Evidence for immunomodulating supplements in sepsis: A systematic review of the recent evidence

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Potential conflicts

Gordon S. Doig

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

• Arginine in sepsis

• Glutamine in sepsis

• Omega-3 fatty acids in sepsis

• Selenium in sepsis
www.Evidencebased.net

Literature search

- Arginine in sepsis (+ specific critical care terms, in clinical queries)
- Glutamine in sepsis (+ specific critical care terms, in clinical queries)
- Omega-3 fatty acids in sepsis (+ specific critical care terms, in clinical queries)
- Selenium in sepsis (+ specific critical care terms, in clinical queries)

Arginine in sepsis

- Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss of microcirculatory regulation, and enhanced production of superoxide and peroxynitrite.
Arginine in sepsis

• Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss of microcirculatory regulation, and enhanced production of superoxide and peroxynitrite.
Patients were randomised to receive:

1) Arginine enhanced EN (Impact) or 2) standard EN

326 patients were enrolled, only 297 were included in analysis

Mortality:

15.5% (23/147) enhanced EN died vs 7.6% (10/132) standard EN

Using Fisher’s Exact Test, mortality was significantly increased in patients receiving the arginine supplemented EN (P=0.045).

Patients were randomised to receive:

1) Arginine enhanced EN (Perative) or 2) standard PN

Interim analysis conducted after 237 patients enrolled. Subgroup analysis planned for septic patients.

<table>
<thead>
<tr>
<th>Mortality in patients with sevr sepsis</th>
<th>EN (n=18)</th>
<th>PN (n=21)</th>
<th>ARD (95% CI)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>ARD (95% CI)</td>
<td>MH</td>
<td>Fisher test</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>8 (44.4%)</td>
<td>3 (14.3%)</td>
<td>30.1 (1.5-58.7)</td>
<td>0.039</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>8 (44.4%)</td>
<td>5 (23.8%)</td>
<td>20.6 (-9.4-50.6)</td>
<td>0.179</td>
</tr>
</tbody>
</table>
Glutamine in sepsis

- Glutamine levels are reduced during critical illness.
- Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation.
- Other potential benefits include enhanced immune cell function, decreased proinflammatory cytokine production, and higher levels of glutathione and antioxidative capacity.
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Glutamine in sepsis

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Glutamine in sepsis

- Two small trials (33 patients and 55 patients) conducted in septic populations failed to demonstrate mortality benefits.

- Due to excess mortality demonstrated in the most recent large scale trial conducted in critically ill patients, use of glutamine in patients with multiple organ dysfunction syndrome, especially renal dysfunction, is warranted.


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The prostaglandins, leukotrienes, and thromboxanes produced from EPA/GLA are less potent than their arachidonic acid-derived equivalents, reducing the proinflammatory impact on the immune response.

Lipids in sepsis


Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials

Oscar D. Rangel-Huerta, Concepcion M. Aguilera, Maria D. Mesa and Angel Gil

Department of Biochemistry and Molecular Biology Molecular II, Institute of Nutrition and Food Technology, Jose Mataix Biomedical Research Centre, University of Granada, Granada, Spain

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<table>
<thead>
<tr>
<th>Author (Country)</th>
<th>CONSORT Score</th>
<th>Participants/Type of Pathology/Age</th>
<th>RCT Type</th>
<th>Dose/Period</th>
<th>Outcome</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbosa et al. (2010) UK</td>
<td>E</td>
<td>n 23; (Exptl = 10; Control = 13); Sepsis (32–80 years)</td>
<td>Randomised, single-blinded.</td>
<td>6-4 g/d fish oil (Average 1-6 g EPA/day + 0-7 g DHA/ day); 5 days</td>
<td>PGE&lt;sub&gt;2&lt;/sub&gt;, Leukotriene, IL-1β, IL-6, IL-10 and TNF-α.</td>
<td>Inclusion of fish oil in parenteral nutrition of septic ICU patients increases plasma EPA, modifies inflammatory cytokine concentration and improves gas exchange.</td>
</tr>
<tr>
<td>Mayer et al. (2003) Germany</td>
<td>VG</td>
<td>n 10; (Exptl = 5; Control = 5); Septic shock (31–71 years)</td>
<td>Randomised, open label.</td>
<td>EPA = 5-2–11.2 g + DHA = 5.6–12.4 g; 10 days (See note 2)</td>
<td>CRP, Leukocytes.</td>
<td>Omega-3 and omega-6 lipid emulsions differentially influence the plasma free fatty acid profile with impact on neutrophil functions. Use of lipid infusions and intravenous feeding have differential impact on inflammatory events.</td>
</tr>
<tr>
<td>Mayer et al. (2003) Germany</td>
<td>VG</td>
<td>n 21; (Exptl = Control = 6); Sepsis (&gt;18 years)</td>
<td>Randomised, open label.</td>
<td>EPA = 4.55–9.8 g/d + DHA = 4.9–10.9 g/d; 5 days (See note 3)</td>
<td>IL-1β, IL-6, IL-8, IL-10, TNF-α.</td>
<td></td>
</tr>
</tbody>
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- Omega-3 FAs significantly reduced IL-6, increased IL-10 and improved gas exchange.
- No comments on mortality or other patient oriented outcomes.

