Consensus Recommendations for the Management of Hyperglycaemia in Critically Ill Patients in the Indian Setting

JJ Mukherjee*, PS Chatterjee**, M Saikia***, A Muruganathan****, Ashok Kumar Das*****

Abstract

Hyperglycaemia occurs frequently in critically-ill patients. Not only does it occur among patients with pre-existing diabetes mellitus but elevated blood glucose values during an acute illness can also be seen in previously glucose-tolerant individuals (stress hyperglycaemia). Numerous observational studies have shown an increase in morbidity and mortality in critically ill patients with hyperglycaemia. Interestingly, outcomes in individuals with stress hyperglycaemia are worse than that in critically ill hyperglycaemic patients with pre-existing diabetes. Proper management of hyperglycaemia has been shown to result in improved clinical outcomes. Critically ill patients with hyperglycaemia should primarily be managed with intravenous insulin infusion to allow dynamic adjustment of treatment to suit the rapid changes in blood glucose values in these patients. Currently, there are in existence a fair number of published protocols to administer intensive intravenous insulin therapy that range from the relatively simple to the fairly complex. Different management strategies have been proposed depending upon whether the critically ill hyperglycaemic patient is stationed in the emergency department, the medical intensive care unit (ICU), the surgical ICU or the coronary care unit. Moreover, the ideal target blood glucose value to maintain in this group of patients remains controversial. Keeping these issues in mind, a group of leading experts in the fields of diabetes and critical care extensively reviewed the literature and framed recommendations with special attention to clinical practice in India. The aim was to formulate recommendations which are based on sound evidence and yet are simple and easy to understand and implement across the ICU throughout the country. In the current recommendations, intensive intravenous insulin therapy has been suggested as the preferred mode of managing hyperglycaemia in patients admitted to critical care settings. The current recommendations suggest using a simple and similar protocol for managing hyperglycaemia in critically-ill patients irrespective of their location among the various critical care units in a hospital. Recommendations have also been made for transition from intravenous to subcutaneous administration of insulin when the patient is transferred out of the critical care setting. It is hoped that the current recommendations shall form the basis for the management of hyperglycaemia in critically ill patients across the country.

Definition of Hyperglycaemia in Critically Ill Patients

Hyperglycaemia occurs frequently in critically ill patients, including in patients with previously known or unrecognised type 1 or type 2 diabetes mellitus, or in those with normoglycaemia (stress hyperglycaemia). Stress hyperglycaemia refers to a transient increase in blood glucose concentration during acute illness in patients with no previous history of diabetes. Several studies in critically ill patients have demonstrated a positive correlation between stress hyperglycaemia and poor clinical outcomes, such as longer hospital stay and increased morbidity and mortality. There is no universally accepted definition for stress hyperglycaemia. For decades, clinical guidelines have recommended to perform an oral glucose tolerance test (OGTT) in all patients to diagnose stress hyperglycaemia. American Diabetes Association (ADA) defined stress hyperglycaemia as an elevation of fasting glucose ≥ 126 mg/dL or 2-hour postprandial glucose ≥ 200 mg/dL in a patient without evidence of previous diabetes. Glycosylated haemoglobin (HbA1c) value has been recommended to distinguish between patients with stress hyperglycaemia and those with previously undiagnosed diabetes. An HbA1c value ≥ 6.5% indicates pre-existing unrecognized diabetes, whereas HbA1c value < 6.5% indicates stress-induced hyperglycaemia. However, the use of HbA1c measurement for diagnosis of hyperglycaemia in critically ill patients is limited due to its unavailability and its relative variability in the presence of haemoglobinopathies, haemodialysis, blood transfusions and iron deficiency anaemia.

Prevalence of Stress Hyperglycaemia/Known Diabetes/Unrecognized Diabetes

The exact prevalence of stress hyperglycaemia in critically ill patients is difficult to estimate because of wide variations in the study populations and definitions used in various reports. A recent review by Deane and Horowitz reported that an approximate 30-40% patients admitted to critical care units suffer from hyperglycaemia, of whom, 10-15% have previously undiagnosed diabetes. In the Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, at least one blood glucose measurement > 180 mg/dL was recorded in 60% of patients without a prior history of diabetes; however, HbA1c was not estimated in this study, and as such, the number of patients with unrecognised diabetes remains unclear.
It is estimated that 15-20% of all adult admissions to intensive care units (ICUs) comprise of patients with known diabetes. There is suboptimal glycaemic control prior to the onset of acute illness in a majority of such patients as reported in a retrospective study that found an HbA1c value < 6% in only < 20% of known diabetic patients. Gornik et al. assessed the prevalence of diabetes 4-6 weeks after discharge of patients from ICU who had hyperglycaemia during hospitalisation and reported that unrecognised type 2 diabetes was evident in approximately 17% of these patients.

A study of elderly patients hospitalised with heart failure in the United States demonstrated hyperglycaemia in 41% of critically ill patients with acute coronary syndromes (ACS), and 44% with heart failure. In a retrospective review of 614 consecutive patients who underwent cardiothoracic surgery, hyperglycaemia was seen in 80% of patients after cardiac surgery. A recent study from the Middle East found stress hyperglycaemia in 9.8% and unrecognised diabetes in 21.1% of patients who were admitted with ACS with no prior diagnosis of diabetes.

