Nutritional 
Immunomodulation 
in Critical Illness

Prof Jonathan Asprer, MD
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University of Santo Tomas
Established in 1611, celebrating 400 years in 2011
From nutrition support to therapy

- **Traditional role of nutrition support:**
  To provide calories, protein, vitamins, minerals, trace elements

- **Current role of nutrition therapy:**
  Modulate immune response in the cascade from SIRS- MOD- MOF
From nutrition support to therapy

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To provide calories, protein, vitamins, minerals, trace elements

**Current role of nutrition therapy:**
Modulate immune response in the IMMUNOMODULATION cascade from SIRS- MOD- MOF
From “support” to “therapy” . . .
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... the more appropriate term for “nutrition support” would be "nutrition therapy" since nutrition care is now recognized to be as important as medicines or therapeutic interventions . . .
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Goals of nutrition support  Goals of nutrition therapy
Goals of nutrition support

- Prevention of starvation-induced complications
- Improvement of nutritional status
- Improvement of metabolic status
- Reduction in LOS and ICU stay
Goals of nutrition support

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Goals of nutrition support

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- Reduction in LOS and ICU stay

Goals of nutrition therapy

- Decreasing local and systemic infections
- Modulation of SIRS, and the cascade to MOD and MOF
- Metabolic support of individual organs
- Reduction in morbidity & mortality
Nutritional immunomodulation

- Early enteral feeding (EN) can stimulate gut immunity & gut function

- Early PN for critically ill patients with poor EN tolerance avoids the infections and other complications associated with caloric deficits

- Hyperglycemia in critical illness is associated with increased mortality and must be controlled

- Pharmacologic effects of glutamine & fish oils directly modulate immune responses
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2009 Guidelines: ASPEN-SCCM, ESPEN

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

ESPEN Guidelines on Parenteral Nutrition: Intensive care

Pierre Singer a, Mette M. Berger b, Greet Van den Berghe c, Gianni Biolo d, Philip Calder e, Alastair Forbes f, Richard Griffiths g, Georg Kreyman h, Xavier Leverve i, Claude Pichard j
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Dysfunctional inflammatory response in ICU-
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Calder, ESPEN, 9/2007
Initially in SIRS phase:
(Systemic Inflammatory Response Syndrome)

Increased generation of inflammatory mediators

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Later in CARS phase:
(compensatory anti-inflammatory response syndrome)
shift towards an anti-inflammatory immunosuppressed state

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Early EN stimulates gut immunity

Lymphoid tissue protection

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- 70-80% of Immune globulin production (IgA)
- Activated & maintained only by feeding stimulation of intestinal mucosa

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Enteral feeding should be started early within 24-48 hr following admission (C). Advance to goal over 48-72 hr (E)

ASPEN-SCCM ICU Guidelines, JPEN, May-June 2009

EN problems in ICU patients-
**EN problems in ICU patients**

- Average energy intakes in ICU patients are 49% to 70% of calculated requirements

- Only 50% to 60% ICU patients tolerate EN successfully

Stapleton RD et al. CCM;2007:35
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![Pie chart showing reasons for EN failure in ICU patients](chart)

- Airway management: 26 days (11%)
- Surgical interventions: 10 days (4%)
- Problems with feeding tube: 17 days (7%)
- Multiple nominations: 44 days (19%)
- No reason: 19 days (8%)
- Gastrointestinal intolerance: 120 days (51%)

*Days on EN <80% of EE after reaching target rate*

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Poor EN tolerance = negative energy balance
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However, with optimized feeding:
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- Cumulative calorie deficit correlates with ICU complications & longer ICU stay (8000kcal - 4000 kcal)


However, with optimized feeding:

- Early energy supply >1500 kcal in day 1-3 in ICU patients was associated with lower mortality & morbidity

MBerger, Curr Opin Clin Nutr Metab Care, Mar 2009  
Kreymann, Weiman et al. ESPEN 2008
Optimize EN delivery with SOPs (ACCEPT trial)

At ICU admission: Should this patient be fed?

- If 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

  - If no: Acceptable conditions:
    - Tolerating adequate oral intake
    - < 24 hours to oral intake
    - Palliative care

- If no: Acceptable conditions:
  - Acute pancreatitis*
  - Enteric anastomosis*
  - Ischemic bowel
  - Enteric fistula
  - Imminent bowel resection
  - Imminent endoscopy
  - Bowel obstruction
  - High nasogastric losses on admission
  - Severe exacerbation of IBD

  *May still opt for elemental feeds

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

- If yes:
  - Is Goal met?
    - Yes: Increase rate to 100%
    - No: Use prokinetic and/or use post-pyloric tube

