How IV Glutamine saves lives and money

Dr. Lorenzo Pradelli - Turin, Italy
Pharmacoeconomics aims at providing a rational trade off between:
  - Rising sanitary needs of the population
  - Limited budget of National Health Systems

Principle of efficient allocation of resources (value for money)

PE also is to value medical and technological innovation in terms of “willingness to pay”
The typical setting of analysis

- We have to assess the relative value of:
  - Strategy S1 → innovative and more expensive
  - Strategy S → control
    - the alternative already available
    - the gold standard in clinical practice
    - the less costly alternative, ...
The rule of the ICER

$$ICER = \frac{C_{S_1} - C_S}{O_{S_1} - O_S}$$

The increase of cost that we have to pay to obtain the unit benefit using the strategy $S_1$ instead of $S$.

Strategy $S$
- Average Outcome ($O_S$)
- Average Cost ($C_S$)

Strategy $S_1$
- Average Outcome ($O_{S_1}$)
- Average Cost ($C_{S_1}$)
Schematic of the Health Policy Space

- S dominates these
  - Costs money
  - Worsens health

- These dominate S
  - Saves money
  - Worsens health

- Costs
  - Incr. cost
  - Incr. effect

- Health
  - ICER
  - S1
Alanyl Glutamine – Economic Model

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Integrating two levels

ICU simulation
- Outcome rates in Italian ICUs from GIVITI

IV Glutamine Effectiveness
- Metanalysis of RCTs

IV Glutamine Economic Model
- Death rates, LOS
- Costs
Progetto Margherita” report 2009, annual publication of the Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GIVITI), includes data from 230 Italian ICUs, for a total of over 77,000 patients.

Data reported for included patients that reflects more accurately the type of patients for which the simulation is performed:

- critically ill patients admitted for Intensive Care therapies
- patients undergoing major surgery

53,831 patients in total
Data sources – transition probabilities

- Probability distributions in the **ICU population** from “Progetto Margherita” 2009 report (data of over 77,000 patients)

<table>
<thead>
<tr>
<th>Probability</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of dying in ICU</td>
<td>19.0%</td>
</tr>
<tr>
<td>Probability of being discharged from ICU directly to home</td>
<td>1.3%</td>
</tr>
<tr>
<td>Probability of being transferred to ward from ICU</td>
<td>79.7%</td>
</tr>
<tr>
<td>Probability of dying in ward</td>
<td>7.9%</td>
</tr>
<tr>
<td>Probability of being discharged alive from ward</td>
<td>92.1%</td>
</tr>
<tr>
<td>Probability of acquiring a nosocomial infection</td>
<td>11.4%</td>
</tr>
</tbody>
</table>
## Data sources – LOS distributions

<table>
<thead>
<tr>
<th>LOS distributions</th>
<th>Progetto Margherita Data</th>
<th>Fitted Weibull Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days pre ICU</strong></td>
<td>Mean (SD) 5.6 (15.5)</td>
<td>5.6 (9.91)</td>
</tr>
<tr>
<td></td>
<td>Median 2</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Days in ICU</strong></td>
<td>Mean (SD) 6.1 (11.0)</td>
<td>6.1 (11.40)</td>
</tr>
<tr>
<td>(alive patients)</td>
<td>Median 2</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Days in ICU</strong></td>
<td>Mean (SD) 8.8 (15.0)</td>
<td>8.8 (16.0)</td>
</tr>
<tr>
<td>(dead patients)</td>
<td>Median 3</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Days post ICU</strong></td>
<td>Mean (SD) 23.2 (23.7)</td>
<td>23.2 (23.70)</td>
</tr>
<tr>
<td>(alive patients)</td>
<td>Median 17</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Days post ICU</strong></td>
<td>Mean (SD) 18.1 (24.1)</td>
<td>18.1 (24.10)</td>
</tr>
<tr>
<td>(dead patients)</td>
<td>Median 10</td>
<td>9.5</td>
</tr>
</tbody>
</table>
History of meta-analyses

- Two previous meta-analyses and their updates demonstrated the effectiveness of ala-glu in reducing mortality and emerging infections in critically ill ICU patients
  - In 2002. Novak et coll conducted a meta-analysis of available trials
  - Canadian Critical Care Practice Guidelines Committee performed a first meta-analysis in 2003, and updated it with new available data in 2006 and earlier this year (2009)

- We pooled the data with a different approach, but yielded largely overlapping results:

- A more recent meta-analysis confirms that ala-glu at a dose >0.20 g per kg of body weight per day in ICU patients is associated with reduced mortality, infection rate and hospital LOS
Data sources – efficacy data/1

