Nutrient requirements during the acute phase: The "baby stomach" concept

Jan Wernerman MD, PhD
Professor of Intensive Care Medicine
Karolinska Huddinge
Stockholm, Sweden
Jan Wernerman

Disclosure of potential conflicts of interest during the last 2 years:

Member of the Medical Advisory Boards and also invited speaker for Baxter, Danone, Fresenius-Kabi, GE Health Care, Grifols, and Nestlé
Nutrient requirements during the acute phase:
The "baby stomach" concept

Provision of Nutrients to the Acutely III
Introducing the “Baby Stomach” Concept

Preiser & Wernerman, AJRCCM 2017;196:1089-90
Role of Glucagon in Catabolism and Muscle Wasting of Critical Illness and Modulation by Nutrition

Steven E. Thiessen¹, Sarah Derde¹, Inge Derese¹, Thomas Dufour¹, Chloé Albert Vega¹, Lies Langouche¹, Chloë Goossens¹, Nele Peersman², Pieter Vermeersch², Sarah Vander Perre¹, Jens J. Holst³,⁴, Pieter J. Wouters¹, Ilse Vanhorebeek¹*, and Greet Van den Berghe¹*

¹Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, and ²Department of Laboratory Medicine, KU Leuven, Leuven, Belgium; and ³Novo Nordisk Foundation Center for Basic Metabolic Research and ⁴Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Copenhagen, Denmark
Rule of the Tumb

1. Set nutrition target (kcal+prot)
2. Start EN when possible
3. Calculate caloric and protein balances
4. Complementary PN on day 4-5-8
Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines

Annika Reintam Blaser\textsuperscript{1,2*}, Joel Starkopf\textsuperscript{1,3}, Waleed Alhazzani\textsuperscript{4,5}, Mette M. Berger\textsuperscript{6}, Michael P. Casaer\textsuperscript{7}, Adam M. Deane\textsuperscript{8}, Sonja Fruehwald\textsuperscript{9}, Michael Hiesmayr\textsuperscript{10}, Carole Ichai\textsuperscript{11}, Stephan M. Jakob\textsuperscript{12}, Cecilia I. Loudet\textsuperscript{13}, Manu L. N. G. Malbrain\textsuperscript{14}, Juan C. Montejo González\textsuperscript{15}, Catherine Paugam-Burtz\textsuperscript{16}, Martijn Poeze\textsuperscript{17}, Jean-Charles Preiser\textsuperscript{18}, Pierre Singer\textsuperscript{19,20}, Arthur R.H. van Zanten\textsuperscript{21}, Jan De Waele\textsuperscript{22}, Julia Wendon\textsuperscript{23}, Jan Wernerman\textsuperscript{24}, Tony Whitehouse\textsuperscript{25}, Alexander Wilmer\textsuperscript{26}, Heleen M. Oudemans-van Straaten\textsuperscript{27} and ESICM Working Group on Gastrointestinal Function
What do we know about energy needs?
Progression of energy delivery in ICU patients over time

Daily energy (kcal)

-1000 0 1000 2000 3000

weeks after admission

Cumulated energy deficit v. infections

Figure 2 Relation between the progressive negative energy balance and the number of infectious complications.

Weijs et al, cc 2014
Figure 1. The cumulative average caloric intake since ICU admission for each of 187 participants is shown. For example, a participant's cumulative average caloric intake for ICU day 5 is the mean for days 1 to 5. Similarly, a participant's cumulative average caloric intake for ICU day 10 is the mean caloric intake for ICU days 1 to 10. The last cumulative average caloric intake for each participant thus represents the average caloric intake from nutritional support over all ICU days for that participant. The mean caloric intake for each ICU day for all participants in the ICU is also shown. The horizontal line at caloric intake represents 100% of the target caloric intake recommended by ACCP guidelines.
Figure 1. The cumulative average caloric intake since ICU admission for each of 187 participants (a) is shown. For example, a participant’s cumulative average caloric intake for ICU day 5 is the mean for days 1 to 5. Similarly, a participant’s cumulative average caloric intake for ICU day 10 is the mean caloric intake for ICU days 1 to 10. The last cumulative average caloric intake for each participant thus represents the average caloric intake from nutritional support over all ICU days for that participant. The mean caloric intake for each ICU day (g) for all participants in the ICU is also shown. The horizontal line at caloric intake represents 100% of the target caloric intake recommended by ACCP guidelines.

