ICU Nutrition - How Many Calories? How Much Proteins?

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Riyadh, Saudi Arabia
I have nothing to disclose.

Within the last 12 months I have not had any type of financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.
• Caloric target in enteral nutrition
• Nutrition across different baseline nutritional status
• The role of PN
• Protein amount
Early Versus Delayed Enteral Nutrition

Early Enteral Nutrition or Not?

Yaseen M. Arabi, MD, FCCP, FCCM, ATSF
Department of Intensive Care
King Abdulaziz Medical City
College of Medicine
King Saud bin Abdulaziz University for Health Sciences and
King Abdullah International Medical Research Center
Riyadh, Saudi Arabia

preventing or gastrointestinal concerns about EN have quest

In this issue the results of e d control lty within 24 hou
Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure

Todd W. Rice, MD, MSc; Susan Mogan, RN; Margaret A. Hays, RN, MSN; Gordon R. Bernard, MD; Gordon L. Jansen, MD, PhD; Arthur P. Wheeler, MD

**N=200**

**Online First**

Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury
The EDEN Randomized Trial

**N= 1000**
Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

Yaseen M. Arabi, M.D., Abdulaziz S. Aldawood, M.D., Samir H. Haddad, M.D., Hasan M. Al-Dorzi, M.D., Hani M. Tarnim, M.P.H., Ph.D., Gwynne Jones, M.D., Sangeeta Mehta, M.D., Lauralyn McIntyre, M.D., Othman Solaiman, M.D., Maram H. Sakkijha, R.D., Musharaf Sadat, M.B., B.S., and Lara Afesh, M.S.N., for the PerMIT Trial Group

N= 894

Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Permissive Underfeeding (N = 448)</th>
<th>Standard Feeding (N = 446)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia — no. (%)</td>
<td>6 (1.3)</td>
<td>7 (1.6)</td>
<td>0.85 (0.29–2.52)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypokalemia — no. (%)</td>
<td>101 (22.5)</td>
<td>91 (20.4)</td>
<td>1.10 (0.86–1.42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypomagnesemia — no. (%)</td>
<td>127 (28.3)</td>
<td>131 (29.4)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypophosphatemia — no. (%)</td>
<td>267 (59.6)</td>
<td>261 (58.5)</td>
<td>1.01 (0.91–1.14)</td>
<td>0.74</td>
</tr>
<tr>
<td>Transfusion of packed red cells — no. (%)</td>
<td>141 (31.5)</td>
<td>142 (31.8)</td>
<td>0.99 (0.82–1.20)</td>
<td>0.91</td>
</tr>
<tr>
<td>Incident renal-replacement therapy — no./total no. (%)</td>
<td>29/406 (7.1)</td>
<td>45/396 (11.4)</td>
<td>0.63 (0.40–0.98)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group*
Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis

Hasan M. Al-Dorzi\textsuperscript{1,2,3}, Abdullah Albarrak\textsuperscript{4}, Mazen Ferwana\textsuperscript{1,2,6}, Mohammad Hassan Murad\textsuperscript{2,8} and Yaseen M. Arabi\textsuperscript{1,2,3,*}

Group A: Studies that did not test calorie restriction as an intervention.
Group B: Studies that tested calorie restriction versus standard feeding strategy.

F for Group A studies: 15.0%  
F for Group B studies: 41.1%  
Overall F: 26.4%
Nutrition across different baseline nutritional status
Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial

Gordon S Dolg, Fiona Simpson, Philippa T Heighes, Rinaldo Bellomo, Douglas Chesher, Ian D Caterson, Michael C Rade, Peter W J Harrison, for the Refeeding Syndrome Trial Investigators Group

A. Mean caloric intake per study day

D. Lowest daily serum phosphates

Primary outcome: ICU free days no difference
The Nutrition Risk in Critically ill (NUTRIC) score: age, APACHE II score, SOFA score, number of co-morbidities, days from hospital admission to ICU admission

In a validation cohort:
- High NUTRIC: positive association between nutritional adequacy and 28 day survival
- Low NUTRIC: no association

Rahman Clin Nutr 2015
Permissive Underfeeding or Standard Enteral Feeding in High- and Low-Nutritional-Risk Critically Ill Adults
Post Hoc Analysis of the PermiT Trial