- If no: Use prokinetic and/or use post-pyloric tube

Begin TPN:
- Consider TPN with glutamine
- Reassess q12h for EN eligibility

Continue EN to Max. tolerated supplement with PN
- Continue EN challenges q12h

“Algorithm for Critical Care Enteral & Parenteral Therapy” - ANZICS CTG
Optimize EN delivery with SOPs (ACCEPT trial)

Start EN w/in 24 hrs

At ICU admission: Should this patient be fed?
- NO
- YES

Can EN be started within 24 hours?
- NO
- YES

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- GOAL: at least 80% of requirements at 72h
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Will at least 80% of requirements be met by 72h?
- YES
- NO

Is Goal met?
- NO
- YES

Increase rate to 100%

Use prokinetic and/or
Use post-pyloric tube

Is Goal met?
- YES
- NO

Continue EN to Max. tolerated Supplement with PN
Continue EN challenges q12h

Acceptable conditions:
- tolerating adequate oral intake
- < 24 hours to oral intake
- palliative care

Acceptable conditions:
- acute pancreatitis*
- enteric anastomosis*
- ischemic bowel
- enteric fistula
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Routinely use strategies to optimize

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        - YES
          - Is Goal met?
            - NO
              - Increase rate to 100%
            - YES
              - Use prokinetic and/or use post- pyloric tube
        - NO
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“Algorithm for Critical Care Enteral & Parenteral Therapy”- ANZICS CTG
Optimize EN delivery with SOPs (ACCEPT trial)

- Start EN w/in 24 hrs
- Routinely use strategies to optimize
- Combine with PN when necessary

“Algorithm for Critical Care Enteral & Parenteral Therapy”- ANZICS CTG
Nutritional immunomodulation

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Combine EN-PN to achieve goals

Clinical course (days)

0 750 1500

100%
Combine EN-PN to achieve goals

EN

PN

Clinical course (days)

ASCP-SCCM ICU Guidelines, JPEN, May-June 2009
ESPEN ICU Guidelines, Clinical Nutrition, Aug 2009
Combine EN-PN to achieve goals

Clinical course (days)

EN
PN

100%

ASPEN-SCCM ICU Guidelines, JPEN, May-June 2009
ESPEN ICU Guidelines, Clinical Nutrition, Aug 2009
All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24 to 48 h if EN is contraindicated or if they cannot tolerate EN. (C) ESPEN

If EN is not feasible, it is appropriate to initiate PN as soon as possible after admission and resuscitation. (C) ASPEN
When to start supplemental PN

- At ICU admission: Should this patient be fed?
  - NO
  - Acceptable conditions:
    - tolerating adequate oral intake
    - < 24 hours to oral intake
    - palliative care
  - YES
  - Can EN be started within 24 hours?
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      - Will at least 80% of requirements be met by 72h?
        - YES
        - Is Goal met?
          - NO
          - Use prokinetic and/or
            Use post-pyloric tube
          - YES
            Increase rate to 100%
        - NO
      - Use prokinetic and/or
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    - NO
      - Is Goal met?
        - YES
          Continue EN to Max. tolerated Supplement with PN
          Continue EN challenges q12h
        - NO

ANZICS CTG
When to start supplemental PN

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       - Will at least 80% of requirements be met by 72h?
         - NO: Begin TPN:
           - consider TPN with glutamine
           - Reassess q12h for EN eligibility
         - YES: Use prokinetic and/or Use post-pyloric tube
       - Is Goal met?
         - NO: Increase rate to 100%
         - YES: Continue EN to Max. tolerated Supplement with PN
       - Is Goal met?
         - NO: Continue EN challenges q12h
         - YES: OK with EN
Start supplemental PN if 60% of the EN target is not reached by the 48th hr, because it is unlikely that 80% of requirements will be met by 72 hrs.

If EN tolerance improves to 80% by 72 hrs, PN may be discontinued, but if not, the resulting calorie deficit can be avoided.

It is easier to discontinue PN than to chase a rapidly increasing calorie deficit.
Benefits of combined EN-PN

- Gut immunity can be stimulated by partial EN
- When tolerance to EN is limited by gut dysfunction, PN can deliver the full requirement of protein, calories & micronutrients
- Adequate calories & protein are important to:
  - Improve wound healing
  - Restore/ maintain immune competence
  - Minimize morbidity & mortality
PN is best given in 3-compartment bags

- Optimal energy utilization (CHO + fat)
- Control respiratory quotient
- Minimize harmful hyperglycemia
- Greater stability and safety; less contamination/delivery errors
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Pichard, Clin Nutr 2000;19:245-51
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- Costs with 3CB were lower than with multibottles; 3CB should be the system of choice to reduce costs

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- Optimal nitrogen sparing is achieved when all components of PN are administered simultaneously over 24 hours (A)

ESPEN PN Guidelines for ICU, 2009
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Hyperglycemia: pro-inflammatory effect

