Early nutritional support in critical illness: evidence, physiology and costs.

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Summary of this talk

- Provide a context for this talk.
- Review the most recent clinical evidence on the topic.
- Present some interesting new physiological evidence supporting the clinical evidence.
- Conclude.
Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults: A Cluster Randomized Controlled Trial

Gordon S. Doig; Fiona Simpson; Simon Finfer; et al.


http://jama.ama-assn.org/cgi/content/full/300/23/2731
The initial MEDLINE/EMBASE electronic search retrieved 2,287 abstracts. Hand-searching of abstracts and reference lists of all overviews and guidelines (GSD and FS) resulted in the retrieval of 465 papers. Of these 465 papers, 337 appeared to be primary nutritional support studies and were identified for detailed review (GSD, FS, and AD). On detailed review 103 studies were found not to report any clinically meaningful outcomes, 42 were not conducted in critically ill patients, 27 were not primary nutritional support studies (i.e., evaluations of recombinant human growth hormone, insulin), 15 were crossover studies, 12 evaluated preoperative interventions, 8 were true observational studies (not controlled trials), 7 were non-English-language studies, 6 were pseudo-randomized, 5 were based on subgroups of patients from a larger published trial, and 1 was a postoperative intervention (oral intake for 10 weeks postsurgery). The remaining 111 articles were found to be primary nutritional support studies reporting clinically meaningful outcomes (11) conducted in critically ill patient populations. A complete listing of all 111 articles is presented in Appendix A.

Box. Evidence-Based Recommendations Approved (Ratified) for Inclusion in the Guideline at the Consensus Conference

**Grade B+**
- Recommendation favoring enteral nutrition over standard care (nothing by mouth)
- Recommendation favoring early parenteral nutrition (<24 hours) over delayed (>24 hours) enteral nutrition
  - 5 Level II RCTs. Supported by positive meta-analysis and validated evidence-based guideline (ACCEPT).

**Grade B**
- Recommendation favoring early enteral nutrition (<24 hours) over delayed (>24 hours) enteral nutrition
  - 3 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring parenteral nutrition over standard care (intravenous glucose)
  - 5 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring early enteral nutrition (<24 hours) over parenteral nutrition
  - 6 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring postpyloric feeding when gastric feeding not tolerated
  - 8 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring prokinetics when gastric feeding not tolerated
  - 5 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring enteral nutrition supplemented with parenteral nutrition if 80% of goals not met by 72 hours with enteral nutrition alone (after consideration of postpyloric feeding, prokinetics, or both)
  - 4 Level II RCTs. Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring protocolized management of diarrhea
  - Supported by validated evidence-based guideline (ACCEPT).
- Recommendation favoring protocolized definition of intolerance of enteral nutrition, which includes gastric residual values > 200 mL
  - Supported by validated evidence-based guideline (ACCEPT).

**Grade B−**
- Consider parenteral nutrition with glutamine instead of standard parenteral nutrition
  - 4 Level II RCTs. Supported by meta-analysis, heterogeneity present.
- Glutamine may be beneficial in select patients. To identify which patients may benefit, each constituent RCT should be reviewed and clinical judgment should be exercised.

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  - American (ASPEN and SCCM) guideline


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- The concept of ‘early’ enteral feeding was popularised in the mid ‘80s.
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< 48 h – **Canadian guideline**, Evidence of trend.
< 24 h – **ACCEPT guideline (also Canadian)**, **Significant evidence.**
< 24 h – **Australian and New Zealand guideline**, **Significant evidence.**
< 24 h – **European (ESPEN) guideline and**
< 48 h – **American (ASPEN and SCCM) guideline** **Evidence of trend.**

Evidence for early EN in critical illness

Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials

Meta-analysis of early EN in critical illness

Comprehensive Literature search

- MEDLINE (http://www.PubMed.org) and EMBASE (http://www.EMBASE.com)
- Academic and industry experts were contacted,
- Reference lists of identified systematic reviews and evidence-based guidelines were hand searched by at least two authors.
- The search was not restricted by Language.

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**Primary outcome**
- Clinically meaningful patient oriented outcomes: (mortality / physical function / quality of life)

Meta-analysis of early EN in critical illness

Chiarelli, 1990: 20 pts, burns
Kompan, 1999: 36 pts, trauma
Kompan, 2004: 52 pts, trauma
Nguyen, 2008: 28 pts, med/surg critically ill
Chuntrasakul, 1996: 38 pts, trauma
Pupelis, 2001: 60 pts, severe pancreatitis and peritonitis

### Results: Primary MA, mortality

**Review:** Early EN (<24h) vs Control (Primary Analysis)
**Comparison:** 01 early EN vs Control
**Outcome:** 01 Mortality, Intention to treat analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>early EN (&lt;24 h) n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiarelli 1990</td>
<td>0/10</td>
<td>0/10</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kompan 1999</td>
<td>0/17</td>
<td>2/19</td>
<td>13.40 0.20 [0.01, 4.47]</td>
<td>100.00</td>
<td>0.34 [0.14, 0.85]</td>
</tr>
<tr>
<td>Kompan 2004</td>
<td>0/27</td>
<td>1/25</td>
<td>8.89 0.30 [0.01, 7.63]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>6/14</td>
<td>6/14</td>
<td>19.95 1.00 [0.22, 4.47]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chuntrasakul 1996</td>
<td>1/21</td>
<td>3/17</td>
<td>18.38 0.23 [0.02, 2.48]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupelis 2001</td>
<td>1/30</td>
<td>7/30</td>
<td>39.38 0.11 [0.01, 0.99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>119</strong></td>
<td><strong>115</strong></td>
<td></td>
<td><strong>100.00</strong></td>
<td><strong>0.34 [0.14, 0.85]</strong></td>
</tr>
</tbody>
</table>

