edi 2011 - Berlin

Künstliche Ernährung bei akuten Erkrankungen

Glukosehomöostase bei kritisch Kranken

M. Adolph
Ab wann beginnt „Hyperglykämie“?
Which level of glycemia should we aim to reach?

Recommendation

Hyperglycemia (glucose > 10 mmol/l) contributes to death in the critically ill patient and should also be avoided to prevent infectious complications (Grade B).

Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/l. No unequivocal recommendation on this is therefore possible at present. There is a higher incidence of severe hypoglycemia in patients treated to tighter limits (Grade A).
Nebenwirkungen einer „Hyperglykämie“?
Adverse Effects of Hyperglycemia

- Electrolytes and fluid imbalance
- Dehydration
- Increased susceptibility to infections
- Increased coagulability
  - platelet aggregation
  - coagulation factors
  - fibrinogen, plasminogen activator inhibitor (PAI)-1, von-Willebrand-Factor
- Impaired wound healing
- Decreased antibacterial function of polymorphonuclear leucocytes
  - adhesion capacity
  - chemotaxis
  - phagocytosis, superoxide radical production

Was sagen die Leitlinien?
Kohlenhydrate

Kohlenhydratanteil und Blutzuckerspiegel:

• In der Regel sollten etwa 60% der Nichteiweißenergie als Kohlenhydrate zugeführt werden (C).

• Die Einhaltung einer Normoglykämie ist anzustreben (A).

DGEM Leitlinie „Parenterale Ernährung“
Kohlenhydrate (Bolder, Ebener, Hauner, Jauch et al) (2007)
Which level of glycemia should we aim to reach?

Recommendation

Hyperglycemia (glucose > 10 mmol/l) contributes to death in the critically ill patient and should also be avoided to prevent infectious complications (Grade B).

Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/l. No unequivocal recommendation on this is therefore possible at present. There is a higher incidence of severe hypoglycemia in patients treated to tighter limits (Grade A).
Die Idee der „Tight Glucose Control“
INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIECT SCHETZ, M.D., PH.D., DIRK VLAESSELERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.
Outcome benefit of intensive therapy in the critically ill: Insulin dose versus glycemic control

Kaplan-Meier cumulative risk of in-hospital death among long-stay (>% days in ICU)

- squares: blood sugar < 110 mg/dl
- circles: blood sugar 110 – 150 mg/dl
- triangles: blood sugar > 150 mg/dl

Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D., Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.
Figure 3. Effect of Intensive Insulin Therapy on Morbidity.

The effect of intensive insulin therapy on time to weaning from mechanical ventilation, time to discharge from the intensive care unit (ICU), and time to discharge from the hospital is shown for all patients (intention-to-treat analysis, Panel A) and for the subgroup of 767 patients staying in the ICU for three or more days (Panel B). P values for the comparison between the two groups were calculated by proportional-hazards regression analysis with censoring for early deaths. Circles represent patients.

Tight blood glucose control: What is the evidence?

Kaplan-Meier curves for in-hospital survival of surgical and medical intensive care unit patients. (*black lines*: conventional insulin therapy group; *gray lines*: intensive insulin therapy group)

Gefahren der „Tight Glucose Control“
Conventional vs intensive insulin therapy - univariate analyses

N= 488 patients

Hypoglycemia = < 2,2 mmol/l (40 mg/dl)

Intensive Insulin Therapy (SepNet)  
- Mortality in Septic Patients -

28-day mortality, ITT  
- Intensive Insulin Therapy (SepNet) -

<table>
<thead>
<tr>
<th>26.0%</th>
<th>24.7%</th>
</tr>
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<td>n=289</td>
<td>n=247</td>
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90-day mortality, ITT  
- Intensive Insulin Therapy (SepNet) -

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„In sedated, severely ill patients with sepsis, the benefits of intensive insulin therapy (administered according to the Leuven protocol) are unproven, but the risk of hypoglycemia is increased by a factor of 5 to 6.“

Symptome einer Hypoglykämie

Plasma glucose level

Upper limit: 6 110
Mean: 5 90
Lower limit: 4 70

- Decreased insulin secretion
- Increased glucagon secretion
- Increased epinephrine secretion
- Symptoms
- Decreased cognition
- Aberrant behavior
- Seizure, coma
  (Functional brain failure)
- Neuronal death
  (Brain death)

Hypoglycemic coma and brain injury are potential complications of insulin therapy.

... these results suggest that high blood glucose concentrations following hypoglycemic coma can initiate neuronal death by a mechanism involving extracellular zinc release and activation of neuronal NADPH oxidase.
Was sagen andere große Studien?

