Parenterale voeding tijdens kritieke ziekte: bijkomende analyses van de EPaNIC studie

Namens alle auteurs
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Early versus Late Parenteral Nutrition in Critically Ill Adults

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Greet Hermans, M.D., Ph.D., Pieter J. Wouters, R.N., M.Sc.,
Miet Schetz, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D.,
Sophie Van Cromphaut, M.D., Ph.D., Catherine Ingels, M.D.,
Philippe Meersseman, M.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D.,
Yves Debaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D.,
Aime Van Assche, M.D., Simon Vanderheyden, B.Sc.,
Alexander Wilmer, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.
ICU patients: unable to feed normally
Malnourished patients in ICU patients: bad outcome
Early underfeeding and cumulative energy deficit

- Alberda: Increased mortality in BMI <25 or ≥ 35
  2009 ICM

- Villet: More infections

- Dvir D.: Complications
Improved outcome through enhanced feeding?
Or better feeding when less ill?
Does nutrition improve outcome?

Adequate number of critically ill patients

Randomization

Nutrition

No Nutrition

M.P.C., K.U.Leuven
Does nutrition improve outcome?

Power

Adequate number of critically ill patients

No selection bias

Randomization
Allocation concealed

Nutrition

No Nutrition

M.P.C., K.U. Leuven
Does nutrition improve outcome?

Power: Adequate number of critically ill patients

No selection bias:
- Randomization
- Allocation concealed

Intention to treat:
- Nutrition
  - LOS
  - QOL
  - Mortality
- No Nutrition
  - LOS
  - QOL
  - Mortality

Blinded assessors:
- M.P.C., K.U.Leuven
Does nutrition improve outcome?

- Randomization
- Allocation concealed
- Nutrition
- No Nutrition

LOS
QOL
Mortality

Adequate number of critically ill patients

Power

No selection bias

Intention to treat

Blinded assessors

M.P.C., K.U.Leuven
Nutrition strategies today

EN only

High risk of underfeeding

Associated with Infections Morbidity Death
Nutrition strategies today

EN only
High risk of underfeeding

EN + PN
Risk of overfeeding and associated metabolic disturbances

Associated with Infections Morbidity Death

M.P.C., K.U.Leuven
Conflicting International Guidelines

**ESPEN**

“Consider PN within 2 days if EN insufficient”

**ASPEN**

“No PN until > day 8, prefer hypocaloric nutrition”
Causality ? RCT !

EPaNIC multicenter randomized controlled trial (N=4640)
clinical trials.gov [NCT00512122]

Nutritional strategy during the first week in ICU: Different strategies

- Early PN group
- Late PN group

M.P.C., K.U.Leuven
De EPaNIC intervention
EPaNIC intervention: PDMS supported

M.P.C., K.U.Leuven
EPaNIC : study population

Adult ICU patients, NRS ≥ 3, BMI ≥ 17

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 2328</strong></td>
<td><strong>N = 2312</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age – years</strong></td>
<td>64 ± 15</td>
<td>64 ± 14</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) Median (IQR)</strong></td>
<td>25.6 (23.0 – 28.8)</td>
<td>25.8 (23.1 – 29.2)</td>
</tr>
<tr>
<td><strong>NRS score ≥ 4 n° (%)</strong></td>
<td>1278 (54.9)</td>
<td>1298 (56.1)</td>
</tr>
<tr>
<td><strong>Sepsis n° (%)</strong></td>
<td>505 (21.7)</td>
<td>510 (22.1)</td>
</tr>
<tr>
<td><strong>Emergency admission n° (%)</strong></td>
<td>970 (41.7)</td>
<td>956 (41.3)</td>
</tr>
<tr>
<td><strong>APACHE II score</strong></td>
<td>23 ± 10</td>
<td>23 ± 11</td>
</tr>
</tbody>
</table>

