Understanding the benefits of Early Enteral Nutrition: From clinical trials to costs.

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University of Sydney, Sydney, Australia
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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.
Background: Review of the Guidelines

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

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- Five major clinical practice guidelines recommend early EN.
  - Canadian guideline,
  - ACCEPT guideline (also Canadian),
  - Australian and New Zealand guideline,
  - 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.

- **Canadian guideline**, **Evidence of trend.**
  - < 48 h
- **ACCEPT guideline (also Canadian)**, **Significant evidence.**
  - < 24 h
- **Australian and New Zealand guideline**, **Significant evidence.**
  - < 24 h
- **European (ESPEN) guideline and**, **Significant evidence.**
  - < 24 h
- **American (ASPEN and SCCM) guideline**, **Evidence of trend.**
  - < 48 h


How early is early?
Evidence for 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.

Meta-analysis of early EN in critical illness

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Primary analysis

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Primary outcome

- clinically meaningful patient oriented outcomes: (mortality / physical function / quality of life)

Potentially relevant papers identified and retrieved (N = 675)

Papers excluded, with reasons (N = 170)
- Not RCTs (Letters, observational studies, systematic reviews, narrative reviews, previous meta-analyses)

RCTs identified for detailed evaluation (N = 505)

RCTs excluded, with reasons (N = 475)
- 329 Did not provide a primary comparison of timing of EN (includes 5 pseudo-randomised trials + 99 trials not reporting clinically meaningful outcomes)
- 72 Not adult critically ill population
- 46 Not primary nutritional support intervention (GH etc)
- 16 Cross-over trials
- 13 Pre-operative interventions

RCTs evaluating timing of EN (N = 30)

Included in primary analysis (N = 6)

Excluded RCTs (N = 24)
- 7 - Early EN not started within 24 h of injury or ICU admission
- 4 - Patient oriented outcomes not reported (no mortality etc)
- 5 - Not critically ill patient population
- 2 - Early post-op oral intake, not early EN
- 2 - EN commenced at same time in both groups
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Included in primary analysis
\((N = 6)\)
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></td>
<td></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>Chuntasaksul 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>Total (95% CI)</td>
<td>119</td>
<td>115</td>
<td>100.00 0.34 [0.14, 0.85]</td>
<td></td>
<td></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**

<table>
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<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>Kompan 2004</td>
<td>9/27</td>
<td>16/25</td>
<td>70.15 0.28 [0.09, 0.88]</td>
<td>46.61</td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>3/14</td>
<td>6/14</td>
<td>29.85 0.36 [0.07, 1.91]</td>
<td>10.92</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>41</strong></td>
<td><strong>39</strong></td>
<td><strong>100.00</strong> 0.31 [0.12, 0.78]</td>
<td><strong>100.00</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

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

Test for heterogeneity: $\chi^2 = 0.06$, df = 1 (P = 0.80), $I^2 = 0$

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

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

Novel MA of gut dysfunction

- Meta-analysis suggests the provision of early EN may reduce the incidence of gut dysfunction:
  - 33% (22/67) of patients vs. 43% (28/65) of patients, p=0.09, no heterogeneity
- One included trial demonstrated a significantly shorter duration of gut dysfunction (p=0.045)
Results: updated MA, ICU length of stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EEN</th>
<th>SoC</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>IV, fixed, 95% CI [days]</td>
</tr>
<tr>
<td>Chuntrasakul et al</td>
<td>8.14</td>
<td>8.35</td>
<td>47.7%</td>
</tr>
<tr>
<td>Pupolis et al</td>
<td>13.9</td>
<td>16</td>
<td>7.3%</td>
</tr>
<tr>
<td>Kompan et al</td>
<td>15.9</td>
<td>20.6</td>
<td>8.9%</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>11.3</td>
<td>15.9</td>
<td>36.1%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>86</td>
<td>100.0%</td>
</tr>
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</table>

Figure 1 Meta-analysis of ICU length of stay: early enteral nutrition vs standard care.  
Notes: Heterogeneity: $\chi^2 = 2.94, df = 3 (P = 0.40);$ $I^2 = 0\%.$ Test for overall effect: $Z = 1.87 (P = 0.06).$  
Abbreviations: CI, confidence interval; EEN, early enteral nutrition; ICU, Intensive Care Unit; IV, inverse variance; SD, standard deviation; SoC, standard of care.