27 kcal/kg


FIGURE 1. The cumulative average caloric intake since ICU admission for each of 187 participants is shown. For example, a participant’s cumulative average caloric intake for ICU day 5 is the mean for days 1 to 5. Similarly, a participant’s cumulative average caloric intake for ICU day 10 is the mean caloric intake for ICU days 1 to 10. The last cumulative average caloric intake for each participant thus represents the average caloric intake from nutritional support over all ICU days for that participant. The mean caloric intake for each ICU day (x) for all participants in the ICU is also shown. The horizontal line at caloric intake represents 100% of the target caloric intake recommended by ACCP guidelines.

27 kcal/kg
9-18 kcal/kg
Zusman et al, Crit Care 2016;20:367
Mortalitet 100 % efter 3 månader

Mortalitet 0 % efter 3 månader
Nutrition status

Relevant co-morbidities

Acute disease

Acute phase

Stable multiple organ failure phase

Rehabilitation phase
Over-fed ICU patient

Energy Expenditure

- Activity induced
- Diet induced
- Basal

Total energy intake

Endogenous energy stores

Stored energy
Wolfe, ejcn 1999;53(suppl 1):S136-S142

Figure 1  Rate of basal glucose production (□) and endogenous glucose production during glucose infusion (■) in a variety of critically ill patients. Values were determined by means of the infusion of 6,6-²H-glucose. *P< 0.05 vs normal volunteers. From: Wolfe et al, 1979a,b; Shaw & Wolfe, 1986a,b, 1987, 1989; Shaw et al, 1985.
### Glucose uptake in septic patients and volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Septic patients</th>
<th>Volunteers</th>
<th>Significance (between groups)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose uptake in step 1</td>
<td>3.61 (2.31–5.58)</td>
<td>11.0 (9.74–12.85)</td>
<td>-</td>
</tr>
<tr>
<td>Glucose uptake in step 2</td>
<td>6.4 (5.25–8.21 )</td>
<td>17.2 (14.05–19.20)</td>
<td>-</td>
</tr>
<tr>
<td>Significance (within groups)²: step 1 versus step 2</td>
<td>$P &lt; 0.001$</td>
<td>$P &lt; 0.01$</td>
<td>-</td>
</tr>
<tr>
<td>Difference between step 2 and step 1</td>
<td>2.5 (0.93, 4.47)</td>
<td>5.3 (4.14, 6.40)</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range). ¹By Wilcoxon’s nonpaired test. ²By Wilcoxon’s paired test.

### Glucose storage in septic patients and volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Septic patients</th>
<th>Volunteers</th>
<th>Significance (between groups)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose storage in step 1</td>
<td>0.4 (-0.4 to +3.19)</td>
<td>7.6 (5.80–9.50)</td>
<td>-</td>
</tr>
<tr>
<td>Glucose storage in step 2</td>
<td>2.3 (0.92–4.16 )</td>
<td>11.6 (9.70–13.60)</td>
<td>-</td>
</tr>
<tr>
<td>Significance (within groups)²: step 1 versus step 2</td>
<td>$P &lt; 0.01$</td>
<td>$P &lt; 0.01$</td>
<td>-</td>
</tr>
<tr>
<td>Difference between step 2 and step 1</td>
<td>1.51 (0.24–2.69)</td>
<td>4.0 (2.95–5.30)</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range). ¹By Wilcoxon’s nonpaired test. ²By Wilcoxon’s paired test.
Olthof et al,
Clin Nutr 2017 (Epubl)
What do we know about energy needs?

In the early phase of critical illness there is a mobilisation of endogenous stores that cannot be inhibited by exogenous nutrition supply.