Nutrition administered

Nutrition administered


M.P.C., K.U.Leuven
**EPaNIC**: In both groups

- Enteral nutrition initiated on the day after ICU admission
- Vitamins, trace elements, minerals administered early
- Overfeeding and hyperglycemia avoided

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin dose</td>
<td>31 (19 – 48) IU</td>
<td>58 (40 – 85) IU</td>
</tr>
<tr>
<td>Blood glucose levels</td>
<td>102 ± 14 mg/dl</td>
<td>107 ± 18 mg/dl</td>
</tr>
</tbody>
</table>

### EPaNIC: safety outcome

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>6.1 %</td>
<td>6.3 %</td>
<td>0.76</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>10.4 %</td>
<td>10.9 %</td>
<td>0.63</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>11.2 %</td>
<td>11.2 %</td>
<td>1.00</td>
</tr>
</tbody>
</table>

EPaNIC : safety outcome

Kaplan-Meier survival Plot

Days after randomization
## EPaNIC : safety outcome

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<tr>
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<td>0.76</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>10.4 %</td>
<td>10.9 %</td>
<td>0.63</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>11.2 %</td>
<td>11.2 %</td>
<td>1.00</td>
</tr>
<tr>
<td>Nutrition related complications</td>
<td>18.2 %</td>
<td>18.8 %</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>3.5 %</td>
<td>1.9 %</td>
<td>0.001</td>
</tr>
</tbody>
</table>

## EPaNIC: primary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged alive within 8 days</td>
<td>75.2 %</td>
<td>71.7 %</td>
<td>0.007</td>
</tr>
<tr>
<td>ICU stay (days) median (IQR)</td>
<td>3 (2 – 7)</td>
<td>4 (2 – 9)</td>
<td>0.02</td>
</tr>
<tr>
<td>mean</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Time to alive discharge from ICU</td>
<td>1.063 (1.002 – 1.128)</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted cox proportional hazard analysis

EPaNIC: primary endpoints


M.P.C., K.U.Leuven
### EPaNIC: infections & inflammation

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with new ICU infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway or lung</td>
<td>16.4 %</td>
<td>19.3 %</td>
<td>0.009</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>6.1 %</td>
<td>7.5 %</td>
<td>0.05</td>
</tr>
<tr>
<td>Wound</td>
<td>2.7 %</td>
<td>4.2 %</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Highest CRP during ICU stay</strong></td>
<td>190.6 (100.8 – 263.2)</td>
<td>159.7 (84.3 – 243.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## EPaNIC: MOF & recovery from MOF

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean duration of CMV</strong></td>
<td>5 days</td>
<td>6 days</td>
<td></td>
</tr>
<tr>
<td><strong>Tracheostomy</strong></td>
<td>5.8 %</td>
<td>7.0 %</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Duration of CVVH – IHD</strong></td>
<td>7 (3 – 16)</td>
<td>10 (5 – 23)</td>
<td>0.008</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>15 days</td>
<td>18 days</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During ICU week 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bilirubine &gt; 3 mg/dl</strong></td>
<td>12.2 %</td>
<td>10.5 %</td>
<td>0.003</td>
</tr>
<tr>
<td>During entire ICU stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gamma GT rise &gt; 79.5 IU/L</strong></td>
<td>32.6 %</td>
<td>38.4 %</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Alk. Phosphatase &gt; 405 IU/L</strong></td>
<td>19.9 %</td>
<td>22.6 %</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Hepatic cytolysis (ALT rise > 123 IU/L or AST rise > 114 IU/L) similar in 2 groups

EPaNIC: hospital stay

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of hospital stay</strong> (days)</td>
<td>14 (9 – 27)</td>
<td>16 (9 – 29)</td>
<td>( \text{P} = 0.004 )</td>
</tr>
<tr>
<td>median (IQR)</td>
<td>14 (9 – 27)</td>
<td>16 (9 – 29)</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Time to alive hospital discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.064 (1.001 – 1.131)</td>
<td>( \text{P} = 0.04 )</td>
<td></td>
</tr>
<tr>
<td>(Adjusted cox proportional hazard)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Discharge from conventional ward was at discretion of attending physicians, who were blinded for treatment allocation*

