NUTRITION and IMMUN SYSTEM

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Nutritional Status

Risk of Mortality

Degenerative diseases

Infection

Kurva J (Bray, 1987)
Infection & Nutrient Status

MALNUTRITION

Impaired Immune function

Acute-phase response

INFECTION

Pathogen

Pathogen
Impact of Infection & Nutrient Status

\[ \downarrow \text{Nutrient intake & absorption} \quad \uparrow \text{Nutrient losses} \]

- anorexia
- malabsorption
- Intestinal damage
- diarrhea

\[ \text{infection} \]

Activation of immune and inflammatory response

- Increase metabolic rate
- Redistribution of nutrient

\[ \uparrow \text{Nutrient requirement} \]
Micronutrients

- Micronutrients are required for an efficient immune response
- **Deficiencies** in one or more of these nutrients diminish immune function.
- **Excessive** intakes of some micronutrients may also impair immune function
Theory of Sepsis

Serial Theory

Stimulus

Pro-inflammatory mediators

SIRS

Normal range of immune homeostasis

CARS

Anti-inflammatory mediators

Theory of Sepsis

Parallel Theory

Stimulus

Pro-inflammatory mediators

SIRS

Normal range of immune homeostasis

CARS

Anti-inflammatory mediators

Immunonutrition


• Immunonutrient = Nutraceuticals = Pharmaconutrients
• Immune-enhancing diet

Definition:

• Nutrition, which can modulate the immune system of critically ill patients
• Several specific substrates with immunological effects have been added, alone or in combination, trying to modify the immune response.
The aim of Immunonutrient

• ↓ morbidity
• ↓ mortality
• ↓ incidence of nosocomial infection
• ↓ LOS
• ↓ treatment fee
Type of immunonutrients

- Arginine
- Glutamine
- Omega-3 FAs
- Nucleotides
- Antioxidant: beta carotene, vitamin C, E, selenium, zinc, cuprum
Arginine
Arginine

- **Semiessential** Amino Acid
- **Conditionally essential AA** nutrients for adult in injured or stressed states.
Metabolic Pathway of Arginine


Body Protein

L-Arginine

L-Citruline + NO

Blood

NO2/NO3

NO

N2OH-L-Arginine

Urea Cycle

L Polyamine

L-Ornithines

Urea Cycle

Carbamoyl phosphatase

L-Proline

L-Glutamate

Kidney

NO3-

URINE

AIR

Lung

NO

Blood

NO
Metabolic Pathway of Arginine during Severe Inflammation / Sepsis


↑ Body Protein
↓ Food
↑ Body Protein

Food
Argino succinate

N^2OH-L-Arginine
L-Citruline
L-Arginine

↑ NOS
↓ NO

Blood
NO2/NO3

NO

Lung
AIR

Kidney
NO3^-

L-Proline
L-Ornithines
L-Polyamine
Carbamoyl phosphatase

Urea Cycle

Plasma [Arginine] ↓
Nitric Oxide (NO)

The role of nitric oxide (NO):

- Vascular relaxation → regulating blood pressure
- Regulates cardiac contractility
- Mediating neurogenic vasodilatation
- Regulating functions of the respiratory, genitourinary and gastrointestinal tracts
- Control platelet aggregation

Nitric Oxide (NO)

During stress & immunologic reaction:

• NO is released in large quantities.
• NO is involved in nonspecific immunity and the patophysiology of septic shock, inflammation and other hyperdynamic states
• The oxide also has cytotoxic effect of macrophages on microbes, parasite and tumors

Arginine Supplementation

• ↑ NO → ↑ microcirculation
• ↑ protein synthesis and ↓ protein breakdown
• Prohibits the increase in pulmonary arterial blood pressure
• Restore the intestinal motility pattern
• ↑ immunocompetence
  – ↑ thymus weight
  – ↑ cell T number
  – ↑ T cell mitogenesis
  – ↑ T cell activity

Arginine supplementation

HARM EFFECTS IN CRITICALLY ILL PATIENTS

- ↑ release of proinflammatory cytokines

May be it will increase systemic inflammation and compromise clinical outcomes in patients who are already experiencing a heightened inflammatory response

Luiking YC, et al, JPEN 2005;29:S70-4
Arginine supplementation

HARM EFFECTS IN CRITICALLY ILL PATIENTS

• ↑ production of NO
  – NO toxic effect:
    • the formation of peroxynitrite may cause tissue damage
    • Inhibition of mitochondrial electron transfer enzymes, which are involved in cell respiration,
    • inhibition of enzymatic substrate use and detoxifying enzymes
    • Inhibition of nuclear DNA synthesizing enzymes.
  – hemodynamic instability with refractory hypotension

Luiking YC, et al, JPEN 2005;29:S70-4
Glutamine
Glutamine

• The most abundant AA in the body and has the highest plasma concentration of all AA ~ ½ free AA pool in skeletal muscle.

• Normal condition: non essential amino acid

• Critically ill: conditionally essential amino acid

Andrew FJ and Griffiths RD, Br J of Nutr; 2002; 87: S3 - 8
Glutamine function

• Source of energy for:
  – Fuel for the cells of the immune system
  – Fuel for GIT system: improved maintenance of gut cellularity and function.

• Providing carbon and nitrogen for precursors of nucleotide synthesis (DNA synthesis)

• Precursor of intracellular glutathione, hepatic glucose, and urinary ammonia

Andrew FJ and Griffiths RD, Br J of Nutr; 2002; 87: S3 - 8
Glutamine – Immune System

Glutamine:
provides nitrogen for synthesis
purine & pyrimidine
⇒
synthesis DNA & RNA
⇒
lymphocyte, macrophage, WBC
Glutamine in Critically Ill

- Plasma glutamine has been shown to be significantly decreased, because:
  - \( \uparrow \) uptake in the kidneys, immune cells and intestinal mucosa
  - \( \downarrow \) skeletal muscle, the main source of glutamine
  - \( \downarrow \) de novo glutamine synthesis may be because reduced availability of intramuscular glutamate as a precursor

Andrew FJ and Griffiths RD, Br J of Nutr; 2002; 87: S3 - 8
Glutamine Supplementation in Critically Ill

• Glutamine may affect the immune system through cytoprotective effects on immune and repair cells.