Yaseen M. Arabi¹, Abdulaziz S. Aldawood¹, Hasan M. Al-Dorzi¹, Hani M. Tamim¹,², Samir H. Haddad¹, Gwynne Jones³, Lauralyn McIntyre³, Othman Solaiman⁴, Maram H. Sakkijha⁴, Musharaf Sadat¹, Shihab Mundekkadian⁵, Anand Kumar⁶, Sean M. Bagshaw⁷, and Sangeeta Mehta⁷,⁸; for the PermiT trial group
The role of PN
**Early versus Late Parenteral Nutrition in Critically Ill Adults**

Michael P. Casaer, M.D., Dieter Mesotten, M.D., Ph.D., 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 Delaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D., Aime Van Assche, M.D., Simon Vanderheyden, B.Sc., Alexander Wilm, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Late-Initiation Group (N = 2328)</th>
<th>Early-Initiation Group (N = 2312)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital status — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged live from ICU within 8 days</td>
<td>1750 (75.2)</td>
<td>1658 (71.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ICU</td>
<td>141 (6.1)</td>
<td>146 (6.3)</td>
<td>0.76</td>
</tr>
<tr>
<td>In hospital</td>
<td>242 (10.4)</td>
<td>251 (10.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Within 90 days after enrollment†</td>
<td>257 (11.2)</td>
<td>255 (11.2)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Kidney failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified RIFLE category — no. (%)</td>
<td>104 (4.6)</td>
<td>131 (5.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Renal-replacement therapy — no. (%)</td>
<td>201 (8.6)</td>
<td>205 (8.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Median duration of renal-replacement therapy (interquartile range) — days</td>
<td>7 (3–16)</td>
<td>10 (5–23)</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Early versus Late Parenteral Nutrition in Critically Ill Children

Torm Fize, M.D., Dorian Kerlaan, M.D., Dieter Mesotter, M.D., Ph.D., Sascha Verbruggen, M.D., Ph.D., Pieter J. Wouters, M.Sc., Ilse Vanhorebeek, Ph.D., Yves Debaeye, M.D., Ph.D., Dirk Vlaeselaers, M.D., Ph.D., Lars Desmet, M.D., Michael P. Casaer, M.D., Ph.D., Gonzalo Garcia Guerra, M.D., Jan Hanot, M.D., Ari Joffe, Ph.D., Dick Tibboel, M.D., Ph.D., Koen Joosten, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early Parenteral Nutrition (N=723)</th>
<th>Late Parenteral Nutrition (N=717)</th>
<th>P Value</th>
<th>Adjusted Odds Ratio or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>New infections — no. (%)</td>
<td>134 (18.5)</td>
<td>77 (10.7)</td>
<td>&lt;0.001</td>
<td>0.48 (0.35–0.66)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total duration of stay in pediatric ICU — days‡</td>
<td>9.2±0.8</td>
<td>6.5±0.4</td>
<td>0.002</td>
<td>1.23 (1.11–1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Duration of mechanical ventilatory support — days</td>
<td>6.4±0.7</td>
<td>4.4±0.3</td>
<td>0.01</td>
<td>1.19 (1.07–1.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of hemodynamic support — days</td>
<td>3.0±0.3</td>
<td>2.4±0.2</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney failure with renal-replacement therapy — no. (%)</td>
<td>26 (3.6)</td>
<td>18 (2.5)</td>
<td>0.28</td>
<td>0.49 (0.24–0.96)‡</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Enteral group (n=1202)</td>
<td>Parenteral group (n=1208)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---</td>
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<td></td>
<td></td>
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<tr>
<td>SAPS II</td>
<td>59 (19)</td>
<td>61 (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA at baseline</td>
<td>11 (3)</td>
<td>11 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressor support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine alone</td>
<td>978 (81%)</td>
<td>973 (81%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine alone</td>
<td>43 (4%)</td>
<td>48 (4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine alone</td>
<td>28 (2%)</td>
<td>37 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least two drugs</td>
<td>144 (12%)</td>
<td>138 (11%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine dose (μg/kg per min)</td>
<td>0.56 (0.30-1.20)</td>
<td>0.50 (0.25-1.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### NUTRIREA-2 Trial

<table>
<thead>
<tr>
<th></th>
<th>Enteral group (n=1202)</th>
<th>Parenteral group (n=1208)</th>
<th>Absolute difference (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28 mortality</td>
<td>443/1202 (37%)</td>
<td>422/1208 (35%)</td>
<td>2.0 (–1.9 to 5.8)</td>
<td>..</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>GI complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>406 (34%)</td>
<td>246 (24%)</td>
<td>1.89 (1.62 to 2.20)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>432 (36%)</td>
<td>393 (33%)</td>
<td>1.20 (1.05 to 1.37)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Bowel ischemia</td>
<td>19 (2%)</td>
<td>5 (&lt;1%)</td>
<td>3.84 (1.43 to 10.3)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Colonic pseudo-obstruction</td>
<td>11 (1%)</td>
<td>3 (&lt;1%)</td>
<td>3.7 (1.03 to 13.2)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>
SCCM webcast: Should patients on vasopressors receive enteral nutrition? PRO/CON debate