These studies demonstrate that hyperglycaemia is common and should be appropriately managed in critically ill patients.

Pathogenesis of Stress Hyperglycaemia and Reasons for Worsening of Hyperglycaemia in the Critically Ill Diabetic Patient

The pathophysiology of stress hyperglycaemia is not completely understood. The current understanding suggests the role of metabolic and hormonal changes associated with the body's response to injury and stress (Figure 1). Several conditions, such as surgery, trauma and acute illness increase the circulatory level of counter-regulatory hormones and pro-inflammatory cytokines, which alter the effect of insulin on hepatic glucose production and skeletal muscle. Increased counter-regulatory hormones (glucagon, cortisol, catecholamines and growth hormone) contribute to alterations in glucose metabolism, including raised hepatic glucose production and impaired peripheral glucose utilisation. Catecholamines inhibit insulin release by pancreatic beta cells and promote glucagon secretion, and cortisol increases hepatic glucose production and stimulates protein catabolism.

Elevated pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 and interleukin-6 not only increase insulin resistance by interfering with insulin signalling but also increase hepatic glucose production through gluconeogenesis by elevating plasma glucagon levels. TNF-α modifies the signalling properties of insulin receptor substrate, resulting in increased insulin resistance in both liver and skeletal muscle. Thus dysregulation of glucose metabolism in a critically ill patient with no prior history of diabetes is a result of a highly complex interplay of counter-regulatory hormones and cytokines precipitated due to the acute stress faced by the patient.

While stress hyperglycaemia is an important complication in critically ill patients, the magnitude of deterioration in glucose control is frequently greater in critically ill patients with known diabetes. In patients with type 2 diabetes, the pathophysiology of worsening hyperglycaemia involves a combination of insulin resistance and beta cell secretory defects. The stress of critical illness introduces acute glycaemic dysregulation in patients who are already hyperglycaemic due to their chronic diabetes condition. The activation of counter regulatory hormones can cause much greater imbalance in glucose metabolism in diabetic patients due to a poor compensatory response. In otherwise stable patients with diabetes, the infusion of counter-regulatory hormones like cortisol and epinephrine at doses similar to stress conditions resulted in five- to seven-fold increase in plasma glucose levels when compared to non-diabetics (P < 0.001).

Impact of Hyperglycaemia on Critically Ill Patients

Patients with stress hyperglycaemia with no previous history of diabetes have worse clinical outcome compared to those with pre-existing diabetes with a comparable degree of hyperglycaemia. The impact of hyperglycaemia on clinical outcomes depends upon a number of factors including the intensity of hyperglycaemic response, the underlying diagnosis, and the prevalent risk of infection.

A retrospective study in a community teaching hospital reported that patients with stress hyperglycaemia had a higher mortality rate and longer hospital stay compared to those with known diabetes and those with normoglycaemia. In another study, a significant association between hyperglycaemia and adjusted mortality was demonstrated; the mortality risk was significantly higher at each quartile range of blood glucose for patients without a history of diabetes.

In a study of critically ill patients admitted to the surgical ward, medical and trauma ICU, the investigators implemented a moderately tight glycaemic control protocol (target blood glucose < 124 mg/dL) and compared outcomes in hyperglycaemic patients with known diabetes and those without known diabetes; although a reduction in mortality was observed in patients without known diabetes, the...
**Table 1**: Summary of clinical trials evaluating glycaemic control in critical care settings

