GENERAL INTENSIVE CARE UNIT CARE
GLYCEMIC CONTROL IN THE INTENSIVE CARE UNIT

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1. Who is at risk for development of hyperglycemia?
Hyperglycemia can occur in patients with known or undiagnosed diabetes mellitus. Hyperglycemia during acute illness can also occur in patients with previously normal glucose tolerance, a condition called stress hyperglycemia.

2. How common is hyperglycemia in critically ill patients?
Acute hyperglycemia is common in critically ill patients. It is estimated that 90% of all patients develop blood glucose concentrations greater than 110 mg/dL during critical illness. Stress-induced hyperglycemia has been associated with adverse clinical outcomes in patients with trauma, acute myocardial infarction, and subarachnoid hemorrhage.

3. What causes hyperglycemia in critically ill patients?
In healthy individuals, blood glucose concentrations are tightly regulated within a narrow range. The cause of hyperglycemia in critically ill patients is multifactorial. Glucose toxicity and activation of inflammatory cytokines, and counterregulatory hormones such as cortisol and epinephrine cause an increase in peripheral insulin resistance and hepatic glucose production. The use of glucocorticoids and parenteral and enteral nutrition is an important contributor to hyperglycemia.

4. What is the relationship between hyperglycemia and acute illness?
The relationship between hyperglycemia and acute illness is complex. Severe hyperglycemia (>250 mg/dL) has been shown to have a negative impact on the vascular, hemodynamic, and immune systems. Hyperglycemia can also lead to electrolyte imbalance, mitochondrial injury, and both neutrophil and endothelial dysfunction. Acute illness increases the risk for hyperglycemia through the release of counterregulatory hormones, increased insulin resistance, and immobility. Fig. 1.1 illustrates the relationship between acute illness and hyperglycemia.

5. Should oral medications used to treat diabetes be continued in the intensive care unit?
Given the high incidence of renal and hepatic impairment, oral medication to treat diabetes should not be continued in the intensive care unit (ICU). Medications such as metformin are contraindicated in patients with renal and/or hepatic dysfunction and congestive heart failure. Long-acting formulations of sulfonylureas have been associated with episodes of prolonged severe hypoglycemia in hospitalized patients. Oral medications are not easily titrated to meet glycemic targets and may take weeks to effectively lower blood glucose levels.

6. Should noninsulin, injectable medications be used in the intensive care unit?
Noninsulin, injectable medications such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) stimulate insulin release in a glucose dependent manner. These medications have been shown to cause nausea and emesis and slow gastric emptying. GLP-1 RAs have similar limitations as oral agents with regards to titration and should not be used in the ICU setting.

7. What is the most effective way to treat hyperglycemia in the intensive care unit?
An intravenous insulin infusion using regular insulin is the safest and most effective way to treat hyperglycemia in critically ill patients. Because of the short half-life of circulating insulin (minutes), an insulin infusion can be frequently adjusted to match the often-variable insulin requirements of critically ill patients. Intravenous insulin therapy should be administered by validated written or computerized protocols that outline predefined adjustments in the insulin dose based on frequent blood glucose measurements.

8. When should treatment with an intravenous insulin infusion be initiated?
Intravenous insulin therapy should be initiated for the treatment of persistent hyperglycemia starting at a blood glucose concentration of no greater than 180 mg/dL.
9. **What is the appropriate glycemic target for critically ill patients?**

Recognizing the importance of glycemic control in critically ill patients, a number of professional societies have developed treatment guidelines and/or consensus statements that provide evidence-based glycemic targets. Although the glycemic targets are not identical, all of the groups advocate for good glycemic control while avoiding hypoglycemia (Table 1.1).

10. **What is the evidence supporting the current glycemic targets?**

The first randomized controlled trial (RCT) comparing tight glycemic control (target blood glucose concentration of 80–110 mg/dL) with conventional insulin therapy (target blood glucose concentration of 180–200 mg/dL) was conducted by Van den Berghe and colleagues (2001). This single-center trial enrolled more than 1500 surgical ICU patients and showed a 34% reduction in mortality associated with tight glycemic control. However, subsequent studies in both medical and surgical ICU populations have not shown consistent reductions in mortality with tight glycemic control. A meta-analysis of RCTs that included 8432 critically ill adult patients did not show a significant difference in mortality between tight glycemic control and control groups.