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate (RR)</td>
<td>0.69</td>
<td>0.09</td>
<td>0.54 – 0.88</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Infection rate (RR)</td>
<td>0.79</td>
<td>0.07</td>
<td>0.67 – 0.93</td>
<td>p=0.006</td>
</tr>
<tr>
<td>LOS reduction</td>
<td>-2.29</td>
<td>0.69</td>
<td>-3.65 - -0.94</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

- We use the mean LOS in control group reported in Bollhalder 2013 to transform absolute reduction in a relative reduction:

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<th>p-value</th>
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<tbody>
<tr>
<td>LOS reduction</td>
<td>0.91</td>
<td>0.03</td>
<td>0.86 - 0.96</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>
Costs included in the model

- Cost of **IV Glutamine** supplementation
- Cost of ICU stay
- Cost of general ward stay
- Cost of new infections acquired in the ICU
Cost of hospital stays and infections

<table>
<thead>
<tr>
<th>Cost (€/day)</th>
<th>Present value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay</td>
<td>1,581.76</td>
<td>Italian empirical study (Tarricone et al. 2010)</td>
</tr>
<tr>
<td>Ward stay</td>
<td>793.30</td>
<td>National Agency for Regional Health Service (ASSR 2003)</td>
</tr>
<tr>
<td>New infection</td>
<td>1,114,87</td>
<td>Italian empirical study (Orsi et al. 2002)</td>
</tr>
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Calculated on the basis of individual stay durations
Present value obtained by official actualization indices
Results from the Economic Model

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## Results: costs and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Standard treatment mean (SE)</th>
<th>IV Glutamine supplementation mean (SE)</th>
<th>Difference mean (SE)</th>
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<tbody>
<tr>
<td><strong>Effectiveness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total LOS – days</td>
<td>30.45 (0,81)</td>
<td>29.38 (0,97)</td>
<td>-1.07 (0,83)</td>
</tr>
<tr>
<td>Infections (N/10,000 pts)</td>
<td>2,598 (406)</td>
<td>1,845 (377)</td>
<td>-753 (250)</td>
</tr>
<tr>
<td>Deaths (N/10,000 pts)</td>
<td>1,165 (243)</td>
<td>918 (209)</td>
<td>-247 (91)</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost (€/pts)</td>
<td>29,724 (4,218)</td>
<td>28,677 (4,066)</td>
<td>-1,047 (823)</td>
</tr>
</tbody>
</table>

SE=standard error
Distribution of mean incremental costs

PSA – Mean Incremental cost

<table>
<thead>
<tr>
<th>Interval</th>
<th>% Simulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>€/pt</td>
<td></td>
</tr>
<tr>
<td>&lt; -3,000</td>
<td>1%</td>
</tr>
<tr>
<td>[-3,000; -2,000]</td>
<td>13%</td>
</tr>
<tr>
<td>[-2,000; -1,000]</td>
<td>39%</td>
</tr>
<tr>
<td>[-1,000]</td>
<td>38%</td>
</tr>
<tr>
<td>[0; 1,000]</td>
<td>8%</td>
</tr>
<tr>
<td>&gt; 1,000</td>
<td>1%</td>
</tr>
</tbody>
</table>
Results: cost/effectiveness

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<th>Difference mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/E (€/pts discharged alive)</td>
<td>40,156 (5,969)</td>
<td>35,165 (5,181)</td>
<td>-4,991 (1,534)</td>
</tr>
<tr>
<td>ICER – dominant cases</td>
<td></td>
<td></td>
<td>91.20% (mean ICER=-14,459)</td>
</tr>
<tr>
<td>(€/death avoided using IV Glutamine instead of standard TPN)</td>
<td></td>
<td></td>
<td>On average IV Glutamine dominates standard TPN; in particular it results dominant in more than 90% of cases</td>
</tr>
</tbody>
</table>

SE=standard error
The cost/effectiveness plane

Incrementals: **IV Glutamine** vs. standard TPN

**IV Glutamine** dominates ST

Mean incremental Effectiveness: 759 deaths avoided
Costs: - € 1,097

1,000 samples estimated in the PsA
95% Confidence Ellipse

Incremental Cost (€/pt)
Deaths avoided/10,000 pts

The cost/effectiveness plane
Conclusions

- **IV Glutamine** treatment is expected to be more effective than standard TPN, as it would avoid almost one third of deaths, about one fifth of infections and slightly reduce overall LOS.

- **IV Glutamine** treatment is expected to be averagely slightly less expensive than standard TPN, with a mean cost saving of about € 1,000 (on a total of almost € 30,000 per patient in ICU).

- According to the model, **IV Glutamine** supplementation in Italian ICUs, besides improving patient outcomes, is very economically attractive.