Early enteral nutrition in critical illness: Clinical evidence and pathophysiological rationale

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Summary of this talk

• Provide a brief background on the origins of the concept of ‘early’ enteral feeding.

• Review the most recent clinical evidence on the topic.

• Present some interesting new physiological evidence supporting the clinical evidence.

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

Background

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- Debate has raged over whether the benefits of ‘early’ EN are real.


**Background**

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

- Debate has raged over whether the benefits of ‘early’ EN are real.

- Previous meta-analyses on the topic have been inconclusive.


How early is early?

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.1-5 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).6-10 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.11 Several studies have
How early is early?

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

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**Research**

**CMAJ**

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


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**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?

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

updated MA of eEN in critically ill

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

**Primary Hypothesis:**

To identify and synthesize the current evidence from *methodologically sound* randomised controlled trials (RCTs) conducted in *critically ill patients* and determine whether the provision of early (*<24h]*) standard EN confers a treatment benefit, on average, in the identified studies.

Methods

Primary analysis

• Included only methodologically sound RCTs.

Methods

Primary analysis

- Included only methodologically sound RCTs.

Simulation analysis

- Duplicated Heyland’s 2003 selection and analysis process, but only included trials where EN was initiated within 24 h of injury or ICU admission.

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 evaluating timing of EN (N = 30)

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

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
1 - Immuno-enhanced EN (Impact)
2 - Excessive loss to follow-up
1 - Subgroup from a larger trial

Included in primary analysis (N = 6)
On topic, included in primary analysis

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>
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<td>100.00</td>
<td>0.34 [0.14, 0.85]</td>
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<td>1/25</td>
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<tr>
<td>Chuntasakul 1996</td>
<td>1/21</td>
<td>3/17</td>
<td>18.38 0.23 [0.02, 2.48]</td>
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</table>

| Total (95% CI) | 119                  | 115         | 100.00 | 0.34 [0.14, 0.85] |

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

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<tr>
<td>Total (95% CI)</td>
<td>41</td>
<td>39</td>
<td>100.00 0.31 [0.12, 0.78]</td>
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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)

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**

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

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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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- **Total events:** 10 (Early EN (<60 h)), 23 (Control)
- **Test for heterogeneity:** Chi$^2 = 4.05$, df = 6 ($P = 0.67$), I$^2 = 0$
- **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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### Total (95% CI)

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<tr>
<td>107</td>
<td>102</td>
<td>100.00</td>
<td>0.26</td>
<td>0.08 [0.08, 0.83]</td>
</tr>
</tbody>
</table>

Total events: 3 (Early EN (<60 h)), 13 (Control)
Test for heterogeneity: Chi² = 0.64, df = 3 (P = 0.89), I² = 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!!!
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- Pneumonia may also be significantly reduced.

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

$1,000,000 question:

**HOW** does early EN reduce mortality and infectious complications?
RM 3,038,993 question:

HOW does early EN reduce mortality and infectious complications?
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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  - Lysozyme, α-defensins plus others

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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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• 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

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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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).

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- Autophagocytosis of the Paneth cells appears to compromise their important immune function, as demonstrated by a reduction in antimicrobial peptide production and increase in bacterial translocation.

Starvation conditions are known to enhance protein breakdown by autophagy, whereas amino acids (either EN or PN), inhibit autophagocytosis.


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- iAP is capable of ‘detoxifying’ Gram negative bacteria by dephosphorylating the lipid A moiety of the lipopolysaccharide (LPS) in their cell walls.

- 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

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

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- 15 CLP + 25 IU i.p. iAP injection 50% survival at day 7
- 15 CLP + 50 IU i.p. iAP injection 50% survival at day 7

iAP and severe peritonitis

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

**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.


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**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.

Summary of the evidence

Recent meta-analysis of current clinical trials demonstrates reduced mortality and reduced pneumonia attributable to early EN, provided within 24 h of the onset of critical illness or major injury.

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Recent physiology breakthroughs demonstrate a significant reduction in gut immune function (reduced activity of Paneth cells and iAP) after only short term fasting.


Recent meta-analysis of current clinical trials demonstrates reduced mortality and reduced pneumonia attributable to early EN, provided within 24 h of the onset of critical illness or major injury.

Recent physiology breakthroughs demonstrate a significant reduction in gut immune function (reduced activity of Paneth cells and iAP) after only short term fasting.

Providing EN within 24 h of the onset of critical illness or injury may prevent functional compromise of the gut’s immune defenses attributable to short term fasting, which translates into the clinical benefits demonstrated in the recent meta-analysis of current clinical trials.


Questions?
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.

**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><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 Curreri formula. 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><strong>Immediately after resuscitation or surgery:</strong> 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><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 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><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</td>
<td>Mechanically ventilated ICU patients Mean 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>