Stress Hyperglycemia in the ICU

November 2, 2016 by Josh Farkas

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**what is stress hyperglycemia?**

- Stress hyperglycemia refers to elevation of glucose as part of the stress response.
  - Glucose is increased by a variety of factors, including elevated levels of cortisol, glucagon, and epinephrine. These hormones may in turn lead to insulin resistance, further increasing hyperglycemia.
- Stress hyperglycemia in the ICU is partially an iatrogenic phenomenon created by ongoing nutrition in the face of critical illness (without invasive nutritional support, most critically ill patients would be cachexic and unable to eat a substantial quantity of calories).
- Hyperglycemia correlates with greater levels of stress and disease severity. Among nondiabetic patients, hyperglycemia generally correlates with mortality (interestingly, this relationship doesn't seem to exist among patients with diabetes). The reason that hyperglycemia often
correlates with worse outcomes is unclear, with some possibilities including:

- Hyperglycemia is a marker of more severe acute illness.
- Hyperglycemia is a marker of underlying insulin resistance (e.g., metabolic syndrome or diabetes).
- Hyperglycemia itself is actually causing harm.

**What should we do about stress hyperglycemia?**

- This is an **enormously** complex question, which eludes any simple answer.
- Management needs to account for four general dimensions discussed below: possible benefits of stress hyperglycemia, possible harms of stress hyperglycemia, risks of hypoglycemia, and other side effects of insulin.
  
  - The balance of risks vs. benefits is enormously complex and **not** predictable. Thus, high-quality clinical evidence is required to answer this question (in the form of RCTs). This is an especially daunting challenge, given that the answer may vary between different contexts (so no single RCT will reveal an answer for all comers).

**(#1) Potential benefits of stress hyperglycemia**

- Increased glucose levels could facilitate glucose transport to tissues, especially those with poor perfusion.
- Glucose administration improves cardiac function and survival in some animal models.
- Marked hyperglycemia may cause osmotic diuresis. Although osmotic diuresis has typically been feared, recent evidence demonstrating benefits from SGLT2 inhibitors suggests that osmotic glucose diuresis isn’t necessarily harmful. Among critically ill patients, it could help counteract volume overload.

**(#2) Potential harms of stress hyperglycemia**

- Osmotic diuresis due to severe hyperglycemia could cause some problems:
  
  - It could hamper the use of urine output as a marker of tissue perfusion.
  - It could promote hypernatremia.
- Hyperglycemia may impair the function of the endothelial glycocalyx, thereby promoting capillary leak.
- Hyperglycemia may impair leukocyte function. In the context of uncontrolled infection, this could be detrimental. (Alternatively, in the context of inflammatory injury due to excessive immune activation, could this conceivably be beneficial?)

**(#3) Potential harms of iatrogenic hypoglycemia**

- Profound hypoglycemia may cause neurologic injury or potentially even death (if sustained). The risks of iatrogenic hypoglycemia due to insulin are well established:
  
  - Insulin is among the most high-risk medications in terms of the potential for medication error. One report found that a third of fatal medication errors involved insulin. ([21486990](https://pubmed.ncbi.nlm.nih.gov/21486990/)) A study in the emergency department found that insulin was the #1 cause of adverse drug events. ([17047216](https://pubmed.ncbi.nlm.nih.gov/17047216/)) Exact numbers will vary, depending on whether insulin-induced hypoglycemia is described as a “medication error” or “side effect.” Regardless, there can be no doubt that insulin is responsible for an outsized amount of patient harm.
  - Intubated and sedated patients won’t manifest any symptom of hypoglycemia. Therefore, it is possible to cause permanent brain damage due to hypoglycemia without any overt signs that harm is occurring. Occult neurologic injury is becoming less common currently with higher glucose targets, but it remains a risk of insulin therapy in the ICU.
- Moderate hypoglycemia may also have adverse effects, including: ([22992074](https://pubmed.ncbi.nlm.nih.gov/22992074/))
  
  - Impaired autonomic function, vasoconstriction.
  - Leukocyte activation and release of inflammatory cytokines.
- Hypoglycemia is associated with mortality in both observational studies and clinical trials. The association of hypoglycemia with death may be stronger among patients with diabetes. ([31246637](https://pubmed.ncbi.nlm.nih.gov/31246637/)) The NICE-SUGAR trial suggests that this link is probably **causal**, rather than merely representing correlation (more on this below).

