Enteral EPA and DHA in ARDS/ALI

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Acute Lung Injury
The Injured Alveolus

N Engl J Med 2000;342(18):1339, fig 3. Adapted with permission. ©2000 Massachusetts Medical Society. All rights reserved.
The Clinical Course of Uncontrolled Inflammation

- Injury or Illness
- SIRS/Sepsis
- ALI/ARDS
- MODS
- Death

Mechanical Ventilation
Therapies proposed:

6 mL/kg vs 12 mL/kg
Pressure limited < 30-35 cm H2O
NO?
Prone position?
High frequency ventilation?
ECMO?
ARDSnet Mechanical Ventilation Protocol

Results: Mortality

Adapted from Figure 1, page 1306, with permission from The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-1378
N-3 FA in ALI/ARDS

Disease Initiation
(e.g. Sepsis, Burns, Acute Pancreatitis, Haemorrhage, Trauma)

- Epithelial and Endothelial Cells
- Neutrophils
- Monocytes

Cytokines, Chemokines, Adhesion Molecules, Lipid Mediators, Neuropeptides (?), C5a(?)

Reactive Oxygen and Nitrogen Species

- Leukocyte Activation
- Chemotaxis
- Leukocyte Adhesion
- Vascular Instability – Vasodilation and Capillary Leak

Acute Respiratory Distress Syndrome
ARDS/ALI associated with

- Excessive release of toxic oxygen radicals from activated intrapulmonary macrophages and neutrophils
- Excessive release of arachidonic acid-derived inflammatory mediators
Rationale for the use of n-3 Fatty acids and GLA

- Animals fed with n-3 FA diets have activated macrophages reducing proinflammatory eicosanoids
- Use of GLA: suppresses acute and chronic inflammation and reduces the synthesis of proinflammatory mediators
Immunonutrition in critically ill patients
Marik and Zaloga Meta analysis

Fig. 3 Odds ratio (with 95% confidence interval) of the treatment effect (for two or more studies) of the immunomodulating diets on mortality (Arg arginine, A–FO arginine + fish oil, FO fish oil, AFG arginine + fish oil + glutamine, G1 glutamine)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS/ALI</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Sepsis</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Level of study</td>
<td>RDBCT Multi Center</td>
<td>RNBCT Single Center</td>
<td>RDBCT Single Center</td>
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<tr>
<td>Randomized Patients</td>
<td>146</td>
<td>100</td>
<td>165</td>
</tr>
<tr>
<td>Included Patients</td>
<td>98</td>
<td>95</td>
<td>103</td>
</tr>
<tr>
<td>Time of recruitment</td>
<td>15 months</td>
<td>14 months</td>
<td></td>
</tr>
</tbody>
</table>
What do the A.S.P.E.N and SCCM. “Guidelines for the Use of Parenteral and Enteral Nutrition In Adult and Pediatric Patients” * say about the EPA+GLA formula?

Patients with ARDS and severe acute lung injury (ALI) should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile (ie, -3 fish oils, borage oil) and antioxidants. (Grade:A)

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.). JPEN 2009; 33 277
ICU Guidelines Australia and New Zealand

EN supplemented with omega-3 FA and anti-oxidants should be used in patients with ARDS
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

Adult ICU Nutrition Guidelines

ESPEN Guidelines

ESPEN Guidelines on Enteral Nutrition: Intensive care

K.G. Kreymann a,⁎, M.M. Berger b, N.E.P. Deutz c, M. Hiesmayr d, P. Jolliet e, G. Kazandjiev f, C. Nitenberg g, G. van den Berghe h, J. Wernerman i, DGEM: B C. Ebner, W. Hartl, C. Heymann, C. Spies
What do guidelines for nutritional support of mechanically ventilated critically ill adult patients* say about the EPA+GLA formula?

"Recommendation 4.1b
According to 1 level 1 study and 2 level 2 studies, we recommend the use of an enteral formula with fish oils, borage oils, and antioxidants in patients with ARDS."

