Glutamine in clinical nutrition: what is the evidence

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Critical illness is associated with low plasma levels of glutamine in most patients (not all...)

### Table 1: Critical illness associated with low plasma levels of glutamine

<table>
<thead>
<tr>
<th>Critical Illness</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Roth et al. 1986</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Decker-Baumann et al. 1999</td>
</tr>
</tbody>
</table>
Glutamine supplementation: patients groups

- Cancer patients undergoing major surgery
- Severe pancreatitis
- Severe burns
- Trauma patients
- Complicated surgery, ICU patients
  (Medical treatment of cancer)
Post-operative TPN + IV-Gln
(0.2-0.35 g/kg bw/day dipeptide)

- Gln-supplemented post-operative TPN is beneficial vs std TPN after **major surgery for GI cancer**:
  - Morlion 1998
  - Powell-Tuck 1999
  - Jiang 1999
  - Fürst 1999 + Mertes 2001
  - Novak et al (Crit Care Med 2002, meta-analysis)

→ significant reduction of length of hospital stay
   infectious complications
Reduced LOS with post-operative Gln-TPN

### Comparison: 03 Total LOS
#### Outcome: 01 Glutamine vs. control

<table>
<thead>
<tr>
<th>Study</th>
<th>Glutamine</th>
<th>Control</th>
<th>WMD (95% CI Random)</th>
<th>Weight %</th>
<th>WMD (95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exner</td>
<td>15</td>
<td>15</td>
<td>-0.30 [-11.54, 10.94]</td>
<td>1.9</td>
<td>-0.30 [-11.54, 10.94]</td>
</tr>
<tr>
<td>Jiang ZM (Asia-CN)</td>
<td>30</td>
<td>30</td>
<td>-3.90 [-7.03, -0.77]</td>
<td>11.5</td>
<td>-3.90 [-7.03, -0.77]</td>
</tr>
<tr>
<td>LI HY (Asia-CN)</td>
<td>20</td>
<td>20</td>
<td>-2.22 [-4.09, -0.35]</td>
<td>15.8</td>
<td>-2.22 [-4.09, -0.35]</td>
</tr>
<tr>
<td>Liang CH (Asia-CN)</td>
<td>12</td>
<td>12</td>
<td>-1.00 [-4.87, 2.87]</td>
<td>9.4</td>
<td>-1.00 [-4.87, 2.87]</td>
</tr>
<tr>
<td>Mertes</td>
<td>15</td>
<td>15</td>
<td>-4.70 [-8.15, -1.25]</td>
<td>10.5</td>
<td>-4.70 [-8.15, -1.25]</td>
</tr>
<tr>
<td>Morlion</td>
<td>15</td>
<td>13</td>
<td>-6.20 [-7.77, -4.63]</td>
<td>16.9</td>
<td>-6.20 [-7.77, -4.63]</td>
</tr>
<tr>
<td>Neri</td>
<td>16</td>
<td>17</td>
<td>-3.50 [-5.38, -1.62]</td>
<td>15.8</td>
<td>-3.50 [-5.38, -1.62]</td>
</tr>
<tr>
<td>Yao GX (Asia-CN)</td>
<td>14</td>
<td>14</td>
<td>-1.40 [-2.51, -0.29]</td>
<td>18.3</td>
<td>-1.40 [-2.51, -0.29]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI)
- Test for heterogeneity chi-square = 27.46, df = 7, p = 0.0003
- Test for overall effect z = 3.92, p = 0.00009

Total (95% CI)
- Test for heterogeneity chi-square = 27.46, df = 7, p = 0.0003
- Test for overall effect z = 3.92, p = 0.00009

Jiang Clin Nutr Suppl 2004
Reduced infections with post-operative Gln-TPN
Impact of Gln-dipeptide supplemented Parenteral Nutrition in surgical patients

- Wang et al, JPEN 2010: meta-analysis of RCT
  - significant reduction of length of hospital stay
    (4 days for alanyl-glutamine, p<0.001)

