Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition:

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*What the evidence really says*

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GS Doig and coauthors

Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition: A Randomized Controlled Trial

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- **B Braun Medical Inc**, Speaker’s Honoraria
Outline

• Brief context and background

• Essential elements of design

• Main results

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

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for the Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group

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rly nutritional support provided within 24 hours of injury or intensive care unit (ICU) admission is a key component in the treatment of critically ill patients and may reduce mortality by 8% to 12%. Nevertheless, practice varies widely between ICUs, and up to 40% of eligible patients may remain unfed after 48 hours in the ICU.

Evidence-practice gaps are common in clinical practice, with 30% of hospitalized patients receiving care inconsistent with current best evidence. Evidence-based guidelines (EBGs) help reduce evidence-practice gaps by promoting awareness of interventions of proven benefit and discouraging ineffective care. However, the ICU is a complex multidisciplinary environment, and reducing evidence-practice gaps through the implementation of evidence-based guidelines is difficult. Evidence supporting whether guidelines can improve ICU feeding practices and patient outcomes is contradictory.

Objective: To determine whether evidence-based feeding guidelines, implemented using a multifaceted practice change strategy, improve feeding practices and reduce mortality in ICU patients.

Design, Setting, and Patients: Cluster randomized trial in ICUs of 27 community and tertiary hospitals in Australia and New Zealand. Between November 2003 and May 2004, 1,116 critically ill adult patients expected to remain in the ICU longer than 2 days were enrolled. All participants completed the study.

Interventions: Intensive care units were randomly assigned to guideline or control groups. Guideline ICUs developed an evidence-based guideline using Brown's Clinical Practice Guideline Development Cycle. A practice-change strategy composed of 13 specific interventions, leveraged by educational outreach visits, was implemented in guideline ICUs.

Main Outcome Measures: Hospital discharge mortality. Secondary outcomes included ICU and hospital length of stay, organ dysfunction, and feeding process measures.

Results: Guideline and control ICUs enrolled 561 and 557 patients, respectively. Guideline ICUs delivered feeding earlier (0.75 vs. 1.37 mean days to enteral nutrition start; difference, -0.62 [95% confidence interval (CI) -0.82 to -0.42]; P < .001) and achieved caloric goals more often (6.10 vs. 5.02 mean days per 10 fed patient-days; difference, 1.07 [95% CI, 0.12 to 2.22]; P = .03). Guideline and control ICUs did not differ with regard to hospital discharge mortality (28.9% vs. 27.4%; difference, 1.4% [95% CI, -6.3% to 12.0%]; P = .75) or to hospital length of stay (24.2 vs. 24.3 days; difference, -0.08 [95% CI, -3.8 to 4.4]; P = .97) or ICU length of stay (9.1 vs. 9.9 days; difference, -0.86 [95% CI, -2.6 to 1.3]; P = .42).

Conclusions: Using a multifaceted practice change strategy, ICU successfully developed and introduced an evidence-based nutritional support guideline that promoted earlier feeding and greater nutritional adequacy. However, use of the guideline did not improve clinical outcomes.

Trial Registration: anzctr.org.au Identifier: ACTRN12608000407392

JAMA 2008 Dec 17;300(23):2731-41.

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

Will at least 80% of requirements be met by 72h?

YES

Is Goal met?

YES

Increase rate to 100%

NO

Use prokinetic and/or use post-pyloric tube

NO

Use prokinetic and/or use post-pyloric tube

Continue EN to max. tolerated
Supplement with FN
Continue EN challenges q12h

Chief Investigator: Dr. Gordon S. Doig, University of Sydney. Contact: g.doig@med.usyd.edu.au
**Equipoise for a large-scale clinical trial**

**Hypothesis:**

In patients who have a short-term relative contraindication to early enteral nutrition, the provision of early parenteral nutrition (within 24 hours of ICU admission) reduces 60-day landmark mortality, and associated measures of morbidity, compared to pragmatic standard care.