**(#4) Potential metabolic side effects of insulin**

- Insulin suppresses **autophagy**, a beneficial process involved in the recycling of cellular organelles.
- Aside from any effects on glucose, continuous or high-level exposure to insulin could be detrimental.
The pendulum of opinion on glycemic control in critical illness has swung back and forth considerably during the 21st century. An overview of landmark trials is as follows:

**Leuven surgical trial in 2001**

- This is a single-center RCT which found that “tight” glycemic control (targeting a glucose of 80-110 mg/dL) could reduce mortality among surgical ICU patients. ([11794168](https://pubmed.ncbi.nlm.nih.gov/11794168/))
- The release of this study in the New England Journal of Medicine led to an enormous amount of enthusiasm for tight glycemic control. It was the stimulus for innumerable guidelines and hospital protocols.
- Unfortunately, the Leuven study had many severe flaws. For example:
  - A single-center, non-blinded design.
  - A low fragility index (two) and a barely significant p-value (0.04).
  - Patients were provided with ~800 kCal/day IV glucose infusion upon arrival in ICU, followed by early initiation of total parenteral nutrition (which is rather bizarre and inconsistent with modern critical care practices).
  - The observed effect was driven largely by cardiac surgery patients (which may not generalize to other critically ill populations).
  - The control group showed an unusually high mortality rate.
  - The study had an open-label design, with some patients receiving more intensive care than others (this generally tends to improve outcomes among the patients receiving more attention).
  - The study was terminated early, following multiple interim analyses.
- More complete discussion of the article can be found at TheBottomLine site [here](https://www.thebottomline.org.uk/summaries/icm/intensive-insulin/).
- The full text of the article is [here](https://www.nejm.org/doi/pdf/10.1056/NEJMoa011300?articleTools=true).

**Leuven medical trial in 2006**

- This is another RCT performed at the same center, involving medical ICU patients. As in the surgical study, tight glycemic control (targeting a level of 80-100 mg/dL) was compared to conventional therapy (targeting a glucose <180-200 mg/dL). ([16452557](https://pubmed.ncbi.nlm.nih.gov/16452557/))
- The primary endpoint (all-cause mortality) was negative, with no significant difference between the groups. However, patients in the intensive glycemic control group did have improvement in several secondary endpoints (including more rapid weaning from mechanical ventilation, lower rates of acute kidney injury).
- This study suffers from many of the same limitations as the Leuven surgical trial above. In particular, patients were treated with early IV glucose loading and parenteral nutrition – factors which could limit the external generalizability to modern practice involving enteral nutrition.

**VISEP trial**

- This was a multi-center RCT investigating tight glycemic control among 537 patients in Germany with severe sepsis. ([18184958](https://pubmed.ncbi.nlm.nih.gov/18184958/))
- The study was terminated early due to harm (patients treated with tight glycemic control experienced an increased rate of severe hypoglycemia and severe adverse events).
- Full text of the article is [here](https://www.nejm.org/doi/pdf/10.1056/NEJMoa070716?articleTools=true).

**NICE-SUGAR trial**

- This is a large multi-center trial reevaluating tight glycemic control (targeting a glucose of 80-100 mg/dL).
- The study is discussed in more detail below. In short, this is currently the best study on glycemic control in the ICU. It refuted the results of the Leuven trial by demonstrating that tighter glycemic control increased mortality.

where we stand currently

- With the wisdom of hindsight, it appears that the Leuven trials were a fluke (single-center, non-blinded trials which could not be replicated).
- The best available evidence suggests that overaggressive glycemic control causes harm (e.g., VISEP and NICE-SUGAR).

https://emcrit.org/ibcc/glucose/
No high-quality evidence exists regarding what a safe upper limit of glucose may be in the ICU. For example, NICE-SUGAR reveals that targeting a glucose level of 140-180 mg/dL is superior to targeting a level of 80-100 mg/dL. However, it's unknown whether allowing an even higher degree of permissive hyperglycemia would be even safer.

**NICE-SUGAR trial**

**basics**

- This is a large, multi-center trial of critically ill patients in New Zealand, Canada, and Australia. Patients were randomized to either:
  - Intensive glucose control, targeting a blood glucose of 81-100 mg/dL (4.5-6 mM).
  - Conventional glucose control, targeting a glucose level below <180 mg/dL (10 mM).
- With 6,104 patients from 42 institutions, this is the largest and most robust RCT of glycemic control in critical care. The study included a variety of medical and surgical patients, making it generalizable across a variety of contexts.
- The primary endpoint was 90-day all-cause mortality.

