Enteral and parenteral nutrition – critically ill patients

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Carol Davila University of General Medicine, Bucharest
<table>
<thead>
<tr>
<th></th>
<th>Luminal Nutrition</th>
<th>Main Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Bowel</td>
<td>30%</td>
<td>Glutamin</td>
</tr>
<tr>
<td>Colon</td>
<td>80%</td>
<td>SCFA‘s</td>
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</table>
Lack of endoluminal substrates

- ↑intestinal permeability
- ↓villous height ⇒ malabsorption, an impaired ability to act as a barrier (endogenous bacteria and toxins)
Lack of endoluminal substrates

- Intestinal epithelial cell apoptosis, villi- and crypt atrophy during PN, even if energy requirements are covered by 100%
- Supports the concept that rather lack of endoluminal substrates than TPN per se is responsible for many of the adverse events seen in patients fed with TPN

Sun X et al. JPEN J Parenter Enteral Nutr. 2006;30:474-9
- ↓stress ulcer
- ↑intestinal peristalsis
- ↓risk of colonization
- ↑hormonal intestinal function
TPN

- Reduction of lymphotoxin-β-receptor expression by TPN

- Evidence that TPN *per se* (not only lack of EN) impairs GALT and mucosal immunity

*Kang W et al. Ann Surg. 2006;244:392-399*
Failure of Enteral Nutrition

- Immunological alterations and impairment of “gut associated lymphatic tissue” (GALT)
  - Bowel becomes source of activated cells and pro-inflammatory stimuli during “gut starvation”
  - Secondary changes in permeability and maybe bacterial translocation challenge GALT

Kudsk KA. Am J Surg 2003;185:16–21
Positive Effects of EN

- IgA-levels and number of circulating lymphocytes of GALT are positively influenced by EN
  - Lymphocytes migrate in non-intestinal tissue (i.e. lung) and modify immune response
  - Neuroendocrine system-/bacteria-host-interaction of the gut influences regulation of inflammation also outside of the GI tract

Message 1

- EN if ever possible
- (T)PN only if EN not possible or insufficient
EN contraindications

- **Absolut CI**
  - Immediate postoperatively or after trauma
  - Shock status (severe acidosis)
  - Severe hypoxia

- **Relative CI**
  - Dynamic ileus
  - Severe vomiting
  - High quantity of gastric aspirate (> 1200 ml/24h)
  - Severe diarrhea
  - Abdominal hypertension
  - Abdominal dysfunction
EN contraindications

- But TPN is permitted
- Mesenteric ischemia
- Mechanical ileus
- Acute abdominal pain
- Abdominal compartment syndrome
Timing of EN

Metaanalysis of 6 RCT’s with 234 patients


Timing of EN

Start with EN < 24 h vs > 24 h

Results

• Significant reduction in mortality (OR 0.34, 95% CI 0.14-0.85) and incidence in pneumonias (OR 0.31, CI 0.12-0.78)

Early vs. Late EN: Mortality

Early EN vs. i.v. fluid/no EN: Mortality

Early EN vs. i.v. Fluid /no EN: Infectious Complications

Earl vs. Late EN: Infectious Complications

No influence on: Ventilator days, LOICUS, LOHS

The problem with randomised studies in all the nutritional literature is the lack of a proper methodology leading to a high risk of bias => over estimation of treatment effects

Despite of that:

Repetitive frequent findings of beneficial effects of early EN (< 24h)
EN complications

- Abdominal distension
- Diarrhea
- Intestinal necrosis (intrajejunal feeding)
- Tracheal aspiration
- Mechanical complication
Timing of PN

- Patients who can be fed adequately within the first 3 days do not need PN.

- Malnourished patients with partial GI intolerance profit from pre- and earlier (> 24-36 h) supplementing PN.

- Patients with prolonged (partial) GI-intolerance profit from PN supplementation.
  - Not immediately after the admission.
  - If ever possible, a minimum of enteral (immuno-) nutrition should be given.
EN vs EN+PN: Systematic Review

• 5 studies; in all studies EN and PN were started simultaneously
  – No significant effect on mortality by combining EN + PN
  – No effect on infectious complications, LOHS, ventilator days

CONCLUSION: In critically ill patients without malnutrition and with working GI tract simultaneous start of EN and PN is useless compared to EN alone

• All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24–48 h if EN is contraindicated or if they cannot tolerate EN. (Grade C)
• In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to target over the next 2–3 days (Grade C)
• All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary PN (Grade C)
PN complications

- Mechanical
- Infectious
- Metabolic
Insulin resistance

- Stress hormones
  - Catecholamines
  - Cortisol
  - Glucagon
  - (Growth hormone)

- Cytokines
  - TNF alpha
  - Interleukin-6
Insulin resistance

- Reduced effect of insulin on glucose turnover –
  > Hyperglycemia

- Related to
  - Substrate oxidation
  - Lipolysis
  - Protein catabolism
Insulin sensitivity and magnitude of operation

Thorell et al: Curr Opin Clin Nutr Metab Care, 1999

Insulin sensitivity (%)

