From the symposium "Sharing Expertise in the ICU: update on blood glucose and volume management" at the Annual meeting 2014 of the Swiss Neurological Society

Glucose control in the ICU

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The two large landmark single-centre randomised controlled trials in Leuven, Belgium, showed a substantial and significant clinical benefit for intensive insulin therapy (IIT, target 80–110 mg/dl) in adult surgical and medical critically ill patients. Therefore, tight glycaemic control was implemented in guidelines and in clinical routine in intensive care units (ICUs) all around the world, often at the cost of an increased incidence of moderate and severe hypoglycaemic episodes. Surprisingly, in subsequent large multicenter trials the same effect could not be replicated. Currently, the debate on how best to implement glucose control in the ICU is lively and ongoing, but a recent consensus paper on glycaemic control in critically ill adults has clarified many aspects [1]. It is likely that the same rules apply to other severely ill patients who are not necessarily in ICU and to hospitalised patients in general [2].

This short review aims to give an overview on current standard treatment, important details in the implementation of insulin therapy and open questions with regard to glucose control in critical illness.

Disturbances in glucose control are associated with excess morbidity and mortality in critical illness

- Both hyperglycaemia and hypoglycaemia are associated with poor outcomes in critically ill patients. Falciglia and colleagues used a database of almost 260,000 intensive care unit (ICU) patients from >170 units to demonstrate that mortality was lowest at mean glucose levels of 110 mg/dl. A U-shape for lower and higher levels was found, but this was less obvious in diabetic patients [3].
- Poor glucose control has been linked to increased mortality and morbidity in a variety of settings:
  - increased rate of infections;
  - disturbed wound healing;
  - longer hospital and ICU length of stay;
  - prolonged mechanical ventilation;
  - poor functional outcome after stroke;
  - excess mortality after stroke, traumatic brain injury, myocardial infarction.
- Hypoglycaemic episodes are also associated with poor outcomes and should be avoided, although overcorrection may contribute to these outcomes and causality is still debated.

Target levels and the best method to achieve optimal glucose control remain controversial (table 1)

Table 1: Summary – what should be considered for optimised glucose control in the ICU.

Insulin	Insulin should be given intravenously in critically ill patients and may be switched to a subcutaneous regimen once the patient has resumed eating. Continuous insulin administration is better than bolus insulin. Ideally, a separate line should be used.
Target level	Currently no uniform target level exists but a target of 100–150 mg/dl is probably safe and feasible for most patients in most units.
Glucose monitoring	Capillary blood is unsuitable. Glucose needs to be monitored frequently (every 1–2 hours). Point of care testing (POCT) developed for diabetics for home use is not suitable in this setting as the accuracy is insufficient. Factors such as anaemia may reduce accuracy further and lead to falsely high glucose readings in POCT. A method of choice is arterial blood gas analysis (ABGA), which has the advantage of providing results rapidly and the possibility for a concomitant potassium check. Alternatively, samples may be sent to the central laboratory.
Diabetes status	It is likely that hyperglycaemia in diabetic patients is less predictive for poor outcomes than in nondiabetics. Therefore, less stringent glucose targets may be applied to diabetics.
Other issues	There are different methods of determining glucose variability. Glucose variability should be minimal. Glucose complexity is a new parameter that can only be determined in continuous glucose analysis and may independently be related to poor outcomes.

- There is currently no uniform target level for glucose control and there is no "one size fits all" regimen [4].
- Intensive insulin therapy targeting normoglycaemia (80–110 mg/dl) is no longer universally recommended.
- In preexisting diabetes, patients seem to benefit less from strict glucose control and therefore the target may be higher (but <180 mg/dl)
- It is possible to diagnose previously unknown diabetes from elevated glycated haemoglobin (HbA_{1c}) >6.5%. Therefore, HbA_{1c} should be tested upon ICU admission.
- Because insulin may shift potassium into the cells, potassium should be checked frequently, especially when high doses of insulin (>5–10 IU per hour) are used.
- Depending on nutrition, severity of critical illness and medications (steroids, immunosuppressive drugs, etc.), insulin sensitivity and thus the insulin dose necessary may change during the course of the illness.
- Hypothermia (e.g. after resuscitation) may cause severe disturbances in metabolism leading to difficulties in glucose control. If this happens, less strict hypothermia may be applied and less nutrition given.
- Workload remains an important issue.
- Most patients have normal glucose levels after recovery from a critical illness.

The closed loop ("artifical pancreas") is being tested in clinical studies and will probably be the treatment of choice in the future

- Current treatment regimens range from no standard to paper-based standards to computer-assisted protocols.
- Computerised glucose control has been found to be superior to standard therapy, but a paper-based protocol is better than no standardisation.
- We recently showed excellent glucose control using the B. Braun Space glucose control device in two European medical ICUs [5].
- Although the closed loop is extensively researched and has shown great promise in clinical trials, we are still years away from its routine use in clinical practice.

Open questions

- What is the best target level for which patients?
- How can we achieve it?
- How can excellent glucose control be achieved without an excessive increase in workload?
- How can we best decrease glucose variability?
- What are the roles of enteral or parenteral nutrition, medication, severity of illness and how can we best account for them?
- When will the artificial pancreas (automated insulin delivery device with continuous glucose monitoring system) be available for clinical use and will it fulfill our expectations?

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Disclosures
KA has received lecture fees from B. Braun.

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