The importance of early EN and the role of early PN in the ICU: Improving outcomes and reducing costs.

Dr. Gordon S. Doig
Associate Professor in Intensive Care
Northern Clinical School Intensive Care Research Unit,
University of Sydney, Sydney, Australia
www.EvidenceBased.net
gdoig@med.usyd.edu.au
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Summary of this talk

- Review the most recent clinical evidence on the topic.

- Discuss physiological ramifications.

- Present clinical evidence that supports the physiology.

- Address costs.

- Conclude.
Background: Review of the Guidelines

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.

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2016 SCCM and ASPEN guideline (eEN < 48h)

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<tbody>
<tr>
<td>Bajer-Holgersen 1999</td>
<td>2</td>
<td>30</td>
<td>4.0%</td>
<td>0.50 [0.10, 2.63]</td>
</tr>
<tr>
<td>Carr 1996</td>
<td>0</td>
<td>14</td>
<td>14.0%</td>
<td>0.33 [0.01, 7.55]</td>
</tr>
<tr>
<td>Ciiarelli 1990</td>
<td>0</td>
<td>10</td>
<td>10.0%</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Choung-Sook 1996</td>
<td>21</td>
<td>17</td>
<td>2.7%</td>
<td>0.27 [0.03, 2.37]</td>
</tr>
<tr>
<td>Kompal 1998</td>
<td>0</td>
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<tr>
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<td>27</td>
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<td>Moore 1996</td>
<td>1</td>
<td>32</td>
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</tr>
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<td>Nguyen 2008</td>
<td>6</td>
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<td>Peck 2004</td>
<td>4</td>
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<td>16</td>
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<tr>
<td>Waters 1997</td>
<td>0</td>
<td>13</td>
<td>13.0%</td>
<td>Not estimable</td>
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<td>Choudhary 2012</td>
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<tr>
<td>Singh 1998</td>
<td>4</td>
<td>21</td>
<td>8.2%</td>
<td>1.05 [0.30, 3.68]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>483</td>
<td>483</td>
<td>100.0%</td>
<td>0.70 [0.49, 1.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%

21 clinical trials

**2016 SCCM and ASPEN guideline (eEN < 48h)**

<table>
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<tr>
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<tbody>
<tr>
<td>Reisser-Hogerson 1998</td>
<td>2</td>
<td>10</td>
<td>0.60 (0.40, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Carr 1998</td>
<td>14</td>
<td>14</td>
<td>1.48 (1.14, 1.92)</td>
<td></td>
</tr>
<tr>
<td>Chiarelli 1998</td>
<td>0</td>
<td>10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Chumraschul 1996</td>
<td>1</td>
<td>15</td>
<td>0.76 (0.47, 1.21)</td>
<td></td>
</tr>
<tr>
<td>Kompan 1998</td>
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<tr>
<td>Pupels 2000</td>
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<td>Schroeder 1991</td>
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<td>Everard 1993</td>
<td>2</td>
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<tr>
<td>Mahler 2004</td>
<td>12</td>
<td>100</td>
<td>0.50 (0.30, 0.87)</td>
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<td><strong>Total (95% CI)</strong></td>
<td><strong>463</strong></td>
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<tr>
<td><strong>Favours (experimental)</strong></td>
<td><strong>Favours (control)</strong></td>
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**21 clinical trials with significant (P=0.05) mortality reduction by 5%**

**Recommended early EN within 24 to 48 h of ICU admission**

**2016 SCCM and ASPEN guideline (eEN < 48h)**

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<td>Sagar 1976</td>
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</table>

**Total (95% CI)**: 483 / 483 100.0% 0.70 [0.49, 1.00]

**Test for overall effect: Z = 1.97 (P = 0.05)**

**Test for subgroup differences: CHI^2 = 1.84, df = 1 (P = 0.36), I^2 = 0%**

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21 clinical trials with significant (P=0.05) mortality reduction by 5%

**Recommends early EN within 24 to 48 h of ICU admission**

2016 SCCM and ASPEN guideline (eEN < 48h)

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<tr>
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<td>&lt; 24h</td>
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<tr>
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<td>&lt; 31h</td>
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<td>&lt; 60h</td>
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<tr>
<td>Minard 2003</td>
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<td>Moses 2003</td>
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<tr>
<td>Sagar 1979</td>
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<td>&lt; 48h</td>
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<td>Singh 1998</td>
<td>4</td>
<td>21</td>
<td>8.2 (0.30, 3.68)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>483</td>
<td>483</td>
<td>100.0% (0.40, 1.00)</td>
</tr>
</tbody>
</table>

21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

2016 SCCM and ASPEN guideline (eEN < 48h)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN</th>
<th>Delayed/None EN</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
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<td>Total</td>
<td>Weight</td>
<td>M H, Random, 95% CI</td>
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<tr>
<td>&lt; 24h</td>
<td>2</td>
<td>30</td>
<td>4.9%</td>
<td>0.50 [0.10, 2.63]</td>
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<tr>
<td>&lt; 24h</td>
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<td>14</td>
<td>1.3%</td>
<td>0.33 [0.01, 7.55]</td>
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<tr>
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</tr>
<tr>
<td>&lt; 24h</td>
<td>1</td>
<td>21</td>
<td>2.7%</td>
<td>0.27 [0.03, 2.37]</td>
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<tr>
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<td>0</td>
<td>14</td>
<td>1.3%</td>
<td>0.33 [0.01, 7.55]</td>
</tr>
<tr>
<td>&lt; 24h</td>
<td>0</td>
<td>27</td>
<td>1.3%</td>
<td>0.31 [0.01, 7.26]</td>
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<tr>
<td>&lt; 24h</td>
<td>1</td>
<td>32</td>
<td>31.0%</td>
<td>0.48 [0.05, 5.07]</td>
</tr>
<tr>
<td>&lt; 24h</td>
<td>6</td>
<td>14</td>
<td>14.1%</td>
<td>1.00 [0.33, 1.35]</td>
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<tr>
<td>&lt; 24h</td>
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<td>11.0%</td>
<td>0.74 [0.25, 2.10]</td>
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<td>3.2%</td>
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<td>0.14 [0.02, 1.09]</td>
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<tr>
<td>&lt; 24h</td>
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<td>16</td>
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<tr>
<td>&lt; 24h</td>
<td>0</td>
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</tr>
<tr>
<td>&lt; 48h</td>
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<td>34</td>
<td>23.4%</td>
<td>1.10 [0.39, 3.69]</td>
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<td>&lt; 72h</td>
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<tr>
<td>&lt; 31h</td>
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<td>19</td>
<td>3.7%</td>
<td>1.00 [0.10, 6.30]</td>
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<td>10</td>
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<tr>
<td>&lt; 60h</td>
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<td>1.03 [0.33, 3.67]</td>
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<tr>
<td>&lt; 48h</td>
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<td>21</td>
<td>22.0%</td>
<td>1.05 [0.30, 3.66]</td>
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</tbody>
</table>