<table>
<thead>
<tr>
<th>Trial, author</th>
<th>Study population, N</th>
<th>Design</th>
<th>Intervention (N, target BG [mg/dL])</th>
<th>Glucose level at endpoint, mg/dL (Mean ± SD)</th>
<th>Mortality (IIT vs. CG)</th>
<th>P-value</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Leuven 1, Van den Berghe et al. 2001</strong>&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Surgical ICU patients on mechanical ventilation, N = 1548</td>
<td>Prospective randomised controlled</td>
<td>IIT group (n=765, BG: 80-110) vs. conventional (n=783, BG: 180-200)</td>
<td>Daily 103 ± 19</td>
<td>ICU mortality: (4.6% vs. 8.0%); In-hospital mortality (7.2% vs. 10.9%); P &lt; 0.01</td>
<td>Single centre, high use of parenteral dextrose (in TPN)</td>
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<td><strong>Leuven 2, Van den Berghe et al. 2006</strong>&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Medical ICU, N = 767</td>
<td>Prospective randomised controlled</td>
<td>IIT group (n=386, BG: 80-110) vs. CG (n=381, BG: 180-200)</td>
<td>Daily 108 ± 26</td>
<td>ICU mortality: P &lt; 0.04 (adjusted); Hospital mortality: P = 0.01</td>
<td>Single-centre, high use of parenteral dextrose (in TPN)</td>
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<tr>
<td><strong>VISEP, Brunkhorst et al. 2008</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Patients with sepsis, N = 537</td>
<td>Multi centre, randomised open-label</td>
<td>IIT group (n=247, BG: 80-110) vs. CG (n=290, BG: 180-200)</td>
<td>130 (IQR 108-167)</td>
<td>28-day mortality: (24.7% vs. 26.0%); 90-day mortality: (39.7% vs. 35.4%); P = 0.05</td>
<td>IIT group did not achieve target; stopped study early for hypoglycaemia risk; underpowered</td>
<td></td>
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<td><strong>NICE-SUGAR, The NICE-SUGAR Investigators 2009</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Medical-surgical ICU patients, N = 6104</td>
<td>Parallel-group, randomised, controlled, computerised treatment algorithm</td>
<td>IIT group (n=3034, BG: 81-108) vs. CG (n=3050, BG: 144-180)</td>
<td>115 ± 18</td>
<td>90-day mortality: (27.5% vs. 24.9%); P = 0.02</td>
<td>IIT group did not achieve target</td>
<td></td>
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<td><strong>GLUCONTROL, Preiser et al. 2009</strong>&lt;sup&gt;47,48,49&lt;/sup&gt;</td>
<td>Medical-surgical ICU patients, N = 1101</td>
<td>Prospective randomised multicentre controlled</td>
<td>IIT group (n=556, BG: 80-110) vs. CG (n=542, BG: 140-180)</td>
<td>144±23 (P &lt; 0.001)</td>
<td>ICU mortality: (17.2% vs. 15.3%); In-hospital mortality: (23.3% vs. 19.4%); 28-day mortality: (18.7% vs. 15.3%); P &lt; 0.001</td>
<td>Stopped study early for hypoglycaemia; many protocol violations</td>
<td></td>
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<tr>
<td><strong>DIGAMI 1, Malmberg et al. 1995</strong>&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Diabetic patients with suspected AMI, N = 620</td>
<td>Multicentre, randomised</td>
<td>Group 1: GI infusion followed by multi dose SC insulin (n = 306, BG: 126-198) vs. group 2: usual care** (n = 314, BG: not specified)</td>
<td>172.8 ± 59.4&lt;sup&gt;**&lt;/sup&gt;</td>
<td>Infusion group vs. CG (18.6% vs. 26.1%); P = 0.027</td>
<td>Administration of additional insulin dose to control group patients; small sample size</td>
<td></td>
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<tr>
<td><strong>DIGAMI 2, Malmberg et al. 2005</strong>&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Diabetic patients with suspected AMI, N = 1253</td>
<td>Multicentre, prospective randomised, open label</td>
<td>Group 1: 163.8 ± 54.0&lt;sup&gt;<strong>&lt;/sup&gt; Group 2: 163.8 ± 50.4&lt;sup&gt;</strong>&lt;/sup&gt;</td>
<td>Group 3: 180 ± 64.8&lt;sup&gt;**&lt;/sup&gt; (P = 0.0001)</td>
<td>Group 1 (23.4%); Group 2 (22.6%); Group 3 (19.3%); Group 1 and 2: P = 0.831; Group 2 and 3: P = 0.203</td>
<td>Patients in study group 1 did not reach the protocol-outlined glucose levels</td>
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</table>

*Median blood glucose level; ″Routine metabolic management according to local practice; ″Blood glucose values during first 24 hours; ″Blood glucose after 24 hours; Abbreviations: ICU: intensive care unit; IIT: intensive insulin therapy; BG: blood glucose; CG: conventional group; GI: glucose-insulin; TPN: total parenteral nutrition; VISEP: Volume Substitution and Insulin Therapy in Severe Sepsis; IQR: interquartile range; NICE-SUGAR: Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation; DIGAMI: Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction; AMI: acute myocardial infarction; GI: glucose-infusion; SC: subcutaneous injection*
threshold mean glucose concentration for increase in mortality was lower in patients with no known history of diabetes (140.4 mg/dL) compared to those with known diabetes (180 mg/dL).36

Non-diabetic patients who had stress hyperglycaemia on admission were found to have a 3.9-fold higher risk of death after myocardial infarction when compared to normoglycaemic non-diabetic patients.37 Similarly, another meta-analysis, which reviewed mortality and functional recovery after stroke in hyperglycaemic patients with or without known diabetes reported an increased risk of in-hospital mortality after stroke in hyperglycaemic patients with no known diabetes as compared to those with diabetes [relative risk = 3.07 (95% CI, 2.50 to 3.79) vs. 1.30 (95% CI, 0.49 to 3.43)]. Moreover, stroke survivors with admission glucose level >121 to 144 mg/dL and no known history of diabetes had a greater risk of poor functional recovery.38

In all these studies, worse clinical outcomes with lower functional status have been demonstrated in patients with stress hyperglycaemia when compared to patients with long standing diabetes. The underlying mechanism(s) behind this discrepancy remains unclear and needs further attention.