**more intensive glucose control increased mortality**

- Patients in the more intensive insulin therapy group had a higher 90-day mortality (27.5% vs. 24.9%, \( p=0.02 \)). This 2.6% mortality difference suggests that intensive insulin therapy killed about one in every forty patients.
- This result is remarkable for a few reasons. First, it's unusual for a modern critical care trial to demonstrate any difference in mortality (more on this [here](https://emcrit.org/pulmcrit/mortality-2/)). Second, it's unusual for the more intensive arm of a trial to have worse outcomes (generally patients in the more work-intensive arm will receive more clinical attention and tend to fare better). Overall, this suggests that intensive insulin therapy was truly causing a substantial amount of harm.

**more intensive glucose control increased the rate of hypoglycemia**

- The rate of severe hypoglycemia (defined as <40 mg/dL or 2.2 mM) was 6.8% in the intensive insulin group, compared to 0.5% in the conventional group (\( p<0.001 \)).
- A subsequent analysis of this data found increased mortality rates in patients with both severe hypoglycemia and also moderate hypoglycemia (glucose 41-70 mg/dL or 2.3-3.9 mM; figure below) ([22992074](https://pubmed.ncbi.nlm.nih.gov/22992074/)). Although retrospective, this suggests some interesting possibilities:
  - (1) Hypoglycemia is a likely mechanism whereby more aggressive glycemic control causes mortality.
  - (2) Even moderate hypoglycemia might be detrimental (e.g., glucose 41-70 mg/dL or 2.3-3.9 mM).
The figure above shows the range of glucose values which was achieved. Patients in the conventional treatment arm were targeted to a goal glucose of <180 mg/dL. However, they often exceeded that goal.

The insulin protocols used in the study are shown below. The protocol for conventional control avoided insulin administration for patients with a glucose below <144 mg/dL (8 mM). Careful insulin titration may have facilitated avoidance of severe hypoglycemia in patients within the conventional treatment arm. These details in the insulin protocol regarding avoidance of hypoglycemia could have been more important than the precise glucose target.
Patients with chronic hyperglycemia

Understanding baseline glucose levels

- Providers who work full-time in the ICU may forget that patients experience a broad range of glucose values when outside the hospital. However, it is important to understand how our glycemic management strategies may fit within the context of the patient's baseline glucose levels.
- Hemoglobin A1C is related to the average glucose level in a linear fashion (figure above). However, individual glucose values will vary quite a bit more (figure below).
  - Many of our patients with diabetes may experience substantial hyperglycemia on a regular basis in the course of their daily lives. This should not be misconstrued as a medical emergency.
correlational relationships between glycemic control and mortality are different in diabetes

- In nondiabetic populations, hyperglycemia and higher glycemic variability correlate with mortality. This has typically been the rationale for using insulin in critically ill patients (although such correlations do not establish causality).
- Among patients with diabetes:
  - Hyperglycemia and often do not correlate with mortality. ([31246637](https://pubmed.ncbi.nlm.nih.gov/31246637/))
  - Hypoglycemia still does correlate with mortality.
  - Glycemic variability may still correlate with mortality.
- Mild hypoglycemia or even "normal" glucose levels may be detrimental in patients with chronic hyperglycemia. Patients with chronic hyperglycemia will adapt to this glucose level over time (e.g., with down-regulation of glucose transport proteins). Suddenly dropping the glucose to a "normal" level may be perceived as (relative) hypoglycemia, leading to a physiological stress response.

emerging evidentiary basis for glycemic control in diabetes

- The lack of a correlation between hyperglycemia and mortality in this patient population undermines the theoretical rationale for aggressive glycemic control.
- An emerging body of evidence supports the safety of targeting a glucose level of 180-250 mg/dL (6-10 mM) among patients with diabetes (and especially patients with hemoglobin A1C >7%). ([30882892](https://pubmed.ncbi.nlm.nih.gov/30882892/)) One study found that targeting a
higher glucose level led to a reduced incidence of hypoglycemia and less glycemic variability.\(^{(27315191)}\) Currently the ANZICS group has a multi-center RCT underway to investigate this further (the LUCID trial).\(^{(32389105)}\)

**what should we do now?**

**no RCT has convincingly shown that lowering glucose in the ICU improves outcomes**

- The Leuven surgical trial was the only study to demonstrate benefit from tighter glycemic control. Subsequently, this study was disproven by the larger and more methodologically rigorous NICE-SUGAR trial.
- Currently there is no convincing evidence that lowering glucose in the ICU is beneficial (outside of specific disease states such as diabetic ketoacidosis or hyperglycemic hyperosmolar state). The degree of glycemic control which might be optimal remains a topic of active debate and clinical investigation.