Total (95% CI) 483 100.0% 0.70 [0.49, 1.00]

Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 1.84, df = 1 (P = 0.36, P = 0.8%)

21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

2016 SCCM and ASPEN guideline (eEN < 48h)

21 clinical trials with significant (P=0.05) mortality reduction by 5%

Recommends early EN within 24 to 48 h of ICU admission

2016 SCCM and ASPEN guideline (eEN < 48h)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Delayed/None EN Events</th>
<th>Delayed/None EN Total</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
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<tbody>
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<tr>
<td>1.2.1 EN &lt; 24 h vs. later</td>
<td>2 30 4 30 4.9%</td>
<td>0.50 (0.10, 2.53)</td>
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<tr>
<td>&lt; 24h</td>
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<td>1.10 (0.20, 5.12)</td>
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</table>

### 2016 SCCM and ASPEN guideline (eEN < 48h)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None EN Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<td>Weight</td>
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<td>Choudhury 1996</td>
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<td>1.3%</td>
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<td>Kompan 2004</td>
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<td>25%</td>
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<td>31%</td>
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<td>6</td>
<td>14%</td>
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<tr>
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<td>13%</td>
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<td>15%</td>
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<td>Moses 2009</td>
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<td>Singh 1998</td>
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## 2016 SCCM and ASPEN guideline (eEN < 48h)

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<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None EN Events</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
<th>Risk Ratio M.H. Random, 95% CI</th>
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<tr>
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<td>0.17 [0.03, 0.83]</td>
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<td>Moore 1988</td>
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<td>2</td>
<td>0.48 [0.05, 4.70]</td>
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<td>6</td>
<td>1.00 [0.43, 2.30]</td>
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<tr>
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<td>0.74 [0.35, 1.60]</td>
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<td>Pupels 2001</td>
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<td>0.14 [0.02, 1.09]</td>
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<td>Schioeder 1993</td>
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<td>Waters 1997</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td><strong>247</strong></td>
<td><strong>0.50 [0.35, 0.98]</strong></td>
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**Total events:** 16 of 35

Heterogeneity: Tau² = 0.00, Chi² = 6.34, df = 9 (P = 0.80); I² = 0%

Test for overall effect: Z = 2.03 (P = 0.04)

| 1.2.2 EN < 48 h vs. later |               |                        |                                |                                |
|---------------------------|----------------|------------------------|--------------------------------|                                |
| Choudakis 2012            | 3              | 25                     | 4.4%                           | 1.10 [0.20, 5.12]              |
| Driscoll 2004             | 0              | 10                     | Not estimable                  |                                |
| Ever 1993                 | 2              | 19                     | 3.7%                           | 1.00 [0.19, 5.38]              |
| Malhotra 2004             | 12             | 100                    | 23.5%                          | 0.75 [0.31, 1.80]              |
| Minard 2000               | 1              | 15                     | 36%                            | 0.31 [0.04, 2.44]              |
| Moses 2008                | 3              | 30                     | 56%                            | 1.03 [0.23, 4.71]              |
| Sagar 1979                | 0              | 15                     | Not estimable                  |                                |
| Singh 1999                | 4              | 22                     | 82%                            | 1.05 [0.30, 3.66]              |

### 2016 SCCM and ASPEN guideline (eEN < 48h)

<table>
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<th>Delayed/None EN Events</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
</tr>
</thead>
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<td>Total</td>
<td>Total</td>
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<td>247</td>
<td>48.6%</td>
<td>0.50 (0.35, 0.98)</td>
</tr>
</tbody>
</table>

Total events 16

Heterogeneity Test $\chi^2 = 6.23, \text{df} = 9 (P = 0.80); I^2 = 0$

Test for overall effect $Z = 1.03 (P = 0.04)$

### 1.2.2 EN < 48 h vs. later

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None EN Events</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
<th>Risk Ratio M.H., Random, 95% CI</th>
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<td>Sagar 1979</td>
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<td>Singh 1999</td>
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## 2016 SCCM and ASPEN guideline (eEN < 48h)

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<tr>
<th>Study or Subgroup</th>
<th>Early EN 24h EN &lt; 24h</th>
<th>Delayed/None EN</th>
<th>Risk Ratio</th>
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<td>Pack 2004</td>
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<td>Schroeder 1991</td>
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<td>Watts 1997</td>
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<td>Subtotal (95% CI)</td>
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<tr>
<td>1.26</td>
<td>246</td>
<td>247</td>
<td>48.6%</td>
<td>0.50 (0.35, 0.98)</td>
</tr>
</tbody>
</table>

| Total events | 16 | 35 |

Heterogeneity: Test 0.00, d.f. 6.2, P = 0 (P = 0.80); I² = 0%

Test for overall effect Z = 2.03 (P = 0.04)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN 48 h</th>
<th>Delayed/None EN</th>
<th>Risk Ratio</th>
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<td>Sagar 1979</td>
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### 2016 SCCM and ASPEN guideline (eEN < 48h)

<table>
<thead>
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<th>Study or Subgroup</th>
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<td>246</td>
<td>247</td>
<td>48.6%</td>
<td>0.50 (0.35, 0.98)</td>
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<th>Study or Subgroup</th>
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<th>Risk Ratio</th>
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<td>Total</td>
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<td>Singh 1999</td>
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</table>

Most recent SCCM/ASPEN guideline includes 21 clinical trials

2016 SCCM and ASPEN guideline (eEN < 48h)

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• Trials that start EN within 24 h of ICU admission show significant reduction in mortality (P=0.04).

