Early nutrition in the ICU patient: 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.
Background: Review of the Guidelines

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

Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma—a prospective, randomized study. 
J Trauma 1986;26:874–881
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  - Canadian guideline,
  - ACCEPT guideline (also Canadian),
  - Australian and New Zealand guideline,
  - European (ESPEN) guideline and
  - American (ASPEN and SCCM) guideline


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


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.

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
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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>
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<tr>
<td>Kompan 1999</td>
<td>0/17</td>
<td>2/19</td>
<td>13.40 0.20 [0.01, 4.47]</td>
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<td></td>
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<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>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

- Review: Early EN (<24h) vs Control (Primary Analysis)
- Comparison: 01 early EN vs Control
- Outcome: 02 Pneumonia, Intention to treat analysis

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<tr>
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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 [0.09, 0.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>3/14</td>
<td>6/14</td>
<td>29.85 0.36 [0.07, 1.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>41</td>
<td>39</td>
<td>100.00 0.31 [0.12, 0.78]</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)**

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**

**Doig et al**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EEN</th>
<th>SoC</th>
<th>Mean difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean [days]</td>
<td>SD [days]</td>
<td>Mean [days]</td>
</tr>
<tr>
<td>Chuntrasakul et al(^a)</td>
<td>8.14</td>
<td>6.28</td>
<td>21</td>
</tr>
<tr>
<td>Pupolisi et al(^b)</td>
<td>13.9</td>
<td>14.6</td>
<td>30</td>
</tr>
<tr>
<td>Kompan et al(^d)</td>
<td>15.9</td>
<td>9.7</td>
<td>27</td>
</tr>
<tr>
<td>Nguyen et al(^e)</td>
<td>11.3</td>
<td>2.99</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>92</td>
<td>86</td>
<td>100.0%</td>
</tr>
</tbody>
</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)

Early EN in Upper GI Sx: Indirect evidence
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- 13 studies, 1,173 patients

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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”

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- 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.


$1,000,000 question:
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1. How could early EN reduce infectious complications and mortality?
With the onset of critical illness:

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

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

• 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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- 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.

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 down regulate autophagy by a factor of 2 to 5 times within 20 minutes.

Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology 1012;153: (ePub ahead of print).
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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 group:
  • 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
- 15 CLP + control i.p. saline injection: 0% survival at day 3

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**iAP and severe peritonitis**

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  0% survival at day 3
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- 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
- 15 CLP + 50 IU i.p. iAP injection  
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- 15 CLP + 25 IU i.p. iAP injection 50% survival at day
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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)

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
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Meta-analysis and 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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EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
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>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 Curreri formula. Rate did not exceed 150 ml/h.</td>
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• SBP > 100 mmHg without need for increasing doses of vasoactive agents for one hour.

Stable shock is not defined by weaning or removing all vasoactive agents.


Summary

Meta-analysis and 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.

Recent physiological evidence provides reasonable mechanistic hypotheses supporting these clinical benefits.

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What if we wait until after 24 h?

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.
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< 48 h – 2016 ASPEN

- 21 clinical trials
- p=0.05 (significant)
- mortality reduction by 5%

We need to understand if there is still benefit if feeding is started after 24 h but before 48 h.

We will remove all the RCTs that start feeding before 24 h and redo the analysis.
2016 ASPEN Guideline

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<td>1</td>
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</table>

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

Total events 41 66

Heterogeneity: Tau^2 = 0.00, Chi^2 = 7.23, df = 15 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
2016 ASPEN Guideline
These RCTs feed ICU patients within 24 h (Doig et al, ICM 2009)
2016 ASPEN Guideline

![Diagram showing risk ratios for early EN versus delayed/none EN.](image)
2016 ASPEN Guideline

These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Early EN Total</th>
<th>Delayed/None Events</th>
<th>Delayed/None Total</th>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>469</td>
<td>467</td>
<td><strong>100.0%</strong></td>
<td></td>
<td>0.70 [0.49, 1.00]</td>
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</table>