Total events: 8 (early EN (<24 h)), 19 (Control)
Test for heterogeneity: \( \chi^2 = 3.20, df = 4 \) (P = 0.52), \( I^2 = 0\% \)
Test for overall effect: \( Z = 2.31 \) (P = 0.02)

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**Significant reduction in mortality (10% absolute reduction, \( P = 0.02 \))**

Results: Primary MA, Pneumonia

Significant reduction in pneumonia (27% absolute reduction, P=0.01)

Results: updated MA, ICU length of stay

Trend towards reduced length of ICU stay with early EN (2.34 days, P = 0.06)


Results: updated MA, duration of MV

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Mean [days]</th>
<th>SD [days]</th>
<th>Total</th>
<th>Mean [days]</th>
<th>SD [days]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, fixed, 95% CI [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuntrasakul et al</td>
<td>5.29</td>
<td>6.28</td>
<td>21</td>
<td>6.12</td>
<td>5.32</td>
<td>17</td>
<td>48.1%</td>
<td>-0.83 [-4.52, 2.86]</td>
</tr>
<tr>
<td>Kompan et al</td>
<td>12.9</td>
<td>8.1</td>
<td>27</td>
<td>15.6</td>
<td>16.1</td>
<td>25</td>
<td>13.3%</td>
<td>-2.70 [-9.71, 4.31]</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>9.2</td>
<td>3.37</td>
<td>14</td>
<td>13.7</td>
<td>7.11</td>
<td>14</td>
<td>38.6%</td>
<td>-4.50 [-8.62, -0.38]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td></td>
<td>56</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-2.49 [-5.05, 0.07]</td>
</tr>
</tbody>
</table>

Figure 2: Meta-analysis of duration of mechanical ventilation: early enteral nutrition vs standard care.

Notes: Heterogeneity: $\chi^2 = 1.69, df = 2$ ($P = 0.43$); $I^2 = 0\%$. Test for overall effect: $Z = 1.91$ ($P = 0.06$).

Abbreviations: CI, confidence interval; EEN, early enteral nutrition; IV, inverse variance; SD, standard deviation; SoC, standard of care.

Trend towards reduced mechanical ventilation with early EN (2.49 days, $P = 0.06$)

Simulation study: Heyland’s 2003 MA

- We conducted a simulation study to test the appropriateness of key assumptions behind our study selection and analysis techniques.

- We duplicated Heyland’s 2003 MA,
  - we used Heyland’s selection process and analysis techniques
  - BUT we only included articles that provided EN within 24 h of injury or ICU admission

Simulation study: Heyland’s 2003 MA

<table>
<thead>
<tr>
<th>Study</th>
<th>Early EN (&lt;60 h) n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
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<tr>
<td>Chiarelli</td>
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<td>Chuntrasakul</td>
<td>1/21</td>
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<td>0.27 [0.03, 2.37]</td>
</tr>
<tr>
<td>Eyer</td>
<td>2/19</td>
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<td>1.00 [0.16, 6.38]</td>
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<td>Minard</td>
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<tr>
<td>Moore</td>
<td>1/32</td>
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<td>9.51</td>
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<td>Total (95% CI)</td>
<td>159</td>
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Total events: 10 (Early EN (<60 h)), 23 (Control)
Test for heterogeneity: Chi² = 4.05, df = 6 (P = 0.67), I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)

Trend towards a reduction in mortality (8% absolute reduction, P=0.08)

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**Comparison:** 01 Mortality  
**Outcome:** 01 Mortality

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<td></td>
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<td>1/32</td>
<td>2/31</td>
<td>9.51 0.48 [0.05, 5.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupelis</td>
<td>1/30</td>
<td>7/30</td>
<td>12.70 0.14 [0.02, 1.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh (&lt;48 h)</td>
<td>4/21</td>
<td>4/22</td>
<td>33.57 1.05 [0.30, 3.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>159</td>
<td>158</td>
<td>100.00 0.52 [0.25, 1.08]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 10 (Early EN (<60 h)), 23 (Control)  
**Test for heterogeneity:** Chi² = 4.05, df = 6 (P = 0.67), I² = 0%  
**Test for overall effect:** Z = 1.76 (P = 0.08)

---

**Trend towards a reduction in mortality (8% absolute reduction, P=0.08)**

Significant reduction in mortality (10% absolute reduction, P=0.02)

Therefore, evidence of benefit has been present in our literature since at least 2003, if early EN is defined as < 24 h from admission or injury!!!
Clinical evidence supporting early EN (< 24 h)

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.
Clinical evidence supporting early EN (< 24 h)

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.

- Updated systematic review of the literature suggests early EN results in an 8 to 10% absolute reduction in mortality (P = 0.02).

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- Pneumonia was significantly reduced.