• Glutamine may affect gut mucosal recovery.
  – ↓ infectious morbidity in patients with critical illness
  – ↓ infection rates (↓ incidence of pneumonia, bacteriemia and sepsis)
  – ↓ bacterial translocation
  – ↓ LOS
  – ↑ survival rate

Andrew FJ and Griffiths RD, Br J of Nutr; 2002; 87: S3 - 8
Glutamine Supplementation

Controversies

• Not all researches indicate benefit of Glutamine supplementation.

• There are no known problems caused by glutamine deficiency in humans.

• There are significant safety issues giving glutamine supplementation in patients with renal or hepatic insufficiency.

• IV glutamine has not been designated generally recognized as safe for human use, by FDA.

Buchman A, ASPEN, 2003
ESPEN Guidelines on Enteral Nutrition: Intensive care

K.G. Kreymann\textsupERS\textsuperscript{a,*}, M.M. Berger\textsupERS\textsuperscript{b}, N.E.P. Deutz\textsupERS\textsuperscript{c}, M. Hiesmayr\textsupERS\textsuperscript{d}, P. Jolliet\textsupERS\textsuperscript{e}, G. Kazandjieva\textsupERS\textsuperscript{f}, G. Nitenbergg, G. van den Berghe\textsupERS\textsuperscript{h}, J. Wernerma,\textsupERS\textsuperscript{i}, DGEM:☆☆ C. Ebner, W. Hartl, C. Heymann, C. Spies

Received 20 January 2006; accepted 20 January 2006

Summary of statements: Intensive care

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recommendations</th>
<th>Grade\textsuperscript{69}</th>
<th>Number</th>
</tr>
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<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>A</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>● trauma patients</td>
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<tr>
<td></td>
<td>There are not sufficient data to support glutamine supplementation in surgical or heterogeneous critically ill patients.</td>
<td>12.2</td>
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Grade: Grade of recommendation; Number: refers to statement number within the text.
Omega 3
### Metabolic conversion of PUFA

<table>
<thead>
<tr>
<th>ω-6 PUFA</th>
<th>ω-3 PUFA</th>
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</thead>
<tbody>
<tr>
<td>Linoleic acid (LA)</td>
<td>α Linoleic acid (ALA)</td>
</tr>
<tr>
<td>-&gt;</td>
<td>Δ-6 desaturase</td>
</tr>
<tr>
<td>γ-linolenic acid (GLA)</td>
<td>Stearidonic acid</td>
</tr>
<tr>
<td>-&gt;</td>
<td>Elongase</td>
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<tr>
<td>Dihomo γ-linolenic acid (DGLA)</td>
<td>Eicosatetraenoic acid</td>
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<td>Δ-5 desaturase</td>
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<td>Arachidonic acid (AA)</td>
<td>Ecosapentaenoic acid (EPA)</td>
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<td>Adrenic acid</td>
<td>Docosapentaenoic acid (DPA)</td>
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<td>Δ-4 desaturase</td>
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<tr>
<td>Docosapentaenoic acid</td>
<td>Docosahexaenoic acid (DHA)</td>
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</table>
IN SEPSIS

**n-6 Family**  
vegetable oils

- LA
- GLA (borage oil)
- DGLA
- PGE1  
  (anti-inflammatory)

**n-3 Family**  
soybean, canola

- ALA
- Stearidonic acid
- Eicosatetraenoic acid
- EPA (fish oil), DHA
  
- TXA3, PGI3  
  (anti-inflammatory)

**Δ-6 desaturase**

**Δ-5 desaturase**

**Cyclooxygenase**

- TXA2, PGI2, PGE2  
  (pro-inflammatory)
Omega - 3

Conflicting result

- Human studies:
  omega 3 inhibit proinflammatory cytokines TNF and IL-1
  (Simopoulos AP, J Am Coll Nutr 2002; 21: 495 – 505)

- Animal studies:
  omega 3 have a stimulatory effect on TNF dan IL-1
Nucleotide
Nucleotide

• Dietary nucleotides are essential for cell mediated immunity and T lymphocyte function


• There is little evident to support the use of dietary RNA supplementation in patients

Conclusion
Systematic review and consensus statement


Immunutrition:

- ↓ infection rate (abdominal abscesses, nosocomial pneumonia and bacteriemia)
- ↓ ICU length of stay
- No effects on mortality

Conclusion:

- The use of diets enriched with pharmaconutrients could be recommended in ICU
- Grade B (fair evidence to support the recommendation)
Immune-modulation formulae (formulae enriched with arginine, nucleotides and ω-3 FAs) are appropriate in most patients

- In patient with a mild sepsis (APACHE II<15) (grade B)
  - ↓ mortality
  - No significance different in LOS
  - ↓ incidence nosocomial infection (bacteriemia)
Immune-modulation formulae (formulae enriched with arginine, nucleotides and ω-3 FAs) are appropriate in most patients

• In patients with severe sepsis, no benefit could be established, in whom an immune modulating formulae may be harmful and are therefore not recommended (grade B)
  – ↑ mortality
ICU patients with very severe illness who do not tolerate more than 700 ml enteral formulae per day should not receive an immune-modulating formula enriched with arginine, nucleotides and ω-3 FAs.

(grade B)