Adjust energy target accordingly in particular when there are symptoms (or suspicion) of refeeding.
What about the Leuven experience?
Casaer et al, nejm 2011;365:506-17
Kaplan-Meier survival Plot

Days after randomization

Early PN
Late PN

Casaer et al, nejm 2011;365:506-17
A Discharge from ICU

Cumulative Proportion Discharged from ICU (%)

Days after Randomization

No. at Risk
Late initiation 2328 574 291 122
Early initiation 2312 646 342 147

Casaer et al, nejm 2011;365:506-17
### Online-table 6. Subgroup Analysis

<table>
<thead>
<tr>
<th></th>
<th>Primary outcome</th>
<th>Safety outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>time to alive discharge from ICU</td>
<td>discharged alive from ICU within 8 days</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Overall (N=4640)</td>
<td>1.063 (1.002-1.128)</td>
<td>1.271 (1.080-1.495)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>A priori defined subgroups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (&lt;25 OR ≥40) (N=1989)</td>
<td>1.045 (0.956-1.143)</td>
<td>1.239 (0.985-1.560)</td>
</tr>
<tr>
<td></td>
<td>0.5725</td>
<td>0.7985</td>
</tr>
<tr>
<td>NRS ≥5 (N=863)</td>
<td>1.059 (0.916-1.224)</td>
<td>1.222 (0.887-1.685)</td>
</tr>
<tr>
<td></td>
<td>0.8454</td>
<td>0.7898</td>
</tr>
<tr>
<td>Cardiac surgery (N=2818)</td>
<td>1.047 (0.971-1.129)</td>
<td>1.232 (0.963-1.599)</td>
</tr>
<tr>
<td></td>
<td>0.8616</td>
<td>0.7445</td>
</tr>
<tr>
<td>Sepsis admission (N=1015)</td>
<td>0.991 (0.866-1.134)</td>
<td>1.068 (0.820-1.439)</td>
</tr>
<tr>
<td></td>
<td>0.3198</td>
<td>0.2701</td>
</tr>
<tr>
<td><strong>Post-hoc defined subgroup</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical contraindication for EN* (N = 517)</td>
<td>1.198 (0.999 -1.437)</td>
<td>1.749 (1.141 - 2.683)</td>
</tr>
<tr>
<td></td>
<td>0.1197</td>
<td>0.1348</td>
</tr>
</tbody>
</table>

Casaer et al, nejm 2011;365:506-17
Early PN  
All patients  
Late PN

Casaer et al, ajrccm 2013;187:247-255
Fivez et al, nejm 2016;374:1111-22
Fivez et al, nejm 2016;374:1111-22
P = 0.25 by log-rank test
P = 0.08 (adjusted in multivariable analysis)

Cumulative Proportion of Patients Alive

Days after Inclusion

Late PN
Early PN

Fivez et al, nejm 2016;374:1111-22
Vanhorebeek et al, lancet resp med 2017;5:475-83
Vanhorebeek et al, Lancet Resp Med 2017;5:475-83
What about the Leuven experience?

Post hoc analysis of Leuven data suggest a less favorable outcome related to protein (amino acid) intake during the acute phase of critical illness.
So is hypocaloric feeding better?
Randomized studies with hypocaloric feeding

Table 1. Trials Comparing Standard Amounts of Enteral Nutrition With Lesser Amounts.

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Energy (kcal/kg/d) Delivered</th>
<th>Mortality, No./Total No. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Infectious Morbidity, No./Total No. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Permissive Underfeeding</td>
<td>Standard Feeding</td>
<td>Permissive Underfeeding</td>
</tr>
<tr>
<td>Arabi et al, 2011&lt;sup&gt;8&lt;/sup&gt;</td>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22/120 (18)</td>
</tr>
<tr>
<td>Rice et al, 2011&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22/98 (22)</td>
</tr>
<tr>
<td>NHLBI ARDS CTN, 2012&lt;sup&gt;6&lt;/sup&gt;</td>
<td>5&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>118/508 (23)</td>
</tr>
<tr>
<td>Rugeles et al, 2013&lt;sup&gt;9&lt;/sup&gt;</td>
<td>12</td>
<td>14</td>
<td>5/53 (9)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Charles et al, 2014&lt;sup&gt;10&lt;/sup&gt;</td>
<td>12.3</td>
<td>17.1</td>
<td>3/41 (7)</td>
</tr>
<tr>
<td>Arabi et al, 2015&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Unable to calculate&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Unable to calculate&lt;sup&gt;g&lt;/sup&gt;</td>
<td>121/445 (27)</td>
</tr>
<tr>
<td>Petros et al, 2016&lt;sup&gt;11&lt;/sup&gt;</td>
<td>11.3</td>
<td>19.7</td>
<td>18/46 (39)</td>
</tr>
</tbody>
</table>
So is hypocaloric feeding better?