[www.evidencebased.net/EarlyPN](http://www.evidencebased.net/EarlyPN)
A large-scale multi-centre trial

- National Health and Medical Research Council Funded RCT
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- Recruitment ran from 19th October 2006 to 30th June 2011.

1,363 patients were enrolled and randomised

- 682 received pragmatic standard care
- 681 received early parenteral nutrition
Eligibility Criteria

Complete inclusion criteria:

- Adult patients admitted to ICU for less than 24 h.
- Expected to remain in ICU today and tomorrow.
- Not expected to receive enteral, parenteral or oral intake today or tomorrow.
- Has a central venous access line through which parenteral nutrition could be delivered.

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Early PN: Study Intervention

- Patients received standard PN
  - ready-to-mix 3-chamber bag containing 34g amino acids, 100g glucose (Glucose 19%), 40g lipid/1026mls, 0.9kcal/ml, and electrolytes

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**Study PN Protocol A: ALL PATIENTS EXCEPT MALNOURISHED PATIENTS**

**Feeding Day 1 (first 24 hours of PN)**
- Commence TPN at 60ml/hr (or goal rate, whichever is lower).
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**Feeding Day 2 (second 24 hours of PN)**
- Increase TPN to 80ml/hr (or goal rate, whichever is lower).
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**Feeding Day 3 (next 24 hours)**
- Increase TPN to goal rate, as appropriate.
- Consider trace element, mineral and vitamin needs, as clinically appropriate.
- Recommend trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour TPN infusion and do not hang another bag.
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**Feeding Day 4 (next 24 hours) plus all additional days after Day 4**
- May switch to parenteral nutrition solution tailored to patient’s specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
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Study PN Protocol B: MALNOURISHED PATIENTS (Ex. BMI ≤ 17 or clinical diagnosis):

Feeding Day 1 (first 24 h of PN)
- Commence TPN at 40ml/hr (or goal rate, whichever lower).
- Strongly recommend administering 100mg thiamine, commencing at least 30 minutes prior to initiation of TPN infusion, as clinically indicated as per product licensing indications.
- Recommend daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

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Feeding Day 4 (next 24 hours) plus all additional days after Day 4
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- Patients received standard PN
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  - Starting rates and daily rate increases were defined by study protocols designed to reflect normal care in Australia and New Zealand.

**Study PN Protocol B: MALNOURISHED PATIENTS (Ex. BMI ≤ 17 or clinical diagnosis):**

**Feeding Day 1 (first 24 h of PN)**
- Commence TPN at 40ml/hr (or goal rate, whichever lower).
- **Strongly recommend** administering 100mg thiamine, commencing at least 30 minutes prior to initiation of TPN infusion, as clinically indicated as per product licensing indications.
- **Recommend** daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

**Feeding Day 2 (second 24 hours of PN)**
- Increase TPN to 60ml/hr (or goal rate, whichever is lower).
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.

**Feeding Day 3 (next 24 hours)**
- Increase TPN to **goal rate** as appropriate.
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  - Used total caloric content (including protein calories) of the study PN to calculate PN infusion rates.
  - Metabolic needs for obese patients, defined as a BMI $\geq 30$, were calculated based on ideal body weight (BMI = 21).
  - Capped to an upper limit of 35 kcal/kg/day.

www.evidencebased.net/EarlyPN
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- Calculated target metabolic needs were usually achieved on study Day 3.
- We did not specify the method to be used to re-estimate targets from Day 4 on, however we did recommend that reasonable ranges should be achieved.

www.evidencebased.net/EarlyPN
Pragmatic Standard Care

- The attending clinician selected the route, starting rate, metabolic targets, measures of tolerance and composition of feeds to be used in standard care patients based on current practice in their ICU.
Who got into the trial:

Main types of patients enrolled:

- 234 (17%) GI perforation (surgical),
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Overall 65% of patients were surgical and 35% of patients were medical.