Stress hyperglycaemia is characterised by an increase in non-insulin-mediated glucose uptake via glucose transporters (GLUT-1 and GLUT-3) and a decrease in insulin-mediated glucose uptake via GLUT-4.1 Evidence suggests that chronic hyperglycaemia, as observed in patients with long-standing diabetes, induces protective cellular conditioning by down-regulating the expression of glucose transporters, which protects the cells from excess glucose ingress. On the other hand, in patients with stress-induced hyperglycaemia, up-regulation of these transporters allows excess glucose ingress into the cells, which in turn causes higher glucose toxicity and possible cell damage.1,39,49

### Controlling Hyperglycaemia Improves Outcomes in Critically Ill Patients—What Targets to Achieve?

In one of the earliest studies on the effect of glycaemic control on clinical outcomes in critically ill patients, namely the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 1 study (DIGAMI 1), three hundred and six patients admitted to coronary care units (CCU) were randomised to insulin-glucose infusion for 24 hours followed by multiple daily subcutaneous insulin injections for ≥3 months and three hundred and fourteen patients were randomised to conventional therapy that consisted of insulin therapy if clinically indicated. During the first 24 hours, there was a statistically significant greater reduction in the mean blood glucose values in the insulin-glucose infusion group (277.2 ± 73.8 to 172.8 ± 59.4 mg/dL) as compared to the group treated conventionally (282.6 ± 75.6 to 210.6 ± 73.8 mg/dL, P < 0.0001). This was reflected in a significantly lower overall mortality in the intensively treated group than the control group at the end of 1 year (18.6% vs. 26.1%; P = 0.027).41 However, as the DIGAMI 1 study included out-patient insulin therapy, it was not possible to assess the effect of isolated in-patient intravenous insulin therapy in critically ill patients. Subsequent studies undertaken in the CCU setting, have failed to show the benefit of intensive intravenous insulin treatment on clinical outcomes.

In the DIGAMI-2 study, four hundred and seventy-four patients with type 2 diabetes and acute myocardial infarction (MI) were randomised to receive insulin-glucose infusion/out-patient intensive subcutaneous insulin-therapy (group 1), four hundred and seventy-three were randomised to receive insulin-glucose infusion/out-patient standard glucose treatment (group 2), and three hundred and six patients were randomised to in-patient and out-patient standard glucose management (group 3). Contrary to expectations, the mortality rates were similar in all three groups. However, there were a number of drawbacks in DIGAMI 2 study, including low event rates and lack of statistical power due to poor recruitment (Table 1).42

In the Hyperglycaemia Intensive Insulin Infusion in Infarction (HI-5) study, which included 240 patients with acute MI and known diabetes or admission blood glucose value greater than 140 mg/dL, there was no difference in mortality at 3 and 6 months between groups treated with insulin/dextrose infusion for at least 24 hours and those treated conventionally.43 However, this study too had a few drawbacks including lack of blinding, insufficient sample size and maintenance of glycaemic control for only 24 hours.

Prior to 2001, little attention was paid to the management of hyperglycaemia in the medical or surgical ICUs because of lack of evidence of beneficial effect of tight glucose control in the critical care setting. The publication of Van den Berghe’s landmark study in 2001 highlighted the importance of tight glucose control in ICU settings. It was a prospective, randomised, controlled, single-centre study that examined the effect of tight glycaemic control (target blood glucose 80-110 mg/dL) with the use of exogenous intravenous insulin infusion on clinical outcomes in 1548 critically ill patients, most of whom had undergone cardiac surgery.44 Seven hundred and sixty five adult patients admitted to surgical ICU (SICU) and receiving mechanical ventilation were randomised to receive intensive insulin therapy and seven hundred and eighty three patients were offered standard care (target blood glucose, 180-200 mg/dL). Patients in the intensive insulin treatment group achieved a mean blood glucose value of 103 mg/dL vs 153 mg/dL in the patients in the conventional group (P < 0.001). Strict glycaemic control using intensive insulin therapy reduced ICU mortality (absolute reduction of mortality rate: 3.4%, P < 0.04) and in-hospital mortality (absolute reduction of mortality rate: 3.7%, P = 0.01) when compared to standard therapy. Intensive therapy also reduced blood stream infections, acute renal failure requiring dialysis or haemofiltration, median number of red-cell transfusions, and critical-illness polyneuropathy.44

The subsequent single-centre study from the same group, the 2006 Leuven-study, using a similar study design, was performed in seven hundred and sixty-seven patients admitted to medical ICU (MICU) for at least 5 days.45 A higher reduction in blood glucose was observed in the intensively treated group (163 ± 67 to 108 ± 26 mg/dL) when compared to those receiving standard care (164 ± 68 to 156 ± 25 mg/dL, P < 0.001). However, in contrast to the first study performed in the surgical ICU, there was no significant decrease in overall in-hospital mortality in the patients treated intensively when compared to those receiving standard care. However, there was reduction in morbidity similar to that seen in the surgical study, including accelerated weaning from mechanical ventilation, less renal injury, and shorter ICU and hospital stays. Moreover, among those patients remaining in ICU for 3 or more days, intensive insulin therapy was associated with a reduction in ICU mortality (absolute reduction of mortality rate: 6.8%, P = 0.05) and in hospital mortality (absolute reduction of mortality rate: 9.5%, P = 0.009) when compared to those in the standard care group (Table 1).