  - significant reduction of infectious complications
    (p=0.02)
Glutamine supplementation: patients groups

- Cancer patients undergoing major surgery
- Severe pancreatitis
- Severe burns
- Trauma patients
- Complicated surgery, ICU patients
TPN + Glutamine in severe acute pancreatitis

- double-blind study
- Gln reduces the severity of acute-phase response
- Gln supports lymphocyte proliferation
Glutamine-TPN in acute pancreatitis:

- reduced acute-phase response and better lymphocyte proliferation
  
  *De Beaux, Nutrition 1998*

- reduced length of TPN (10 vs 16 days, p< 0.05)
  reduced length of hospital stay (21 vs 25 days)

*Ockenga et al, Clin Nutr 2002*
Glutamine-TPN in acute pancreatitis: other RCTs

- less infections and reinterventions
  Fuentes-Orozco et al, JPEN 2008

- less patients with complications

- lower incidence of complications, prevention of pancreatic infections
  He et al, Clin Nutr Suppl 2004
Glutamine supplementation: patients groups

- Cancer patients undergoing major surgery
- Severe pancreatitis
- Severe burns
- Trauma patients
- Complicated surgery, ICU patients
(Medical treatment of cancer)
IV Glutamine in severely burned patients:

- 31 patients with severe burns (50 % of body surface)
- standard enteral diet
- randomized to supplemental intravenous glutamine (0.57 g/kg.d) or control amino acids

Results:
- improved prealbumin, reduced CRP
- reduced gram negative bacteremia: 1/12 vs 6/14 (p=0.04)

Wischmeyer et al, Crit Care Med 2001
Enteral glutamine in adult burn patients:

<table>
<thead>
<tr>
<th></th>
<th>No. of deaths (intention to treat)</th>
<th>No. of deaths (per protocol analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Glutamine</td>
<td>2*</td>
<td>0*</td>
</tr>
</tbody>
</table>

* = P < 0.05

→ Decreased mortality and infectious morbidity

Enteral glutamine in burns: other RCTs
(0.35-0.5 g/kg bw /day)

• reduced wound infections and length of hospital stay
  *Pattanshetti et al, IJ Surg 2009*

• improved wound repair and shorter hospital stay
  *Peng et al, Burns 2004*

• improved wound healing, reduced infections, shorter hospital stay
  *Zhou et al, JPEN 2003*
Glutamine supplementation: patients groups

- Cancer patients undergoing major surgery
- Severe pancreatitis
- Severe burns
- Trauma patients
- Complicated surgery, ICU patients
  (Medical treatment of cancer)
Reduced infections in patients receiving *enteral glutamine*

*Houdijk et al. Lancet 1998*
Recommandations for enteral Glutamine


ESPEN GUIDELINES

ESPEN Guidelines on Enteral Nutrition: Intensive care

Summary of statements: Intensive care

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recommendations</th>
<th>Grade</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamine</td>
<td>Should be added to standard enteral formula in</td>
<td>A</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>- burned patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- trauma patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>There are not sufficient data to support glutamine supplementation in surgical or heterogenous critically ill patients.</td>
<td>A</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Parenteral glutamine reduces insulin resistance in trauma patients