EPaNIC : time to (alive) hospital discharge

EPaNIC: functionality at hospital discharge

EPaNIC : functionality at hospital discharge

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Minutes Walking Distance (m)</td>
<td>277 (210 – 345)</td>
<td>283 (205 – 336)</td>
<td>0.69</td>
</tr>
<tr>
<td>N tested</td>
<td>624</td>
<td>603</td>
<td></td>
</tr>
<tr>
<td>Patients independent for all ADL</td>
<td>73.5 %</td>
<td>75.5 %</td>
<td>0.31</td>
</tr>
<tr>
<td>N tested</td>
<td>1060</td>
<td>996</td>
<td></td>
</tr>
</tbody>
</table>

Similar effects of **late PN** in predefined subgroups:

- Cardiac surgery \( (N = 2818) \)
- BMI ≤ 25 OR ≥ 40 kg/m² \( (N = 1989) \)
- NRS 5, 6 and 7 \( (N = 863) \)
- Sepsis \( (N = 1015) \)

Subgroup: surgical contra-indication for EN

M.P.C., K.U.Leuven
Subgroup: surgical contra-indication for EN

Posthoc subgroup, identifiable upon admission
**Subgroup : surgical contra-indication for EN**

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 261</td>
<td>N = 256</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral intake day 7 (kcal/day) median (IQR)</td>
<td>0 (0 – 263)</td>
<td>0 (0 – 142)</td>
<td>0.54</td>
</tr>
<tr>
<td>Patients with new ICU infection</td>
<td>29.9 %</td>
<td>40.2 %</td>
<td>0.01</td>
</tr>
<tr>
<td>Discharged alive from ICU ≤8 days Odds ratio (95%CI)</td>
<td>1.749 (1.141 – 2.683)</td>
<td>+ 75%</td>
<td></td>
</tr>
<tr>
<td>Time to alive discharge from ICU Hazard ratio (95%CI)</td>
<td>1.198 (0.999 – 1.437)</td>
<td>+ 20%</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup: surgical contra-indication for EN

What does this mean?

- More PN is more toxic?
- No feeding, irrespective of route, is better?

M.P.C., K.U.Leuven
## Health economy impact?

<table>
<thead>
<tr>
<th></th>
<th>Late PN</th>
<th>Early PN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital stay cost</strong></td>
<td>16863 (8793-17774)</td>
<td>17973 (8749-18677)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Between patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td>1110 EUR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td>2,300,000 EUR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cost of PN & hospital stay: flat compensation in Belgian healthcare system*

*Difference explained by antibiotics and laboratory tests*

2 more questions?

Is PN only beneficial in the most severely ill patients?

Is PN only beneficial at moderate energy doses?
Patient specific? The wrong dose for the wrong patient? Perhaps less harmful when more severely ill

✓ EPaNIC subgroup analyses
  ✓ NRS ≥ 5
  ✓ Contra indication EN
  ✓ Subgroups by severity of illness
Patient specific? The wrong dose for the wrong patient?
Perhaps less harmful when more severely ill

- EPaNIC subgroup analyses
  - NRS > 5
  - Contra indication EN
- Subgroups by severity of illness
Patient specific? The wrong dose for the wrong patient? Perhaps less harmful when more severely ill

- EPaNIC subgroup analyses
- NRS ≥ 5
- Contra indication EN
- Subgroups by severity of illness
Total Population
(N = 4640)

Apache II

In favour of Early PN  Late PN

Likelihood earlier alive ICU discharge (HR)

M.P.C. & G.V.d.B., K.U.Leuven
### Total Population
(N = 4640)