Welche Ergebnisse liefern die Metaanalysen?
Clinical experience with tight glucose control by intensive insulin therapy

Design and end-points of three prospective, randomized, controlled trials

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<td>Open label, randomized, controlled, stratified</td>
<td>90-day mortality</td>
<td>6,100</td>
<td>80–110</td>
<td>140–180</td>
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IIT, intensive insulin therapy; CIT, conventional insulin therapy; ICU, intensive care unit.
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*
## NICE-SUGAR Trial
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intensive Insulin</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled (n)</td>
<td>3054</td>
<td>3050</td>
</tr>
<tr>
<td>Surgical (%)</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Apache II &gt; 25 (%)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td><strong>Severe Sepsis (%)</strong></td>
<td><strong>22</strong></td>
<td><strong>21</strong></td>
</tr>
<tr>
<td>Mech Ventilator (%)</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

In 6014 critically ill patients, tight glucose control was associated with hypoglycemia and increased mortality at 90 days. “On the basis of [these] results we do not recommend use of the lower target (81 -110 mg/dl) in critically ill patients.”

<table>
<thead>
<tr>
<th></th>
<th>Intensive Insulin (%)</th>
<th>Conventional (%)</th>
<th>Odds ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>6.8</td>
<td>0.5</td>
<td>(1.02 - 1.28)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)
Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

Interpretation: Intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, this therapy may be beneficial to patients admitted to a surgical ICU.
Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial

Kaplan-Meier survival curves for the permissive under feeding and target feeding groups (A) and for the intensive insulin therapy and conventional insulin therapy groups (B).

Meta-Analysis
Modified from Wiener RS, et al. JAMA 2008; 300:933

Tight glucose control had no significant beneficial effect on hospital mortality in 27 trials of 8315 critically ill patients.

Sensitivity analysis suggests this is true whether the level of glucose control is < 150 or < 110 mg/dl and independent of the type of ICU (medical, surgical or combined).

Glucose < 110 mg/dl
Glucose < 150 mg/dl
Surgical
Medical
Med / Surg
Overall
Hypoglykämierate bei Intensivierter Insulintherapie

<table>
<thead>
<tr>
<th>Study</th>
<th>No. events / total no. patients</th>
<th>IIT</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson et al.</td>
<td>7/32</td>
<td>1/35</td>
<td></td>
<td>7.66 (1.00–58.86)</td>
</tr>
<tr>
<td>Bland et al.</td>
<td>1/5</td>
<td>1/5</td>
<td></td>
<td>1.00 (0.08–11.93)</td>
</tr>
<tr>
<td>Van den Berghe et al.</td>
<td>111/595</td>
<td>19/605</td>
<td></td>
<td>5.94 (3.70–9.54)</td>
</tr>
<tr>
<td>Mitchell et al.</td>
<td>5/35</td>
<td>0/35</td>
<td></td>
<td>11.00 (0.63–191.69)</td>
</tr>
<tr>
<td>Azevedo et al.</td>
<td>27/168</td>
<td>6/169</td>
<td></td>
<td>4.53 (1.92–10.68)</td>
</tr>
<tr>
<td>De La Rosa Godl et al.</td>
<td>21/254</td>
<td>2/250</td>
<td></td>
<td>10.33 (2.45–43.61)</td>
</tr>
<tr>
<td>Devos et al.</td>
<td>54/550</td>
<td>15/551</td>
<td></td>
<td>3.61 (2.06–6.31)</td>
</tr>
<tr>
<td>Oksanen et al.</td>
<td>7/39</td>
<td>1/51</td>
<td></td>
<td>9.15 (1.17–71.35)</td>
</tr>
<tr>
<td>Brunkhorst et al.</td>
<td>42/247</td>
<td>12/290</td>
<td></td>
<td>4.11 (2.21–7.63)</td>
</tr>
<tr>
<td>Iapichino et al.</td>
<td>8/45</td>
<td>3/45</td>
<td></td>
<td>2.67 (0.76–9.41)</td>
</tr>
<tr>
<td>Arabi et al.</td>
<td>76/266</td>
<td>8/257</td>
<td></td>
<td>9.18 (4.52–18.63)</td>
</tr>
<tr>
<td>Mackenzie et al.</td>
<td>50/121</td>
<td>9/119</td>
<td></td>
<td>5.46 (2.82–10.60)</td>
</tr>
<tr>
<td>NICE-SUGAR</td>
<td>206/3016</td>
<td>15/3014</td>
<td></td>
<td>13.72 (8.15–23.12)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>654/6138</td>
<td>98/6209</td>
<td></td>
<td>5.99 (4.47–8.03)</td>
</tr>
</tbody>
</table>

Griesdale DE, CMJA 2009
Blutzucker Variabilität – oft unterschätzt ?!
Viewpoint

Is reducing variability of blood glucose the real but hidden target of intensive insulin therapy?

Moritoki Egi¹, Rinaldo Bellomo² and Michael C Reade²

¹Department of Anesthesiology and Resuscitology, Okayama University Hospital, Shikata City, Japan 700-8558
²Department of Intensive Care, Austin Hospital, Melbourne, 145 Studley Road, Heidelberg, Victoria, Australia 3084

Corresponding author: Rinaldo Bellomo, rinaldo.bellomo@austin.org.au

Published: 6 April 2009

Blood Glucose Variability
Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

Moritoki Egi, M.D.,* Rinaldo Bellomo, M.D., F.J.F.I.C.M.,† Edward Stachowski, M.D.,‡ Craig J. French, M.D.,§ Graeme Hart, M.D.||

Relation between blood glucose control and intensive care unit (ICU) and hospital mortality in the total cohort.