So far there is poor evidence for a systematic hypocaloric feeding.
What do we know about protein needs?
Cumulated nitrogen balance over 1 w (g N)

daily nitrogen supply (g/kg bw)

-100
-80
-60
-40
-20
0
0.10
0.20
0.25
0.30

Larsson et al, Br J Surg 1990;77:413
Change in Total Body Protein

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Protein (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 7)</td>
<td>1.14 ± 0.13&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>B (n = 8)</td>
<td>1.47 ± 0.11&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>C (n = 8)</td>
<td>1.86 ± 0.14&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>p&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Ishibashi et al, CCM 1998;26:1529-35
Zusman et al, Crit Care 2016;20:367
Weijis et al, Crit Care 2014;18:701
Figure 2. Effect of protein delivery on mortality*

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns (2000)</td>
<td>1.13 (0.29–4.44)</td>
<td>3.10</td>
</tr>
<tr>
<td>Goeters (2002)</td>
<td>1.70 (0.57–5.10)</td>
<td>4.38</td>
</tr>
<tr>
<td>Ibrahim (2002)</td>
<td>1.45 (0.68–3.12)</td>
<td>7.14</td>
</tr>
<tr>
<td>Oztuna (2008)</td>
<td>1.11 (0.37–3.31)</td>
<td>4.41</td>
</tr>
<tr>
<td>Hsu (2009)</td>
<td>0.80 (0.39–1.65)</td>
<td>7.58</td>
</tr>
<tr>
<td>Rice (2011)</td>
<td>1.19 (0.60–2.35)</td>
<td>8.11</td>
</tr>
<tr>
<td>Singer (2011)</td>
<td>2.33 (1.07–5.09)</td>
<td>6.94</td>
</tr>
<tr>
<td>Huang (2012)</td>
<td>0.77 (0.34–1.75)</td>
<td>6.50</td>
</tr>
<tr>
<td>Heyland (2013)</td>
<td>0.78 (0.61–1.00)</td>
<td>15.09</td>
</tr>
<tr>
<td>Braunschweig (2014)</td>
<td>0.28 (0.10–0.83)</td>
<td>4.51</td>
</tr>
<tr>
<td>Ferrie (2015)</td>
<td>0.69 (0.27–1.79)</td>
<td>5.39</td>
</tr>
<tr>
<td>Doig (IV AA) (2015)</td>
<td>1.22 (0.76–1.98)</td>
<td>11.04</td>
</tr>
<tr>
<td>Doig (refeeding) (2015)</td>
<td>0.37 (0.19–0.70)</td>
<td>8.52</td>
</tr>
<tr>
<td>Qiu (2015)</td>
<td>1.20 (0.57–2.54)</td>
<td>7.29</td>
</tr>
<tr>
<td>Overall $(I^2 = 48.2%, P = 0.023)$</td>
<td>0.93 (0.72–1.22)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*Favours low protein vs favours high protein
Allingstrup et al, ICM 2017;43:1637-47
controls (n=235)  
protein (n=239)

mortality rate (%)  

P = 0.78  
P = 0.46  
P = 0.56

Doig et al, ICM 2015;41:1197-1208
What do we know about protein needs?

There is very limited evidence for a beneficial effect from a high protein intake in the early phase of critical illness, and it rests solely on observational data.

Also safety data are limited, and the Leuven experience is contradictory.
1. Set nutrition target (kcal+prot)
2. Start EN when possible
3. Calculate caloric and protein balances
4. Complementary PN on day 4-5-8

Nutrition target by indirect calorimetry (or 20 kcal/kg), (50-80) 100%, 1.0-1.5 g protein/kg
Our research is dedicated to the metabolic and nutritional problems of critically ill patients treated in the ICU.

We are a small research group dedicated to the metabolic and nutritional problems of critically ill patients in the intensive care unit (ICU).

**Latest news/meetings**

Program for our weekly Wednesday research meeting can be found [here](#).

Jonathan Grip will present his poster at the ESCIM meeting in Barcelona next week on Wednesday.
Thank you for listening!