Table 4. Comparison of glucose homeostasis parameters between groups

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group AG</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>6.6 ± 0.9; 6.45; 5.2, 8.6</td>
<td>6.9 ± 1.3; 6.35; 4.9, 9.9</td>
<td>.84</td>
</tr>
<tr>
<td></td>
<td>7.6 ± 2.6; 6.85; 4.8, 13.9</td>
<td>6.5 ± 1.6; 6.4; 3.1, 10.6</td>
<td>.27</td>
</tr>
<tr>
<td>C-peptide, μmol/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.52 ± 0.44; 1.5; 0.85, 2.3</td>
<td>1.99 ± 1.41; 1.71; 0.73, 6.31</td>
<td>.49</td>
</tr>
<tr>
<td></td>
<td>2.04 ± 0.63; 2.1; 1.06, 4.04</td>
<td>1.54 ± 0.52; 1.43; 0.92, 3.2</td>
<td>.026</td>
</tr>
<tr>
<td>Fasting insulin resistance, microunits · mg&lt;sup&gt;-1&lt;/sup&gt; · kg&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>5.5 ± 4.5; 5; 1.21</td>
<td>6.1 ± 2.4; 6; 3.13</td>
<td>.084</td>
</tr>
<tr>
<td></td>
<td>10.0 ± 3.1; 10.4; 4.16</td>
<td>7.8 ± 6.8; 5.5; 1.28</td>
<td>.015</td>
</tr>
<tr>
<td>Glucose disposal, mg · kg&lt;sup&gt;-1&lt;/sup&gt; · min&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.9 ± 0.6; 1.87; 0.65, 3.4</td>
<td>2.4 ± 0.7; 2.3; 1.2, 3.8</td>
<td>.044</td>
</tr>
<tr>
<td></td>
<td>1.2 ± 0.6; 1.11; 0.42, 3.15</td>
<td>2.2 ± 0.7; 2.05; 0.4, 3.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Group C, control group; group AG, alanyl-glutamine group.<br>Plasmatic concentration. Data are provided as mean ± sd; median; minimum, maximum.

Bakalar et al Crit Care Med 2006

→ Reduced pneumoniae in trauma patients with Gln+TPN

Déchelotte et al, Crit Care Med 2006
The Rumanian Dipeptiven study

82 multiple *trauma patients* with an indication for TPN

Prospective controlled trial
isocaloric isonitrogenous TPN

+ *Alanyl-glutamine*: $0.5 \text{ g x kg}^{-1} \times \text{day}^{-1}$

+ control

$N=41$  
$N=41$

→ *reduced incidence of hyperglycemia* $(p<0.05)$
→ *reduced insulin needs* $(<0.05)$

Luca Vasiliu et al, ESPEN 2011, abstract P014
Glutamine supplementation: patients groups

- Cancer patients undergoing major surgery
- Severe pancreatitis
- Severe burns
- Trauma patients
- Complicated surgery, ICU patients
Studies with enteral glutamine in ICU patients:

- reduced costs  
  Jones 1999
- reduced infection rate  
  Conejero 2002
- no clinical benefit  
  Hall 2003
- faster recovery (SOFA)  
  Beale 2008
- lower hospital mortality benefit  
  Carvalho 2008

→ no clear evidence of benefit for enteral glutamine in mixed populations of ICU patients (ESPEN guidelines on EN, 2006)
→ reasons: insufficient dose, underfeeding?
→ further studies needed before update of guidelines
Studies with IV glutamine + TPN in ICU:

The french Dipeptiven study

L-alanyl-L-glutamine dipeptide–supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: The French controlled, randomized, double-blind, multicenter study*

Pierre Déchelotte, MD; Michel Hasselmann, MD; Luc Cynober, PharmD; Bernard Allaouchiche, MD; Moïse Coëffier, PhD; Bernadette Hecketsweiler, PharmD; Véronique Merle, MD; Michel Mazerolles, MD; Désiré Samba, MD; Yves Marie Guillou, MD; Jean Petit, MD; Odile Mansoor, MD; Gabriel Colas, MD; Robert Cohendy, MD; Didier Barnoud, MD; Pierre Czernichow, MD; Gérard Bleichner, MD

Crit Care Med 2006 Vol. 34, No. 3
114 ICU patients
multiple trauma (38) complicated surgery (65)
others (11) with an indication for TPN over > 5 days

Prospective randomized double-blind controlled trial
isocaloric isonitrogenous TPN supplemented with