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- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.
- Updated systematic review of the literature suggests early EN results in an 8 to 10% absolute reduction in mortality ($P = 0.02$).
- Pneumonia was significantly reduced.
- Strong trend towards a reduction in duration of mechanical ventilation.


Clinical evidence supporting early EN (< 24 h)

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.
- Updated systematic review of the literature suggests early EN results in an 8 to 10% absolute reduction in mortality (P = 0.02).
- Pneumonia was significantly reduced.
- Strong trend towards a reduction in duration of mechanical ventilation.
- Strong trend towards a reduction in ICU stay.


Clinical evidence supporting early EN (< 24 h)

- Evidence supporting the presence of a significant mortality benefit from the provision of early EN (< 24 h of injury or ICU admission) has been present in our literature since 2003.

- Updated systematic review of the literature suggests early EN results in an 8 to 10% absolute reduction in mortality (P = 0.02).

- Pneumonia was significantly reduced.

- Strong trend towards a reduction in duration of mechanical ventilation.

- Strong trend towards a reduction in ICU stay.

- There were no suggestions of any increase in any adverse events or harms.


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
        - GOALS 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
      - 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

- **NO**
  - 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
Evidence-based ICU feeding algorithm

At ICU admission: Should this patient be fed?

- **NO**
  - Acceptable conditions:
    - tolerating adequate oral intake
    - < 24 hours to oral intake
    - palliative care

- **YES**
  - Can EN be started within 24 hours?

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

- **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?

- **NO**
  - Is Goal met?
    - **NO**
      - Use prokinetic and/or Use post-pyloric tube
    - **YES**
      - Increase rate to 100%
  - Is Goal met?
    - **NO**
      - Continue EN to Max. tolerated supplement with PN
      - Continue EN challenges q12h
    - **YES**
      - 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

**Background: Review of the Guidelines**

- Early parenteral feeding was popularised in the early ‘80s.

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  – *ACCEPT* guideline (*also* Canadian),
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---


Background: Review of the Guidelines

- Early parenteral feeding was popularised in the early ‘80s.
- Three major clinical practice guidelines recommend early PN.
  - ACCEPT guideline (also Canadian),
  - Australian and New Zealand guideline,
  - European (ESPEN) guideline


Background: Review of the Guidelines

- Early parenteral feeding was popularised in the early ‘80s.
- Three major clinical practice guidelines recommend *early* PN.
  - < 24 h – *ACCEPT guideline (also Canadian)*, Significant evidence.
  - < 24 h – *Australian and New Zealand guideline*, Significant evidence.
  - < 24 h – *European (ESPEN) guideline*, Significant evidence.


Simpson F and Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of high-quality trials.


**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 $I^2$ 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**

**Review:** TPN vs EN  
**Comparison:** 01 TPN vs. EN Sensitivity Analysis  
**Outcome:** 01 Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>TPN</th>
<th>EN</th>
<th>OR (fixed) 95% CI</th>
<th>Weight</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Early EN (&lt;24 hrs post ICU admission or injury)</td>
<td>Adams 3/23, 1/23</td>
<td>2.23, 3.30 [0.32, 34.35]</td>
<td>2.23</td>
<td>3.30 [0.32, 34.35]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dunham 2/16, 1/12</td>
<td>2.57, 1.57 [0.13, 19.67]</td>
<td>5.02</td>
<td>1.00 [0.14, 7.26]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gianotti 2/87, 2/87</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kudsk 0/34, 1/34</td>
<td>3.80, 0.32 [0.01, 8.23]</td>
<td>5.06</td>
<td>0.47 [0.04, 5.44]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rayes 0/30, 0/30</td>
<td>5.06, 0.47 [0.04, 5.44]</td>
<td>5.06</td>
<td>0.47 [0.04, 5.44]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reynolds 1/34, 2/33</td>
<td>5.06, 0.47 [0.04, 5.44]</td>
<td>5.06</td>
<td>0.47 [0.04, 5.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>224, 219</td>
<td>18.67, 1.07 [0.39, 2.95]</td>
<td>224</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong> 8 (TPN), 7 (EN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity: Ch² = 1.94, df = 4 (P = 0.75), I² = 0%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 0.14 (P = 0.89)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>TPN</th>
<th>EN</th>
<th>OR (fixed) 95% CI</th>
<th>Weight</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Late EN</td>
<td>Borzotta 2/23, 9/36</td>
<td>16.45, 0.29 [0.06, 1.47]</td>
<td>22</td>
<td>0.29 [0.06, 1.47]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerra 10/37, 9/33</td>
<td>17.82, 0.39 [0.06, 9.24]</td>
<td>6.93</td>
<td>0.63 [0.09, 4.24]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kalfarentzos 2/20, 3/20</td>
<td>6.93, 0.63 [0.09, 4.24]</td>
<td>6.93</td>
<td>0.63 [0.09, 4.24]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapp 3/20, 9/18</td>
<td>20.67, 0.18 [0.04, 0.82]</td>
<td>20.67</td>
<td>0.18 [0.04, 0.82]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Woodcock 5/21, 9/17</td>
<td>19.46, 0.28 [0.07, 1.11]</td>
<td>19.46</td>
<td>0.28 [0.07, 1.11]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>121, 124</td>
<td>81.33, 0.44 [0.24, 0.81]</td>
<td>121</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong> 22 (TPN), 39 (EN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity: Ch² = 4.44, df = 4 (P = 0.35), I² = 10.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.63 (P = 0.008)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

| **Total (95% CI)** | 345, 343 | 100.00, 0.56 [0.33, 0.93] | 345 | 343 |
| **Total events:** 30 (TPN), 46 (EN) |  |  |  |  |
| Test for heterogeneity: Ch² = 8.23, df = 9 (P = 0.51), I² = 0% |  |  |  |  |
| Test for overall effect: Z = 2.22 (P = 0.03) |  |  |  |  |

Favours TPN Favours EN

Simpson F and Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: A meta-analysis of high-quality trials.  
Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition: A Randomized Controlled Trial

Early PN 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.
Early PN 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.