The SD of blood glucose was used as marker of blood glucose control for A, and the mean blood glucose level was used for B.

GluAve mean blood glucose concentration; GluSD SD of blood glucose concentration.
Conclusions:

The Standard Deviation of glucose concentration is a significant independent predictor of intensive care unit and hospital mortality.

Decreasing the variability of blood glucose concentration might be an important aspect of glucose management.
Automatisierte Blutzuckerkontrolle
Kontinuierliche subkutane Glukosemessung
Kontinuierliche Glukosemessung:
Erwartungshaltung der Intensivmediziner

- 100% Zuverlässigkeit
- Minimal invasiv
- Einfache Handhabung
- Erhöhung der Patientensicherheit
- Reduzierung der IIT-assozierten Hypoglykämierate
- Reduzierung der Arbeitsbelastung
- Verbesserte Glukosekontrolle (Zielbereich)
- Reduzierung der Glukosevariabilität
Kontinuierliche Glukosemessung auf der ICU: Klinische Studien

- Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring

- Accuracy and reliability of a subcutaneous continuous glucose monitoring system in critically ill patients
  » Brunner R, Critical Care Med 2010: in press

- Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial.

- The impact of real time continuous glucose monitoring on glycaemic variability in critically ill patients
  » Brunner R, European Journal of Endocrinology: under review
Welche Blutzuckerspiegel erscheinen sinnvoll?
Glucose Control and Mortality in Critically Ill Patients

Results

... the regression models suggest that a mortality benefit accrues below a threshold glucose level of 144 to 200 mg/dl (8.0 – 11.1 mmol/l), with a speculative upper limit of 145 mg/dl for the target blood glucose level.

Conclusions

Increased insulin administration is positively associated with death in the ICU regardless of the prevailing blood glucose level.

Thus, control of glucose levels rather than of absolute levels of exogenous insulin appear to account for the mortality benefit associated with intensive insulin therapy demonstrated by others.

Special Article

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee
Glucose control

- Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU (1B)

- Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment (2C)

- Provide a glucose calorie source and monitor blood glucose values every 1–2 hrs (4 hrs when stable) in patients receiving intravenous insulin (1C)

- Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values (1B)
Univariate analysis comparing risk of adverse outcome between decreasing incremental mean glucose levels during the intraoperative period (GlcOR).

- *P* < 0.001 overall between mean glucose levels for each individual outcome.
- #P* < 0.001 between GlcOR more than 200 mg/dl and GlcOR 141–170 mg/dl.
Alternativen zur „Tight Glucose Control“
Olive oil based nutrition in multiple trauma patients: a pilot study

Blood glucose level in the lipid (circles) and the glucose group (triangles). Values are mean ± SEM and the mean of multiple measurements (minimum of three, maximum of six measurements); n number of patients; * p<0.05; ** p<0.01;
ESPEN Guidelines on Parenteral Nutrition: Intensive Care

Should we use all-in-one bags for PN administration?

Recommendation

PN admixtures should be administered as a complete all-in-one bag (Grade B).
Changes in plasma insulin and glucose in patients who received intermittent fat followed by continuous fat (1400 kcal/day, 9.4 gN/day).

Herzlichen Dank für Ihre Aufmerksamkeit!
The Effect on Energy and Nitrogen Metabolism by Continuous, Bolus, or Sequential Infusion of a Defined TPN Formulation in Patients after Major Surgical Procedures

Patients: 65 patients receiving TPN after acute or elective major surgery

TPN: 1) nonprotein calories: 100% of predicted preoperative REE
   60% glucose and 40% fat
2) amino acids: 0.2 gN/kg bw/day

Kinetics:
- Yellow: Sequential: AA + lipids
- Green: Continuous: all nutrients in one bag
- Red: Bolus: all nutrients in 5 bags

The Effect on Energy and Nitrogen Metabolism by Continuous, Bolus, or Sequential Infusion of a Defined TPN Formulation in Patients after Major Surgical Procedures

![Graph showing cumulative nitrogen balance over days for continuous, sequential, and bolus infusion methods.](image-url)
Continuous Versus Intermittent Infusion of Fat Emulsions During Total Parenteral Nutrition: Clinical Trial

**Conclusions**

... our results suggest that the utilization of fat emulsions may be enhanced if they are given on a continuous basis.

Furthermore, this means of administration will probably be associated with less TPN related morbidity because complications of excess glucose loading will be avoided.

Finally this study provides a metabolic justification for the use of so-called bag systems during TPN wherever possible because it guarantees the continuous infusion of fat over a 24 hour period.
Which level of glycemia should we aim to reach?

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Crit Care Med 2008; 36:296–327
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