Effects of enteral feeding with eicosapentaenoic acid, \( \gamma \)-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock*

Alessandro Pontes-Arruda, MD, PhD; Afra Maria Albuquerque Aragão, RD; Juliana Deusdará Albuquerque, RD
A total of 165 patients were recruited.

- 62 patients (37.6% of all enrolled patients) were excluded from analysis due to protocol violations.
- Outcomes are not reported on these 62 patients.

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Although this trial reported a significant reduction in mortality in the 103 ‘evaluable’ patients, due to failure to report outcomes on a large number of patients with protocol violations, confirmation in a subsequent trial was required before clinical recommendations could be made.
Enteral nutrition with eicosapentaenoic acid, ω-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study.


Department of Nutrition and Intensive Care, Fernandes Távora Hospital, Avenida Francisco Sá, 5445, Fortaleza, Ceará, 6030-002, Brazil. pontes-arruda@secatl.com.br
A total of 115 patients were recruited from 5 sites in Brazil.
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- Duration of ventilation was reduced, and ICU free days and hospital free days were increased in study diet patients.
- There was no difference in mortality between groups.

Although these results were interesting, they did not confirm the findings of the 2006 trial. Due to the small size of this trial, clinical recommendations cannot be made. More research is needed.
Selenium in Sepsis

- Selenium could be beneficial in sepsis through reversible inhibition of NF-κB binding to DNA, cytokine production blockade, or apoptosis induction in proinflammatory cells.
- Critically ill patients with systematic inflammatory response syndrome (SIRS) and severe sepsis were found to have 40% lower selenium levels compared to critically ill patients without SIRS or severe sepsis.


Selenium in Sepsis

Fig. 3. Summary of relative risks of all-cause mortality in septic patients between the selenium group and the control group.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Selenium</th>
<th>Placebo</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Zimmermann 1997</td>
<td>3</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>1997</td>
</tr>
<tr>
<td>Angstwurm 1999</td>
<td>7</td>
<td>21</td>
<td>11</td>
<td>21</td>
<td>1999</td>
</tr>
<tr>
<td>Angstwurm 2007</td>
<td>46</td>
<td>116</td>
<td>61</td>
<td>122</td>
<td>2007</td>
</tr>
<tr>
<td>Mishra 2007</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>22</td>
<td>2007</td>
</tr>
<tr>
<td>Forceville 2007</td>
<td>14</td>
<td>31</td>
<td>13</td>
<td>29</td>
<td>2007</td>
</tr>
<tr>
<td>Montoya 2009</td>
<td>6</td>
<td>34</td>
<td>8</td>
<td>34</td>
<td>2009</td>
</tr>
<tr>
<td>Valenta 2011</td>
<td>19</td>
<td>75</td>
<td>24</td>
<td>75</td>
<td>2011</td>
</tr>
<tr>
<td>Manzanares 2011</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>10</td>
<td>2011</td>
</tr>
<tr>
<td>Andrews 2011</td>
<td>30</td>
<td>67</td>
<td>27</td>
<td>65</td>
<td>2011</td>
</tr>
</tbody>
</table>

