Early enteral nutrition in critical illness:
A full economic analysis using European costs

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Faculty Disclosures

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Relevant financial relationships with a commercial interest:

• **Fresenius Kabi**, Academic Research Grants (Past), Consultant and Speaker’s Honoraria (Current)

• **Baxter Healthcare**, Academic Research Grant (Current), Consultant and Speaker’s Honoraria (Current)

• **Nestle Healthcare**, Academic Research Grant (Current), Consultant and Speaker’s Honoraria (Current)
Overview

- Short background on previous studies costing enteral nutrition

- Describe the current study
  - a large scale Monte Carlo simulation of stochastic model based on European costs

- Briefly review financial implications of providing early enteral nutrition to critically ill patients
Systematic review of previous costing studies

“There is a lack of well-designed studies taking a broad view of relevant comparators, costs and outcomes.”

Systematic review of previous costing studies

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“The cost-effectiveness of different forms of nutrition in different patient groups remains to be established.”

**Purpose of this project**

- **Full economic analysis** involves the comparison of alternative courses of action in terms of both **costs** (resource use) and **consequences** (patient outcomes, adverse effects).

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- A well-conducted meta-analysis based on a systematic review of randomized trials is the **least-biased** source of data to establish treatment **consequences** (resource use, patient outcomes, adverse effects) for use in an economic model.

Meta-analysis of early EN in critical illness

Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials

Meta-analysis of 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.

Primary analysis
• Included only methodologically sound RCTs.

Primary outcome
• clinically meaningful patient oriented outcomes: (mortality / physical function / quality of life)

**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;24h) 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>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><strong>Total (95% CI)</strong></td>
<td><strong>119</strong></td>
<td><strong>115</strong></td>
<td><strong>100.00 0.34 [0.14, 0.85]</strong></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 with early EN** (95%CI 8.6% to 17.2%, 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>
<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, 0.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>3/14</td>
<td>6/14</td>
<td>29.85 [0.07, 1.91]</td>
<td></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></td>
<td><strong>0.31</strong></td>
<td><strong>[0.12, 0.78]</strong></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 with early EN  (27% reduction, P=0.01)

Results: updated MA, ICU length of stay

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

**Results: updated MA, duration of MV**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>EEN Mean [days]</th>
<th>EEN SD [days]</th>
<th>Total Mean [days]</th>
<th>Total SD [days]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, fixed, 95% CI [days]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuntrasakul et al(^a)</td>
<td>5.29</td>
<td>6.28</td>
<td>21</td>
<td>6.12</td>
<td>5.32</td>
<td>17</td>
<td>48.1%</td>
</tr>
<tr>
<td>Kompan et al(^b)</td>
<td>12.9</td>
<td>8.1</td>
<td>27</td>
<td>15.6</td>
<td>18.1</td>
<td>25</td>
<td>13.3%</td>
</tr>
<tr>
<td>Nguyen et al(^c)</td>
<td>9.2</td>
<td>3.37</td>
<td>14</td>
<td>13.7</td>
<td>7.11</td>
<td>14</td>
<td>38.6%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td></td>
<td>56</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>−2.49 [−5.05, 0.07]</td>
</tr>
</tbody>
</table>

**Figure 2** Meta-analysis of duration of mechanical ventilation: early enteral nutrition vs standard care.

**Notes:** Heterogeneity: $\chi^2 = 1.69$, df = 2 ($P = 0.43$); $I^2 = 0\%$. Test for overall effect: $Z = 1.91$ ($P = 0.06$).

**Abbreviations:** CI, confidence interval; EEN, early enteral nutrition; IV, inverse variance; SD, standard deviation; SoC, standard of care.

Trend towards reduced mechanical ventilation with early EN (2.49 days, $P = 0.06$)

Results: updated MA, hospital stay

No difference in hospital stay (2.46 days, P =0.72).

