Early nutritional support in critical illness:
From clinical trials to physiology.

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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.

Effect of Evidence-Based Feeding Guidelines on Mortality of Critically Ill Adults: A Cluster Randomized Controlled Trial

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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
      - If at least 80% of requirements be met by 72h
        - Begin TPN:
          - Consider TPN with glutamine
          - Reassess q12h for EN eligibility
      - Is Goal met?
        - Yes
          - Increase rate to 100%
        - No
          - Use prokinetic and/or Use post-gastric tube
          - Is Goal met?
            - Yes
              - Continue EN to Max. tolerated
            - No
              - Continue EN challenge q12h
    - No
      - Acceptable conditions:
        - tolerating adequate oral intake
        - < 24 hours to oral intake
        - palliative care
  - No


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

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The initial MEDLINE/EMBASE search retrieved 2,287 abstracts. Handsearching and reference lists of all other articles (GSD and FS) resulted in the identification of 465 papers. Of these 465 papers, 337 were nutritional support studies and 128 were critical care nutrition research articles. Ninety-three of these 103 studies were found not to meet inclusion criteria for meaningful outcomes, 42 papers were randomized control trials, 27 were preoperative nutrition support studies (i.e., evaluating assessment tools, growth hormone, insulin), 15 were nutritional studies of critically ill patients, and clinical trials (not controlled trials). Only 26 English-language studies, 6 of which were systematic reviews, were based on subgroups of patients included in the published trial, and 1 was a post hoc analysis. Only 10 articles reporting on 10 randomized trials for feeding for critically ill patients were found to be published. The following tables provide a complete listing of all 111 articles.

Background: Review of the Guidelines

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

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  - European (ESPEN) guideline and
  - American (ASPEN and SCCM) guideline


**Background: Review of the Guidelines**

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

  - **< 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**, Significant evidence.
  - **< 48 h – American (ASPEN and SCCM) guideline** Evidence of trend.


Evidence for early EN in critical illness

Doig GS, Heighes PT, Simpson F, Sweetman EA and Davies AR. Enteral nutrition within 24 h of ICU admission significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. 

DOI 10.1007/s00134-009-1664-4
**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 analysis

- Included only methodologically sound RCTs.

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>13.40</td>
<td>0.20 [0.01, 4.47]</td>
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<td>Kompan 2004</td>
<td>0/27</td>
<td>1/25</td>
<td>8.89 0.30 [0.01, 7.63]</td>
<td>8.89</td>
<td>0.30 [0.01, 7.63]</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>19.95</td>
<td>1.00 [0.22, 4.47]</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>18.38</td>
<td>0.23 [0.02, 2.48]</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>39.38</td>
<td>0.11 [0.01, 0.99]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>119</td>
<td>115</td>
<td>100.00 0.34 [0.14, 0.85]</td>
<td>100.00</td>
<td>0.34 [0.14, 0.85]</td>
</tr>
</tbody>
</table>

Total events: 8 (early EN (<24 h)), 19 (Control)
Test for heterogeneity: Chi² = 3.20, df = 4 (P = 0.52), I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

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

### Results: Primary MA, Pneumonia

**Review:** Early EN (<24h) vs Control (Primary Analysis)

**Comparison:** 01 early EN vs Control

**Outcome:** 02 Pneumonia, Intention to treat analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>early EN (&lt;24h) n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kompan 2004</td>
<td>9/27</td>
<td>16/25</td>
<td>70.15 [0.28, 0.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>3/14</td>
<td>6/14</td>
<td>29.85 [0.07, 1.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>41</td>
<td>39</td>
<td><strong>100.00 [0.31, 0.78]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 12 (early EN (<24 h)), 22 (Control)

Test for heterogeneity: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%

Test for overall effect: Z = 2.47 (P = 0.01)

---

**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>EEN</th>
<th>SoC</th>
<th>Mean difference IV, fixed, 95% CI [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuntrasakul et al(a)</td>
<td>5.29</td>
<td>6.12</td>
<td>-0.83 [-4.52, 2.86]</td>
</tr>
<tr>
<td>Kompan et al(b)</td>
<td>12.9</td>
<td>15.6</td>
<td>-2.70 [-9.71, 4.31]</td>
</tr>
<tr>
<td>Nguyen et al(c)</td>
<td>9.2</td>
<td>13.7</td>
<td>-4.50 [-8.62, -0.38]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td>56</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**