Mortality at Day 60: 301/1358 (22.2%)
Average ICU stay: 8.9 days
Average hospital stay: 25.0 days

This is a critically ill patient population.
Nutrition therapy process measures

Early parenteral nutrition (681 patients):

- 679/681 patients (99.7%) commenced PN 44 minutes after enrolment
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  • 80 /186 (43.0%) progressed to EN 5.08 days after PN start
• 278/682 patients (40.8%) never received EN or PN during their 3.72 day ICU stay
Pre-specified algorithm was used to identify baseline characteristics for inclusion in a multivariate model to control for confounding.

Final multivariate model controlled for strong predictors and baseline imbalance: Age, gender, BMI, APACHE 2 score, Chronic Liver, Chronic Respiratory and Source of Admission.
Table 2. Mortality

<table>
<thead>
<tr>
<th></th>
<th>Standard Care (n = 680)(^a)</th>
<th>Early PN (n = 678)(^a)</th>
<th>Risk Difference, % (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths before study day 60, No. (%)</td>
<td>155 (22.8)</td>
<td>146 (21.5)</td>
<td>-1.26 (-6.6 to 4.1)</td>
<td>.60</td>
</tr>
<tr>
<td>Covariate-adjusted deaths before study day 60(^b)</td>
<td></td>
<td></td>
<td>0.04 (-4.2 to 4.3)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

\(^a\) 5 patients (2 Standard Care, 3 Early PN) could not be contacted on study Day 60 to determine vital status. Considered ‘missing at random’ for ITT Primary and Adjusted primary outcome analysis.

\(^b\) Multivariate model controlled for confounding due to baseline imbalance and strong predictors: Age, gender, BMI, APACHE 2 score, Chronic Liver, Chronic Respiratory and Source of Admission.

Table 4. New Infections During Study

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<th>Patients With New Infections&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup> new infections based on cultures obtained in the study ICU.
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<sup>c</sup> venous or arterial catheters

<sup>e</sup> CPIS ≥ 6 plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72hrs after starting a new antibiotic regimen.

<sup>f</sup> CPIS ≥ 6 (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from <sup>a</sup> an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); <sup>b</sup> the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jiroveci (carinii)*; <sup>c</sup> recovery of a likely/possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, BAL, or protected specimen brush); or <sup>d</sup> positive serology.
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<td>Catheterc</td>
<td>32 (4.69)</td>
<td>31 (4.55)</td>
<td>-0.14 (-5.45 to 5.12)</td>
<td>&gt; .99</td>
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<td>Catheter tipc</td>
<td>28 (4.11)</td>
<td>26 (3.82)</td>
<td>-0.29 (-5.60 to 5.01)</td>
<td>.89</td>
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<tr>
<td>Surgical wound</td>
<td>27 (3.96)</td>
<td>22 (3.23)</td>
<td>-0.73 (-6.04 to 4.57)</td>
<td>.56</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>33 (4.84)</td>
<td>39 (5.73)</td>
<td>0.89 (-4.43 to 6.18)</td>
<td>.47</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3 (0.44)</td>
<td>6 (0.88)</td>
<td>0.44 (-4.89 to 5.74)</td>
<td>.34</td>
</tr>
<tr>
<td>Clinically significant UTI</td>
<td>1 (0.15)</td>
<td>2 (0.29)</td>
<td>0.15 (-5.16 to 5.45)</td>
<td>.62</td>
</tr>
<tr>
<td>Airway or lungd</td>
<td>123 (18.04)</td>
<td>101 (14.83)</td>
<td>-3.20 (-8.52 to 2.08)</td>
<td>.12</td>
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<td>CPIS-probable pneumoniaa</td>
<td>96 (14.08)</td>
<td>81 (11.89)</td>
<td>-2.18 (-7.50 to 3.11)</td>
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<tr>
<td>CPIS-confirmed pneumoniaf</td>
<td>45 (6.60)</td>
<td>43 (6.31)</td>
<td>-0.28 (-5.60 to 5.01)</td>
<td>.91</td>
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<tr>
<td>Any major infectiong</td>
<td>78 (11.4)</td>
<td>74 (10.9)</td>
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a new infections based on cultures obtained in the study ICU.