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.

www.evidencebased.net/EarlyPN
Early PN Trial

Study Intervention

- Patients received standard PN supplied by Fresenius Kabi
  - Kabiven G19%, ready-to-mix 3-chamber bag containing 34g amino acids (Vamin 18 Novum), 100g glucose (Glucose 19%), 40g lipid (Intralipid 20%)/ 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.
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  - Starting rates and daily rate increases were defined by study protocols designed to reflect normal care in Australia and New Zealand.

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.
Early PN Trial

• Recruitment ran from **19th October 2006** to **30th June 2011**.
• 31 participating hospitals throughout Australia and New Zealand.
• 1,363 patients were enrolled and randomised
  • 682 received pragmatic standard care
  • 681 received early parenteral nutrition
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),
- 98 (7%) ruptured aorta (surgical),
- 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).
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
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- 91 (7%) other GI (surgical),
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- 62 (5%) GI bleeding (med/surg),

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.
a 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.

b 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 4. New Infections During Study

<table>
<thead>
<tr>
<th>Patients With New Infections(^a)</th>
<th>No. (%)</th>
<th>Standard Care (n = 682)</th>
<th>Early PN (n = 681)</th>
<th>Risk Difference (Exact 95% CI)</th>
<th>Exact P Value(^b)</th>
</tr>
</thead>
</table>

\(^a\) new infections based on cultures obtained in the study ICU.
a new infections based on cultures obtained in the study ICU.

c  venous or arterial catheters

e 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.

g Attributable excess case mortality greater than 15%.

<table>
<thead>
<tr>
<th>Patients With New Infections&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. (%)</th>
<th>Standard Care (n = 682)</th>
<th>Early PN (n = 681)</th>
<th>Risk Difference (Exact 95% CI)</th>
<th>Exact P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32 (4.69)</td>
<td>31 (4.55)</td>
<td>-0.14 (-5.45 to 5.12)</td>
<td>&gt; .99</td>
<td></td>
</tr>
<tr>
<td>Catheter tip&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28 (4.11)</td>
<td>26 (3.82)</td>
<td>-0.29 (-5.60 to 5.01)</td>
<td>.89</td>
<td></td>
</tr>
<tr>
<td>Surgical wound</td>
<td>27 (3.96)</td>
<td>22 (3.23)</td>
<td>-0.73 (-6.04 to 4.57)</td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td>Bloodstream</td>
<td>33 (4.84)</td>
<td>39 (5.73)</td>
<td>0.89 (-4.43 to 6.18)</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>3 (0.44)</td>
<td>6 (0.88)</td>
<td>0.44 (-4.89 to 5.74)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Clinically significant UTI</td>
<td>1 (0.15)</td>
<td>2 (0.29)</td>
<td>0.15 (-5.16 to 5.45)</td>
<td>.82</td>
<td></td>
</tr>
<tr>
<td>Airway or lung&lt;sup&gt;d&lt;/sup&gt;</td>
<td>123 (18.04)</td>
<td>101 (14.83)</td>
<td>-3.20 (-8.52 to 2.08)</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<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>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Table 3. Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)(^a)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Mean (95% CI), Days per 10 Patient × ICU Days</td>
<td>(P) Value (^b)</td>
<td></td>
<td></td>
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<tr>
<td>---------------------------------</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Standard Care (n = 682)</td>
<td>7.73 (7.55 to 7.92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early PN (n = 681)</td>
<td>7.26 (7.09 to 7.44)</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean (95% CI), Days per 10 Patient × ICU Days</th>
<th>( P ) Value\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>7.73 (7.55 to 7.92)</td>
<td>.01</td>
</tr>
<tr>
<td>Pressure ulcer treatment</td>
<td>0.87 (0.74 to 1.02)</td>
<td>.54</td>
</tr>
<tr>
<td>Low serum albumin (&lt;2.5 g/dL)</td>
<td>5.47 (5.28 to 5.67)</td>
<td>.15</td>
</tr>
<tr>
<td>Systemic antibiotic use</td>
<td>7.95 (7.78 to 8.12)</td>
<td>.55</td>
</tr>
<tr>
<td>Witnessed aspiration</td>
<td>1.59 (0.98 to 2.54)</td>
<td>.66</td>
</tr>
<tr>
<td>With new pulmonary infiltrates</td>
<td>0.48 (0.20 to 1.15)</td>
<td>.65</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>0.99 (0.82 to 1.81)</td>
<td>.25</td>
</tr>
</tbody>
</table>

\( P \) values are for comparison between Standard Care and Early PN.
<table>
<thead>
<tr>
<th>Length of Stay</th>
<th>(n = 682)</th>
<th>(n = 681)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<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>
<td>.06</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>
<td>.50</td>
</tr>
</tbody>
</table>
Clinical evidence supporting early PN (< 24 h)

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  - Best estimate of treatment effect, adjusted for confounding, suggests Early PN may not alter mortality (0.0%, 95%CI -4.2% to 4.3%).