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Why?

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- After glycogen is depleted, protein becomes the primary energy source.

When are glycogen stores depleted?
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- So, the rest of our metabolic needs must be met by liver glycogen.
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  - gastrointestinal barrier cells
  - brain

Sequential Changes in the Metabolic Response in Critically Injured Patients During the First 25 Days After Blunt Trauma


From the University Department of Surgery* and Department of Critical Care Medicine, †Auckland Hospital, Auckland, New Zealand


Diaphragmatic function
Diaphragmatic function is compromised within 24 h:

- Light microscopy of diaphragm biopsies show proteolysis is increased in critically ill patients after only **18 h** of mechanical ventilation

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*What do we know about autophagy?*


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During starvation, autolysosomes do not just target damaged structures. Their action is ‘non-selective’.

“In nutrient deprivation, autophagy activates bulk protein (non-selective) degradation to harvest amino acids as a fuel for ATP production through the tricarboxylic acid (TCA) cycle.”

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“We speculate that blocking or attenuating diaphragm proteolytic pathways in patients on mechanical ventilation might mitigate the weaning problems that occur in some patients.”


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**Protein intake down regulates autophagy by a factor of 2 to 5 times within 20 minutes.**


Gut barrier function
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  - Lysozyme, α-defensins plus
- These antimicrobial peptides protect against bacterial translocation and also protect the gut stem cells from damage.

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- *structural changes that explained these functional correlates.*

Gut barrier function

Globules to be secreted into lumen of small intestine

Antimicrobial protein globules

Gut barrier function

Fasting led to proteolysis in Paneth cells, with significant increase in late-stage degradative autophagolysosomes (autophagy).

Fasting led to **proteolysis** in Paneth cells, with significant increase in **late-stage degradative autophagolysosomes** (*autophagy*).

Increase in autophagy compromised Paneth cell gut-barrier function.

Traumatic brain injury (TBI)
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Autophagy can be detected using biochemical markers.
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CSF was collected from children with TBI on day 1, 3 and 7 post-injury.

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Tissue samples were obtained from adults who underwent a decompressive craniectomy as management for high intracranial pressure after TBI

- Assays for protein LC3-II and Beclin 1 found evidence of ongoing proteolysis (autophagy) that peaked at 24 h post-injury.
- None of these patients had started feeding prior to the time of the biopsy.


Starting feeding *later than* 24 h
Starting feeding **later than 24 h**

- 2016 SCCM/ASPEN guideline
- Trials that commence EN within 48 h of ICU admission show NO reduction in mortality (P=0.44).
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- Furthermore, delay for longer than 24 h depletes liver glycogen stores and stimulates proteolysis:
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  - gut barrier function,
  - and perhaps even brain function (delirium, long-term cognitive impairment).

Starting feeding within 24 h
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  - Preserves gut barrier function (reduced GI haemorrhage P=0.0005; sepsis P<0.0001; and pneumonia P=0.01).
  - *In a mouse model of TBI, partially inhibited autophagy leading to improvements in behavioural and histological outcomes.*


The importance of Early EN

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
- At least five major clinical practice guidelines recommend *early* EN.

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<th>Guideline Details</th>
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There is no evidence of mortality benefit if EN is started later than 24 h.
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Based on clinical trials in updated meta-analyses, we recommend that EN should begin within 24 h of ICU admission.
The importance of Early EN

- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
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There is no evidence of mortality benefit if EN is started *later than 24 h*.

Based on clinical trials in updated meta-analyses, we recommend that EN should begin within 24 h of ICU admission, as soon as shock is stabilised:

- Shock Index ≤ 1 (Heart rate / SBP) for one hour or
- SBP > 100 mmHg without need for *increasing* doses of vasoactive agents for one hour.

*Stable shock is not defined by weaning or removing all vasoactive agents.*
Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults
A Cluster Randomized Controlled Trial


Evidence demonstrates that providing nutritional support to intensive care unit (ICU) patients within 24 hours of ICU admission reduces mortality. However, early feeding is not universally practiced. Changing practice in complex multidisciplinary environments is difficult. Evidence supporting whether guidelines can improve ICU feeding practices and patient outcomes is contradictory.

Objectives To determine whether evidence-based feeding guidelines, implemented using a multifaceted practice change strategy, improve feeding practices and reduce mortality in ICU patients.

Design, Setting, and Patients Cluster randomized trial in ICUs of 27 community and tertiary hospitals in Australia and New Zealand. Between November 2003 and May 2004, 1118 critically ill adult patients expected to remain in the ICU longer than 2 days were enrolled. All participants completed the study.

Interventions Interventions were randomly assigned to guideline or control groups. Guideline ICUs developed an evidence-based guideline using Browman’s Clinical Practice Guideline Development Cycle. A practice-change strategy composed of 18 specific interventions, leveraged by educational outreach visits, was implemented in guideline ICUs.

Main Outcome Measures Hospital discharge mortality. Secondary outcomes included ICU and hospital length of stay, organ dysfunction, and feeding process measures.

Results Guideline and control ICUs enrolled 561 and 557 patients, respectively. Guideline ICUs fed patients earlier (0.75 vs 1.37 mean days to enter enteral nutrition start; difference = -0.62 [95% confidence interval (CI), -0.82 to -0.42]; P < 0.001) and achieved caloric goals more often (61.0 vs 50.2 mean days per 10 fed patient-days; difference = 1.07 [95% CI, 0.12 to 2.22]; P = 0.03). Guideline and control ICUs did not differ with regard to hospital discharge mortality (28.9% vs 27.4%; difference = 1.4% [95% CI, -6.3% to 12.0%]; P = 0.75) or to hospital length of stay (24.2 vs 24.3 days; difference = -0.08 [95% CI, -3.8 to 3.4]; P = 0.79) or ICU length of stay (9.1 vs 9.9 days; difference = -0.86 [95% CI, -2.6 to 1.3]; P = 0.62).