- Lap Chol
- Hernia
- Open Chol
- Major Colorectal

P < 0.001, ANOVA
n = 6-13
Time course of insulin resistance

Relative insulin sensitivity (%) vs. Postoperative day

Thorell et al: Curr Opin Clin Nutr Metab Care, 1999
Insulin resistance & length of stay

$r = 0.53$, $P < 0.0001$

$n = 60$

Thorell et al: Curr Opin Clin Nutr Metab Care, 1999
Factors predicting length of stay

- Type of surgery
- Perioperative blood loss
- Postoperative insulin resistance

\[ R^2 = 0.71, \ p < 0.01 \]

Thorell et al: *Curr Opin Clin Nutr Metab Care*, 1999
Risk of hyperglycemia

BG levels were strongly correlated with severity of septic shock estimated by APACHE II score ($r=+0.241; p=0.005$) or SAPS II ($r=0.280; p=0.001$) - Pearson Correlation

Mirea L et al. Discontinuous corticosteroids administration increase the risk of hyperglycaemia in septic shock, Clinical Nutrition 2014; 33: S125
Mirea L et al. The impact of corticosteroids administration in septic shock on glycaemic variability, Crit Care 2014; A333
Mirea L et al. Discontinuous corticosteroids administration increase the risk of hyperglycaemia in septic shock, Clinical Nutrition 2014; 33: S125
Mirea L et al. The impact of corticosteroids administration in septic shock on glycaemic variability, Crit Care 2014; A333
### Glycaemic variability

Mirea L et al. *The impact of corticosteroids administration in septic shock on glycaemic variability*, *Crit Care* 2014; A333

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Insulin treatment in surgical ICU

Prospective randomized trial
1548 consecutive postop ICU patients
Target glucose 4.5-6.1 mM vs. treat >12mM

- Mortality ICU: 43%
- Mortality in hospital: 34%

G van den Berghe, N Engl J Med 2001
Insulin treatment in surgical ICU

Prospective randomized trial
1548 consecutive postop ICU patients
Target glucose 4.5-6.1 mM vs. treat >12 mM

- Bacteremia: 46%
- Ventilatory support: 37%
- Renal failure: 41%
- Polyneuropathy: 44%

G van den Berghe, N Engl J Med 2001
VISEP Trial, 2008

NICE SUGAR 1

## NICE SUGAR 1

### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (N=3010)</th>
<th>Conventional Control (N=3012)</th>
<th>Odds Ratio for Death (95% CI)</th>
<th>P Value for Heterogeneity</th>
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<td>1.31 (1.07–1.61)</td>
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<td>Diabetes</td>
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<td>Severe sepsis</td>
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<td>APACHE II score</td>
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<td>≥25</td>
<td>386/927</td>
<td>363/944</td>
<td>1.14 (0.95–1.37)</td>
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<td>&lt;25</td>
<td>442/2080</td>
<td>387/2066</td>
<td>1.17 (1.01–1.36)</td>
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<td>Corticosteroids</td>
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<td>Yes</td>
<td>134/392</td>
<td>140/378</td>
<td>0.88 (0.66–1.19)</td>
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<td>No</td>
<td>695/2616</td>
<td>611/2634</td>
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<td>All deaths at day 90</td>
<td>829/3010</td>
<td>751/3012</td>
<td>1.14 (1.02–1.28)</td>
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# NICE SUGAR 2

<table>
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<tr>
<th>Subgroup</th>
<th>Deaths</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td><strong>Cardiovascular cause of death</strong></td>
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<tr>
<td>Distributive shock</td>
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<tr>
<td>No hypoglycemia</td>
<td>110</td>
<td>1.00</td>
<td>&lt;0.001</td>
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<tr>
<td>Moderate hypoglycemia</td>
<td>177</td>
<td>2.34 (1.69–3.25)</td>
<td>&lt;0.001</td>
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<tr>
<td>Severe hypoglycemia</td>
<td>21</td>
<td>4.35 (2.49–7.61)</td>
<td>&lt;0.001</td>
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<tr>
<td>Arrhythmia</td>
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<td>No hypoglycemia</td>
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<td>Moderate hypoglycemia</td>
<td>41</td>
<td>1.31 (0.71–2.43)</td>
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<td>Severe hypoglycemia</td>
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<td>Other</td>
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<tr>
<td>No hypoglycemia</td>
<td>96</td>
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<tr>
<td>Moderate hypoglycemia</td>
<td>119</td>
<td>1.41 (0.98–2.08)</td>
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<tr>
<td>Severe hypoglycemia</td>
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<td>1.29 (0.56–2.99)</td>
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<td><strong>Neurologic cause of death</strong></td>
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<td>No hypoglycemia</td>
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<td>Severe hypoglycemia</td>
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<td>1.74 (0.90–3.36)</td>
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<td><strong>Respiratory cause of death</strong></td>
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<td><strong>Other cause of death</strong></td>
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<td>Moderate hypoglycemia</td>
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<td>Severe hypoglycemia</td>
<td>17</td>
<td>2.98 (1.51–5.88)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Metanalysis

- Griesdale et al., 2009
- Friedrich et al., 2010
- Wiener et al., 2008
- Marik et al., 2010
- Kansagara et al., 2011