Summary of the consequences of early EN use

- Significant reduction in mortality (95%CI 8.6% to 17.2%, P=0.02)
- Trend towards reduction in length of ICU stay (2.34 days, P=0.06)
- Trend towards reduction in mechanical ventilation (2.49 days, P=0.06)
  - Significant reduction in VAP (27%, P=0.01)
Establishing costs

- Costs of ICU care:
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Establishing costs

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  *Microcosting* requires recording all costs at the most detailed level.


  [Review of A Large Clinical Series: A Microcosting Study of Intensive Care Unit Stay in the Netherlands](http://jic.sagepub.com/)

  *Journal of Intensive Care Medicine*


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  - Conducted in the mixed med-surg ICUs of 3 hospitals in the Netherlands
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  - **Microcosting** requires recording all costs at the most detailed level.
  - Conducted in the mixed med-surg ICUs of 3 hospitals in the Netherlands
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    - Costed 576 patients, consuming 2,868 ICU days

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  Average total costs of 1 ventilated-ICU day reported as €2,349

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- Costs of ICU care:

  - Average total costs of 1 ventilated-ICU day reported as €2,349
  - Average total costs of 1 non-ventilated ICU day reported as €1,835
    - indexed to 2012 Euros, using the European Central Bank Harmonised Index of Consumer Prices, Overall Index

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Adrien Strickland, Anita Brogan, Janis Krauss, Robert Martindale and Gail Cresci
JPEN J Parenter Enteral Nutr. 2005 29: S81
DOI: 10.1177/01486071050290S1S81

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- Single centre study from the US reported the total costs of a 7 day course of EN in medical ICU or trauma patients
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- $35 per day
  - indexed to 2012 US dollars using US Consumer Price Index, Medical Consumers

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Costs of 1 day of EN:

To account for variability between hospitals, and to allow for a conservative over-estimation of EN costs, the $35 estimate was inflated by 50% to $52.50.

Converts to €39.30 per day, at 1 USD = 0.748597 EUR (mid-market rates, June 13, 2013 at 2:22 am coordinated universal time [UTC]).

Establishing costs

If one day of EN costs €39.30, and the provision of *early* EN requires EN to be started within 24 h of ICU admission, how many *extra days of EN* will the average patient receive?
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- To ensure conservative overcosting of the number of extra days of EN support provided by starting EN within 24 hours of ICU admission, the worst performing hospital case was used.
- Assumes that early EN patients received 6.21 extra days of EN, compared with standard care patients.

Calculation of crude costs

Crude calculations of costs (based on averages):

\[ 6.21 \text{ more days of EN} \times \€39.30 = \€244 \]
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- 6.21 more days of EN \times €39.30 = + €244
- 2.49 less mechanical ventilation days \times €2,349 = €5,849
- 2.49 ventilated days \times €1,835 = €4,569
- Difference - €1,280
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**Total savings** per treated patient = €5,330


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* savings per treated patient

...... but .........


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- The total accumulated costs is the sum of a series of cross products of sets of numbers, each with considerable variability

- In addition, costs and length of stay are known to have long tailed distributions

  - Gamma distributed random numbers are generated with mean $\mu$ and shape $\alpha$, where $\alpha = \mu^2 / \sigma^2$, (SAS, ver 6.12)
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  • large scale Monte Carlo simulation

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95% CI €2,475 to €8,224*

*95% CI obtained via the Percentile method (non-parametric)

Summary

• The provision of early enteral nutrition to critically ill patients dominant:
  • Early EN reduces mortality (95% CI 8.6% to 17.2%) and
  • Early EN reduces costs (€5,325 per patient, 95% CI €2,475 to €8,224)

Summary

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- Sensitivity analyses confirms these results
  - Varying discount rate
  - Using log-normal distributions instead of gamma
  - Using US costs

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  - Worst case scenario, assuming no (zero) decrease in ICU stay or MV days:
    - Assuming 8.6% mortality, the incremental cost of providing early EN to all eligible patients was €2,836 (95% CI €2,087 to €4,297) per life saved.

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Questions?

ClinicoEconomics and Outcomes Research

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