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- No difference in any type of infectious complications.
- No significant harmful effects attributable to the use of Early PN.


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$1,000,000 question:

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1. *Could early EN reduce infectious complications and mortality?*
The gut as the motor of MODs

With the onset of critical illness:

- Loss of functional and structural integrity of the intestinal epithelium.

The gut as the motor of MODs: recent advances

Recent advances in our understanding:

1. Paneth cell function.

2. Intestinal Alkaline Phosphatase.
Paneth cells

- Highly specialized epithelial cells located in the crypts of the small intestine.

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- Paneth cells are the main producers of antimicrobial proteins in the gut.
- ‘Sense’ bacterial cells and secrete granules containing antimicrobial peptides.
  - Lysozyme, α-defensins plus others
- Play a crucial role in preventing bacterial translocation in situations of physical intestinal barrier loss.

Paneth cells and fasting

- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
Paneth cells and fasting

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- 30 male C57BL/6 mice aged 12 weeks were randomised to 48 h of food restriction (fasting) or standard *ad libetum* food access.
- After 48 h, all mice were anesthetized with ketamine / xylazine and sacrificed by bleeding.
- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.

Paneth cells and fasting

Fasting led to a significant reduction of lysozyme expression (P<0.01 by quantitative western blot assay and quantitative PCR for lysozyme mRNA).

Why?

Fasting led to significant increase in autophagy activity in Paneth cells, with more late-stage degradative autophagolysosomes.

Autophagocytosis

Autophagy

A catabolic process that delivers intracellular constituents sequestered in double-membrane vesicles to lysosomes for degradation.

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

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Paneth cells and fasting

- Fasting led to significant increase in autophagy activity in Paneth cells, with more late-stage degradative autophagolysosomes.

- Increase in bacterial translocation as indicated by a 2-fold increase in CFUs cultured from mesenteric lymph node tissue (p < 0.01).

Paneth cells and fasting

- Autophagy is induced in all cells on starvation and serves to mobilize amino acids for transport to the liver to fuel gluconeogenesis.
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*Starvation conditions are known to enhance protein breakdown by autophagy, whereas systemic amino acids (continued feeds ad lib), inhibit autophagocytosis.*


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- iAP is secreted into the gut lumen and remains functional as it is carried distally through the lumen of the small and large intestine.

iAP and severe peritonitis

• 90 C57BL/6 mice were randomly divided into 6 groups:
  • 15 Sham surgical procedure
  • 15 Cecal-ligation and perforation (CLP) + control i.p. saline injection
  • 15 CLP + 5 IU i.p. iAP injection
  • 15 CLP + 10 IU i.p. iAP injection
  • 15 CLP + 25 IU i.p. iAP injection
  • 15 CLP + 50 IU i.p. iAP injection
• Survival rates were determined up to 7 days post CLP surgery.

iAP and severe peritonitis

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  100% survival at day 7

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**iAP and severe peritonitis**

- Peritoneal injection of iAP was found to be protective in a lethal model of abdominal peritonitis leading to sepsis.

- Measures of inflammation and deaths were reduced (IL-6 and TNF-α).

* iAP has very strong anti-gram negative activity.

---

iAP and fasting

• 15 C57BL/6 mice randomly assigned to 3 groups:
  • Fed for 2 days (n = 5)
  • Fasted for 2 days (n = 5)
  • Fasted for 2 days then fed for 2 days (n = 5)

• Segments of bowel studied for iAP levels and iAP activity (LPS dephosphorylation)

iAP and fasting

• Fasting results in a reduction in iAP levels and iAP functional activity.

• iAP levels and function can be returned to normal by enteral feeding after fasting.

$1,000,000 question:

**HOW** could early nutrition *reduce* infectious complications, mortality, duration of ventilation and ICU stay?

1. Could early EN *reduce* infectious complications and mortality?
$1,000,000 question:

**HOW** could early nutrition reduce infectious complications, mortality, duration of ventilation and ICU stay?

1. **Could early EN reduce infectious complications and mortality?**

   It is plausible that early EN could help prevent or ameliorate lesions leading to a compromised gut host defense system (Paneth cells, iAP etc) thus reducing infectious complications which confers a mortality advantage.
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1. Could early EN reduce infectious complications and mortality?

2. Could early nutrition support reduce duration of ventilation and ICU stay?
Body composition: Changes over time

- Mild to Moderate evidence of muscle (and fat) loss during critical illness
Body composition: Changes over time

- 38 – 88% of critically ill patients are malnourished at admission.

Body composition: Changes over time

- 38 – 88% of critically ill patients are malnourished at admission.

- Even well nourished and well fed major trauma patients lose 15.5% of their total body protein over the first three weeks of their ICU stay
  - Majority of loss coming from skeletal muscle early during the ICU stay (up to 1.2% per day).


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
Fully factorial repeated measures ANOVA:
p < 0.0001 change over time
Body composition: Changes over time

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- Mild to Moderate evidence of muscle (and fat) loss during critical illness
- Diaphragmatic thinning evident on ultrasound after 48 h of mechanical ventilation.

Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. 
Chest 2012 Dec;142(6):1455-60.
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- Significant increase in presence of autophagosomes (autophagy) by electron micrograph of diaphragmatic biopsies after as little as 15 h of mechanical ventilation
- Amino acids inhibit autophagy rapidly (within 20 minutes) and greatly (up to fivefold)

**Body composition**

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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

Weeks in study ICU

G r a d e   c h a n g e

G r a d e   c h a n g e

1  2  3  4  5 +

Fully factorial repeated measures ANOVA:
p < 0.0001 change over time
Subjective Global Assessment: Muscle wasting

Fully factorial repeated measures ANOVA:

\[ p < 0.0001 \text{ change over time, } p = 0.014 \text{ difference between groups (0.16 grade per week)} \]
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**HOW** could early nutrition reduce infectious complications, mortality, duration of ventilation and ICU stay?

1. Could early EN reduce infectious complications and mortality?

2. Could early nutrition support reduce duration of ventilation and ICU stay?

Given evidence of skeletal muscle sparing, it is plausible that Early nutrition (EN or PN) attenuates diaphragmatic proteolysis (autophagy), mitigating diaphragmatic loss, leading to improved weaning.
Summary
Meta-analysis and large-scale clinical trials demonstrate reduced infectious complications, reduced mortality, reduced duration of ventilation and reduced ICU stay attributable to early nutrition support, provided within 24 h of the onset of critical illness or major injury.
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We would like to invite you to participate:

Nutrition Support in Critical Illness

This Audit of Nutrition Support in Critical Illness is being conducted by the University of Sydney’s Northern Clinical School Intensive Care Research Unit. The primary purpose of this project is to benchmark current practice within hospitals throughout the world in order to provide useful information to participating sites to support local quality improvement initiatives to achieve best practice targets. Click here for additional information about this project. After reading the additional information, if you would like to participate, contact Gordon S. Doig or Philippa F. Heighes.

This is a secure, password protected web site. Access is restricted to participating hospitals only.

[ Login to secure site ]

Using this site for the first time: You will need to install the most recent version of Java to use all features of this site. Click here to verify and update your browser's version of Java.

Endorsed by:

[Logos for various organizations]

Any questions or comments please contact Gordon S. Doig

Implemented and designed by Gordon Doig

Page last modified on 18 May 2012.

Your browser is: Microsoft Internet Explorer

MSIE Version 7 or higher: true

MSIE Version 6 or higher: true

MSIE Version 5 or higher: true

Netscape / Mozilla Version 4 or higher: false

Your browser supports Javascript 1.3
How is your ICU performing?

- A Global audit of time from ICU admission to commencing nutrition therapy.
www.EvidenceBased.net/Nutrition

How is your ICU performing?

• A Global audit of time from ICU admission to commencing nutrition therapy.

• Very simple data collection.
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Data Collection Form: ICU Nutrition Audit

Please record all patients remaining in your ICU at least 3 calendar days, who did not receive oral nutrition on day of ICU admit (Day 1) or the day after ICU admission (Day 2).

<table>
<thead>
<tr>
<th>Initials</th>
<th>Sequential Number</th>
<th>ICU Admission</th>
<th>Feeding Start or ICU discharge</th>
<th>Type of Feeding Started</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1) Enteral Nutrition; (2) Parenteral Nutrition; (3) EN+PN; (4) Oral feeding; (5) No feeding started.</td>
</tr>
</tbody>
</table>
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• If your data suggests you could improve practice, Phase II of the project will help you improve by providing you with a comprehensive change management strategy to focus on the aspect of nutrition therapy that needs change.
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Questions?
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A catabolic process that delivers intracellular constituents sequestered in double-membrane vesicles to lysosomes for degradation.

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

Metabolism in critical illness

Glycogenolysis

• Generation of glucose from glycogen
  • Muscle glycogen likely only available to muscle
  • Liver stores approx 100 g to 120 g
  • Other sources (RBCs, WBCs, kidneys, glial cells) store no more than 20 to 50 g
  • Total energy (not including muscle)
    \[= 4 \text{ kcals/g} \times 170 \text{ g}\]
    \[= 680 \text{ kcals}\]

Gluconeogenesis

• Generation of glucose from non-carbohydrate substrates
  • pyruvate, lactate, glycerol, odd-chain fatty acids and gluconeogenic amino acids
# How was early (< 24 h) EN initiation achieved?