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

Results: updated MA, duration of MV

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>
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<tr>
<th>Study or sub-category</th>
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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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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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Total (95% CI) 159 158 100.00 0.52 [0.25, 1.08]

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

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

<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>
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<td>0.48 [0.05, 5.07]</td>
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<td>12.70</td>
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<tr>
<td>Singh (&lt;48 h)</td>
<td>4/21</td>
<td>4/22</td>
<td>33.57</td>
<td>1.05 [0.30, 3.66]</td>
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</tbody>
</table>

Total (95% CI) 107 102 100.00 0.26 [0.08, 0.83]

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!!!**
Early EN in Upper GI Sx: Indirect evidence
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- A Meta-analysis comparing RCT’s of early feeding (within 24h) versus no feeding in patients undergoing gastrointestinal surgery.
- 13 studies, 1,173 patients

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  - Mortality (2.4% eEN vs 6.9%, p=0.03)

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- Early feeding was not associated with any harms:
  - Wound infections (7.1% eEN vs 9.3%, p=0.26)
  - Anastomotic dehiscence (2.8% eEN vs 4.3%, p=0.27)
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“There is no obvious benefit for keeping patients “nil by mouth” after gastrointestinal surgery”

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


$1,000,000 question:
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1. How 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

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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

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- 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?

Paneth cells and fasting

Paneth cells and fasting

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

Autophagocytosis

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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).

Paneth cells and fasting

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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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- 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

- 15 Sham surgical procedure

100% survival at day 7

iAP and severe peritonitis

- 15 Sham surgical procedure    100% survival at day 7
- 15 CLP + control i.p. saline injection  0% survival at day 3

iAP and severe peritonitis

- 15 Sham surgical procedure  100% survival at day 7
- 15 CLP + control i.p. saline injection  0% survival at day 3
- 15 CLP + 5 IU i.p. iAP injection  26% survival at day 7
- 15 CLP + 10 IU i.p. iAP injection  40% survival at day 7

iAP and severe peritonitis

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- 15 CLP + control i.p. saline injection: 0% survival at day 3
- 15 CLP + 5 IU i.p. iAP injection: 26% survival at day 7
- 15 CLP + 10 IU i.p. iAP injection: 40% survival at day 7
- 15 CLP + 25 IU i.p. iAP injection: 50% 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:

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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.
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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www.EvidenceBased.net

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How early is early?

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

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


**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 the 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

---

**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.

How early is early?

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**Research**

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**CMAJ** 2004;170(2):197-204.

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**Updated US Guideline: Early EN**

All RCTs, Early EN

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<td>Chourdakis 2012</td>
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</table>

**Total (95% CI):**

- Events: 469
- Delayed/None: 467
- Weight: 100.0%
- Risk Ratio: 0.70 [0.49, 1.00]

**Heterogeneity:**
- Tau² = 0.00
- Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

**Test for overall effect:** Z = 1.97 (P = 0.05)
### Updated US Guideline: Early EN

Zero mortality: do not contribute any information

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN</th>
<th>Delayed/None</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<td>2/25</td>
<td>1.10 [0.20, 6.12]</td>
<td>2012</td>
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</tbody>
</table>

**Total (95% CI):**

- Early EN: 469 events, 467 total
- Delayed/None: 41 events, 56 total

**Heterogeneity:**
- Tau² = 0.00
- Chi² = 7.23, df = 15 (P = 0.95)
- I² = 0%

**Test for overall effect:**
- Z = 1.97 (P = 0.05)
Updated US Guideline: Early EN

All RCTs, Early EN

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
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<td><strong>Total (95% CI)</strong></td>
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<td></td>
<td><strong>469</strong></td>
<td><strong>467</strong></td>
<td><strong>0.70 [0.49, 1.00]</strong></td>
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<td><strong>Total events</strong></td>
<td>41</td>
<td>66</td>
<td><strong>100.0%</strong></td>
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Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Updated US Guideline: Early EN

Duplicate publication

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None Events</th>
<th>Total Events Weight</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
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<td>5</td>
<td>18</td>
<td>0.33 [0.04, 2.45] 2000</td>
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<td>30</td>
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<td>0.31 [0.01, 7.26] 2004</td>
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<td>13</td>
<td>0.74 [0.25, 2.18] 2004</td>
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<td>16</td>
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<td>0.75 [0.37, 1.50] 2004</td>
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<td>25</td>
<td>1.10 [0.20, 6.12] 2012</td>
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</table>

Total (95% CI) 469 467 100.0% 0.70 [0.49, 1.00]

Total events 41 66

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

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

enteral group and the controls (Fig. 2). Of the 11 patients with severe pancreatitis who were given enteral nutrition, five developed a paralytic ileus, one of whom developed complete necrotic obstruction of the sigmoid colon. He died on the 45th day (despite many interventions including a colostomy) having been given enteral nutrition for 41 days (mean daily intake 1052 ml, total 43,150 ml). Another patient developed necrosis of the transverse colon, but

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.
Updated US Guideline: Early EN
Surgical patients, not managed in ICU

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Total Events</th>
<th>Delayed/None Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
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<td>31</td>
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<td>14</td>
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<td>17</td>
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<td>14</td>
<td>1.00 [0.43, 2.35] 2008</td>
</tr>
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</table>

Total (95% CI) | 469 | 467 | 100.0% | 0.70 [0.49, 1.00]

Total events: 41 | 66

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
Updated US Guideline: Early EN