Friedrich JO, Chant C, Adhikari NK. Crit Care 2010; 14:324
Wiener RS, Wiener DC, Larson RJ. JAMA 2008; 300:933–944
Marik PE, Preiser JC. Chest 2010; 137:544–551
Normoglycemia

- Preiser JC “Restoring normoglycemia: not so harmless”

(Crit Care 2008, 12:116)
Actual recommendations

- Start insulin drip protocol when 2 consecutive BG > 180mg/dL
- Glucose goal ≤ 180 mg/dL, not ≤ 110 mg/dL BG
- Monitoring every 1-2 hour until stable, then q4hrs after
- Capillary BG may not be as accurate as blood BG

Glutamine supplementation
Effects of Glutamine

- Major energy source for endothelial cell - Jing 2007
- ↓ALI / ARDS in sepsis - Singleton 2005
- Protection to oxidative stress - Kelly 2003
- Major energy source for miocyte - Kelly 2003
- Protection to ischemia-reperfusion injury - Khogali 2002
- Glutathione synthesis
- Regulatory for nitrogen metabolism - Kelly 2003
- Major energy source for mucosal cell, ↑ IgA - Singleton 2007
- Maintains structure (van der Hulst 1993), integrity and permeability of intestinal mucosa - de Souza 2005
- Protection to oxidative stress, antiapoptotic - Singleton 2007
- Major energy source
- Stimulates PMN and macrophages - Singleton 2007
- ↓ Synthesis of proinflammatory cytokines and peroxide
- Acid-base regulation
- NH₃ metabolism
Gln

- Oxidative stress postinjury
- Glutathione synthesis
- Hexosamine synthesis
- ↓ NO (anti-inflammatory effects)

↓ Oxidative stress postinjury

Preserves metabolic function

Energy source ↑ cellular ATP

↑ HSP70

↓ proinflamm cytokines

Nf-kB

Maintains immune function

Elimination of pathogen bacteria and fungi

Maintains mucosal integrity

Energy source for enterocyte

Precursor for nucleotides synthesis

Energy source for lymphocytes

↓ bacterial translocation

modified after Kelly & Wischmeyer 2003
Parenteral Glutamine vs Control

Mortality

- Dechelotte 2006
- Fuentes-Orozco 2004
- Griffiths 1997
- Powell-Tuck 1999
- Wischmeyer 2001
- Xian-Li 2004
- Ziegler unpub

![Diagram showing the relationship between RR (random) and 95% CI for mortality study results. The study's weight is also indicated.](image-url)
Parenteral Glutamine vs Control
Infectious Complications

Study
- Dechelotte 2006
- Fuentes-Orozco 2004
- Griffiths 1997
- Wischmeyer 2001
- Zhou 2004
- Ziegler unpub
Parenteral Glutamine vs Control
Length of Hospital Stay

Study
- Fuentes-Orozco 2004
- Powell-Tuck 1999
- Wischmeyer 2001
- Xian-Li 2004
- Zhou 2004
- Ziegler unpub

![Graph showing SMD (random) and 95% CI for the studies mentioned. Each study's data point is represented with its corresponding SMD and 95% CI range. The x-axis represents the difference in favor of PN Glutamine or control, while the y-axis shows the weight for each study, ranging from 16.26 to 16.84. The graph indicates that PN Glutamine has a slight advantage in reducing length of hospital stay, with SMD values ranging from -0.02 to -2.44, and 95% CI ranges from [-0.71, 0.66] to [-3.13, -1.76].]
Safety and Tolerance

- No study ever demonstrated any adverse effects at Gln supplementation in healthy volunteers or in patients (critically ill, surgical, etc)!
  

- Even supra-physiological levels are well tolerated
  

- Ideally: monitoring daily plasma levels (concentration > 0.42 mmol/l) → only for detecting lower levels
  

- Patients with severe head trauma (GCS<8 and cerebral edema) - Gln supplementation doesn’t modify intracerebral glutamate !!!
  
Guidelines & Recommendations

- All patients on parenteral nutrition should receive supplemental parenteral glutamine.
- In patients on enteral nutrition, parenteral glutamine might be supplemented.
- There is not enough evidence up to now to recommend enteral glutamine supplementation in all critically ill patients.
- Enteral glutamine is recommended in trauma and burn patients.

0.2 - 0.57 g/kg/day, starting within first 24 hs, for at least 7 days

Glutamine supplementation

A. Glutamine supplementation

$y = 2.407x + 98.148$

$R^2 = 0.9643$

B. Standard supplementation

$y = 2.5601x + 95.022$

$R^2 = 0.9523$

Glutamine supplementation

Conclusions- EN

- If EN is started early, a higher proportion of ICU patients can be adequately nourished enterally after a few days.
- The literature suggests that EN should be started within the first 24 hours.
- Only a few CI for EN.
- Not so severe complications.
Conclusions- TPN

- Severe complications
- Not reduce mortality and overall morbidity
- Expensive
Thank you!
14- 16 noiembrie 2014
Al 15-lea Simpozion Național de Nutriție Clinică
1-7 November 2015 – București European Course of Clinical Nutrition