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<thead>
<tr>
<th>Study or sub-category</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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<tbody>
<tr>
<td>Chiarelli</td>
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<td>Not estimable</td>
<td></td>
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<td>Chuntrasakul</td>
<td>1/21</td>
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</tr>
<tr>
<td>Eyer</td>
<td>2/19</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>Pupelis</td>
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<td>Singh</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>159</strong></td>
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Total events: 10 (Early EN (<60 h)), 23 (Control)
Test for heterogeneity: $\chi^2 = 4.05$, 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)**

**Simulation study: Heyland’s 2003 MA**

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

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

Simulation study: Heyland’s 2003 MA

Review: Heyland Early EN
Comparison: 01 Mortality
Outcome: 01 Mortality

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</tr>
<tr>
<td>Eyer (average time to early EN: 31 h)</td>
<td>2/19</td>
<td>2/19</td>
<td>15.27</td>
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<td>12.70</td>
<td>0.14</td>
<td>[0.02, 1.09]</td>
</tr>
<tr>
<td>Singh (&lt;48 h)</td>
<td>4/21</td>
<td>4/22</td>
<td>33.57</td>
<td>1.05</td>
<td>[0.30, 3.66]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>159</td>
<td>158</td>
<td>100.00</td>
<td>0.52</td>
<td>[0.25, 1.08]</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)

**Simulation study: Heyland’s 2003 MA**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Early EN (&lt;60 h) n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiarelli</td>
<td>0/10</td>
<td>0/10</td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Chuntrasakul</td>
<td>1/21</td>
<td>3/17</td>
<td>11.14 0.27 [0.03, 2.37]</td>
<td>11.27</td>
<td>1.00 [0.16, 6.38]</td>
</tr>
<tr>
<td>Eyer (average time to early EN: 31 h)</td>
<td>2/19</td>
<td>2/19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kompan</td>
<td>0/14</td>
<td>1/14</td>
<td>5.39 0.33 [0.01, 7.55]</td>
<td>15.27</td>
<td>1.00 [0.16, 6.38]</td>
</tr>
<tr>
<td>Minard (&lt;60 h)</td>
<td>1/12</td>
<td>4/15</td>
<td>12.42 0.31 [0.04, 2.44]</td>
<td>5.39</td>
<td>0.33 [0.01, 7.55]</td>
</tr>
<tr>
<td>Moore</td>
<td>1/32</td>
<td>2/31</td>
<td>9.51 0.48 [0.05, 5.07]</td>
<td>12.42</td>
<td>0.31 [0.04, 2.44]</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>9.51</td>
<td>0.48 [0.05, 5.07]</td>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>107</strong></td>
<td><strong>102</strong></td>
<td><strong>100.00 0.26 [0.08, 0.83]</strong></td>
<td><strong>33.57</strong></td>
<td><strong>1.05 [0.30, 3.66]</strong></td>
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Total events: 3 (Early EN (<60 h)), 13 (Control)
Test for heterogeneity: $\chi^2 = 0.64$, df = 3 ($P = 0.89$), $I^2 = 0$
Test for overall effect: $Z = 2.27$ ($P = 0.02$)

**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.
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- 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.


$1,000,000 question:

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

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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.

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- Mesenteric lymph nodes and ileum were instantly harvested and prepared for study.

Paneth cells and fasting

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?

Paneth cells and fasting

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

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

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Starvation conditions are known to enhance protein breakdown by autophagy, whereas systemic amino acids down regulate autophagy by a factor of 2 to 5 times within 20 minutes.


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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

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- Even well nourished and well fed ICU 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: Changes over time

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- Amino acids inhibit autophagy rapidly (within 20 minutes) and greatly (up to fivefold)


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*It is plausible that Early nutrition attenuates diaphragmatic proteolysis (autophagy), mitigating diaphragmatic loss, leading to improved weaning.*
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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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