Sriram, PENSA 2009, Kuala Lumpur
Hyperglycemia: pro-inflammatory effect

Oxidative stress:
- Increase in oxygen free radical (ROS) generation by leukocytes

Inflammatory stress:
- ROS activate proinflammatory transcription factors
  - NF-κB
  - Activator protein-1
  - Early growth response-1
  - Hypoxia-inducible factor α

Increased expression:
- Pro-inflammatory cytokines (TNF-α, IL-1, IL-6)

ROS - Reactive Oxygen Species

Sriram, PENSA 2009, Kuala Lumpur
Glycemic control in ICU: ↓morbidity & mortality

- Intensive vs conventional insulin therapy*
- Tight glucose control = improved survival (80-110mg/dl)

** NICE-SUGAR study, NEJM 2009: Vol 160, No. 13
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- **NICE-SUGAR study***(<180mg/dl)

  Normoglycemia in Intensive Care Evaluation-
  Survival Using Glucose Algorithm Regulation


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- NICE-SUGAR study: Normoglycemia in Intensive Care: Survival Using Glucose Algorithm Regulation

Glycemic control is easier to achieve by:
- dual energy concept (glucose + lipids)
- preoperative oral nutrition supplements
- glutamine to lower insulin resistance

Asprer, PhilSPEN, Nov 2009

** NICE-SUGAR study, NEJM 2009: Vol 160, No. 13
Value of combining lipids with glucose
Value of combining lipids with glucose

- **Energy from lipids allows lower glucose supply, thereby enhancing glycemic control**
  
  Asprer, PhilSPEN Annual Convention, Nov 2009

- **Lipids are tolerated better in sepsis**
  

- **Helps to control respiratory quotient by reduced CO2 production**
  

- **In cancer, tumors utilize glucose as the main energy source but are unable to use lipids**
  
  Bongaerts et al. Medical Hypotheses. 67, 1213–1222, 2006
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When PN is indicated in ICU the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide). (A)
When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine. (C)

The addition of enteral glutamine to an EN regimen should be considered in burns, trauma, and mixed ICU patients. (B)

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Beneficial effects of glutamine

- Fuel for Enterocytes
- Nucleotide Synthesis
- Fuel for Lymphocytes

As presented at PENSA 2007, Manila
Beneficial effects of glutamine

- Fuel for Enterocytes
- Nucleotide Synthesis
- Fuel for Lymphocytes
- Maintenance of Intestinal Mucosal Barrier
- Maintenance of Lymphocyte Function

Kelly & Wischmeyer,
Curr Opin Clin Nutr Metab Care 2003, 6:217–222
As presented at PENSA 2007, Manila
Beneficial effects of glutamine

Glutamine

- Fuel for Enterocytes
- Nucleotide Synthesis
- Fuel for Lymphocytes
- Maintenance of Intestinal Mucosal Barrier
- Maintenance of Lymphocyte Function
- Reduced Translocation of Enteric Bacteria or Endotoxins
- Reduction of Infectious complications

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Beneficial effects of glutamine

- Decreased Free Radical availability (Anti-inflammatory action)
- Glutathione Synthesis
- Fuel for Enterocytes
- Preservation of Muscle mass
- Fuel for Lymphocytes
- Maintenance of Intestinal Mucosal Barrier
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- Fuel for Lymphocytes

- Maintenance of Lymphocyte Function

- Reduced Translocation Enteric Bacteria or Endotoxins

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- Preservation of TCA Function

- Anti-catabolic effect

- Preservation of Cellular Energetics- ATP content

- Preservation of Muscle mass

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- Fuel for Lymphocytes
- Maintenance of Intestinal Mucosal Barrier
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- Preservation of TCA Function
- Anti-catabolic effect
- Enhanced Heat Shock Protein
- Inflammatory Cytokine Attenuation
- Reduced Translocation Enteric Bacteria or Endotoxins
- Reduced Infectious complications
- NF-κB
- Preservation of Muscle mass
- Preserved Cellular Energetics- ATP content

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- Fuel for Enterocytes
- Nucleotide Synthesis
- Fuel for Lymphocytes
- Maintenance of Intestinal Mucosal Barrier
- Maintenance of Lymphocyte Function
- Reduced Translocation Enteric Bacteria or Endotoxins
- Reduced Infectious complications
- Enhanced Heat Shock Protein
- Inflammatory Cytokine Attenuation
- Preservation of TCA Function
- Preservation of Muscle mass
- Preserved Cellular Energetics- ATP content
- Enhanced insulin sensitivity

Kelly & Wischmeyer, Curr Opin Clin Nutr Metab Care 2003, 6:217–222
As presented at PENSA 2007, Manila
**Beneficial effects of glutamine**

- **Critical Illness**
  - Glutathione Synthesis
  - Enhanced Heat Shock Protein
  - Inflammatory Cytokine Attenuation
  - Reduced Translocation Enteric Bacteria or Endotoxins
  - Reduction of Infectious complications