Conclusions Using a multifaceted practice change strategy, ICUs successfully developed and introduced an evidence-based nutritional support guideline that promoted earlier feeding and greater nutritional adequacy. However, use of the guideline did not improve clinical outcomes.

Trial Registration anzctr.org.au Identifier: ACTRN12608000407392 (JAMA. 2008;300(23):2731-41.)
**Evidence-based ICU feeding algorithm**

At ICU admission: Should this patient be fed?
- **YES**
  - Can EN be started within 24 hours?
    - **YES**
      - GASTRIC CHALLENGE
        - Use full strength concentration
        - Consider prokinetic with challenge
        - GOAL: at least 80% of requirements at 72h
        - Assess q12h
      - Will at least 80% of requirements be met by 72h?
        - **YES**
          - Is Goal met?
            - **YES**
              - Increase rate to 100%
            - **NO**
              - Use prokinetic and/or use post-pyloric tube
        - **NO**
          - Is Goal met?
            - **YES**
              - Continue EN to Max, tolerated
            - **NO**
              - Supplement with PN
              - Continue EN challenges q12h
- **NO**
  - Acceptable conditions:
    - tolerating adequate oral intake
    - < 24 hours to oral intake
    - Palliative care
  - Acceptable conditions:
    - Acute pancreatitis¹
    - Enteric anastomosis
    - Ischemic bowel
    - Enteric fistula
    - Imminent bowel resection
    - Imminent endoscopy
    - Bowel obstruction
    - High nasogastric losses on admission
    - Severe exacerbation of IBD
  - May still opt for elemental feeds
  - Begin TPN:
    - Consider TPN with glutamine
    - Reassess q12h for EN eligibility

Chief Investigator: Dr. Gordon S. Doig, University of Sydney. Contact: gdoig@med.usyd.edu.au
ICU GUIDELINES

Evidence-based ICU feeding algorithm

At ICU admission: Should this patient be fed?

YES  NO

Can EN be started within 24 hours?

YES  NO

GASTRIC CHALLENGE
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Will at least 80% of requirements be met by 72h?

YES  NO

Is Goal met?

NO  YES

Use prokinetic and/or
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- < 24 hours to oral intake
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- Enteric fistula
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- Imminent endoscopy
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- Severe exacerbation of IBD
- May still opt for elemental feeds

Continue EN to Max. tolerated
Supplement with PN
Continue EN challenges q12h

Chief Investigator: Dr. Gordon S. Doig, University of Sydney. Contact: g.doig@med.usyd.edu.au
Parenteral vs. enteral nutrition in the critically ill patient: A meta-analysis of high-quality trials using the intention to treat principle

Fiona Simpson
Gordon Stuart Doig

Received: 29 April 2004
Accepted: 2 November 2004
Published online: 9 December 2004
© Springer-Verlag 2004

Abstract Objective: Controversy surrounds the use of parenteral nutrition in critical illness. Previous overviews used composite scales to identify high-quality trials, which may mask important differences in true methodological quality. Using a component-based approach this meta-analysis investigated the effect of trial quality on overall conclusions reached when standard enteral nutrition is compared to standard parenteral nutrition in critically ill patients. Methods: An extensive literature search was undertaken to identify all eligible trials. We retrieved 465 publications, and 11 qualified for inclusion. Nine trials presented complete follow-up, allowing the conduct of an intention to treat analysis. Results: Aggregation revealed a mortality benefit in favour of parenteral vs. early enteral nutrition compared to parenteral vs. late enteral. Six trials with complete follow-up reported infectious complications. Infectious complications were increased with parenteral use. The I² measure of heterogeneity was 37.7%. Conclusions: Intention to treat trials demonstrated reduced mortality associated with parenteral nutrition use. A priori subgroup analysis attributed this reduction to trials comparing parenteral to delayed enteral nutrition. Despite an association with increased infectious complications, a grade B+ evidence-based recommendation (level II trials, no heterogeneity) can be generated for parenteral nutrition use in patients in whom enteral nutrition cannot be initiated within 24 h of ICU admission or injury.