**Alanyl-glutamine** (Dipeptiven°):
0.5 g x kg\(^{-1}\) x day\(^{-1}\)

N=58

**Isonitrogenous control** (alanine + proline):
0.7 g x kg\(^{-1}\) x day\(^{-1}\)

N=56

Statistics: intention to treat analysis

*Déchelotte, Crit Care Med 2006*
### Better clinical outcome (primary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Dipeptiven</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>complicated outcome</td>
<td>24</td>
<td>34</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>(41.4%)</td>
<td>(60.7%)</td>
<td></td>
</tr>
<tr>
<td>nosocomial infections</td>
<td>0.45</td>
<td>0.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound alterations</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>death during study</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

TISS score decreased over time in both groups (NS)
Median ICU (12.5 vs 11.5 d), hospital LOS (30 vs 26 d),
6-months survival rate (72% vs 83%) : NS

*Déchelotte, Crit Care Med 2006*
## Reduced infectious complications

<table>
<thead>
<tr>
<th></th>
<th>Dipeptiven</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>total number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of infectious episodes</td>
<td>26</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>pneumonia</td>
<td>10</td>
<td>19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>surgical wound infection</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>septic shock or sepsis</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>urine infection</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>IV catheter</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Déchelotte, Crit Care Med 2006*
## Better metabolic tolerance

<table>
<thead>
<tr>
<th></th>
<th>Dipeptiven</th>
<th>Control</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>total metabolic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total metabolic disorders</td>
<td>38</td>
<td>56</td>
<td>(40 %)</td>
<td>(60 %)</td>
</tr>
<tr>
<td>hyperglycemia</td>
<td>20</td>
<td>30</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>requiring insulin</td>
<td>9</td>
<td>18</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>hypertriglyceridemia</td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>liver disorders</td>
<td>24</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total adverse events</td>
<td>116</td>
<td>159</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Déchelotte et al, Crit Care Med 2006*
Glutamine-TPN in secondary peritonitis:

33 patients with secondary peritonitis

Prospective randomized double-blind controlled trial
isocaloric isonitrogenous TPN with

1.1 amino acid + Alanyl-glutamine
0.4 g x kg\(^{-1}\) x day\(^{-1}\)
n = 17

Isonitrogenous control standard amino acid,
1.5 g x kg\(^{-1}\) x day\(^{-1}\)
n = 16

*Fuentes-Orozco, Clin Nutr 2004*
Reduces infectious complications:

![Graph showing comparison between Glt-TPN and STD-TPN for infectious complications. The graph indicates a significant difference (*P = 0.005*) with a lower number of infectious complications in the Glt-TPN group.]

Fuentes-Orozco, Clin Nutr 2004
Ala-Gln-TPN in complicated surgical patients:

- 59 patients with major surgery (cardiac, pancreatic, colonic)
- TPN + progressive standard enteral diet
- PRCT: IV alanyl-glutamine (0.5 g/kg.d) vs std amino acids

Results in non-pancreatic surgery:
- improved gln and GSH
- reduced nosocomial infections: 13 vs 36 (p<0.005) (bacteremia, pneumonia, Staph A, fungal)

Estivariz et al JPEN 2008
The Spanish Dipeptiven study

132 ICU patients
multiple trauma (35) complicated surgery (79)
+ others with an indication for TPN over > 4 days

Prospective randomized double-blind controlled trial
isocaloric isonitrogenous TPN supplemented with

<table>
<thead>
<tr>
<th>Alanyl-glutamine:</th>
<th>Isonitrogenous control:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=59 0.5 g x kg(^{-1}) x day(^{-1})</td>
<td>0.6 g x kg(^{-1}) x day(^{-1}) N=68</td>
</tr>
</tbody>
</table>