11. **What was the normoglycemia in intensive care evaluation–survival using glucose algorithm regulation study?**

The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) was a multicenter, multinational RCT that evaluated the effect of tight glycemic control (target glucose level of 81–108 mg/dL) to conventional glucose control (<180 mg/dL) on a number of clinical outcomes in 6104 critically ill adults, greater than 95% of whom required mechanical ventilation. The 90-day mortality was significantly higher in the tight glycemic control group (78 more deaths; Table 1.1).

### Table 1.1. Summary of Glycemic Targets from the Medical Literature

<table>
<thead>
<tr>
<th>Professional society/consensus statement</th>
<th>Glycemic target for critically ill patients</th>
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<tbody>
<tr>
<td>American Diabetes Association</td>
<td>140–180 mg/dL</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>140–180 mg/dL</td>
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<tr>
<td>Surviving Sepsis Campaign</td>
<td>150–180 mg/dL</td>
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<tr>
<td>American College of Physicians</td>
<td>140–200 mg/dL</td>
</tr>
<tr>
<td>American Thoracic Society</td>
<td>&lt;180 mg/dL (in patients undergoing cardiac surgery)</td>
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27.5% vs. 24.9%; \( P = .02 \). Cardiovascular mortality and severe hypoglycemic events were also more common in the tight glycemic control group. The results of the NICE-SUGAR trial have resulted in a shift from tight glycemic control to good control in critically ill patients, and standard of care is now to target glucose level between 140 and 180 mg/dL.

12. How should patients be transitioned from an intravenous insulin infusion to subcutaneous insulin therapy?
Patients should be transitioned from an insulin infusion to a subcutaneous insulin program when clinically stable. In patients who are eating, once- or twice-daily administration of basal insulin in combination with scheduled mealtime rapid-acting insulin and a supplemental (correction) component has been shown to maintain adequate glycemic control without clinically significant hypoglycemia. Subcutaneous insulin therapy should be initiated at least 2 hours before the discontinuation of the insulin infusion to reduce the risk of hyperglycemia. The use of a sliding-scale insulin regimen as the sole means of treatment of hyperglycemia is ineffective and should be avoided.

13. How is hypoglycemia defined?
Hypoglycemia is defined as any blood glucose level less than 70 mg/dL. This level correlates with the initial release of counterregulatory hormones. Cognitive impairment begins at a blood glucose concentration of approximately 50 mg/dL, and severe hypoglycemia occurs when blood glucose concentrations are less than 40 mg/dL.

14. What is the clinical impact of hypoglycemia?
Hypoglycemia has been associated with mortality, although whether it serves as a marker of illness or a causal agent remains to be established. Patients with diabetes who experience hypoglycemia during hospitalization have longer lengths of stay, higher costs, and greater odds of being discharged to a skilled nursing facility than their counterparts without hypoglycemia. Insulin-induced hypoglycemia and subsequent endothelial injury, abnormal coagulation, and increases in counterregulatory hormones are all associated with increased risk for cardiovascular events and sudden death. The true incidence of inpatient hypoglycemia is underestimated because of a lack of standardized definitions and varying models of data collection and reporting among hospitals. Despite this, iatrogenic hypoglycemia remains a top source of inpatient adverse drug events.

15. How do we prevent severe hypoglycemic events in the intensive care unit?
Critically ill patients are likely not able to report symptoms of hypoglycemia; thus it is important that patients be closely monitored. Early recognition and treatment of mild hypoglycemia can prevent the adverse outcomes associated with severe hypoglycemia. The establishment of a system for documenting the frequency and severity of hypoglycemic events and the implementation of policies that standardize the treatment of hypoglycemia are essential components of an effective glycemic management program.

16. Is intensive treatment of hyperglycemia cost-effective?
Intensive treatment of hyperglycemia not only reduces morbidity and mortality but is also cost-effective. The cost savings have been attributed to reductions in laboratory and radiology costs, decreased ventilator days, and reductions in ICU and hospital length of stay.

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KEY POINTS: GLYCEMIC CONTROL IN THE INTENSIVE CARE UNIT

Management of Hyperglycemia in Critically Ill Patients
1. Hyperglycemia is common in critically ill patients and has been independently associated with increased ICU mortality.
2. Oral medications and noninsulin injectable therapies should not be used to treat hyperglycemia in critically ill patients.
3. An intravenous insulin infusion is the safest and most effective way to treat hyperglycemia in critically ill patients.
4. A glycemic target of 140 to 180 mg/dL is recommended for critically ill patients.
5. Early recognition and treatment of mild hypoglycemia can prevent the adverse outcomes associated with severe hypoglycemia.
BIBLIOGRAPHY