#### Apache II

<table>
<thead>
<tr>
<th>Score</th>
<th>n</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 [10-13]</td>
<td>1252</td>
<td>p = 0.6</td>
</tr>
<tr>
<td>17 [16-18]</td>
<td>1072</td>
<td>p = 0.2</td>
</tr>
<tr>
<td>26 [22-30]</td>
<td>1247</td>
<td>p = 0.008</td>
</tr>
<tr>
<td>37 [35-41]</td>
<td>1069</td>
<td>p = 0.3</td>
</tr>
</tbody>
</table>

In favour of Early PN  
Late PN  

**OR for acquisition of a new infection**

**Patients acquiring a new infection during ICU stay**
**Total Population (N = 4640)**

- **Apache II**
  - 12
  - 17
  - 26
  - 37
  - In favour of Early PN: 1.4
  - OR for acquisition of a new infection
  - Patients acquiring a new infection during ICU stay

**Other Patients (N = 1822)**

- **Apache II**
  - 13
  - 17
  - 28
  - 37
  - In favour of Early PN: 2.8
  - OR for acquisition of a new infection
  - Patients acquiring a new infection during ICU stay

E.PaN.I.C., unpublished data

M.P.C. & G.V.d.B., K.U.Leuven
Type and severity of illness?

- No population doing better with early PN was identified.
- Benefit of Late PN most pronounced in the severely ill.
- No difference between cardiac surgery and others.

EPaNIC, unpublished data
Mismatch = more or less than the optimal dose
RCT’s aiming at optimum nutrition intake

Adapted from:
Singer P. 2011 ICM
RCT's aiming at optimum nutrition intake

McClave 110% REE

N = 130

Adapted from:
Singer P. 2011 ICM

M.P.C., K.U.Leuven
RCT’s aiming at optimum nutrition intake

- Prolonged ICU stay
- Prolonged Mechanical ventilation
- Increased Infections
- ? Reduced mortality ?

N = 130
RCT’s aiming at optimum nutrition intake

McClave 110% REE

N = 4640
RCT’s aiming at optimum nutrition intake

N = 4640

M.P.C., K.U.Leuven
RCT’s aiming at optimum nutrition intake

Cummulative Energy Deficit

N = 4640
RCT’s aiming at optimum nutrition intake

- Prolonged ICU stay
- Prolonged Mechanical ventilation
- Increased Infection

N = 4640
RCT’s aiming at optimum nutrition intake

Interpretation of energy intake

Based on the 2012 ESPEN presentation by Doig GS

Displayed exclusively for the purpose of this discussion with kind permission of dr. Doig

N = 1372
RCT’s aiming at optimum nutrition intake in:

- No effect on primary endpoint
- Shorter mechanical ventilation?
- Improved subjective wellbeing

N = 1372
 Patients expected to stay more than 5 days and live more than 7 days

SPN started if EN < 60% of target on day 3

SPN group

Control group

Nutritional Target (°IC)
RCT’s aiming at optimum nutrition intake

Patients expected to stay more than 5 days and live more than 7 days

SPN started if EN < 60% of target on day 3

SPN group

Control group

Nutritional Target (° IC)

Day 1
Day 7
Day 4

EN
PN

Day 4

EN

Patients expected to stay more than 5 days and live more than 7 days

Less infections
Same ICU stay
N = 305

Heidegger CP.
2012

M.P.C., K.U.Leuven
A new concept of overfeeding? observational data

Hise <80%
Preiser <50%

- Hise ME
  2007 J Am Diet Assoc
- Preiser JC
  Glucontrol data
  Poster at ESPEN 2012
A new concept of overfeeding?

- Hise <80%
- Preiser <50%

- Hise ME
  2007 J Am Diet Assoc

- Preiser JC
  Glucontrol data
  Poster at ESPEN 2012

M.P.C., K.U.Leuven
Dose-response?

Estimating the effect of

increasing cumulative energy intake on

likelihood of earlier discharge from the ICU

AND

detecting an eventual superior energy dose

EPaNIC, unpublished data

M.P.C., K.U.Leuven
Dose-response?

