Early enteral nutrition in the major trauma patient requiring intensive care:
An overview of the evidence.

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Summary of this talk

• Provide a context.

• Review the most recent clinical evidence.

• Generate concise clinical recommendations.

• Summarize.
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

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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.

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Evidence updated by the ANZICS CTG Feeding Investigators Group Oct 28th, 2003. Chief Investigator: Dr. Gordon S. Doig, University of Sydney. Contact: gdoig@msd.usyd.edu.au

JAMA 2008 Dec 17;300(23):2731-41.
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  - < 48 h – *American (ASPEN and SCCM) guideline*


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

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One major trauma CPG recommends *early* EN.
Background: Review of the Guidelines

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“enteral feeding can be instituted in most patients after resuscitation is complete and hemodynamic stability has been gained.”

Early EN in trauma: Direct evidence
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- RCT’s conducted in:

  - adult trauma patients requiring intensive care and;
  - standard EN begun within 24hrs of injury compared to standard care (oral intake upon return of bowel sounds, TPN, or TPN + delayed EN);
  - the literature search supporting our 2008 JAMA guideline was updated and expanded with a specific focus on trauma patients.

Early EN in trauma: Direct evidence

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Early EN in trauma: Direct evidence

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- Primary analysis is based on RCTs that do not have major flaws:
  - Moore et al enrolled 75 patients, but 12 were excluded from analysis within the first 72 hr post-injury because of reoperation (six), death (four), or transfer to another hospital (two). We do not know which group these 12 patients were randomised to.
  - Excessive loss to follow-up is a major validity flaw.


Primary analysis: RCTs without major flaws

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<tr>
<th>Study or sub-category</th>
<th>Early EN (&lt;24 h) n/N</th>
<th>Standard Care n/N</th>
<th>Peto OR 95% CI</th>
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<tr>
<td>Kompan 1999</td>
<td>0/17</td>
<td>2/19</td>
<td>29.48</td>
<td>0.14 [0.01, 2.38]</td>
<td></td>
</tr>
<tr>
<td>Kompan 2004</td>
<td>0/27</td>
<td>1/25</td>
<td>15.20</td>
<td>0.12 [0.00, 6.31]</td>
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<tr>
<td>Chuntrasakul 1996</td>
<td>1/21</td>
<td>3/17</td>
<td>55.32</td>
<td>0.26 [0.03, 2.06]</td>
<td></td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>65</strong></td>
<td><strong>61</strong></td>
<td><strong>100.00</strong></td>
<td><strong>0.20 [0.04, 0.91]</strong></td>
<td></td>
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Total events: 1 (Early EN (<24 h)), 6 (Standard Care)
Test for heterogeneity: Chi² = 0.18, df = 2 (P = 0.91), I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)

Mortality reduced by 8.3%, p=0.04

Sensitivity analysis: Including Moore et al.

Review: Early EN (<24h) vs Standard Care (TRAUMA - Sensitivity)
Comparison: 01 Early (<24h) EN vs Standard Care
Outcome: 01 Mortality, Sensitivity Analysis

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<td>1/25</td>
<td></td>
<td>10.54</td>
<td>0.12 [0.00, 6.31]</td>
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<tr>
<td>Moore 1986 (16%ltf)</td>
<td>1/32</td>
<td>2/31</td>
<td></td>
<td>30.64</td>
<td>0.49 [0.05, 4.85]</td>
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<tr>
<td>Total (95% CI)</td>
<td>97</td>
<td>92</td>
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<td>100.00</td>
<td>0.26 [0.07, 0.93]</td>
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Total events: 2 (Early EN (<24 h)), 8 (Standard Care)
Test for heterogeneity: Chi² = 0.59, df = 3 (P = 0.90), I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

Mortality reduced by 6.7%, p=0.04

Early EN in trauma: Direct evidence

- Early EN also resulted in:
  - Reduced incidence of pneumonia (33% eEN vs 64%, p=0.050)
  - A trend towards a reduction in the severity of MODS (2.5 vs 3.1 organ failures per patient, p=0.057)

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There were no signs of any harms.

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  - 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”

A special case: The Open Abdomen

“deliberately leaving a laparotomy wound open is now the standard of care in clinical situations that require either planned reoperations or decompression of intra-abdominal hypertension”

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Fear of bowel oedema and ileus, with subsequent aspiration pneumonia.
Feeding the Open Abdomen: Dogma?

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- Fear of increasing bowel distension, making it harder for the surgeon to obtain fascial closure.

*Therefore many open abdomen patients receive no nutrition until fascial closure.*

Should we fear enteral nutrition?
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Observational study reviewing 597 trauma patients from 11 US trauma centres who were managed with *open abdomen*.

- average age 38, 77% male
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39% (232/597) received EN before first attempt at closure of the abdomen

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Receiving EN before first attempt at closure resulted in significant improvements in outcome.

Should we fear enteral nutrition?

• 3 other smaller observational studies in open abdomen patients, comparing EN started prior to fascial closure with delayed nutrition


Byrnes MC, Reicks P, Irwin E. Early enteral nutrition can be successfully implemented in trauma patients with an “open abdomen”. The *American Journal of Surgery* 2010;199:359-363.
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  - Higher rates of primary fascia closure
  - Lower rates of fistula
  - Lower total hospital charges

There were no reported adverse events with the use of EN started prior to fascial closure

Physiology: Why should patients benefit?
The gut as the motor of MODs

With the onset of shock, major surgery or critical illness:

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

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- Reduced contractility promotes bacterial overgrowth.
- Gut stasis, bacterial overgrowth and loss of structural integrity leads to bacterial translocation (even more bacterial cross intestinal barrier!!!).
- Gut neutrophils become ‘primed’ and release cytokines into lymphatic drainage and also may travel to distant sites
  - Increases overall oxidative stress, predisposing to infection and MODs


**Figure 2.** Paradigm for development of multiple organ failure (MOF). PGE$_2$, prostaglandin E$_2$; IL-6, interleukin-6; TNF, tumor necrosis factor; O$_2$, oxygen; ATN, acute tubular necrosis; ARDS, acute respiratory distress syndrome. Reprinted from Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma-reduced septic morbidity. *J Trauma*. 1989;29(7):916-923, with permission of Wolters Kluwer.
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The gut as the motor of MODs: recent advances

Recent advances in our understanding:

1. Paneth cell function.

2. Intestinal Alkaline Phosphatase.
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- Highly specialized epithelial cells located in the crypts of the small intestine.
- 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.
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- Fasting led to a significant reduction in lysozyme (P<0.01 by quantitative western blot assay and quantitative PCR for lysozyme mRNA).

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- 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 (continued feeds ad lib), inhibit autophagocytosis.


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

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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.

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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

**Diagram:**

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

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.

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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

- Direct evidence (RCTs in Trauma patients), indirect evidence (RCTs in upper GI Sx), observational studies and physiology supports the benefits of early EN for trauma patients requiring ICU care.


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- Head Trauma
  - Mounting evidence suggests we create gut dysmotility by feeding late.
  - If you are concerned, start with post-pyloric feeding.
- Role of Parenteral Nutrition
  - Patients with contraindications to early EN may benefit from early PN.
  - PN does not increase infectious complications.


Questions?

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


- **Demonstrates strength of acceptance of the importance of early feeding by trauma surgeons.**


- **Extensive search and systematic review of best available evidence for early EN in trauma.**


- **Major multi-centre observational study demonstrating patients often assumed to be ‘most difficult to feed’ benefit from early EN.**


- **Major RCT demonstrating PN does NOT increase infections and improves patient outcomes.**