Several subsequent randomised controlled trials (RCTs)
further explored the relationship between tight glycaemic control (target blood glucose, 80-110 mg/dL) or conventional therapy and outcomes in critically ill patients, \(^{14,46-49}\) and failed to replicate the remarkable benefits in morbidity and mortality as seen in the 2001 Leuven-SICU study.

The NICE-SUGAR study is the largest, multicentre, multinational, parallel-group, randomised, controlled trial till date on six thousand one hundred and four critically ill adult patients admitted to medical-surgical ICU, the majority (> 95%) of whom required mechanical ventilation. The study was designed to test the effect of tight glycaemic control (target blood glucose, 81-108 mg/dL) on clinical outcomes.\(^{14}\) Contrary to the 2001 Leuven-SICU study, the patients in the intensive glycaemic control (81-108 mg/dL) group in the NICE-SUGAR study had a significantly increased mortality at 90 days compared to the conventional therapy (144-180 mg/dL) group (27.5% vs. 24.9%, \(P = 0.02\)).\(^{14}\) Severe hypoglycaemia was also more common in the intensively treated group (6.8% vs. 0.5%, \(P < 0.001\)) (Table 1).

The GLUCONTROL study\(^ {44}\) was a prospective, randomized, multicentre trial that compared the effects of two glucose control regimens in medical-surgical ICU patients. In this study, one thousand one hundred and four critically ill adult patients were stratified to receive either intensive insulin therapy (target blood glucose, 80-110) or conventional therapy (target blood glucose 140-180 mg/dL). In the study, the ICU mortality (17.2% vs. 15.3%, \(P = 0.41\)) and in-hospital mortality (23.3% vs. 19.4%, \(P = 0.11\)) were higher in the intensively treated group when compared to the conventional group, although this difference was not statistically significant. However, the study was prematurely terminated due to a high rate of unintended protocol violations and an unacceptably high incidence of hypoglycaemia in intensively treated group (8.7% vs. 2.7%, \(P < 0.001\)).\(^ {44,50}\)

The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was a multicentre, randomised study that examined the effects of intensive insulin therapy in patients with septic shock or severe sepsis.\(^ {47}\) In this study, two hundred forty seven patients were randomised to intensive insulin therapy (target blood glucose, 80-110 mg/dL) and two hundred and ninety patients were randomised to conventional therapy (target blood glucose 180-200 mg/dL). Results of the study indicated a significantly higher rates of severe hypoglycaemia (17.0% vs. 4.1%, \(P < 0.001\)), and serious adverse events (10.9% vs. 5.2%, \(P = 0.01\)) in the intensive group compared to conventional group (Table 1).\(^ {47}\)

In summary, although the 2001 Leuven-SICU study reported a significant reduction in morbidity and mortality with tight glycaemic control (80-110 mg/dL) in comparison to standard therapy in SICU patients,\(^ {44}\) several subsequent studies\(^ {14,46,47,49}\) failed to replicate these benefits. Rather, the largest study to date, the NICE-SUGAR study showed that targeting a blood glucose value of 80-110 mg/dL increased mortality and was associated with significantly higher rates of hypoglycaemia.

The reasons for the disparity in the results between the 2001 Leuven-SICU study\(^ {44}\) and the other landmark studies remain unclear but may be related to several methodological differences. Large doses of parenteral glucose (200-300 gm per 24 hours) was given to the patients in 2001 Leuven-SICU study, whereas enteral feeding is generally the norm in critically ill patients in most ICUs, and was used in most of the other studies. Moreover, there was a higher than expected mortality in the conventionally treated group in the 2001 Leuven-SICU study which might have been due to administration of insulin only when blood glucose values exceeded 215 mg/dL as against blood glucose targets of < 180 mg/dL in NICE-SUGAR and GLUCONTROL studies. Also, the 2001 Leuven-SICU study was a single-centre study with patients predominantly from the surgical ICU, whereas the other studies (NICE-SUGAR, GLUCONTROL and VISEP studies) included patients from both medical and surgical ICUs from multiple centres.

Thus, the optimal blood glucose target for safe and effective hyperglycaemia management in critically ill patients remains unclear till date. However, this does not mean that one should not attempt to control hyperglycaemia in the critically ill patients. There is no doubt that uncontrolled hyperglycaemia is associated with poor outcomes. It would appear that it is prudent to control hyperglycaemia in critically ill patients while aiming for targets less stringent than 80-110 mg/dL in the majority of patients.