Statistics: Intention To Treat analysis & Per Protocol

Grau et al, Crit Care Med 2011
### Reduced infections and insulin resistance

<table>
<thead>
<tr>
<th></th>
<th>Dipeptiven</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>nosocomial infections / pt</td>
<td>1.5</td>
<td>2.1</td>
<td>0.20</td>
</tr>
<tr>
<td>pneumonia</td>
<td>22</td>
<td>31</td>
<td>0.02</td>
</tr>
<tr>
<td>UTI/1000 cath days</td>
<td>2.5</td>
<td>16.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Reduced insulin dose and insulin resistance

<0.001

Death, LOS, SOFA : NS

Grau et al, Crit Care Med 2011
IV Gln : reduced mortality in severe ICU patients

*Improved survival,
\[ p = 0.049 \]

Glutamine 57% *

Control 33%

Days from admission to 6 months

Griffiths, Nutrition 1997
IV-Gln improves outcome in ICU patients:

- Gln-TPN in severe ICU patients reduced 6-month mortality
  
  Griffiths Nutrition 1997
  Goeters CCM 2002

- reduced catheter related infections:
  12/25 vs 21/27
  reduced lethal fungal infections:
  0/25 vs 6/27

- enhanced IFNγ and maintained Il-4 production by PBMC of ICU patients

  Griffiths Nutrition 2002
  Boelens Clin Nutr 2004
IV glutamine in ICU: reduced infectious complications

Heyland et al. 2009
www.criticalcarenutrition.com
IV glutamine in ICU: reduced mortality

Heyland et al. 2009

www.criticalcarenutrition.com
IV glutamine + PN in ICU: recommendations

**European (ESPEN)**
« When PN is indicated in ICU patients, the AA solution should contain 0.2-0.4 g/kg/day of L-glutamine (e.g. 0.3-0.6 g/kg/day of alanyl-glutamine dipeptide) » - grade A

*Singer et al Clin Nutr 2009, 28:387-400*

**French (SFNEP/ASFAR)**
In case of major post-operative complications, it is recommended to prescribe glutamine intravenously and at high dosage (0.2 à 0.4 g/kg/day i.e. 0.3 à 0.6 g/kg/day of dipeptide).

*Chambrier et al Ann Fr Anesth Réanim 2011; 30:381-389*
IV glutamine + PN in ICU: recommendations

**Canadian (CSCN/CSCCM)**

Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended.

www.criticalcarenutrition.com 2009

- Parenteral glutamine administration is associated with a decrease in infectious complications, decrease in hospital length of stay, and possibly a decrease in mortality in critically ill postoperative or ventilator dependent patients requiring parenteral nutrition (PN).

**USA (ASPEN/ASCCM)**

*Nutr Clin Pract* 2011; 26: 479-494
Recent trials with IV glutamine in ICU: (0.35-0.5 g dipeptide/kg bw /day)

- reduced ICU mortality (PP) in patients fed PN, EN or both + IV alanyl-glutamine given in parallel
  *Wernerman, Acta Anesth Scand 2011*

- no effect on TLR-2, TLR-4 expression
  *Peres-Barcena, Nutr Hospit 2010*

- improved GSH levels in trauma patients
  *Eroglu, Anesth Analg 2009*
Global meta-analysis of RCTs of parenteral Gln

- 40 RCTs, 3107 patients, high heterogeneity: surgery, critical illness, mixed
- reduction of mortality in critically ill group (p=0.024),
- reduction of infection risk (p=0.009) in global population
- reduction of hospital length of stay (p=0.001, global)
- in high dose studies (> 0.3 g/kg bw/day of dipeptide): significant reduction of short term mortality, infections and LOS.