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Early EN intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiarelli</td>
<td>Thermal injury (25% to 60% TBSA). No inhalational injury. Mean survival probability 0.73±0.10.</td>
<td>Immediately after admission: 50 ml/h ‘homemade’ EN (1900kcal/L and 79 g protein/L) via NGT increasing over 3-4 days. Goals set with <strong>Curren formula</strong>. Rate did not exceed 150 ml/h.</td>
</tr>
<tr>
<td>Chuntrasakul</td>
<td>Trauma (ISS &gt; 20 and &lt; 40). Mean ISS 29±1.5</td>
<td>Immediately after resuscitation or surgery: 30 mls/h ¾-strength EN (Traumacal™) via NGT, concentration increased over time. Goals estimated using modified Harris-Benedict equation. TPN was added if goals were not met.</td>
</tr>
<tr>
<td>Kompan</td>
<td>Trauma (ISS &gt; 25) Mean ISS 33.6±10 Mean APACHE II 11.5±5.8</td>
<td>Immediately after resuscitation: EN (Jevity™) started at 20 ml/h via NGT. Increased to 50% of estimated goal on Day 1, 75% of estimated goal on Day 2 and 100% of goal on Day 3. Estimated goal was set at 25-35 nonprotein kcal/kg per day and 0.2 – 0.3 g nitrogen / kg per day at 72 hours post ICU admission. TPN was added to meet estimated requirements.</td>
</tr>
<tr>
<td>Pupelis</td>
<td>Severe pancreatitis and peritonitis Mean APACHE II 11.5±5.4</td>
<td><strong>Within 12 h of surgery:</strong> EN (Nutrison Standard™ or Nutrison Pepti™) via NJT started at 20-25ml/h. Increase based in individual tolerance to 1 L per day by Day 3 post-op. Patients also received an average of 500kcals/day from IV dextrose.</td>
</tr>
<tr>
<td>Kompan</td>
<td>Trauma (ISS &gt; 20). Mean APACHE II 11.3±4.8</td>
<td>Immediately after resuscitation: Same protocol as Kompan 1999 except goal set at an average of 25 nonprotein kcal/kg.</td>
</tr>
<tr>
<td>Nguyen</td>
<td>Mechanically ventilated ICU patients APACHE II 22.4±1.2</td>
<td><strong>Within 24 h of admission:</strong> EN via NGT at 40 ml/h and increased by 20ml/h q6h to goal, if tolerated (aspirates &lt;250mls). <strong>Goal was determined by a dietitian</strong>, based on patient’s BMI.</td>
</tr>
</tbody>
</table>
Immediately after resuscitation:

Stable shock can be defined as:

Shock Index ≤ 1 (heart rate ÷ systolic blood pressure = Shock Index)

or

Systolic blood pressure > 90 mmHg or mean blood pressure > 70 mmHg for at least one hour.

Should I trust a meta-analysis?

- Searched NEJM, Lancet, Annals and JAMA for all large Level I trials (> 1,000 patients with appropriate sample size estimates) published between 1991 and 1994.
- Searched for meta-analyses on the same topic as each trial, published prior to the trial’s conduct.
- 12 large Level I trials were matched to 19 corresponding meta-analyses.

Most important findings:
- None of the meta-analyses originally demonstrating significant benefit were later shown to be causing significant harm.

**Detailed reasons for trial exclusion from our MA**

<table>
<thead>
<tr>
<th><strong>Trial Name</strong></th>
<th><strong>Reasons for exclusion</strong></th>
<th><strong>DH MA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyer 1993</td>
<td>1. Excessive ltf: 27% (14/52 pts ltf, missing)</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>2. Early EN not started within 24 h of injury or ICU admit (Early EN average time 31 hours)</td>
<td></td>
</tr>
<tr>
<td>Minard 2000</td>
<td>1. Early EN not started within 24 h of injury or ICU admit (Early EN defined as within 60 hours, average time 33 h)</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>2. Patients received immune-enhanced EN (Impact), not standard EN</td>
<td></td>
</tr>
<tr>
<td>Singh 1998</td>
<td>1. Not conducted in a critically ill patient population</td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>2. Early EN not started within 24 hours of injury or ICU</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(EN begun 24 – 48 post-op)</td>
<td></td>
</tr>
<tr>
<td>Ibrahim 2002</td>
<td>1. Enteral nutrition commenced at the same time in both groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Early full goal feeding versus early restricted)</td>
<td></td>
</tr>
<tr>
<td>Schroeder 1991</td>
<td>1. No patient oriented outcomes</td>
<td></td>
</tr>
<tr>
<td>Hasse 1995</td>
<td>1. No patient oriented outcomes</td>
<td></td>
</tr>
<tr>
<td>Watters 1997</td>
<td>1. No patient oriented outcomes</td>
<td></td>
</tr>
<tr>
<td>Seri 1984</td>
<td>1. Not conducted in a critically ill patient population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. No patient oriented outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(No deaths reported as of study day 7, no outcomes reported beyond day 7)</td>
<td></td>
</tr>
<tr>
<td>Taylor 1999</td>
<td>1. Enteral nutrition commenced at the same time in both groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Gastric versus post-pyloric feeding)</td>
<td></td>
</tr>
<tr>
<td>Sagar 1979</td>
<td>1. No patient oriented outcomes</td>
<td></td>
</tr>
<tr>
<td>Beier-Holgersen 1996</td>
<td>1. Not conducted in a critically ill patient population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Early post-op oral intake, not early EN</td>
<td></td>
</tr>
<tr>
<td>Carr 1996</td>
<td>1. Not conducted in a critically ill patient population (elective intestinal resection)</td>
<td></td>
</tr>
<tr>
<td>Heslin 1997</td>
<td>1. Not conducted in a critically ill patient population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Patients received immune-enhanced EN (Impact), not standard EN</td>
<td></td>
</tr>
<tr>
<td>Schilder 1997</td>
<td>1. Not conducted in a critically ill patient population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Early post-op oral intake, not early EN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Pseudo-randomised</td>
<td></td>
</tr>
<tr>
<td>Grahm 1989</td>
<td>1. Early EN not started within 24 h of injury or ICU admit (commenced within 36 hours)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Pseudo-randomised</td>
<td></td>
</tr>
</tbody>
</table>
Pupelis 2000 vs Pupelis 2001