**Intravenous vs. Subcutaneous Administration of Insulin in the Management of Hyperglycaemia in Critically Ill Patients**

In critically ill patients, the prime goal of hyperglycaemia management is to achieve optimal efficacy with maximum safety. A number of variables, including inconsistent and variable calorie intake, limitations regarding the timing of glucose monitoring and insulin administration, the effect of associated co-morbid medical and surgical conditions predisposing to hypo- and hyperglycaemia, and the use of various medications having an adverse effect on blood glucose values including steroids and various vasopressor agents, make safe management of hyperglycaemia in critically ill patients a difficult proposition.\(^ {51}\) As such, in critically ill patients, insulin remains the mainstay of treatment for the management of hyperglycaemia, and oral hypoglycaemic agents do not have a role to play.\(^ {21}\)

The expert panel deliberated the route of insulin administration in critically ill patients in the Indian context at length keeping in mind the resource challenges faced by many of the ICUs in our country. After considerable discussions, the panel decided upon intravenous administration of insulin for the management of hyperglycaemia in critically ill patients as opposed to subcutaneous administration of insulin. Subcutaneous administration of insulin has not been formally studied in critically ill patients with hyperglycaemia. Subcutaneous administration of insulin is best avoided in critical care settings because of its unreliable absorption and unpredictable effects, especially in patients with peripheral oedema, hypotension, or shock.\(^ {52-54}\) Moreover, repeated administration of insulin in the subcutaneous space may result in “stacking” of insulin effect, resulting in delayed hypoglycaemia.\(^ {52,55}\) On the other hand, intravenous administration of insulin results in rapid onset of action, allows quicker dosage adjustments, has a better safety profile, and predictable glucose-lowering effect.\(^ {53,56}\)

A prospective, non-randomised, study performed in patients undergoing coronary artery bypass grafting demonstrated that intravenous administration of insulin reduced deep sternal wound infections and risk-adjusted mortality compared to patients treated with subcutaneous insulin.\(^ {22}\) Intravenous insulin should be continued during the critical care period when patients are unstable.\(^ {19}\) One should shift to subcutaneous administration of insulin when the patient is more stable and has started to accept calories orally.\(^ {58}\)
Existing Protocols for Administering IV Insulin in the Management of Hyperglycaemia in Critically Ill Patients

An ideal intravenous insulin protocol should control hyperglycaemia in a reasonable timeframe with minimal hypoglycaemic events, low operator error rate, and minimal nursing time required. A large number of protocols currently exist for administering intravenous insulin for the management of hyperglycaemia in the critically ill patient, which range from simple to very complex. In a systematic review, Wilson et al. identified twelve different intravenous insulin protocols for the management of hyperglycaemia in critically ill patients from different institutions, and reviewed them with respect to target goals, autonomy, steps for initiation and titration of insulin, and methods of adjustment (Table 2). They concluded that despite the extensive use of various intravenous insulin protocols, there is no uniformity of practice in this regard. They also found a wide variability in patterns of insulin administration and stated that it was difficult to recommend any one particular protocol over the another.

More recently, computer-based algorithms have also become available to direct nursing staff to adjust insulin infusion rates. Newton et al. reported that a computer-guided algorithm results in tighter glycaemic control in medical ICU patients compared to standard paper protocol. However, these protocols implemented a variety of insulin delivery strategies and complex set of instructions that could be confusing for the nursing staff and junior doctors. Computer-based algorithms and/or complex protocols require high degree of expertise and clinical decision-making to adjust the rate of insulin infusion, and substantially increase the cost of care. Barring a few well equipped ICUs in urban tertiary care hospitals, most other ICUs in the Indian context are challenged with poor nurse-to-patient ratio, poor availability of sophisticated equipment, and lack of expertise among the nursing staff.

### Table 2: Comparison of insulin infusion protocols

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<tbody>
<tr>
<td>Target glucose (mg/dL)</td>
<td>100-150</td>
<td>120-180</td>
<td>90-144</td>
<td>&lt; 180</td>
<td>100-150</td>
<td>100-139</td>
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<td>Bolus insulin</td>
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<td>Dose (units)</td>
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<td>0</td>
<td>0</td>
<td>12</td>
<td>4.5</td>
<td>3</td>
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**Changes in insulin infusion based on changes in glucose**

- **Direction/Velocity/Resistance**
  - Insulin infused with BG > 200 mg/dL: R/U R/U R/U + %
  - Percentage of insulin infused with BG > 200 mg/dL: 41, 90% 143, 53% 42, 66% 52, 39% 59, 57% 26, 81%
  - Basis of changes in insulin rate: R or I/U ± %
  - Time to goal glucose: NR 7.5-10.5 h 9.0 h 11.3 ± 7.9 h NR NR 12-24 h 8.0 h 2.1 h
  - Highest hourly dose (units): 11.0 4.3 15.0 12.3 18.5 9.0 12.0 10.0 18.0 15.0 10.5 21.0
  - Total insulin dose (units): 45.0 26.9 63.5 66.3 78.0 32.0 77.0 44.0 107.0 98.5 49.0 115.0

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1. Protocol permitted a bolus amount at the discretion of the attending physician. For the purpose of this stimulation, no bolus was incorporated into analysis. Y* = variable dose based on physician input; R = rate changes based on the glucose range; I = rate change based on insulin infusion rate; U = changes made in units of insulin; % = changes based on a percentage of the current insulin infusion rate; Multiplier = adjustment of insulin dose using a multiplier incorporated into a formula for calculation. Insulin adjustment: include number of steps and calculations as needed. Time to goal: reported as median values, range, or mean SD. NR, not reported.
Table 3: Titration of insulin dose according to BG levels