All RCTs, Early EN
### Updated US Guideline: Early EN

**RCTs defining Early EN as < 48 h**

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Delayed/None Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
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<td>19</td>
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<td>3.7%</td>
<td>1.00 [0.16, 6.30]</td>
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<td>467</td>
<td>100.0%</td>
<td>0.70</td>
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<tr>
<td><strong>Total events</strong></td>
<td>41</td>
<td>66</td>
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</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)
Updated US Guideline: Early EN
All RCTs, Early EN < 24 h (same as our 2009 publication)
Updated US Guideline: Early EN

RCTs, Early EN < 48 h

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Total</th>
<th>Delayed/None Events</th>
<th>Total</th>
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<tbody>
<tr>
<td>Sagar 1979</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>Not estimable</td>
<td>1979</td>
</tr>
<tr>
<td>Chiarelli 1990</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>Not estimable</td>
<td>1990</td>
</tr>
<tr>
<td>Schroeder 1991</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>Not estimable</td>
<td>1991</td>
</tr>
<tr>
<td>Eyer 1993</td>
<td>2</td>
<td>19</td>
<td>2</td>
<td>19</td>
<td>3.7%</td>
<td>1.00 [0.16, 6.39] 1993</td>
</tr>
<tr>
<td>Watters 1997</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>14</td>
<td>Not estimable</td>
<td>1997</td>
</tr>
<tr>
<td>Singh 1998</td>
<td>4</td>
<td>21</td>
<td>4</td>
<td>22</td>
<td>8.2%</td>
<td>1.05 [0.30, 3.66] 1998</td>
</tr>
<tr>
<td>Minard 2000</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>15</td>
<td>3.0%</td>
<td>0.31 [0.04, 2.44] 2000</td>
</tr>
<tr>
<td>Dvorak 2004</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>10</td>
<td>Not estimable</td>
<td>2004</td>
</tr>
<tr>
<td>Malhotra 2004</td>
<td>12</td>
<td>100</td>
<td>16</td>
<td>100</td>
<td>26.5%</td>
<td>0.75 [0.37, 1.50] 2004</td>
</tr>
<tr>
<td>Moses 2009</td>
<td>3</td>
<td>29</td>
<td>3</td>
<td>30</td>
<td>5.6%</td>
<td>1.03 [0.23, 4.71] 2009</td>
</tr>
<tr>
<td>Chourdakis 2012</td>
<td>3</td>
<td>34</td>
<td>2</td>
<td>25</td>
<td>4.4%</td>
<td>1.10 [0.20, 6.12] 2012</td>
</tr>
</tbody>
</table>

Total events: 41, 66

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)
### Updated US Guideline: Early EN

**RCTs, Early EN < 48 h**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early EN</th>
<th>Delayed/None</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watters 1997</td>
<td>0</td>
<td>14</td>
<td>Not estimable 1997</td>
</tr>
<tr>
<td>Singh 1998</td>
<td>4</td>
<td>21</td>
<td>1.05 [0.30, 3.66] 1998</td>
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**Total events**: 41 / 66

Heterogeneity: Tau² = 0.00; Chi² = 7.23, df = 15 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.97 (P = 0.05)
### 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 1990</td>
<td>Thermal injury (25% to 60% TBSA). No inhalational injury. Mean survival probability 0.73±0.10.</td>
<td><strong>Immediately after admission:</strong> 50 ml/h ‘homemade’ EN (1900kcal/L and 79 g protein/L) via NGT increasing over 3-4 days. Goals set with <strong>Currenri formula</strong>. Rate did not exceed 150 ml/h.</td>
</tr>
<tr>
<td>Chuntrasakul 1996</td>
<td>Trauma (ISS &gt; 20 and &lt; 40). Mean ISS 29±1.5</td>
<td><strong>Immediately after resuscitation or surgery:</strong> 30 mls/h ¾-strength EN (Traumacal™) via NGT, concentration increased over time. Goals estimated using <strong>modified Harris-Benedict</strong> equation. TPN was added if goals were not met.</td>
</tr>
<tr>
<td>Kompan 1999</td>
<td>Trauma (ISS &gt; 25) Mean ISS 33.6±10 Mean APACHE II 11.5±5.8</td>
<td><strong>Immediately after resuscitation:</strong> 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 <strong>goal was set at 25-35 nonprotein kcal/kg per day</strong> 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 2001</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 <strong>started at 20-25ml/h</strong>. Increase based in individual tolerance to <strong>1 L per day</strong> by Day 3 post-op. Patients also received an average of 500kcaes/day from IV dextrose.</td>
</tr>
<tr>
<td>Kompan 2004</td>
<td>Trauma (ISS &gt; 20). Mean APACHE II 11.3±4.8</td>
<td><strong>Immediately after resuscitation:</strong> Same protocol as Kompan 1999 except goal set at an average of 25 nonprotein kcal/kg.</td>
</tr>
<tr>
<td>Nguyen 2008</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 <strong>40 ml/h</strong> and increased by 20ml/h q6h to goal, if tolerated (aspirates &lt;250mls). <strong>Goal was determined by a dietician</strong>, based on patient’s BMI.</td>
</tr>
</tbody>
</table>