- **GLN Pool**
  - Decreased Free Radical availability (Anti-inflammatory action)
  - Fuel for Enterocytes
  - Maintenance of Intestinal Mucosal Barrier
  - Fuel for Lymphocytes
  - Maintenance of Lymphocyte Function
  - Reduced Translocation Enteric Bacteria or Endotoxins

- **Preservation of Muscle mass**
  - Preservation of TCA Function
  - Enhanced Heat Shock Protein
  - Inflammatory Cytokine Attenuation
  - Reduced Translocation Enteric Bacteria or Endotoxins
  - Reduction of Infectious complications

- **Kelly & Wischmeyer,**
  - *Curr Opin Clin Nutr Metab Care* 2003, 6:217–222
  - As presented at PENSA 2007, Manila

- **Critical Illness**
  - GLN Pool
  - Enhanced insulin sensitivity
  - Glutathione Synthesis
  - Preserved Cellular Energetics-ATP content
  - Preservation of Muscle mass

- **Critical Illness**
  - GLN Pool
  - Enhanced insulin sensitivity
  - Glutathione Synthesis
  - Preserved Cellular Energetics-ATP content
  - Preservation of Muscle mass
**Beneficial effects of glutamine**

- Enhanced insulin sensitivity
- Reduced translocation of enteric bacteria or endotoxins
- Reduced inflammatory complications

**Glutamine Therapy**

- Critical Illness
- Preserved cellular energetics - ATP content
- Preservation of TCA function
- Enhanced insulin sensitivity
- Anti-catabolic effect
- Fuel for enterocytes
- Maintenance of intestinal mucosal barrier
- Fuel for lymphocytes
- Maintenance of lymphocyte function
- Inflammatory cytokine attenuation
  - Enhanced heat shock protein
  - Preservation of muscle mass

**Kelly & Wischmeyer,**
*Curr Opin Clin Nutr Metab Care* 2003, 6:217–222

As presented at PENSA 2007, Manila
Glutamine: mechanisms of action
Glutamine: mechanisms of action

- Modulation of cytokine production
- Modulation of cellular immunity
- Protection of gut integrity & barrier function
- Cell protection (elaboration of heat-shock protein)
- Reduction in oxidative stress; glutathione
- Counteracting insulin resistance
- Counteracting apoptosis
Proposed organ-specific effects of glutamine in critical illness

**LUNG**
- Major fuel for endothelial cell
- Preserves cell metabolism following endotoxin injury

**HEART**
- Major fuel for cardiomyocytes

**IMMUNE CELLS**
- Major fuel for lymphocytes
- Supports neutrophil killing and macrophage function

**KIDNEY**
- Acid/base regulation
- Central role in N transport within the body
- $\text{NH}_3$ metabolism

**GASTROINTESTINAL TRACT**
- Major fuel; Supports nucleotide biosynthesis
- Protects epithelial cells against endotoxin/oxidant related injury
- Enhances glutathione concentration post-stress
Proposed organ-specific effects of glutamine in critical illness

LUNG
- Major fuel for endothelial cell
- Preserves cell metabolism following endotoxin injury

HEART
- Major fuel for cardiomyocytes

IMMUNE CELLS
- Major fuel for lymphocytes
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- Acid/base regulation
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GASTROINTESTINAL TRACT
- Major fuel; Supports nucleotide biosynthesis
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- Enhances glutathione concentration post-stress
IV glutamine may stimulate gut immunity

McClave & Heyland, NCP, 2009.
IV glutamine may stimulate gut immunity

Early feeding can stimulate gut function & gut immunity within 24–48 hrs after the critical event (surgery, ICU, etc)

McClave & Heyland, NCP, 2009.
IV glutamine may stimulate gut immunity

McClave & Heyland, NCP, 2009.

Addition of IV glutamine to PN therapy may be the single most important strategy for closing the gap between the physiologic effects of EN & PN.

Early feeding can stimulate gut function & gut immunity within 24 – 48 hrs after the critical event (surgery, ICU, etc)
Is there actual evidence of depletion?

<table>
<thead>
<tr>
<th>Patient group/ catabolic state</th>
<th>GLUTAMINE DEPLETION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intramuscular</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>MOF</td>
<td></td>
</tr>
<tr>
<td>Severe acute pancreatitis</td>
<td>Roth 1986</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td></td>
</tr>
</tbody>
</table>
Is there actual evidence of depletion?

- **ICU patients w/ pancreatitis**
  Roth, *Klin Em* 1982

- **ICU trauma patients**

- **ICU patients**

- **Burns & trauma, incl sepsis patients**
  Wischmeyer et al, *NCP*, 2003

- **ICU patients**
  Oudemans-Van Straaten, *ICM* 2001
Glutamine depletion = higher mortality!