<table>
<thead>
<tr>
<th>Blood glucose value (mg/dL)</th>
<th>Dosage of insulin infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 110</td>
<td>No insulin to be given</td>
</tr>
<tr>
<td>110-149</td>
<td>1.0 unit/hour</td>
</tr>
<tr>
<td>150-199</td>
<td>2.0 units/hour</td>
</tr>
<tr>
<td>200-249</td>
<td>2.5 units/hour</td>
</tr>
<tr>
<td>250-299</td>
<td>3.0 units/hour</td>
</tr>
<tr>
<td>300-349</td>
<td>3.5 units/hour</td>
</tr>
<tr>
<td>350-399</td>
<td>4.0 units/hour</td>
</tr>
<tr>
<td>400-449</td>
<td>4.5 units/hour</td>
</tr>
<tr>
<td>450-499</td>
<td>5.0 units/hour</td>
</tr>
<tr>
<td>500-549</td>
<td>5.5 units/hour</td>
</tr>
<tr>
<td>550-599</td>
<td>6.0 units/hour</td>
</tr>
</tbody>
</table>

American College of Physicians (ACP),79 Australian Diabetes Society (ADS),76 Canadian Diabetes Association (CDA),77 Surviving Sepsis Campaign (SSC),78 and American Heart Association (AHA).79 However, due to the complexity of some of these available protocols, confounding biases, and their non-applicability in the Indian scenario, these guidelines cannot be widely recommended for management of hyperglycaemia in critically ill patient in the Indian context. The existing Indian guideline, formulated by API80 is brief, and concentrates critically ill patient in the Indian context. the existing indian applicability in the indian scenario, these guidelines cannot be managed appropriately (Grade A; EL 4).

Methodology

A systematic review of literature was conducted to provide the best possible evidence base for the recommendations. Existing guidelines, meta-analyses, systematic reviews and key cited articles were reviewed by a group of doctors and recommendations relevant to Indian scenario were framed. The recommendations were discussed by a panel of 30 experts including intensivists, endocrinologists and key opinion leaders at the National Insulin Summit, held in August 2013. At this summit, recommendations for each section of the guidelines, and overall recommendations were agreed upon. Where there was little or no evidence, the committee relied on experience, judgement and consensus to make their recommendations. The consensus document was drafted and circulated for further feedback from the participants and others who could not attend.

Grading system

These consensus guidelines have been developed in accordance with the AACE protocol for standardised production of clinical practice guidelines.81 Recommendations are organized by topic and are assigned evidence level (EL) ratings on the basis of the quality of supporting evidence, all of which have also been rated for strength. Recommendations are based on clinical importance and graded as A (strongly recommended), B (intermediate), C (weak) and D (not evidence based), and these are coupled by four intuitive levels of evidence: 1, 2, 3, and 4. They have been positioned on the basis of available evidence to be used for grading recommendations as follows:

• “1”: Meta-analysis of randomised controlled trials
• “2”: Meta-analysis of nonrandomised prospective or case-controlled trials, non-randomised controlled trial, prospective cohort study, retrospective case-control study
• “3”: Cross-sectional study, surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modelling of database), consecutive case series, single case reports
• “4”: No evidence (theory, opinion, consensus, review, or preclinical study)

Glycaemic Targets

Recommendations

• In critically ill patients with hyperglycaemia, it is recommended to aim for a target blood glucose value in the range of 140-180 mg/dL. (Grade A; EL 1).
• In selected critically ill patients with hyperglycaemia, (such as post-CABG and uncomplicated surgical patients), it is recommended to aim for a target blood glucose value in the range of 110-140 mg/dL. (Grade A; EL 3).
• It is recommended to avoid aiming for blood glucose values < 110 mg/dL in critically ill patients with hyperglycaemia (Grade A; EL 4).

Medical Surgical ICU

Initiation of insulin therapy

Recommendations

• It is recommended to start intensive intravenous insulin therapy in critically ill patients when blood glucose value is > 180 mg/dL. (Grade A; EL 1).
• It is recommended to re-check the blood glucose value before starting intensive intravenous insulin therapy in patients with no prior history of diabetes (Grade A; EL 4).
• It is recommended to start intensive intravenous insulin therapy with short-acting regular human insulin, preferably using an infusion pump (Grade A; EL 4).
• It is recommended to start insulin infusion (U/L) by dividing the blood glucose value in (mg/dL) by 100 and rounding it off to the nearest decimal (Grade A; EL 4).
  e.g. If blood glucose value is 237 mg/dL, then start insulin infusion at a rate of 2 units/hour
  e.g. If blood glucose value is 387 mg/dL, then start insulin infusion at a rate of 4 units/hour
• Administration of a bolus insulin dose is not recommended (Grade A; EL 4).
• It is recommended to titrate intravenous insulin dosage according to the prevailing blood glucose value as shown in Table 3 (Grade A; EL 4).