**Background**

**Comparison:** 01 TPN vs. EN Sensitivity Analysis

**Outcome:** 01 Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>TPN n/N</th>
<th>EN n/N</th>
<th>OR (fixed) 95% CI</th>
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<td><strong>01 Early EN (&lt;24 hrs post ICU admission or injury)</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Adams</td>
<td>3/23</td>
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<td>2.23 3.30 [0.32, 34.35]</td>
<td></td>
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</tr>
<tr>
<td>Dunham</td>
<td>2/16</td>
<td>1/12</td>
<td>2.57 1.57 [0.13, 19.67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gianotti</td>
<td>2/87</td>
<td>2/87</td>
<td>5.02 1.00 [0.14, 7.26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kudsk</td>
<td>0/34</td>
<td>1/34</td>
<td>3.80 0.32 [0.01, 8.23]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rayes</td>
<td>0/30</td>
<td>0/30</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reynolds</td>
<td>1/34</td>
<td>2/33</td>
<td>5.06 0.47 [0.04, 5.44]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>224</td>
<td>219</td>
<td>18.67 1.07 [0.39, 2.95]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>8 (TPN), 7 (EN)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity: Chi² = 1.94, df = 4 (P = 0.75), I² = 0%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.14 (P = 0.89)</td>
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<tr>
<td><strong>02 Late EN</strong></td>
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<tr>
<td>Borzotta</td>
<td>2/23</td>
<td>9/36</td>
<td>16.45 0.29 [0.06, 1.47]</td>
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<tr>
<td>Cerra</td>
<td>10/37</td>
<td>9/33</td>
<td>17.82 0.99 [0.34, 2.84]</td>
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<tr>
<td>Kalfarentzos</td>
<td>2/20</td>
<td>3/20</td>
<td>6.93 0.63 [0.09, 4.24]</td>
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<tr>
<td>Rapp</td>
<td>3/20</td>
<td>9/18</td>
<td>20.67 0.18 [0.04, 0.82]</td>
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<tr>
<td>Woodcock</td>
<td>5/21</td>
<td>9/17</td>
<td>19.46 0.28 [0.07, 1.11]</td>
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<td></td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>121</td>
<td>124</td>
<td>81.33 0.44 [0.24, 0.81]</td>
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<tr>
<td><strong>Total events:</strong></td>
<td>22 (TPN), 39 (EN)</td>
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<tr>
<td>Test for heterogeneity: Chi² = 4.44, df = 4 (P = 0.35), I² = 10.0%</td>
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<tr>
<td>Test for overall effect: Z = 2.63 (P = 0.008)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>345</td>
<td>343</td>
<td>100.00 0.56 [0.33, 0.93]</td>
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<td>30 (TPN), 46 (EN)</td>
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<td>Test for heterogeneity: Chi² = 8.23, df = 9 (P = 0.51), I² = 0%</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.14 (P = 0.89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Late EN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borzotta</td>
<td>2/23</td>
<td>9/36</td>
<td>16.45 0.29 [0.06, 1.47]</td>
<td>31.33</td>
<td></td>
</tr>
<tr>
<td>Cerra</td>
<td>10/37</td>
<td>9/33</td>
<td>17.82 0.99 [0.34, 2.84]</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Kalfarentzos</td>
<td>2/20</td>
<td>3/20</td>
<td>6.93 0.63 [0.09, 4.24]</td>
<td>31.33</td>
<td></td>
</tr>
<tr>
<td>Rapp</td>
<td>3/20</td>
<td>9/18</td>
<td>20.67 0.18 [0.04, 0.82]</td>
<td>16.45</td>
<td></td>
</tr>
<tr>
<td>Woodcock</td>
<td>5/21</td>
<td>9/17</td>
<td>19.46 0.28 [0.07, 1.11]</td>
<td>17.82</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>121</td>
<td>124</td>
<td>81.33 0.44 [0.24, 0.81]</td>
<td>6.93</td>
<td></td>
</tr>
<tr>
<td>Total events: 22 (TPN), 39 (EN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 4.44, df = 4 (P = 0.35), I² = 10.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.63 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>345</td>
<td>343</td>
<td>100.00 0.56 [0.33, 0.93]</td>
<td>17.82</td>
<td></td>
</tr>
<tr>
<td>Total events: 30 (TPN), 46 (EN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 8.23, df = 9 (P = 0.51), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.22 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

![Graph showing comparison between TPN and EN](image)
### Background


<table>
<thead>
<tr>
<th>Study on subcategory</th>
<th>EN n/N</th>
<th>TPN n/N</th>
<th>CR (fixed) 95% CI</th>
<th>Weight %</th>
<th>CR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 No. Patients with infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gianotti</td>
<td>16/87</td>
<td>19/86</td>
<td>35.64</td>
<td>1.26 [0.60, 2.65]</td>
<td></td>
</tr>
<tr>
<td>Kalfarentzos</td>
<td>5/18</td>
<td>10/20</td>
<td>7.57</td>
<td>2.60 [0.67, 10.06]</td>
<td></td>
</tr>
<tr>
<td>Rayes</td>
<td>2/30</td>
<td>9/30</td>
<td>4.03</td>
<td>6.00 [1.17, 30.32]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>135</td>
<td>136</td>
<td>47.24</td>
<td>1.88 [1.04, 3.38]</td>
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</tr>
<tr>
<td><strong>Total events: 38 (TPN), 23 (EN)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 Total Number of Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adams</td>
<td>14/23</td>
<td>10/23</td>
<td>22.76</td>
<td>0.49 [0.15, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Reynolds</td>
<td>13/33</td>
<td>20/34</td>
<td>15.62</td>
<td>2.20 [0.63, 5.84]</td>
<td></td>
</tr>
<tr>
<td>Woodcock</td>
<td>10/32</td>
<td>16/32</td>
<td>14.38</td>
<td>2.20 [0.79, 6.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>88</td>
<td>89</td>
<td>52.76</td>
<td>1.46 [0.81, 2.64]</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong></td>
<td>Chi² = 3.28, df = 2 (P = 0.19), I² = 39.0%</td>
<td>Test for overall effect: Z = 2.10 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong></td>
<td>Chi² = 4.56, df = 2 (P = 0.10), I² = 56.1%</td>
<td>Test for overall effect: Z = 1.27 (P = 0.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong></td>
<td>Chi² = 8.02, df = 5 (P = 0.16), I² = 37.7%</td>
<td>Test for overall effect: Z = 2.39 (P = 0.02)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Equipoise for a large-scale clinical trial

Hypothesis:

In patients who have a short-term relative contraindication to early enteral nutrition, the provision of early parenteral nutrition (within 24 hours of ICU admission) reduces 60-day landmark mortality, and associated measures of morbidity, compared to pragmatic standard care.

www.evidencebased.net/EarlyPN
A large-scale multi-centre trial

• National Health and Medical Research Council Funded RCT
A large-scale multi-centre trial

- National Health and Medical Research Council Funded RCT
- 31 participating hospitals throughout Australia and New Zealand.
A large-scale multi-centre trial

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- Recruitment ran from 19th October 2006 to 30th June 2011.
A large-scale multi-centre trial

- National Health and Medical Research Council Funded RCT
- 31 participating hospitals throughout Australia and New Zealand.
- Recruitment ran from 19th October 2006 to 30th June 2011.
- 1,363 patients were enrolled and randomised
  - 682 received pragmatic standard care
  - 681 received early parenteral nutrition
Eligibility Criteria

Complete inclusion criteria:

- Adult patients admitted to ICU for less than 24 h.
- Expected to remain in ICU today and tomorrow.
- Not expected to receive enteral, parenteral or oral intake today or tomorrow.
- Has a central venous access line through which parenteral nutrition could be delivered.

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[www.evidencebased.net/EarlyPN](http://www.evidencebased.net/EarlyPN)
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Early PN: Study Intervention

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Study PN Protocol A: ALL PATIENTS EXCEPT MALNOURISHED PATIENTS
Feeding Day 1 (first 24 hours of PN)
• Commence TPN at 60ml/hr (or goal rate, whichever is lower).
• Consider trace element, mineral and vitamin needs as clinically appropriate.