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c CPIS ≥ 6 plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72hrs after starting a new antibiotic regimen.

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g Attributable excess case mortality greater than 15%.
## Table 4. New Infections During Study

<table>
<thead>
<tr>
<th>Patients With New Infections(^a)</th>
<th>Standard Care (n = 682)</th>
<th>Early PN (n = 681)</th>
<th>Risk Difference (Exact 95% CI)</th>
<th>Exact P Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter(^c)</td>
<td>32 (4.69)</td>
<td>31 (4.55)</td>
<td>-0.14 (-5.45 to 5.12)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Catheter tip(^c)</td>
<td>28 (4.11)</td>
<td>26 (3.82)</td>
<td>-0.29 (-5.60 to 5.01)</td>
<td>.89</td>
</tr>
<tr>
<td>Surgical wound</td>
<td>27 (3.96)</td>
<td>22 (3.23)</td>
<td>-0.73 (-6.04 to 4.57)</td>
<td>.56</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>33 (4.84)</td>
<td>39 (5.73)</td>
<td>0.89 (-4.43 to 6.18)</td>
<td>.47</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3 (0.44)</td>
<td>6 (0.88)</td>
<td>0.44 (-4.89 to 5.74)</td>
<td>.34</td>
</tr>
<tr>
<td>Clinically significant UTI</td>
<td>1 (0.15)</td>
<td>2 (0.29)</td>
<td>0.15 (-5.16 to 5.45)</td>
<td>.62</td>
</tr>
<tr>
<td>Airway or lung</td>
<td>123 (18.04)</td>
<td>101 (14.83)</td>
<td>-3.20 (-8.52 to 2.08)</td>
<td>.12</td>
</tr>
<tr>
<td>CPIS-probable pneumonia(^g)</td>
<td>96 (14.08)</td>
<td>81 (11.89)</td>
<td>-2.18 (-7.50 to 3.11)</td>
<td>.26</td>
</tr>
<tr>
<td>CPIS-confirmed pneumonia(^f)</td>
<td>45 (6.60)</td>
<td>43 (6.31)</td>
<td>-0.28 (-5.60 to 5.01)</td>
<td>.91</td>
</tr>
<tr>
<td>Any major infection(^g)</td>
<td>78 (11.4)</td>
<td>74 (10.9)</td>
<td>-0.57 (-5.89 to 4.72)</td>
<td>.80</td>
</tr>
</tbody>
</table>

\(^a\) new infections based on cultures obtained in the study ICU.

\(^c\) venous or arterial catheters

\(^e\) CPIS \(\geq 6\) plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), or the presence of a negative lower respiratory tract culture if collected within 72hrs after starting a new antibiotic regimen.

\(^f\) CPIS \(\geq 6\) (using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from a) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate); b) the recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jiroveci (carinii)*); c) recovery of a likely/possible respiratory pathogen in cultures of a lower respiratory tract sample (endotracheal aspirate, BAL, or protected specimen brush); or d) positive serology.

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<thead>
<tr>
<th>Quality of life and physical function, mean (SD)</th>
<th>Standard Care (n = 680)</th>
<th>Early PN (n = 678)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life and physical function, mean (SD)</td>
<td>(n = 525)</td>
<td>(n = 532)</td>
<td></td>
</tr>
<tr>
<td>RAND-36 general health status</td>
<td>45.5 (26.8) (n = 516)</td>
<td>49.8 (27.6) (n = 525)</td>
<td>.01</td>
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Minimally Important Difference $= \frac{1}{2} \text{SD} = 13.5$

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Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of a half a standard deviation. Medical Care 2004;41:582-592.