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Late PN patient

Early PN patient

EPaNIC, unpublished data

M.P.C., K.U.Leuven
Dose-response?

Day 1

Day 3

Day 5

Day 7

EPaNIC, unpublished data
Dose-response?

Day 1  Day 3  Day 5  Day 7

EPaNIC, unpublished data
Dose-response?

Day 1  Day 3  Day 5  Day 7

EPaNIC, unpublished data
Dose-response?

Day 1  Day 3  Day 5  Day 7

EPaNIC, unpublished data  M.P.C., K.U.Leuven
Dose-response?

Day 1  Day 3  Day 5  Day 7

EPaNIC, unpublished data
Dose-response?

Day 1  Day 3  Day 5  Day 7

EPaNIC, unpublished data
Dose-response?

Likelihood for an earlier discharge from ICU ~ nutrition dose

EPaNIC, unpublished data
Dose-response?

10% of target /day increase in cumulative energy intake

was associated with

2 – 8% decrease in likelihood for an earlier discharge from ICU

~ p < 0,0001
Likelihood of an earlier alive ICU discharge for intervals of cumulative energy in % of target reached per day

Early PN (N = 2312)  Total Population (N = 4640)  Late PN (N = 2328)

<30% 30-60 60-70 70-90 >90%
Likelihood of an earlier alive ICU discharge for intervals of cumulative energy in % of target reached per day

Early PN (N = 2312)  
Total Population (N = 4640)  
Late PN (N = 2328)

EPaNIC, unpublished data

M.P.C. & G.V.d.B., K.U.Leuven
Likelihood of an earlier alive ICU discharge for intervals of cumulative energy in % of target reached per day

<table>
<thead>
<tr>
<th>Early PN (N = 2312)</th>
<th>Total Population (N = 4640)</th>
<th>Late PN (N = 2328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N analyzed = 1358 / 1438 (80 PO)</td>
<td>N analyzed = 823 / 913 (80 PO)</td>
<td>N analyzed = 1312 / 1390 (87 PO)</td>
</tr>
<tr>
<td>N analyzed = 893 / 975 (82 PO)</td>
<td>N analyzed = 823 / 913 (90 PO)</td>
<td>N analyzed = 823 / 913 (80 PO)</td>
</tr>
<tr>
<td>N analyzed = 677 / 738 (59 PO)</td>
<td>N analyzed = 823 / 913 (80 PO)</td>
<td>N analyzed = 823 / 913 (80 PO)</td>
</tr>
</tbody>
</table>

EPaNIC, unpublished data

M.P.C. & G.V.d.B., K.U.Leuven
Is less more when you are really ill?

Is less more when you are really ill?

Relative effect of glucose versus protein intake

### Likelihood of an earlier ICU discharge

<table>
<thead>
<tr>
<th>Day</th>
<th>Glucose Intake HR (CI)</th>
<th>Protein Intake HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 1</td>
<td>0.95 (0.85-1.05)</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>day 3</td>
<td>0.85 (0.75-0.95)</td>
<td>0.95 (0.85-1.05)</td>
</tr>
<tr>
<td>day 5</td>
<td>1.0 (0.9-1.1)</td>
<td>1.05 (0.95-1.15)</td>
</tr>
<tr>
<td>day 7</td>
<td>1.1 (1.0-1.2)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
</tbody>
</table>

- **HR (CI) per 10% of target increase in glucose intake** (± 28 g / day)
- **HR (CI) per 10% of target increase in protein intake** (± 7 g / day)
Postponing PN to beyond day 8 (while providing micronutrients) in ICU pts at risk for malnutrition:

- is superior to preventing caloric deficit with early PN
- accelerates recovery from organ failure
- reduces number of infections
- shortens hospital stay, without compromising functionality at hospital discharge
- is less costly for patient, hospital and society

Summary of clinical study findings

The untoward effect of Early PN:

- is independent of **type and severity of disease**
- Is present at **all nutrition doses** except the lowest: less is more even for enteral nutrition
- The association between enhanced intake and **delayed recovery** is **more pronounced for protein** than glucose.