Short-chain: 2-4 carbons long

Medium-chain: 6-12 carbons long

Long-chain: ≥14 carbons long

Saturated: 0 double bonds in carbon chain

Monounsaturated: 1 double bond in carbon chain

Polyunsaturated: ≥2 double bonds in carbon chain

ω-9: first double bond is 9 carbons from the ω end

ω-6: first double bond is 6 carbons from the ω end

ω-3: first double bond is 3 carbons from the ω end

Oleic acid: ω-9

Linoleic acid: ω-6

α-Linolenic acid: ω-3
The omega-3 family includes α-linolenic acid (18:3 ω-3) and stearidonic acid (18:4 ω-3), which are converted into eicosatetraenoic acid (20:4 ω-3). This is followed by the conversion to eicosapentaenoic acid (EPA, 20:5 ω-3) and docosapentaenoic acid (DPA, 22:5 ω-3), both of which can be converted into docosahexaenoic acid (DHA, 22:6 ω-3). EPA and DHA can be transformed into A/J-Ring Neuroprostane 17S Resolvins and blocks prostanoids.

The omega-6 family includes linoleic acid (18:2 ω-6), which is converted into γ-linolenic acid (GLA, 18:3 ω-6) and dihomoy-linolenic acid (DGLA, 20:3 ω-5). GLA and DGLA can be converted into arachidonic acid (AA, 20:4 ω-6), which is the main substrate for the synthesis of numerous prostanoids and leukotrienes.

The Δ6 desaturase converts linoleic acid to γ-linolenic acid and EPA to DPA. The Δ5 desaturase converts γ-linolenic acid to dihomoy-linolenic acid and DPA to DHA. The Δ4 desaturase converts dihomoy-linolenic acid to arachidonic acid and DHA to docosatetraenoic acid.
<table>
<thead>
<tr>
<th>Lipids</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total calories</td>
<td>55.2</td>
<td>55.2</td>
</tr>
<tr>
<td>g/L</td>
<td>93.4</td>
<td>93.7</td>
</tr>
<tr>
<td>Source</td>
<td>55.8% canola oil 14% corn oil 20% MCT 7% high oleic safflower oil 3.2% soy lecithin</td>
<td>31.8% canola oil 25% MCT 20% borage oil 20% fish oil 3.2% soy lecithin</td>
</tr>
<tr>
<td>Ω6:Ω3</td>
<td>3.8:1</td>
<td>1.85:1</td>
</tr>
<tr>
<td>Ω3 (g/L)</td>
<td>4.7</td>
<td>10</td>
</tr>
<tr>
<td>EPA (g/L)</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td>GLA (g/L)</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td>DHA (g/L)</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>Vitamin E (IU/L)</td>
<td>65</td>
<td>320</td>
</tr>
<tr>
<td>Vitamin C (mg/l)</td>
<td>317</td>
<td>840</td>
</tr>
</tbody>
</table>

No significant differences regarding other vitamins, electrolytes and trace minerals, CHO and protein