@YaseenarabiYa  @Paul_Wischmeyer
Thursday Jan 23, 2020 at 1p Central time
Phase 3 Pilot Randomized Controlled Trial Comparing Early Trophic Enteral Nutrition With “No Enteral Nutrition” in Mechanically Ventilated Patients With Septic Shock

Jayshil J. Patel, MD¹; Michelle Kozeniecki, MS, RD, CNSC²; William J. Peppard, PharmD³; Sarah R. Peppard, PharmD⁴,⁵; Stephanie Zellner-Jones, MS, CCRC⁶; Jeanette Graf, CCRP⁶; Aniko Szabo, PhD⁷; and Daren K. Heyland, MD⁸

**Diagram:**
- **Patient Admitted With Septic Shock**
  - No Feeding
  - Randomize
  - Trophic EN, <600 kcal/day
  - Vasopressors Off 3 Hours
    - No
    - Are GRV >500 mL? (Yes: Hold EN; No: Advance to Goal Per RD)
    - Yes: Follow GRV protocol
  - Yes

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¹²³⁴⁵⁶⁷⁸: Authors or institutions associated with the study.
How about protein?
Catabolic state and proteolysis, primarily in the skeletal muscles.

The amino acids released into the circulation are used for tissue repair and synthesis of acute phase proteins and other inflammatory mediators.

This may be associated with

- Immunosuppression
- Poor wound healing
- Intensive care unit (ICU)–acquired weakness
- Increased mortality
- Delayed recovery.

Liebau F, Am J Clin Nutr 2015
Arabi YM, Intensive Care Med 2017
Fock RA, Nutrition 2010
Rai J, Orthopedics 2002
Latronico N, Intensive Care Med 2017
Higher protein intake has been thought to mitigate the negative protein catabolic state by increasing the availability of exogenous amino acids.

Several observational studies suggested that outcomes are improved with higher protein intake.

Current clinical practice guidelines suggest protein intake in the range of 1.2–2.5 g/kg/d.

Casaer MP, Am J Respir Crit Care Med 2013
McClave SA, JPEN J Parenter Enteral Nutr 2016
• Daily supplement of up to 100 g of IV amino acids or standard care.

• No difference in the primary outcome (mean duration of renal dysfunction)

• No difference in mortality (or other secondary or tertiary outcomes)
Role of Disease and Macronutrient Dose in the Randomized Controlled EPaNIC Trial: A Post Hoc Analysis

Michael P. Casaer\textsuperscript{1,2}, Alexander Wilmer\textsuperscript{3}, Greet Hermans\textsuperscript{2,3}, Pieter J. Wouters\textsuperscript{1,2}, Dieter Mesotten\textsuperscript{1,2}, and Greet Van den Berghe\textsuperscript{1,2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Time to live discharge from the intensive care unit (ICU): Relation to glucose dose as compared with protein dose. Effect size per 10\% increments of target per day in cumulative glucose intake (~\pm 28 g/d) (yellow) and cumulative protein intake (~\pm 7 g/d) (green) in a time-to-alive ICU discharge analysis corrected for severity and type of disease. Normalized glucose target was 276.4 (\pm 70.8) g/day and}
# Association of protein intake with the outcomes of critically ill patients: a post hoc analysis of the PermiT trial

YM Arabi,1,2 HM Al-Dorzi,1,2 S Mehta,3 HM Tamim,1,2,4 SH Haddad,3 G Jones,5 L McIntyre,5 O Solaiman,6 MH Sakkija,2 M Sadat,1,2 L Afesh,1,2 A Kumar,2 SM Bagshaw,6 AS Aldawood,1,2 and the PermiT Trial Group

<table>
<thead>
<tr>
<th></th>
<th>Higher-protein group (&gt; 0.80 g/kg)</th>
<th>Lower-protein group (≤ 0.80 g/kg)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>N=365</td>
<td>N=364</td>
<td>0.80 (0.56, 1.16)</td>
<td>-</td>
</tr>
<tr>
<td>Low NUTRIC score</td>
<td>88/364 (24.2)</td>
<td>94/363 (25.9)</td>
<td>0.80 (0.56, 1.16)</td>
<td>-</td>
</tr>
<tr>
<td>High NUTRIC score</td>
<td>47/251 (18.7)</td>
<td>35/209 (16.8)</td>
<td>1.05 (0.63, 1.75)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>41/113 (36.3)</td>
<td>59/154 (38.3)</td>
<td>0.60 (0.33, 1.09)</td>
<td></td>
</tr>
</tbody>
</table>
### Number of Patients