- Glutamine <420 µmol/l: 25 patients
- Glutamine >420 µmol/l: 55 patients

Hospital mortality (%):
- Glutamine <420 µmol/l: 29%
- Glutamine >420 µmol/l: 60%

Plasma Glutamine (µmol/l):
- <420 µmol/l: 29%
- >420 µmol/l: 60%

Severity of illness (APACHE II Score):
- <420 µmol/l: 29
- >420 µmol/l: 25

Glutamine depletion = higher mortality!

Glutamine depletion = higher mortality!

Depleted plasma glutamine is a predictor of mortality (more sensitive than APACHE II score)

Glutamine depletion = higher mortality!

Pre-op parenteral glutamine resulted in increased white blood cell, granulocyte, and lymphocyte counts.

When supplementation was discontinued before surgery, this increase was not sustained in the post-op period.

Glutamine is best when given both pre- & post-op.
Pre-op parenteral glutamine resulted in increased white blood cell, granulocyte, and lymphocyte counts

When supplementation was discontinued before surgery, this increase was not sustained in the post-op period

Glutamine is best when given both pre- & post-op

Glutamine in surgical patients: meta-analysis

The impact of glutamine dipeptides on outcome of surgical patients: systematic review of randomized controlled trials from Europe and Asia

Glutamine dipeptide for parenteral nutrition in abdominal surgery: A meta-analysis of randomized controlled trials

Clinical Nutrition Supplements (2004) 1, 17-23

World J Gastroenterol 2006; 12 (46): 7537 - 7541
Glutamine in surgical patients: meta-analysis

The impact of glutamine dipeptides on outcome of surgical patients: systematic review of randomized controlled trials from Europe and Asia

Results of glutamine dipeptide therapy:

- Significant reduction in length of hospital stay
- Significant reduction in infectious complications

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Results of glutamine dipeptide therapy:

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- Significant reduction in infectious complications

Glutamine dipeptide for parenteral nutrition in abdominal surgery: A meta-analysis of randomized controlled trials

World J Gastroenterol 2006; 12 (46): 7537 - 7541

Glutamine-supplemented PN in abdominal surgery

- Improved N- balance (significant)
- Decreased infection rate (significant)
- Reduced length of hospital stay (significant)
**Effect of glutamine in critical illness: Systematic review of literature**

### Infectious complications

**Review:** glutamine New review (Version 01)  
**Comparison:** 03 Glutamine vs Control  
**Outcome:** 02 Infectious Complications

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Glutamine n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Griffiths</td>
<td>28/42</td>
<td>26/42</td>
<td>17.16 1.08 [0.78, 1.48]</td>
<td>17.16</td>
<td>1.08 [0.78, 1.48]</td>
<td>1997</td>
</tr>
<tr>
<td>Houdijk</td>
<td>20/35</td>
<td>26/37</td>
<td>14.79 0.81 [0.57, 1.16]</td>
<td>14.79</td>
<td>0.81 [0.57, 1.16]</td>
<td>1998</td>
</tr>
<tr>
<td>Wischmeyer</td>
<td>7/12</td>
<td>9/14</td>
<td>6.02 0.91 [0.49, 1.68]</td>
<td>6.02</td>
<td>0.91 [0.49, 1.68]</td>
<td>2001</td>
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<tr>
<td>Hall</td>
<td>38/179</td>
<td>43/184</td>
<td>13.15 0.91 [0.62, 1.33]</td>
<td>13.15</td>
<td>0.91 [0.62, 1.33]</td>
<td>2003</td>
</tr>
<tr>
<td>Zhou</td>
<td>2/20</td>
<td>6/20</td>
<td>1.16 0.33 [0.08, 1.46]</td>
<td>1.16</td>
<td>0.33 [0.08, 1.46]</td>
<td>2003</td>
</tr>
<tr>
<td>Fuentes-Orozco</td>
<td>4/17</td>
<td>12/16</td>
<td>3.00 0.31 [0.13, 0.77]</td>
<td>3.00</td>
<td>0.31 [0.13, 0.77]</td>
<td>2004</td>
</tr>
<tr>
<td>Zhou 2004</td>
<td>3/15</td>
<td>4/15</td>
<td>1.46 0.75 [0.20, 2.79]</td>
<td>1.46</td>
<td>0.75 [0.20, 2.79]</td>
<td>2004</td>
</tr>
<tr>
<td>Dechelotte 2006</td>
<td>23/58</td>
<td>32/56</td>
<td>12.87 0.69 [0.47, 1.03]</td>
<td>12.87</td>
<td>0.69 [0.47, 1.03]</td>
<td>2006</td>
</tr>
<tr>
<td>Palmese</td>
<td>2/42</td>
<td>6/42</td>
<td>1.07 0.33 [0.07, 1.56]</td>
<td>1.07</td>
<td>0.33 [0.07, 1.56]</td>
<td>2006</td>
</tr>
<tr>
<td>Estivariz</td>
<td>13/30</td>
<td>16/29</td>
<td>7.99 0.79 [0.46, 1.33]</td>
<td>7.99</td>
<td>0.79 [0.46, 1.33]</td>
<td>2008</td>
</tr>
<tr>
<td>Fuentes-Orozco 2008</td>
<td>9/22</td>
<td>16/22</td>
<td>7.06 0.56 [0.32, 0.99]</td>
<td>7.06</td>
<td>0.56 [0.32, 0.99]</td>
<td>2008</td>
</tr>
<tr>
<td>Perez-Barcena</td>
<td>11/15</td>
<td>13/15</td>
<td>14.28 0.85 [0.59, 1.22]</td>
<td>14.28</td>
<td>0.85 [0.59, 1.22]</td>
<td>2008</td>
</tr>
</tbody>
</table>