Bollhalder et al Clin Nutr 2013
New meta-analysis (Wischmeyer et al, ASPEN, 2013)

IV glutamine in ICU: reduced hospital mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PN GLN Events</th>
<th>PN GLN Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffiths</td>
<td>18</td>
<td>42</td>
<td>25</td>
<td>42</td>
<td>44.2%</td>
<td>0.72 [0.47, 1.11]</td>
<td>1997</td>
</tr>
<tr>
<td>Powell-Tuck</td>
<td>14</td>
<td>83</td>
<td>20</td>
<td>85</td>
<td>21.7%</td>
<td>0.72 [0.39, 1.32]</td>
<td>1999</td>
</tr>
<tr>
<td>Wischmeyer</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>16</td>
<td>3.7%</td>
<td>0.43 [0.10, 1.88]</td>
<td>2001</td>
</tr>
<tr>
<td>Xian-Li</td>
<td>0</td>
<td>20</td>
<td>3</td>
<td>21</td>
<td>1.0%</td>
<td>0.15 [0.01, 2.73]</td>
<td>2004</td>
</tr>
<tr>
<td>Fuentes-Orozco 2004</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>16</td>
<td>3.0%</td>
<td>0.63 [0.12, 3.28]</td>
<td>2004</td>
</tr>
<tr>
<td>Dechelotte</td>
<td>2</td>
<td>58</td>
<td>2</td>
<td>56</td>
<td>2.2%</td>
<td>0.97 [0.14, 6.62]</td>
<td>2006</td>
</tr>
<tr>
<td>Sahin</td>
<td>2</td>
<td>20</td>
<td>6</td>
<td>20</td>
<td>3.7%</td>
<td>0.33 [0.08, 1.46]</td>
<td>2007</td>
</tr>
<tr>
<td>Perez-Barcena 2008</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>1.0%</td>
<td>7.00 [0.39, 124.83]</td>
<td>2008</td>
</tr>
<tr>
<td>Estivariz</td>
<td>1</td>
<td>32</td>
<td>6</td>
<td>31</td>
<td>1.9%</td>
<td>0.16 [0.02, 1.26]</td>
<td>2008</td>
</tr>
<tr>
<td>Luo</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>9</td>
<td></td>
<td>Not estimable</td>
<td>2008</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>1</td>
<td>25</td>
<td>3</td>
<td>25</td>
<td>1.7%</td>
<td>0.33 [0.04, 2.99]</td>
<td>2008</td>
</tr>
<tr>
<td>Perez-Barcena 2010</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td>20</td>
<td>0.8%</td>
<td>0.29 [0.01, 6.78]</td>
<td>2010</td>
</tr>
<tr>
<td>Ziegler</td>
<td>11</td>
<td>75</td>
<td>13</td>
<td>75</td>
<td>15.0%</td>
<td>0.85 [0.41, 1.77]</td>
<td>2012</td>
</tr>
</tbody>
</table>

Total (95% CI) 436 | 431 100.0%
Total events 56 | 87

Heterogeneity: Tau² = 0.09; Chi² = 8.62, df = 11 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
New meta-analysis (Wischmeyer et al, ASPEN, 2013)

**IV glutamine in ICU: reduced hospital length of stay**

### Figure 2: Overall Complications

**Hospital Length of Stay**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PN Glutamine</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powel-Tuck</td>
<td>43.4</td>
<td>48.9</td>
<td>-5.50 [-16.48, 5.48]</td>
<td>1999</td>
</tr>
<tr>
<td>Wischmeyer</td>
<td>40</td>
<td>40</td>
<td>0.00 [-7.36, 7.36]</td>
<td>2001</td>
</tr>
<tr>
<td>Xian-Li</td>
<td>25.3</td>
<td>28.6</td>
<td>-3.30 [-7.75, 1.15]</td>
<td>2004</td>
</tr>
<tr>
<td>Fuentes-Orozco 2004</td>
<td>13.5</td>
<td>18.7</td>
<td>-5.20 [-5.65, 5.25]</td>
<td>2004</td>
</tr>
<tr>
<td>Zhou 2004</td>
<td>42</td>
<td>48</td>
<td>-4.00 [-8.87, 0.87]</td>
<td>2004</td>
</tr>
<tr>
<td>Sahin</td>
<td>14.2</td>
<td>18.4</td>
<td>-2.20 [-4.78, 0.38]</td>
<td>2007</td>
</tr>
<tr>
<td>Estivarz</td>
<td>20</td>
<td>30</td>
<td>-10.00 [-13.54, -6.48]</td>
<td>2008</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>13.48</td>
<td>15.1</td>
<td>-1.70 [-2.41, -0.09]</td>
<td>2008</td>
</tr>
<tr>
<td>Perez-Baroena 2008</td>
<td>35.5</td>
<td>42.9</td>
<td>-7.40 [-9.80, 15.00]</td>
<td>2008</td>
</tr>
<tr>
<td>Ziegler</td>
<td>25.1</td>
<td>20.5</td>
<td>4.60 [-2.17, 11.37]</td>
<td>2012</td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 319 - 320