Figure 4. The effect of selenium versus placebo on mortality (random effects model). M-H = Mantel-Haenszel.
<table>
<thead>
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<th>Study or Subgroup</th>
<th>Selenium</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Zimmermann 1997</td>
<td>3</td>
<td>20</td>
<td>3.8%</td>
</tr>
<tr>
<td>✓ Angstwurm 1999</td>
<td>7</td>
<td>21</td>
<td>5.6%</td>
</tr>
<tr>
<td>✓ Angstwurm 2007</td>
<td>46</td>
<td>116</td>
<td>32.9%</td>
</tr>
<tr>
<td>✓ Mishra 2007</td>
<td>11</td>
<td>18</td>
<td>5.1%</td>
</tr>
<tr>
<td>✓ Forceville 2007</td>
<td>14</td>
<td>31</td>
<td>8.4%</td>
</tr>
<tr>
<td>Montoya 2009</td>
<td>6</td>
<td>34</td>
<td>6.2%</td>
</tr>
<tr>
<td>✓ Valenta 2011</td>
<td>19</td>
<td>75</td>
<td>17.2%</td>
</tr>
<tr>
<td>Manzanares 2011</td>
<td>3</td>
<td>12</td>
<td>2.6%</td>
</tr>
<tr>
<td>Andrews 2011</td>
<td>30</td>
<td>67</td>
<td>18.3%</td>
</tr>
</tbody>
</table>

**Figure 4.** The effect of selenium versus placebo on mortality (random effects model). M-H = Mantel-Haenszel.

The authors of two trials kindly provided us with data on the subgroup of patients with sepsis, which we included in the primary analysis (17, 26).

**Figure 4.** The effect of selenium versus placebo on mortality (random effects model). M-H = Mantel-Haenszel.
### Table 1: Subgroup Data

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Selenium</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Zimmermann 1997</td>
<td>3</td>
<td>8</td>
<td>0.26 [0.06, 1.21]</td>
</tr>
<tr>
<td>Angstwurm 1999</td>
<td>7</td>
<td>11</td>
<td>0.45 [0.13, 1.58]</td>
</tr>
<tr>
<td>Angstwurm 2007</td>
<td>46</td>
<td>61</td>
<td>0.66 [0.39, 1.10]</td>
</tr>
<tr>
<td>Mishra 2007</td>
<td>11</td>
<td>15</td>
<td>0.73 [0.20, 2.70]</td>
</tr>
<tr>
<td>Forceville 2007</td>
<td>14</td>
<td>13</td>
<td>1.01 [0.37, 2.80]</td>
</tr>
<tr>
<td>Montoya 2009</td>
<td>6</td>
<td>8</td>
<td>0.70 [0.21, 2.28]</td>
</tr>
<tr>
<td>Valenta 2011</td>
<td>19</td>
<td>24</td>
<td>0.72 [0.35, 1.47]</td>
</tr>
<tr>
<td>Manzanares 2011</td>
<td>3</td>
<td>4</td>
<td>0.50 [0.08, 3.08]</td>
</tr>
<tr>
<td>Andrews 2011</td>
<td>30</td>
<td>27</td>
<td>1.14 [0.57, 2.27]</td>
</tr>
</tbody>
</table>

### Figure 4

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**Figure 4.** The effect of selenium versus placebo on mortality (random effects model). M-H = Mantel-Haenszel.
Selenium in Sepsis

- Planned to recruit 1,180 patients.
- Recorded as ‘completed’ in June 2013.
- May only have recruited 380 patients?
Selenium in Sepsis

In the mean time:

- Selenium is relatively cheap.
- Sepsis carries a high risk of mortality.
- Although the authors report concerns about the analytic metrics used with the results being very close to 0.05 with Relative Risk and more significant when an Odds Ratio is used, the Odds Ratio is generally more stable and robust.
- > 500 µgm Selenium per day was associated with a significant reduction in mortality.

Summary

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- Glutamine in sepsis
- Omega-3 fatty acids in sepsis
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  - A well conducted meta-analysis of 9 clinical trials including 792 septic patients demonstrates > 500 μgm Selenium per day was associated with a significant reduction in mortality.
  - Read the MA, and individual RCTs, for additional dosing/patient selection details.

Questions?

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