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<th>Mean (95% CI), Days per 10 Patient × ICU Days</th>
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<tr>
<td>Standard Care (n = 682)</td>
<td>7.73 (7.55 to 7.92)</td>
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<td>7.26 (7.09 to 7.44)</td>
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<td>Invasive mechanical ventilation</td>
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Table 3. Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)
<p>| Table 3. Concomitant Interventions, Adjusted for Time at Risk (ICU Stay)\textsuperscript{a} |
|-----------------------------------------------|---|---|---|
| | Mean (95% CI), Days per 10 Patient \times ICU Days | | |
| | Standard Care (n = 682) | Early PN (n = 681) | (P) Value\textsuperscript{b} |
| Invasive mechanical ventilation | 7.73 (7.55 to 7.92) | 7.26 (7.09 to 7.44) | .01 |
| Pressure ulcer treatment | 0.87 (0.74 to 1.02) | 0.78 (0.67 to 0.92) | .54 |
| Low serum albumin (&lt;2.5 g/dL) | 5.47 (5.28 to 5.67) | 5.76 (5.56 to 5.97) | .15 |
| Systemic antibiotic use | 7.95 (7.78 to 8.12) | 8.05 (7.88 to 8.22) | .55 |
| Witnessed aspiration | 1.59 (0.98 to 2.54) | 1.96 (1.21 to 3.13) | .66 |
| With new pulmonary infiltrates | 0.48 (0.20 to 1.15) | 0.71 (0.30 to 1.72) | .65 |
| Renal replacement therapy | 0.99 (0.82 to 1.81) | 0.80 (0.67 to 0.96) | .25 |</p>
<table>
<thead>
<tr>
<th>Length of Stay</th>
<th>(n = 682)</th>
<th>(n = 681)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>ICU stay, mean (95% CI), d</td>
<td>9.3 (8.9 to 9.7)</td>
<td>8.6 (8.2 to 9.0)</td>
<td>.06</td>
</tr>
<tr>
<td>Hospital stay, mean (95% CI), d</td>
<td>24.7 (23.7 to 25.8)</td>
<td>25.4 (24.4 to 26.6)</td>
<td>.50</td>
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$1,000,000 question:

**HOW** could early nutrition reduce duration of ventilation and ICU stay?
Body composition

ICU admission:

- Enrolment within 24 h of admit

Body composition measures obtained at enrolment and every Monday and Thursday while in study ICU:

- MAMC, SGA muscle wasting, SGA fat store loss
Subjective Global Assessment: Muscle wasting

Fully factorial repeated measures ANOVA:
$p < 0.0001$ change over time
Subjective Global Assessment: Muscle wasting

Fully factorial repeated measures ANOVA:
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Subjective Global Assessment: Fat loss

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Body composition: Changes over time

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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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Given evidence of skeletal muscle sparing, it is plausible that Early PN attenuates diaphragmatic proteolysis (autophagy), mitigating the diaphragmatic loss which leads to improved weaning

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*But what about costs?*
Economic analysis: US costs

Marginal differences in patient outcomes from Early PN Trial:

Economic analysis: US costs

Marginal differences in patient outcomes from Early PN Trial:
Costs of ICU care in the US healthcare system:

• Database of 51,009 ICU patients from 253 US hospitals (NDCHealth).
• Costs estimated using hospital specific cost-to-charge ratios

Economic analysis: US costs

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Notes: Mean costs (standard deviation); indexed to 2012 US dollars. Costs of care whilst admitted to the intensive care unit were abstracted from Dasta JF et al.15

Abbreviation: MV, mechanical ventilation.

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US costs of PN delivered in the ICU:

- Using the Premier Healthcare Alliance database, Turpin et al identified 44,358 hospital patients from 194 hospitals who had at least one transaction level cost recorded for PN.


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<p>| Table 1 Matrix of the distributions of daily costs of care whilst admitted to the intensive care |
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<td>$15,625 ($11,955)</td>
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<td>Day 2</td>
<td>$6,535 ($4,678)</td>
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<td>$7,414 ($6,683)</td>
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<td>$4,765 ($5,624)</td>
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- For the purposes of our study, the costs for providing ready to hang PN were blended with the costs of pharmacy compounded PN to give an estimated cost of US$229.66, with a standard deviation of US$60.44.


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www.EvidenceBased.net/EarlyPN