Total events: 41

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

Test for overall effect: Z = 1.97 (P = 0.05)
2016 ASPEN Guideline
These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)

- Beier-Holgersen 1996, Carr 1996

**Influence of postoperative enteral nutrition on postsurgical infections**
R Beier-Holgersen, S Boesby

**Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection**
Cornelia S Carr, KD Eddie Ling, Paul Boulos, Mervyn Singer

Abstract
Background—This study was undertaken to test the hypothesis that early enteral nutrition might reduce the incidence of serious complications after major abdominal surgery versus parenteral nutrition. The effectiveness of early versus delayed enteral nutrition in reducing serious complications after surgery has been shown in numerous studies. However, there is evidence that early enteral nutrition can be delayed for up to 72 hours without adverse consequences. Therefore, the aim of this study was to assess the safety and efficacy of early versus delayed enteral nutrition in reducing serious complications after surgery.

Objective—To assess the safety and efficacy of early versus delayed enteral nutrition in reducing serious complications after surgery.

Design—Randomised trial of two groups of patients undergoing major abdominal surgery: group 1 received early enteral nutrition from the day of surgery, and group 2 received delayed enteral nutrition from 72 hours after surgery. All patients received intravenous fluids until the reintroduction of a normal diet.

Results—The incidence of serious complications was significantly lower in group 1 compared to group 2. There were no differences in mortality, reoperation rate, or length of stay between the two groups.

Conclusion—Early enteral nutrition is safe and effective in reducing serious complications after major abdominal surgery. It is recommended that all patients undergoing major abdominal surgery receive early enteral nutrition.
• Beier-Holgersen 1996, Carr 1996
  - Both trials start feeding immediately after surgery (< 24 h).

---

2016 ASPEN Guideline
These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)
2016 ASPEN Guideline
These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)

- Beier-Holgersen 1996, Carr 1996
  - Both trials start feeding immediately after surgery (< 24 h).
  - Neither study reports any patients requiring care in the ICU, post-op mechanical ventilation or any other interventions requiring ICU admission.
Beier-Holgersen 1996, Carr 1996
- Both trials start feeding immediately after surgery (< 24 h).
- Neither study reports any patients requiring care in the ICU, post-op mechanical ventilation or any other interventions requiring ICU admission.
- These are elective surgery patients!

2016 ASPEN Guideline
These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)
These RCTs feed GI Sx patients within 24 h (Lewis et al, J Gast Sx 2009)
These RCTs start feeding after 24 h, but before 48 h
2016 ASPEN Guideline

These RCTs start feeding after 24 h, but before 48 h
2016 ASPEN Guideline
These RCTs start feeding after 24 h, but before 48 h

<table>
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<th>Study or Subgroup</th>
<th>Early EN Events</th>
<th>Early EN Total</th>
<th>Delayed/None Events</th>
<th>Delayed/None Total</th>
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<td>2012</td>
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Total (95% CI) 469 467 100.0% 0.70 [0.49, 1.00]
Total events 41 66
Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.23, df = 15 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 1.97 (P = 0.05)
2016 ASPEN Guideline
These RCTs start feeding after 24 h, but before 48 h

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Total events: 29 / 36
Heterogeneity: Chi² = 1.46, df = 6 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.32)
2016 ASPEN Guideline

These RCTs start feeding after 24 h, but before 48 h
Summary

Meta-analysis and 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.

Recent physiological evidence provides reasonable mechanistic hypotheses supporting these clinical benefits.

EN should begin within 24 h of ICU admission, as soon as shock is stabilised:

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

What if we wait until after 24 h?

Meta-analysis and 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.

Recent physiological evidence provides reasonable mechanistic hypotheses supporting these clinical benefits.

