassium concentrations should be monitored every 12 hours and maintained between 3.5-5.5 mEq/L. (Potassium Infusion rates as per Serum potassium levels: K&lt;3.5 mEq/L -40 mEq in each 500 mL of NS; K between 3.5-5.5 mEq/L – 20 mEq in each 500 mL of NS; K&gt;5.5 – No correction).</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• <b>Target of glycemic goal:</b> <ol style="list-style-type: none"> <li>1. Glycemic goal of 140 -180 mg/dl is recommended in accordance with most of the standard guidelines, with relaxed goals up to 250 mg/dl in selected populations (terminally ill with short life expectancy, advanced kidney failure, high risk for hypoglycemia and/or labile glycemic excursions).</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <ul style="list-style-type: none"> <li>• <b>Transition to subcutaneous insulin:</b> <ol style="list-style-type: none"> <li>1. Patient should be kept on insulin infusion as long as needed and should be converted to oral insulin only when following have been achieved: <ul style="list-style-type: none"> <li>✓ Absence of hemodynamic instability or need for mechanical ventilation</li> <li>✓ Absence of acidosis</li> <li>✓ Stable and within target blood glucose profile</li> <li>✓ Predictable oral intake</li> <li>✓ Absence of vomiting or ileus.</li> </ul> </li> <li>2. Subcutaneous basal insulin should be given 2 hours before discontinuing intravenous infusion, with the aim of minimizing rebound hyperglycemia. For transitioning, the total daily dose of subcutaneous insulin can be calculated based on the insulin infusion rate during the prior 6 -8 hours of stable glycemic goals or based on prior home insulin dose or following a weight based approach.</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>• <b>Addressing hyperglycemia associated with parenteral nutrition:</b> <ol style="list-style-type: none"> <li>1. For individuals receiving peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if &gt; 20 units of correctional insulin have been required in the past 24 hours. A starting dose of 1 unit of regular human insulin for every 10 gm of dextrose has been recommended. Adding insulin to the parenteral solution is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted.</li> <li>2. Correctional insulin doses should be administered subcutaneously to address any hyperglycemia above 180 mg/dl.</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• <b>Change in regimen for patients on glucocorticoids:</b> <ol style="list-style-type: none"> <li>1. For patients on intermediate acting glucocorticoids (e.g. Prednisone which reaches peak plasma levels at 46 hours) administering NPH insulin (peaks about 4 -6 hour after administration) is a standard approach. Patients on multiple subcutaneous insulin injection (MSII) may require a morning dose of NPH insulin along with glucocorticoids to address morning hyperglycemia.</li> <li>2. For long-acting glucocorticoids such as dexamethasone and multi -dose or continuous glucocorticoid use, twice basal insulin with higher doses of prandial insulin will be required.</li> </ol> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Daily patient clinical status, including the changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g. glucocorticoids), must be incorporated into day-to-day decisions.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

## CONCLUSION

Hyperglycemia encountered in hospital settings can stem from either known or previously undiagnosed diabetes, or it may be a result of hospital-related factors. Extensive evidence indicates a strong association between hyperglycemia in critically ill patients, regardless of their diabetes status, and adverse outcomes. Therefore, it is crucial to identify and manage hyperglycemia in hospitalized patients to mitigate the risk of poor outcomes. This can be accomplished by achieving optimal glycemic control through the use of suitable insulin therapy. With numerous basal and bolus insulin options available, selecting the appropriate insulin with characteristics such as reduced glycemic variability, improved glycemic control, flexible dosing, and lower risk of hypoglycemia can lead to better clinical outcomes. Additionally, evaluating nutritional needs and selecting an appropriate insulin regimen are integral aspects of effective management.

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