<table>
<thead>
<tr>
<th></th>
<th>Study day 1</th>
<th>Study day 7</th>
<th>Study day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-protein</td>
<td>266</td>
<td>249</td>
<td>196</td>
</tr>
<tr>
<td>Lower-protein</td>
<td>297</td>
<td>262</td>
<td>185</td>
</tr>
</tbody>
</table>

### Study Day

- **Transferrin (g/L)**
  - Study day 1: 1.0
  - Study day 7: 1.2
  - Study day 14: 1.4

- **Prealbumin (g/L)**
  - Study day 1: 0.05
  - Study day 7: 0.10
  - Study day 14: 0.15

- **24-hour Nitrogen Balance (grams)**
  - Study day 1: -14
  - Study day 7: -12
  - Study day 14: -10

- **24-hour Urinary Urea Nitrogen (mmol/d)**
  - Study day 1: 100
  - Study day 7: 200
  - Study day 14: 300

### P-values

- **Transferrin (g/L)**: *P* = 0.08 for the main effect of the group
  - *P* < 0.0001 for the main effect of time
  - *P* = 0.12 for the time by group difference

- **Prealbumin (g/L)**: *P* = 0.003 for the main effect of the group
  - *P* < 0.0001 for the main effect of time
  - *P* < 0.0001 for the time by group difference

- **Nitrogen Balance (grams)**: *P* = 0.002 for the main effect of the group
  - *P* < 0.0001 for the main effect of time
  - *P* < 0.0001 for the time by group difference

- **Urea Nitrogen (mmol/d)**: *P* = 0.0002 for the main effect of the group
  - *P* < 0.0001 for the main effect of time
  - *P* < 0.0001 for the time by group difference

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**Critical Care Forum**

[Logo]
High vs. Low Protein Dose in Critical Ill Patients

Heyland DK, Nutrients

Fetterplace, JPEN 2019
Ongoing Trials
The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-Based Randomized Trial: The EFFORT Trial

- **High protein dose** (≥ 2.2 g/kg/day)
- **Low protein dose** (≤ 1.2 g/kg/day)

**4000 nutritionally high risk ICU patients**

**OUTCOMES**
- 60-day mortality
- Time to discharge alive from hospital
Patients mechanically ventilated on ICU day 4

Protein 0.8-1.2 g/kg/day from the feeding formula

Protein 0.8-1.2 g/kg/day from the feeding formula + 1.2 g/kg/day supplemental enteral protein

PRIMARY OUTCOME
• 90 day all-cause mortality

SECONDARY OUTCOMES
• Days alive at day 90 without life support
• Days alive and out of hospital at day 90
• New or progression of Skin Pressure Ulcers
• Bacteremia until 2 days post ICU
• Functional assessment using SARC-F screen for sarcopenia on 90 day
• EuroQol (EQ)-5D-5L on day 90
• Safety outcomes
• Stage 2 or higher AKI by KDIGO criteria after enrollment
• Re-feeding syndrome
• Severe diarrhea,
• Grade III or IV Acute Gastrointestinal injury (AGI)
RESEARCH AGENDA

The intensive care medicine research agenda in nutrition and metabolism


Pre-morbid condition  Acute illness  ICU  Recovery phase  Post-recovery phase

Underlying nutritional risk/ underlying functional status
Inflammation  Insulin resistance  Catabolism/ anabolism  Energy expenditure  Rehabilitation

GI intolerance  Oxidative stress  Autophagy

Nutritional therapy in the ICU
- Energy and protein amount
- Macronutrients
- Micronutrients
- Antioxidants
- Route of nutrition
EDITORIAL

Less is more in nutrition: critically ill patients are starving but not hungry

Yaseen M. Arabi1*, Annika Reintam Blaser2,3 and Jean-Charles Preiser4
Conclusions

- Early EN, no need to push for full feeding. Trophic or permissive underfeeding are OK in early days.
- In patients with re-feeding syndrome: restricted caloric intake may be preferred
- Early PN is not recommended.
- In patients with severe shock, postpone EN or start trophic or permissive underfeeding
- Follow current guidelines regarding amount of protein, but evidence from RCT is needed
Thank you.

@YaseenarabiYa