Feeding Day 2 (second 24 hours of PN)
• Increase TPN to 80ml/hr (or goal rate, whichever is lower).
• Consider trace element, mineral and vitamin needs as clinically appropriate.

Feeding Day 3 (next 24 hours)
• Increase TPN to goal rate, as appropriate.
• Consider trace element, mineral and vitamin needs, as clinically appropriate.
• Recommend trialing enteral/oral nutrition, if clinically appropriate.
• Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour TPN infusion and do not hang another bag.
• If patient tolerates any oral caloric intake from food, complete remainder of 24 hour TPN infusion and do not hang another bag.

Feeding Day 4 (next 24 hours) plus all additional days after Day 4
• May switch to parenteral nutrition solution tailored to patient’s specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
• Consider long term needs regarding trace element, mineral and vitamins as clinically appropriate.
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<tbody>
<tr>
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<tr>
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</tr>
<tr>
<td>• Increase TPN to 80ml/hr (or goal rate, whichever is lower).</td>
</tr>
<tr>
<td>• Consider trace element, mineral and vitamin needs as clinically appropriate.</td>
</tr>
<tr>
<td><strong>Feeding Day 3 (next 24 hours)</strong></td>
</tr>
<tr>
<td>• Increase TPN to goal rate, as appropriate.</td>
</tr>
<tr>
<td>• Consider trace element, mineral and vitamin needs, as clinically appropriate.</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>• If patient tolerates any oral caloric intake from food, complete remainder of 24 hour TPN infusion and do not hang another bag.</td>
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</tr>
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- **Consider** trace element, mineral and vitamin needs as clinically appropriate.

**Feeding Day 3 (next 24 hours)**
- Increase TPN to the **goal rate**, as appropriate.
- **Consider** trace element, mineral and vitamin needs, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates $\geq 475$ kcal/day EN, complete remainder of 24 hour TPN infusion and do not hang another bag.
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- Target metabolic needs were calculated using the Harris-Benedict equation.
  - Used total caloric content (including protein calories) of the study PN to calculate PN infusion rates.
  - Metabolic needs for obese patients, defined as a BMI ≥ 30, were calculated based on ideal body weight (BMI = 21).
  - Capped to an upper limit of 35 kcal/kg/day.

www.evidencebased.net/EarlyPN
Patients received standard PN: a ready-to-mix 3-chamber bag containing 34g amino acids, 100g glucose (Glucose 19%), 40g lipid/1026mls, 0.9kcal/ml, and electrolytes. Starting rates and daily rate increases were defined by study protocols designed to reflect normal care in Australia and New Zealand. Target metabolic needs were calculated using the Harris-Benedict equation. Used the total caloric content (including protein calories) of the study PN to calculate PN infusion rates. Metabolic needs for obese patients, defined as a BMI ≥ 30, were calculated based on ideal body weight (BMI = 21) and capped to an upper limit of 35 kcal/kg/day.
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  - Capped to an upper limit of 35 kcal/kg/day.
- Calculated target metabolic needs were usually achieved on study Day 3.
- We did not specify the method to be used to re-estimate targets from Day 4 on, however we did recommend that reasonable ranges should be achieved.
Pragmatic Standard Care

- The attending clinician selected the route, starting rate, metabolic targets, measures of tolerance and composition of feeds to be used in standard care patients based on current practice in their ICU.
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
- 91 (7%) GI neoplasm (surgical),
**Who got into the trial:**

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
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- 91 (7%) GI neoplasm (surgical),
- 91 (7%) other GI (surgical),
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
- 91 (7%) GI neoplasm (surgical),
- 91 (7%) other GI (surgical),
- 87 (6%) Sepsis other than urinary (med),
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
- 91 (7%) GI neoplasm (surgical),
- 91 (7%) other GI (surgical),
- 87 (6%) Sepsis other than urinary (med),
- 62 (5%) GI bleeding (med/surg).
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Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
- 91 (7%) GI neoplasm (surgical),
- 91 (7%) other GI (surgical),
- 87 (6%) Sepsis other than urinary (med),
- 62 (5%) GI bleeding (med/surg).

Overall 65% of patients were surgical and 35% of patients were medical.
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
- 140 (10%) GI obstruction (surgical or medical management),
- 98 (7%) ruptured aorta (surgical),
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- 87 (6%) Sepsis other than urinary (med),
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Overall 65% of patients were surgical and 35% of patients were medical.

Mortality at Day 60: 301/1358 (22.2%)
Average ICU stay: 8.9 days
Average hospital stay: 25.0 days

This is a critically ill patient population.
Nutrition therapy process measures

Early parenteral nutrition (681 patients):

• 679/681 patients (99.7%) commenced PN 44 minutes after enrolment
Nutrition therapy process measures

Early parenteral nutrition (681 patients):

- 679/681 patients (99.7%) commenced PN 44 minutes after enrolment
- 405/679 (59.6%) progressed to EN 3.83 days after PN start
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Pragmatic standard care (682 patients):
Nutrition therapy process measures

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- 679/681 patients (99.7%) commenced PN 44 minutes after enrolment
  - 405/679 (59.6%) progressed to EN 3.83 days after PN start

Pragmatic standard care (682 patients):

- 199/682 patients (29.2%) commenced EN 1.98 days after enrolment,
Nutrition therapy process measures

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Pragmatic standard care (682 patients):
- 199/682 patients (29.2%) commenced EN 1.98 days after enrolment,
  - 48/199 (24.1%) received supplemental PN 5.58 days after EN start
**Nutrition therapy process measures**

Early parenteral nutrition (681 patients):

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    • 48/199 (24.1%) received supplemental PN 5.58 days after EN start
  • 186/682 patients (27.3%) commenced PN 1.99 days after enrolment,
    • 80/186 (43.0%) progressed to EN 5.08 days after PN start
Nutrition therapy process measures

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Pragmatic standard care (682 patients):