**current guidelines are contradictory and not evidence-based**

- The ideal target glucose is unknown; in particular, it is unclear what the highest “safe” glucose is (or if such a limit exists). This has led to disagreement between “evidence-based” guidelines:
  - The Society of Critical Care Medicine recommends targeting a glucose level of 140-180 mg/dL.\(^{(23164767)}\)
  - The American College of Physicians recommends targeting a glucose level of 140-200 mg/dL.\(^{(23709472)}\)
- As shown by *disagreement* between different guidelines, these targets are arbitrary. The guidelines are based upon the same evidentiary basis, so if they were truly evidence-based they should reach the same conclusions.
  - One of the foundational principles of science is *repeatability* – if two different investigators perform the same experiment, they should obtain the same results. When different guideline creators generate conflicting recommendations, they are failing this foundational principle of replicability.

**factors which may affect glycemic target in an individual patient**

- (1) Baseline glycemic status
  - Patients with chronic hyperglycemia may be better served with a more permissive strategy.
  - A history of diabetes and (when available) hemoglobin A1C levels may help guide management.
- (2) Safety of preventing hypoglycemia
  - Continuous glucose monitoring or q1hr monitoring may improve safety, compared to less frequent monitoring.
  - Measuring glucose from phlebotomized blood directly may be more accurate than a fingerstick glucose.
  - The risk of insulin will be greater in settings which are unable to provide intense and reliable glucose monitoring.

**current approach to practice?**

- There is no proven benefit from glycemic control, but there are *definitely* proven harms. Therefore, based on the principle of *primum non nocere*, allowing a permissive hyperglycemia may be safest. In the absence of evidence, the following strategy might be reasonable:
- (1) Allow for relatively permissive hyperglycemia. For example:
  - Among nondiabetic patients, a target glucose of ~100-220 mg/dL or ~100-200 mg/dL might be reasonable.\(^{(23470218)}\) Targeting a glucose <220 mg/dL is controversial today, but this was actually considered conventional therapy in 2001 prior to the disastrous Leuven study.
  - In patients with Type II diabetes (especially those with hemoglobin A1C > 7 mg/dL), a range of 180-250 mg/dL (XXX-xxx MM)(REF) could be reasonable. Hopefully, the LUCID trial will provide further validation for this target.
- (2) Efforts to reduce glucose should be *gentle* and *cautious*.
  - Low doses of subcutaneous insulin may be used, with a goal of *gently* lowering the glucose into the range of ~150-200 mg/dL.
  - Avoid insulin infusions when possible (continuous infusion may cause overshoot hypoglycemia if not precisely monitored, especially in patients without ongoing nutritional intake).
  - When in doubt, it’s safer to underdose insulin than to overdose it (“better sweet than sour”).
  - Note that *glycemic variability* correlates with mortality – so inducing rapid swings in glucose could be harmful.
• (3) Remove causes of hyperglycemia when possible.
  • Steroid dose may be limited or down-titrated, as possible.
  • *Intermittent feeding* may tend to cause less hyperglycemia than 24/7 continuous feeding.

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**podcast**


**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/glucose/).

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Don't give too much insulin. The ability of insulin to kill patients is proven, whereas the ability of glycemic control to save lives isn't supported by reliable evidence.

Don't be dogmatic about specific glucose targets. Nobody knows what we should be targeting here.

Don't over-utilize insulin infusions. These are easy for physicians to order, but they often expose patients to unnecessarily rapid glucose shifts.

Be careful when patients are made NPO or when steroid is discontinued. If the same insulin dose is continued, this may lead to hypoglycemia.

**Going further:**

• More on NICE-SUGAR
  • The original manuscript is available [here](https://www.nejm.org/doi/pdf/10.1056/NEJMoa0810625?articleTools=true).
  • **Glycemic control in diabetic ICU patients**([https://intensivecarenetwork.com/bellomo-glycemic-control-icu-patients/](https://intensivecarenetwork.com/bellomo-glycemic-control-icu-patients/)) (Bellomo on the Intensive Care Network). This is epic, and should be required education for any provider ordering an insulin infusion in the ICU.

**references**


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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.