Pupelis 2000:
Mortality
1/11 early EN vs 5/18 standard care

Pupelis 2001:
Mortality
1/30 early EN vs 6/30 standard care

The only patient in the JF group who died was admitted with a partly ruptured pancreatic gland after trauma and total enzymatic peritonitis. Emergency surgical intervention was performed. The patient subsequently experienced two repeated reexplorations of the abdominal cavity because of unresolved peritonitis, intestinal fistula, and obstruction of the left side colon. The patient developed MODS and died from profuse gastrointestinal bleeding on 45 d after admission. Despite a very complicated clinical course, it was possible to provide 43 L of the feeding formula jejunally for this patient.
Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs

Gordon S Doig
Fiona Simpson
On behalf of the Early PN Trial Investigators Group
Northern Clinical School Intensive Care Research Unit, University of Sydney, Sydney, NSW, Australia

Purpose: The provision of early enteral (gut) nutrition to critically ill patients, started within 24 hours of injury or intensive care unit admission, is accepted to improve health outcomes. However, not all patients are able to receive early enteral nutrition. The purpose of the economic analysis presented here was to estimate the cost implications of providing early parenteral (intravenous) nutrition to critically ill patients with short-term relative contraindications to early enteral nutrition.

Materials and methods: From the perspective of the US acute care hospital system, a cost-minimization analysis was undertaken based on large-scale Monte Carlo simulation (N = 1,000,000 trials) of a stochastic model developed using clinical outcomes and measures of resource consumption reported in a 1,363-patient multicenter clinical trial combined with cost distributions obtained from the published literature. The mean costs of acute care attributable to each study group (early parenteral nutrition versus pragmatic standard care) and the mean cost difference between groups, along with respective 95% confidence intervals, were obtained using the percentile method.

Results and conclusion: The use of early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition may significantly and meaningfully reduce total costs of acute hospital care by US$3,150 per patient (95% confidence interval US$1,314 to US$4,990). These findings were robust, with all sensitivity analyses demonstrating significant savings attributable to the use of early parenteral nutrition, including sensitivity analysis conducted using European cost data.

Keywords: intensive care, acute hospital care, intravenous nutrition, US acute hospital system

How early is early?

- Early EN defined as *within 24 hours* of injury or ICU admission

**Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT)**

*Claudio M. Martin, Gordon S. Doig, Daren K. Heyland, Teresa Morrison, William J. Sibbald, for the Southwestern Ontario Critical Care Research Network*

**Abstract**

**Background:** The provision of nutritional support for patients in intensive care units (ICUs) varies widely both within and between institutions. We tested the hypothesis that evidence-based algorithms to improve nutritional support in the ICU would improve patient outcomes.

**Methods:** A cluster-randomized controlled trial was performed in the ICUs of 11 community and 3 teaching hospitals between October 1997 and September 1998. Hospital ICUs were stratified by hospital type and randomized to the intervention or control arm. Patients at least 16 years of age with an expected ICU stay of at least 48 hours were enrolled in the study.

If EN is preferable, starting sooner may be better. Data from a few animal and clinical studies on this topic support this hypothesis. However, recent observational studies have documented low rates of “optimal” use of EN in the critical care setting. EN is often started several days after admission, patients do not tolerate adequate amounts of EN, and PN is used excessively in some patients (up to 60% in some countries). Using an audit of intensive care units (ICUs) in community and teaching hospitals, our Critical Care Research Network (CCR-Net) also documented delays in the institution of nutritional support that included both enteral and parenteral routes. Several studies have
How early is early?

- Early EN defined as within 24 hours of injury or ICU admission

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**Multicentre, cluster randomized clinical trial of algorithms for critical care enteral and parenteral therapy (ACCEPT)**

Claudio M. Martin for the Southwest

**Abstract**

**Background:** The provision of critical care enteral nutrition (EN) for patients in intensive care units (ICUs) is time-sensitive. However, compared to parenteral therapy (TP), EN is often delayed. Whether critical care EN algorithms can improve EN delivery in the ICU remains unknown. We compared the time from injury to EN delivery in patients with early EN (within 24 hours of injury) and those with delayed EN (after 24 hours).

**Methods:** A cluster-randomized trial comparing EN algorithms vs hospital-based algorithms was conducted in 11 ICUs of 5 hospitals between October 1997 and September 1998. Patients 16 years of age with a predicted ICU stay of at least 48 hours were enrolled in the study (ICUs) in community and teaching hospitals, our Critical Care Research Network (CCR-Net) also documented delays in the institution of nutritional support that included both enteral and parenteral routes. Several studies have

**Results:** Two hospitals crossed over and were excluded from the primary analysis. Compared with the patients in the control hospitals ($n = 214$), the patients in the intervention hospitals ($n = 248$) received significantly more days of enteral nutrition (6.7 v. 5.4 per 10 patient-days; $p = 0.042$), had a significantly shorter mean stay in hospital (25 v. 35 days; $p = 0.003$) and showed a trend toward reduced mortality (27% v. 37%; $p = 0.058$). The mean stay in the ICU did not differ between the control and intervention groups (10.9 v. 11.8 days; $p = 0.7$).

**Interpretation:** Implementation of evidence-based recommendations improved the provision of nutritional support and was associated with improved clinical outcomes.

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How early is early?

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Research

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