Total (95% CI) 487 492 100.00 0.79 [0.68, 0.93]  
Total events: 160 (Glutamine), 209 (Control)  
Test for heterogeneity: Chi² = 13.14, df = 11 (P = 0.28), I² = 16.3%  
Test for overall effect: Z = 2.81 (P = 0.005)
**Effect of glutamine in critical illness: Systematic review of literature**

**Length of stay**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Glutamine N</th>
<th>Glutamine Mean (SD)</th>
<th>Control N</th>
<th>Control Mean (SD)</th>
<th>WMD (random) 95% CI</th>
<th>Weight %</th>
<th>WMD (random) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houdijk</td>
<td>35</td>
<td>32.70 (17.10)</td>
<td>37</td>
<td>33.00 (23.80)</td>
<td>2.83 (2.83, 6.66)</td>
<td>0.30</td>
<td>-0.30 (-9.83, 9.23)</td>
<td>1998</td>
</tr>
<tr>
<td>Powell-Tuck</td>
<td>83</td>
<td>43.40 (34.10)</td>
<td>85</td>
<td>48.90 (38.40)</td>
<td>2.26 (0.50, 5.35)</td>
<td>1.00</td>
<td>-5.50 (-16.46, 5.48)</td>
<td>1999</td>
</tr>
<tr>
<td>Brantley</td>
<td>31</td>
<td>19.50 (8.80)</td>
<td>41</td>
<td>20.80 (11.50)</td>
<td>6.87 (0.00, 13.21)</td>
<td>1.30</td>
<td>-1.30 (-5.99, 3.39)</td>
<td>2000</td>
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<tr>
<td>Witschmeier</td>
<td>12</td>
<td>40.00 (10.00)</td>
<td>14</td>
<td>40.00 (9.00)</td>
<td>4.12 (0.00, 7.12)</td>
<td>0.00</td>
<td>-7.36 (7.36, 21.36)</td>
<td>2001</td>
</tr>
<tr>
<td>Zhou</td>
<td>20</td>
<td>67.00 (4.00)</td>
<td>20</td>
<td>73.00 (6.00)</td>
<td>9.14 (0.00, 18.04)</td>
<td>6.00</td>
<td>-9.16 (-18.24, 0.00)</td>
<td>2003</td>
</tr>
<tr>
<td>Fuentes-Orozco</td>
<td>17</td>
<td>16.50 (8.90)</td>
<td>16</td>
<td>16.70 (7.00)</td>
<td>5.93 (0.00, 11.85)</td>
<td>0.20</td>
<td>-5.65 (5.25, 0.00)</td>
<td>2004</td>
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<tr>
<td>Peng</td>
<td>25</td>
<td>46.59 (12.58)</td>
<td>23</td>
<td>55.68 (17.16)</td>
<td>3.24 (0.00, 6.48)</td>
<td>9.09</td>
<td>-17.82 (-0.36, 0.00)</td>
<td>2004</td>
</tr>
<tr>
<td>Zhou 2004</td>
<td>15</td>
<td>42.00 (7.00)</td>
<td>15</td>
<td>46.00 (6.60)</td>
<td>6.64 (0.00, 13.28)</td>
<td>4.00</td>
<td>-8.87 (-12.87, 0.00)</td>
<td>2004</td>
</tr>
<tr>
<td>Palmezse</td>
<td>42</td>
<td>12.00 (4.60)</td>
<td>42</td>
<td>13.00 (3.40)</td>
<td>11.32 (0.00, 22.64)</td>
<td>1.00</td>
<td>-2.70 (9.70, 0.00)</td>
<td>2006</td>
</tr>
<tr>
<td>Sahin</td>
<td>20</td>
<td>14.20 (4.40)</td>
<td>20</td>
<td>16.40 (3.90)</td>
<td>10.07 (0.00, 20.14)</td>
<td>2.20</td>
<td>-4.78 (4.08, 0.00)</td>
<td>2007</td>
</tr>
<tr>
<td>Cai</td>
<td>55</td>
<td>22.10 (4.90)</td>
<td>55</td>
<td>23.80 (5.10)</td>
<td>11.13 (0.00, 22.26)</td>
<td>1.70</td>
<td>-3.57 (5.07, 0.00)</td>
<td>2008</td>
</tr>
<tr>
<td>Estivariz</td>
<td>15</td>
<td>20.00 (2.00)</td>
<td>12</td>
<td>30.00 (6.00)</td>
<td>8.54 (0.00, 16.01)</td>
<td>10.00</td>
<td>-13.54 (-23.54, 0.00)</td>
<td>2008</td>
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<tr>
<td>Fuentes-Orozco 2008</td>
<td>22</td>
<td>30.18 (10.42)</td>
<td>22</td>
<td>26.59 (13.30)</td>
<td>4.36 (0.00, 8.72)</td>
<td>3.59</td>
<td>-5.47 (10.65, 0.00)</td>
<td>2008</td>
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<tr>
<td>Luo 2008</td>
<td>11</td>
<td>7.60 (0.90)</td>
<td>9</td>
<td>6.90 (0.90)</td>
<td>12.36 (0.00, 24.72)</td>
<td>0.70</td>
<td>0.00 (-0.02, 1.42)</td>
<td>2008</td>
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<tr>
<td>McGugan</td>
<td>10</td>
<td>32.00 (13.60)</td>
<td>10</td>
<td>39.30 (36.30)</td>
<td>0.55 (0.00, 1.10)</td>
<td>7.30</td>
<td>-31.33 (16.73, 0.00)</td>
<td>2008</td>
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<tr>
<td>Perez-Barcena</td>
<td>15</td>
<td>35.50 (33.60)</td>
<td>15</td>
<td>42.90 (28.80)</td>
<td>0.63 (0.00, 1.26)</td>
<td>7.40</td>
<td>-29.80 (15.00, 0.00)</td>
<td>2008</td>
</tr>
</tbody>
</table>