EN should begin within 24 h of ICU admission, as soon as shock is stabilised:

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

*If we commence EN after 24 h, there may be no significant benefit on mortality!*

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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)


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

---

**Research**

**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?

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

Research

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 \((6.7 \text{ v. } 5.4 \text{ per } 10 \text{ patient-days}; p = 0.042)\), had a significantly shorter mean stay in hospital \((25 \text{ v. } 35 \text{ days}; p = 0.003)\) and showed a trend toward reduced mortality \((27\% \text{ v. } 37\%; p = 0.058)\). The mean stay in the ICU did not differ between the control and intervention groups \((10.9 \text{ v. } 11.8 \text{ days}; p = 0.7)\).

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

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

How early is early?

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

Abstract

Background: The provision of adequate nutrition in the ICU is critical. Evidence suggests that patients receiving early EN (within 24 hours of injury or ICU admission) have improved outcomes. However, defining "early" is not always straightforward. The aim of this study was to determine the optimal timing for initiating EN in critically ill patients.

Methods: A cluster-randomized controlled trial was conducted in 11 ICUs across Canada. Patients were randomized to receive EN within 24 hours of injury or ICU admission or to receive EN later. The primary outcome was mortality at 28 days.

Results: Two hospitals crossed over and were excluded from the primary analysis. Compared with the patients in the control group, the patients in the intervention group 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.

Mortality by subgroup

Favours control

Favours Guideline

All patients $n=492$

Medical Admit $n=132$

Emerg Dept Admit $n=150$

Surgical Admit $n=147$

Elective Sx $n=66$

Emergent Sx $n=81$

From other hospital $n=39$

From other ICU $n=15$

Absolute Risk Reduction for Mortality with 95% confidence interval (test based), accounting for clustering
Assorted loose ends
Assorted loose ends

- Rates and Targets
Assorted loose ends

- Rates and Targets
  - There is no robust evidence to mandate specific rates or goals.
  - In general, start slow and achieve reasonable goals within 3 to 7 days.
Assorted loose ends

- Rates and Targets
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- Gut Dysmotility
Assorted loose ends

- Rates and Targets
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- Gut Dysmotility
  - Mounting evidence suggests we create gut dysmotility by feeding late.
**Rates and Targets**
- There is no robust evidence to mandate specific rates or goals.
- In general, start slow and achieve reasonable goals within 3 to 7 days.

**Gut Dysmotility**
- Mounting evidence suggests we create gut dysmotility by feeding late.
- Gastric tubes are easier to place and allow you to start earlier.
**Assorted loose ends**

- **Rates and Targets**
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  - Mounting evidence suggests *we* create gut dysmotility by feeding late.
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Assorted loose ends

• Rates and Targets
  • There is no robust evidence to mandate specific rates or goals.
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• Gut Dysmotility
  • Mounting evidence suggests we create gut dysmotility by feeding late.
  • Gastric tubes are easier to place and allow you to start earlier.
  • In general, start slow and achieve reasonable goals within 3 to 7 days.
  • Do not allow the placement of a post-pyloric tube to delay or interrupt EN.
**Assorted loose ends**

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- EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
Assorted loose ends

- Rates and Targets
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  - Do not allow the placement of a post-pyloric tube to delay or interrupt EN.
- EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
  - Shock Index ≤ 1 (Heart rate / SBP) for one hour or
  - SBP > 100 mmHg without need for increasing doses of vasoactive agents for one hour.
Assorted loose ends

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  • There is no robust evidence to mandate specific rates or goals.
  • In general, start slow and achieve reasonable goals within 3 to 7 days.

• Gut Dysmotility
  • Mounting evidence suggests we create gut dysmotility by feeding late.
  • Gastric tubes are easier to place and allow you to start earlier.
  • In general, start slow and achieve reasonable goals within 3 to 7 days.
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• EN should begin within 24 h of ICU admission, as soon as shock is stabilised:
  • Shock Index ≤ 1 (Heart rate / SBP) for one hour or
  • SBP > 100 mmHg without need for increasing doses of vasoactive agents for one hour.

*Stable shock is not defined by weaning or removing all vasoactive agents.*
Economic Analysis: Early EN reduces costs

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

- **EN US$14,462** (95% CI $5,464 to $23,669) savings per patient treated
- **¥ 9,000 RMB per patient savings** using local costs of ICU care

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