Heterogeneity: Tau² = 8.35, Chi² = 26.03, df = 10 (P = 0.001); I² = 35%

Test for overall effect: Z = 2.18 (P = 0.03)

Favours PN Glutamine  
Favours control
Effectiveness and cost-effectiveness of supplemental glutamine dipeptide in total parenteral nutrition therapy for critically ill patients:

- 200 Italian ICUs database
- Reduced mortality (24.6% ± 1.6% vs. 34.5% ± 2.1%), infection rate (13.8% ± 2.9% vs. 18.8% ± 3.9%), and hospital LOS (24.9 ± 0.3 vs. 26.0 ± 0.3 days)
- A lower total cost per patient (23,409 ± 3,345 vs. 24,161 ± 3,523 Euro).
- Treatment cost offset by savings on ICU and antibiotic costs.

Pradelli et al.
Trials with IV glutamine in ICU using other study designs and doses:

- SIGNET trial: fixed low dose of glutamine (20 g/day x 5 d) or Se, fixed PN regimen: NS on new infections and mortality
  
  *Andrews, BMJ 2011*

- Multicenter trial in surgical “ICU” patients: Gln dipeptide in TPN with **progressive weaning to EN** → no significant effect on outcome

  *Ziegler, ESPEN, 2012*
Trials with IV glutamine in ICU using other study designs and doses:

• REDOXS study with very high Gln (around 0.7 g/kg bw/d from IV and enteral routes) and/or AOX, 2x2 design
• Gln supply separated from nutrition, started D1
• outcome: **NS on 28 day mortality** (ITT),
• trend for increased 6-mo mortality (?) (high number of patients lost in the follow-up)

*Heyland, NEJM, 18th april 2013*
Specificities of the REDOXS study:

- **very severe** ICU patients: 2 or more organ failures, high proportion (32-38%) with renal failure, high incidence of vasopressors; more patients with ¾ organ failures in the Gln group
- **high total dose of Gln, different from guidelines**
- Early provision of full Gln while feeding was minimal (mostly enteral, < 50% of nutritional goals)
- **subgroup analysis for predictors of mortality:** renal dysfunction, <30% of caloric needs (p<0.03) + trends for GI diagnostic, vasopressors, steroids, early supply of Gln

*Heyland, ASPEN, 2013, abstract 1517432*
Conclusion: Enteral glutamine in ICU?

→ recommendations for trauma and burns patients fed enterally (0.35-0.5 g gln/kg bw/d)

→ some recent studies in mixed populations of ICU patients suggest a benefit on the reduction of infectious complications: but need for additional evidence to update guidelines

→ no evidence that giving enteral Gln in addition to IV glutamine is beneficial
Conclusion: IV glutamine-dipeptide in ICU

- confirmed benefits and safety in TPN-patients:
  - after major surgery (0.2-0.35 g dipeptide/kg bw/d)
  - for acute pancreatitis (idem)

- confirmed benefits and safety in ICU patients (mixed populations, medical and surgical) fed adequately with TPN (or EN+TPN), receiving the recommended dosage of 0.5g dipeptide/kg bw/d, in the absence of contraindication (renal failure!)

- lower or much higher doses in ICU patients: no benefit