Total (95% CI) 428 | 436 | 100.00 | -2.56 (-4.39, -0.74)

Test for heterogeneity: Chi² = 62.15, df = 15 (P < 0.00001), I² = 75.9%

Test for overall effect: Z = 2.76 (P = 0.006)
Effect of glutamine in critical illness: Systematic review of literature

Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Glutamine n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffiths</td>
<td>18/42</td>
<td>25/42</td>
<td>23.68</td>
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<td>0.72 [0.47, 1.11]</td>
<td>1997</td>
</tr>
<tr>
<td>Houdijk</td>
<td>4/41</td>
<td>3/39</td>
<td>2.13</td>
<td></td>
<td>1.27 [0.90, 1.81]</td>
<td>1996</td>
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<tr>
<td>Jones</td>
<td>10/26</td>
<td>9/24</td>
<td>8.66</td>
<td></td>
<td>1.03 [0.50, 5.31]</td>
<td>1999</td>
</tr>
<tr>
<td>Powell-Tuck</td>
<td>14/83</td>
<td>20/85</td>
<td>11.63</td>
<td></td>
<td>0.72 [0.39, 1.32]</td>
<td>1999</td>
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<tr>
<td>Brantley</td>
<td>0/31</td>
<td>0/41</td>
<td>Not estimable</td>
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<td>Garrel</td>
<td>2/21</td>
<td>12/24</td>
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<td></td>
<td>0.19 [0.05, 0.76]</td>
<td>2003</td>
</tr>
<tr>
<td>Hall</td>
<td>27/179</td>
<td>30/184</td>
<td>19.12</td>
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<td>0.93 [0.57, 1.49]</td>
<td>2003</td>
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<td>Zhou</td>
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<td>0/20</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fuentes-Orozco</td>
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<td>0.52</td>
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<td>2004</td>
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<td>Dechelotte 2006</td>
<td>2/58</td>
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<td>1.18</td>
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<td>0.97 [0.14, 6.62]</td>
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<td>8/42</td>
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<tr>
<td>Sahin</td>
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<td>6/20</td>
<td>2.00</td>
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<td>0.33 [0.08, 1.46]</td>
<td>2006</td>
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<tr>
<td>Cai</td>
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<td>20/55</td>
<td>15.66</td>
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<td>Duska</td>
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<td>0.16 [0.02, 1.27]</td>
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<td>1.86</td>
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<td>2/10</td>
<td>0.51</td>
<td></td>
<td>0.20 [0.01, 3.70]</td>
<td>2008</td>
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<tr>
<td>Perez-Barcena</td>
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<td>0/15</td>
<td>0.53</td>
<td></td>
<td>7.00 [0.39, 124.83]</td>
<td>2008</td>
</tr>
</tbody>
</table>