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- 186/682 patients (27.3%) commenced PN 1.99 days after enrolment,
  - 80/186 (43.0%) progressed to EN 5.08 days after PN start
- 278/682 patients (40.8%) never received EN or PN during their 3.72 day ICU stay

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<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Standard Care (n = 682)</th>
<th>Early PN (n = 681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>68.6 (14.3)</td>
<td>68.4 (15.1)</td>
</tr>
<tr>
<td>Female gender, No. (%)</td>
<td>262 (38.4)</td>
<td>281 (41.3)</td>
</tr>
<tr>
<td>BMI, mean (SD)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>28.5 (6.9)</td>
<td>27.9 (6.8)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>21.5 (7.8)</td>
<td>20.5 (7.4)</td>
</tr>
<tr>
<td>Mechanically ventilated, No. (%)</td>
<td>549 (80.6)</td>
<td>572 (83.9)</td>
</tr>
</tbody>
</table>
5 patients (2 Standard Care, 3 Early PN) could not be contacted on study Day 60 to determine vital status. Considered ‘missing at random’ for ITT Primary and Adjusted primary outcome analysis.

Multivariate model controlled for confounding due to baseline imbalance and strong predictors: **Age, gender, BMI, APACHE 2 score, Chronic Liver, Chronic Respiratory and Source of Admission.**

<table>
<thead>
<tr>
<th>Patients With New Infections&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup> New infections based on cultures obtained in the study ICU.
Table 4. New Infections During Study

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c  CPIS $\geq 6$ plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72hrs after starting a new antibiotic regimen.

f  CPIS $\geq 6$ (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from a) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); b) the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jiroveci (carinii)*; c) recovery of a likely/possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, BAL, or protected specimen brush); or d) positive serology.


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<td>CPIS-probable pneumonia&lt;sup&gt;g&lt;/sup&gt;</td>
<td>96 (14.08)</td>
<td>81 (11.89)</td>
<td>-2.18 (-7.50 to 3.11)</td>
<td>.26</td>
<td></td>
</tr>
<tr>
<td>CPIS-confirmed pneumonia&lt;sup&gt;f&lt;/sup&gt;</td>
<td>45 (6.60)</td>
<td>43 (6.31)</td>
<td>-0.28 (-5.60 to 5.01)</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>Any major infection&lt;sup&gt;g&lt;/sup&gt;</td>
<td>78 (11.4)</td>
<td>74 (10.9)</td>
<td>-0.57 (-5.89 to 4.72)</td>
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<sup>g</sup> Attributional excess case mortality greater than 15%.
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<td>RAND-36 general health status&lt;sup&gt;d&lt;/sup&gt;</td>
<td>45.5 (26.8) (n = 516)</td>
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Minimally Important Difference = ½ SD = 13.5

Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of a half a standard deviation. *Medical Care* 2004;41:582-592.
**Table 3. Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)**

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<th>Mean (95% CI), Days per 10 Patient × ICU Days</th>
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<td>0.78 (0.67 to 0.92)</td>
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<td>Low serum albumin (&lt;2.5 g/dL)</td>
<td>5.47 (5.28 to 5.67)</td>
<td>5.76 (5.56 to 5.97)</td>
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<td>8.05 (7.88 to 8.22)</td>
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<td>1.96 (1.21 to 3.13)</td>
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<td>With new pulmonary infiltrates</td>
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<td>0.99 (0.82 to 1.81)</td>
<td>0.80 (0.67 to 0.96)</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>(n = 682)</td>
<td>(n = 681)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>ICU stay, mean (95% CI), d</td>
<td>9.3 (8.9 to 9.7)</td>
<td>8.6 (8.2 to 9.0)</td>
</tr>
<tr>
<td>Hospital stay, mean (95% CI), d</td>
<td>24.7 (23.7 to 25.8)</td>
<td>25.4 (24.4 to 26.6)</td>
</tr>
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$1,000,000 question:

*HOW* could early nutrition *reduce* duration of ventilation and ICU stay?
Body composition

ICU admission:
- Enrolment within 24 h of admit

Body composition measures obtained at enrolment and every Monday and Thursday while in study ICU:
- MAMC, SGA muscle wasting, SGA fat store loss
Subjective Global Assessment: Muscle wasting

Fully factorial repeated measures ANOVA:
\[ p < 0.0001 \text{ change over time} \]
Subjective Global Assessment: Muscle wasting

Fully factorial repeated measures ANOVA:
$p < 0.0001$ change over time, $p = 0.014$ difference between groups (0.16 grade per week)
Subjective Global Assessment: Fat loss

Fully factorial repeated measures ANOVA:
p < 0.0001 change over time
Fully factorial repeated measures ANOVA:
$p < 0.0001$ change over time, $p = 0.045$ difference between groups (0.13 grade per week)
Body composition: Changes over time

- Mild to Moderate evidence of muscle (and fat) sparing with Early PN use
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- Diaphragmatic thinning evident on ultrasound after 48 h of mechanical ventilation.

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Given evidence of skeletal muscle sparing, it is plausible that Early PN attenuates diaphragmatic proteolysis (autophagy), mitigating the diaphragmatic loss which leads to improved weaning

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*But what about costs?*
Economic analysis: US costs

Marginal differences in patient outcomes from Early PN Trial:

Costs of ICU care in the US healthcare system based on 51,000 ICU patients:

<table>
<thead>
<tr>
<th>Medical patients</th>
<th>Surgical patients</th>
<th>Trauma patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Received MV</td>
<td>No MV received</td>
</tr>
<tr>
<td>Day 1</td>
<td>$8,141 ($5,584)</td>
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<tr>
<td>Day 2</td>
<td>$6,535 ($4,678)</td>
<td>$4,783 ($4,678)</td>
</tr>
<tr>
<td>Day 3 plus</td>
<td>$5,703 ($4,666)</td>
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Notes: Mean costs (standard deviation); indexed to 2012 US dollars. Costs of care whilst admitted to the intensive care unit were abstracted from Dasta JF et al.15
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<td>$15,625 ($11,955)</td>
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<td>$9,916 ($14,319)</td>
<td>$9,062 ($11,955)</td>
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<tr>
<td>$6,535 ($4,678)</td>
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Costs were calculated for each of the 1,363 Early PN Trial patient's ICU stay, mechanical ventilation days and PN usage accounting for variability by considering the published standard deviations of costs using a Stochastic model with Gamma distributed costs.