Why?

No indirect calorimetry?

No Glutamine?

Protein dosing?

...
Underlying mechanisms?

M.P.C., K.U.Leuven
Withholding PN while providing parenteral micronutrients

Ziegler T
2011 N Engl J Med

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Ziegler T
2011 N Engl J Med

Less infections
Enhanced Recovery

+Micronutrients

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Withholding PN while providing parenteral micronutrients

Macronutrient restriction

+ 

Early Micronutrients

✓ Ziegler T
2011 N Engl J Med
Withholding PN while providing parenteral micronutrients

Macronutrient restriction

Early Micronutrients

Derde S
2012
Endocrinology
Balance between damage induction & removal

Critical illness
- Inflammation
- Hypoperfusion
- Hypoxia

Nutrients (Insulin) (Growth factors)

Hyperglycemia

INDUCTION OF DAMAGE

DAMAGE REMOVAL

Autophagy

M.P.C., K.U. Leuven
Under investigation…
Conclusions

• **Postponing PN to beyond day 7** in ICU patients at risk of malnutrition is superior to preventing caloric deficit with early PN

• **Underlying mechanisms** could relate to cellular damage removal, which is **suppressed by nutrients**
Conclusion

3 RCT’s, together > 6000 patients:
EPaNIC, SPN, Early PN
All agree
Conclusion

3 RCT’s, together > 6000 patients:
EPaNIC, SPN, Early PN

All Agree

Parenteral nutrition before day 8, prevents caloric deficit but

✓ Does not improve survival
✓ Does not shorten ICU or hospital stay
✓ Long term functional outcome results will learn us more
A new concept of overfeeding: also true for EN

The EDEN Randomized Trial

If less is equally beneficial than more, I’d prefer less

- No functional outcome
- Highly selected patients

Rice T
2011 JAMA

M.P.C., K.U.Leuven
FUNDING

**Methusalem** (Flemish Government)

**FWO** (Flemish Government)

**KULeuven GOA**

**UZLeuven KOF**

Baxter (< 30%) Unconditional research grant and speaker fee
Thank You

Laboratory and Department of Intensive Care Medicine
Thank you
Not enough protein in Early PN?


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Not enough protein in Early PN?


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Not enough protein in Early PN?


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Not enough protein in Early PN?


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Balance between damage induction & removal

High Energy Hyperglycemia
- Mortality: 8%

High Energy
- TGC 80 – 110 mg/dl
- Mortality: 6%

GVdB 1 & 2
Balance between damage induction & removal

High Energy

Hyperglycemia

Mortality: 8%

High Energy

TGC 80 – 110 mg/dl

Mortality: 6%

LOS ICU 4 [2 - 9]

Low Energy

TGC 80 – 110 mg/dl

Mortality: 6%

LOS ICU 3 [2 - 7]

GVdB 1 & 2

EPaNIC

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Balance between damage induction & removal

- **High Energy Hyperglycemia**
  - Mortality: 8%

- **Low Energy Other Glycemic Target**
  - ???
  - ???

- **High Energy**
  - TGC 80 – 110 mg/dl
  - Mortality: 6%
  - LOS ICU 4 [2 - 9]

- **Low Energy**
  - TGC 80 – 110 mg/dl
  - Mortality: 6%
  - LOS ICU 3 [2 - 7]

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How much energy, how much insulin?

- **No Early PN** in ICU

- **Early EN?** Recent trials showed no benefit…

  Rice TW. CCM 2011
  Ibrahim EH. JPEN 2002

- **Glycemic target** based on **accuracy of tools** and adequacy of insulin provision.
Critical illness is a state of excessive availability of glucose and lipids.