Total (95% CI) 782 782 100.00 0.75 [0.61, 0.93]

Total events: 115 (glutamine), 159 (Control)
Test for heterogeneity: Chi² = 16.81, df = 18 (P = 0.54), I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)
Glutamine role in nutrition therapy - supported by current practice guidelines

- Canadian Critical Care Grp - www.criticalcarenutrition.com
- American Society of Parenteral & Enteral Nutrition ASPEN - www.nutritioncare.org
- Society of Critical care Medicine (SCCM)
- European Society of Parenteral & Enteral Nutrition ESPEN - www.espen.org
High dose, parenteral glutamine appears to demonstrate the highest potential benefit

Recommendations for clinical use of glutamine:

- Critical illness
- Surgery- pre- & post-op
- Oncology

No evidence of harm has been observed in studies

0.35- 0.57 g GLN/ kg BW per day for at least 5 days

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ESPEN Guidelines on Parenteral Nutrition: Intensive care

Pierre Singer, Mette M. Berger, Greet Van den Berghe, Gianni Biolo, Philip Calder, Alastair Forbes, Richard Griffiths, Georg Kreyman, Xavier Leverve, Claude Pichard
ESPEN Guidelines: Fish oil

ESPEN Guidelines on Parenteral Nutrition: Intensive care

Pierre Singer, Mette M. Berger, Greet Van den Berghe, Gianni Biolo, Philip Calder, Alastair Forbes, Richard Griffiths, Georg Kreyman, Xavier Leverve, Claude Pichard

ESPEN ICU Guidelines, Clinical Nutrition, Aug 2009
Addition of EPA & DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes.

Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. (B)
Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:
Immune-modulating EN formulas (w/ agents such as glutamine, arginine*, ω-3 fatty acids, AOx, NA) should be used for:

- major elective surgery
- head & neck cancer
- trauma (ATI >20)
- burns (>30% BSA)
- critically ill patients on mechanical ventilation

Surgical ICU patients (A)  Medical ICU patients (B)  *Caution in severe sepsis

ASPEN Guidelines: Fish oil

Surgical ICU patients (A)  Medical ICU patients (B)  *Caution in severe sepsis

ASPEN-SCCM ICU Guidelines, JPEN, May-June 2009
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Surgical ICU patients (A)  Medical ICU patients (B)  *Caution in severe sepsis

Patients with ARDS & severe ALI should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile (ie, ω-3 fish oils, borage oil) and antioxidants. (Grade A)
**Benefits of ω-3 FA in clinical nutrition**

- **Biologic effects of ω-3 FA:** immune-modulating, organ-protective

- **ω-3 FA are incorporated in phospholipid pool of cell membranes and replace the ω-6 FA thereby increasing membrane fluidity and favorably influencing lipid mediator and cytokine production**

*Koch & Heller, Clin Nutr Supp, Jan 2005*
Lipid mediators from $\omega$-6 & $\omega$-3 fatty acids

Bilipid layer

Wendell & Heller. Anti-Cancer Agents in Medicinal Chemistry, 2009, Vol. 9, No. 4
Lipid mediators from ω-6 & ω-3 fatty acids

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Invited Review

Fish Oil Lipid Emulsions and Immune Response: What Clinicians Need to Know

Dan Linetzky Waitzberg, MD, PhD; and Raquel Susana Torrinhas, RB, MSc

- $\omega$-3 PUFA (EPA & DHA) in fish oil can modulate inflammation through its effects on the immune response

- Parenteral infusion of $\omega$-3 PUFAs is advantageous, especially in severely ill patients

- Fish oil lipid emulsion decreases the length of hospital and ICU stay in surgical patients

- Currently available lipid emulsions containing fish oil:
  (1) Only fish oil (Omegaven);
  (2) Fish oil in a balanced fat mixture (SMOF lipid) (soybean oil-- MCT-LCT -- olive oil -- fish oil)
Clinical benefits of fish oils

- Improved ventilation parameters
- Reduced infectious complications
- Better preservation of organ function
- Reduced number of new organ failures
- Shorter ICU stay
- Shorter hospital stay
- Possible mortality benefit
- Potential anti-cancer effects
Key messages from guidelines

- Assess nutrition risk in all surgical/hospital patients
- Initiate EN early (within 24-48hr) to stimulate gut immunity
- Supplement PN early (within 48-72hr) when gut dysfunction prevents reaching targets with EN alone
- Determine requirements accurately; avoid hyperglycemia
- Optimize nutrition strategy by using dual-energy with lipids & glucose in a 3-chamber bag (AIO) over 24 hrs
- Consider pharmaconutrients esp. glutamine, fish oils
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- systematically developed
- to assist practitioners
- making patient care decisions
- in specific clinical circumstances
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There is sufficiently robust evidence to support astute, well-informed clinicians in the rational implementation of clinical nutrition therapy.