Monitoring

Recommendation

• It is recommended to monitor capillary blood glucose every hour (Grade A; EL 4).
• In selected cases, it is suggested to monitor capillary blood glucose more frequently (Grade A; EL 4).
• If capillary blood glucose does not show an expected declining trend, it is suggested to increase the dose of insulin infusion according to the patient’s response (Grade A; EL 4).
• If blood glucose value is < 70 mg/dL, cessation of insulin infusion should be ensured and hypoglycaemia should be managed appropriately (Grade A; EL 4).
Table 4: Comparison of the current consensus guideline with existing guidelines for management of hyperglycaemia in critically ill patients

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Consensus guideline</th>
<th>AACE-ADA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>API&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ACP&lt;sup&gt;c&lt;/sup&gt;</th>
<th>CDA&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ADS&lt;sup&gt;e&lt;/sup&gt;</th>
<th>SSC&lt;sup&gt;f&lt;/sup&gt;</th>
<th>AHA&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemic target</td>
<td>140-180 mg/dL, &lt; 110 mg/dL is not recommended; 110-140 mg/dL in post-CABG, uncomplicated surgical patients</td>
<td>140-180 mg/dL in patients with medical morbidity and 110-140 mg/dL for patients with surgical morbidity</td>
<td>140-180 mg/dL in patients with medical morbidity and 110-140 mg/dL for patients with surgical morbidity</td>
<td>140-200 mg/dL, (MICU/SICU patients on insulin therapy)</td>
<td>144-180 mg/dL (MICU/SICU patients), intraoperative: 99-180 mg/dL (patients with diabetes undergoing CABG) and perioperative: 90-180 mg/dL (for most other surgical patients)</td>
<td>&lt; 180 mg/dL in patients with hyperglycaemia along with AMI or acute thrombotic stroke</td>
<td>&lt; 180 mg/dL in ICU patients with severe sepsis</td>
<td>90-140 mg/dL</td>
</tr>
<tr>
<td>Initiating insulin therapy</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL; Short-acting regular insulin, preferably with infusion pump; re-check BG before starting IIT in patients without diabetes, start insulin infusion at: BG/100 U/hour</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL</td>
<td>Do not use IIT to strictly control or normalise BG in MICU/SICU patients with or without diabetes</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL. Rest same as consensus</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL. Rest same as consensus</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL. Rest same as consensus</td>
<td>Initiate IIT (continuous IV insulin infusion) when BG level &gt; 180 mg/dL. Rest same as consensus</td>
</tr>
<tr>
<td>Monitoring of blood glucose</td>
<td>Monitor capillary BG every 1 hour; every 20-30 mins till hypoglycaemia resolves, re-start IIT in modified doses as necessary once BG rises</td>
<td>Frequent glucose monitoring in patients with IV insulin therapy, to minimize the risk of hypoglycaemia</td>
<td>Initial monitoring should be done on an hourly basis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transition from IV to SC insulin</td>
<td>Once patient is stable and taking enteral/oral feeds, start transition wherever needed; Start SC insulin therapy at least 1 hour prior to discontinuing IV insulin therapy</td>
<td>Start SC insulin at least 1-2 hours before discontinuing IV insulin or 15-30 min if rapid-acting analogues are used</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


- It is recommended to monitor blood glucose every 20-30 minutes until hypoglycaemia resolves (Grade A; EL 4).
- If blood glucose values start rising, it is recommended to restart intensive intravenous insulin therapy in modified doses as required (Grade A; EL 4).

Coronary Care and Emergency Units Recommendations

In critically ill patients with hyperglycaemia in the coronary care unit with or without an acute coronary event, and in critically ill patients waiting for a critical unit bed in the emergency department, it is recommended to follow the same recommendations as made for the management of...
hyperglycaemia in critically ill patients admitted to the medical/surgical ICU.

Transition from IV to SC Insulin

Recommendations:
- Once the patient is stable and has been started on enteral/oral feeds, transition to SC insulin therapy is recommended, wherever appropriate (Grade A; EL 1).
- It is recommended to start subcutaneous insulin therapy at least 1 hour prior to discontinuing intravenous insulin therapy (Grade A; EL 4).
- In patients transitioning from intravenous insulin, it is recommended to initiate subcutaneous basal-bolus regimen (Grade A; EL 4).
- It is recommended to individualise the dose of insulin in the subcutaneous basal-bolus regimen (Grade A; EL 4).

Summary

Although uncontrolled hyperglycaemia in critically ill patients predisposes them to adverse clinical outcomes, attention towards achieving good glycaemic control continues to remain a neglected part of their management in the critical care units in our country. Administration of intravenous insulin therapy to maintain target blood glucose values, together with close monitoring of glycaemic status, can achieve these goals, safely. The current recommendations for the management of hyperglycaemia in critically ill patients have been developed following extensive review of the existing protocols and guidelines, and have been specifically modified for the critically ill hyperglycaemic patients in the Indian context (Table 4). The simplicity of the recommendations, together with its proposed uniform application for the management of hyperglycaemia in critically ill patients irrespective of their location (medical, surgical or cardiac intensive care units or emergency department) makes it easy to apply and follow.

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References