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- **For every $1 spent on PN, $5 are saved in subsequent healthcare costs**

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Evidence-based ICU feeding algorithm

At ICU admission: Should this patient be fed?

- **YES**
  - Can EN be started within 24 hours?
    - **YES**
      - GASTRIC CHALLENGE
        - use full strength concentration
        - Consider prokinetic with challenge
        - GOAL: at least 80% of requirements at 72h
        - assess q12h
      - Will at least 80% of requirements be met by 72h?
        - **YES**
          - Is Goal met?
            - **YES**
              - Increase rate to 100%
            - **NO**
              - Use prokinetic and/or Use post-pyloric tube
        - **NO**
          - Use prokinetic and/or Use post-pyloric tube
    - **NO**
      - Acceptable conditions:
        - tolerating adequate oral intake
        - < 24 hours to oral intake
        - palliative care

- **NO**
  - Acceptable conditions:
    - acute pancreatitis*
    - enteric anastomosis*
    - ischemic bowel
    - enteric fistula
    - imminent bowel resection
    - imminent endoscopy
    - bowel obstruction
    - high nasogastric losses on admission
    - severe exacerbation of IBD
    - *may still opt for elemental feeds

Begin TPN:
- consider TPN with glutamine
- Reassess q12h for EN eligibility

Continue EN to Max. tolerated
Supplement with PN
Continue EN challenges q12h

Chief Investigator: Dr. Gordon S. Doig, University of Sydney. Contact: gdoig@med.usyd.edu.au
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The importance of Early EN
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Stable shock is not defined by weaning or removing all vasoactive agents.
Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2)

Trial of the Route of Early Nutritional Support in Critically Ill Adults


BACKGROUND
 Uncertainty exists about the most effective route for delivery of early nutritional support in critically ill adults. We hypothesized that delivery through the parenteral route is superior to that through the enteral route.

METHODS
 We conducted a pragmatic, randomized trial involving adults with an unplanned admission to one of 33 English intensive care units. We randomly assigned patients who could be fed through either the parenteral or the enteral route to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to 5 days. The primary outcome was all-cause mortality at 30 days.

RESULTS
 We enrolled 2400 patients; 2368 (99.5%) were included in the analysis (1191 in the parenteral group and 1177 in the enteral group). By 30 days, 395 of 1168 patients (33.1%) in the parenteral group and 409 of 1195 patients (34.2%) in the enteral group had died (relative risk in parenteral group, 0.97; 95% confidence interval, 0.86 to 1.08; P=0.57). There were significant reductions in the parenteral group, as compared with the enteral group, in rates of hypoglycemia (44 patients [3.7%] vs. 74 patients [6.2%]; P=0.006) and vomiting (100 patients [8.4%] vs. 194 patients [16.2%]; P=0.001). There were no significant differences between the parental and enteral groups in the mean number of treated infectious complications (0.22 vs. 0.21; P=0.79), 90-day mortality (442 of 1184 patients [37.3%] vs. 464 of 1188 patients [39.1%]; P=0.40), in rates of 14 other secondary outcomes, or in rates of adverse events. Caloric intake was similar in the two groups, with the target intake not achieved in most patients.

CONCLUSIONS
 We found no significant difference in 30-day mortality associated with the route of delivery of early nutritional support in critically ill adults. (Funded by the United Kingdom National Institute for Health Research; CALORIES Current Controlled Trial’s number, ISRCTN17386141.)

From the Clinical Trials Unit, Intensive Care National Audit and Research Centre (EFH, P.P., D.A.H., K.M.R.), the Department of Nutrition and Dietetics (D.E.B.) and Adult Critical Care (D.L.B., R.B.), Guy’s and St. Thomas’ NHS Foundation Trust, the Department of Intensive Care, Imperial College Healthcare NHS Trust (B.S., R.L.), the Division of Asthma, Allergy and Lung Medicine, King’s College London (R.B.), National Institute for Health Research Biomedical Research Centre, University College London Hospitals NHS Foundation Trust and University College London London (G.B., M.G.M.), and the Department of Surgery and Cancer, Imperial College London (R.L.) — all in London. Address reprint requests to Dr Rowan at the Intensive Care National Audit and Research Centre, Napsyle House, 24 High Holborn, London WC1V 6AT, United Kingdom, or at kathy.rowan@icnarc.org.

A complete list of the investigators and committee members in the CALORIES trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 1, 2014, at NEJM.org.

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Economic Analysis: Early EN reduces costs

Full economic analyses based on large-scale Monte Carlo simulations of stochastic cost models demonstrate clinical benefits can be achieved whilst at the same time reducing costs.

- EN US$14,462 (95% CI $5,464 to $23,669) savings per patient treated

www.EvidenceBased.net/talks

Study PN Protocol B: MALNOURISHED PATIENTS (Ex. BMI ≤ 17 or clinical diagnosis):

**Feeding Day 1 (first 24 h of PN)**
- Commence TPN at 40ml/hr (or goal rate, whichever lower).
- **Strongly recommend** administering 100mg thiamine, commencing at least 30 minutes prior to initiation of TPN infusion, as clinically indicated as per product licensing indications.
- **Recommend** daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

**Feeding Day 2 (second 24 hours of PN)**
- Increase TPN to 60ml/hr (or goal rate, whichever is lower).
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.

**Feeding Day 3 (next 24 hours)**
- Increase TPN to goal rate, as appropriate.
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour TPN infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour TPN infusion and do not hang another bag.

**Feeding Day 4 (next 24 hours) plus all additional days after Day 4**
- **May switch** to parenteral nutrition solution tailored to patient’s specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- **Strongly recommend** addressing long term needs regarding trace elements, minerals and vitamins as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour TPN infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour TPN infusion and do not hang another bag.