ARDS
Rules

- No idea is a bad idea
- Be creative
- Take risks
- No criticism allowed
<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Day</th>
<th>Weighted Differences$^a$</th>
<th>Mean Effect$^b$</th>
<th>Standard Error</th>
<th>LCL</th>
<th>UCL</th>
<th>Z Value$^c$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{FiO}_2 (%O_2)$</td>
<td>Baseline</td>
<td>0.02</td>
<td>0.12</td>
<td>0.12</td>
<td>-0.11</td>
<td>0.35</td>
<td>1.05</td>
<td>.293</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-0.07</td>
<td>-0.39</td>
<td>0.12</td>
<td>-0.63</td>
<td>-0.16</td>
<td>-3.25</td>
<td>.001</td>
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<tr>
<td></td>
<td>7</td>
<td>-0.07</td>
<td>-0.40</td>
<td>0.14</td>
<td>-0.69</td>
<td>-0.11</td>
<td>-2.67</td>
<td>.007</td>
</tr>
<tr>
<td>$\text{PEEP (cm H}_2\text{O)}$</td>
<td>Baseline</td>
<td>0.34</td>
<td>0.06</td>
<td>0.12</td>
<td>-0.17</td>
<td>0.29</td>
<td>0.51</td>
<td>.608</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-0.92</td>
<td>-0.24</td>
<td>0.12</td>
<td>-0.48</td>
<td>0.00</td>
<td>-1.94</td>
<td>.053</td>
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<tr>
<td></td>
<td>7</td>
<td>-1.39</td>
<td>-0.26</td>
<td>0.14</td>
<td>-0.55</td>
<td>0.03</td>
<td>-1.74</td>
<td>.081</td>
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<tr>
<td>$\text{PIP (cm H}_2\text{O)}$</td>
<td>Baseline</td>
<td>-0.68</td>
<td>-0.08</td>
<td>0.12</td>
<td>-0.32</td>
<td>0.14</td>
<td>-0.71</td>
<td>.480</td>
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<tr>
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<td>4</td>
<td>0.23</td>
<td>-0.13</td>
<td>0.12</td>
<td>-0.38</td>
<td>0.11</td>
<td>-1.07</td>
<td>.283</td>
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<td>-1.16</td>
<td>-0.19</td>
<td>0.15</td>
<td>-0.50</td>
<td>0.11</td>
<td>-1.26</td>
<td>.209</td>
</tr>
<tr>
<td>Minute ventilation (L/min)$^2$</td>
<td>Baseline</td>
<td>-0.91</td>
<td>0.04</td>
<td>0.12</td>
<td>-0.19</td>
<td>0.28</td>
<td>0.37</td>
<td>.714</td>
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<td>4</td>
<td>-0.92</td>
<td>0.43</td>
<td>0.13</td>
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<td>0.68</td>
<td>3.33</td>
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<tr>
<td></td>
<td>7</td>
<td>-1.16</td>
<td>-0.14</td>
<td>0.15</td>
<td>-0.44</td>
<td>0.15</td>
<td>-0.97</td>
<td>.334</td>
</tr>
<tr>
<td>$\text{PaO}_2/\text{FiO}_2$</td>
<td>Baseline</td>
<td>-14.62</td>
<td>-0.23</td>
<td>0.12</td>
<td>-0.46</td>
<td>0.00</td>
<td>-1.97</td>
<td>.049</td>
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<tr>
<td></td>
<td>4</td>
<td>70.61</td>
<td>1.49</td>
<td>0.14</td>
<td>1.21</td>
<td>1.78</td>
<td>10.33</td>
<td>&lt;.0001</td>
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<td>7</td>
<td>54.88</td>
<td>0.98</td>
<td>0.17</td>
<td>0.65</td>
<td>1.31</td>
<td>5.87</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>Baseline</td>
<td>-10.89</td>
<td>-0.09</td>
<td>0.12</td>
<td>-0.32</td>
<td>0.14</td>
<td>-0.72</td>
<td>.469</td>
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<tr>
<td></td>
<td>4</td>
<td>31.13</td>
<td>0.44</td>
<td>0.12</td>
<td>0.20</td>
<td>0.69</td>
<td>3.54</td>
<td>&lt;.0001</td>
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<tr>
<td></td>
<td>7</td>
<td>55.37</td>
<td>0.61</td>
<td>0.16</td>
<td>0.31</td>
<td>0.92</td>
<td>3.92</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

LCL, lower confidence limit; UCL, upper confidence limit; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

$^a$Weighted mean differences (EPA + GLA + antioxidant weighted raw mean - Control weighted raw mean).

$^b$Expressed as standardized mean difference using fixed-effects model.

$^c$Test for overall effect (Z test).
Edema – generalized
Disturbances of gas diffusion
Permeability of the lung measured by Lung/Heart radioactivity ratio in rats.
CCM 1997
Effects of select fatty acids on cardiopulmonary dysfunction in acute lung injury in pigs

Pulmonary vascular resistance and arterial PO2 (PaO2) before and after endotoxin infusion in pigs fed enteral diets contain linoleic acid■, EPA●, or EPA + GLA▲ for 8 days.

Effects of select fatty acids on cardiopulmonary dysfunction in acute lung injury in pigs

Pulmonary vascular resistance and arterial PO2 (PaO2) before and after endotoxin infusion in pigs fed enteral diets contain linoleic acid ■, EPA ●, or EPA + GLA ▲ for 8 days.

Fig. 3. Similarities in $\text{PaO}_2/\text{FiO}_2$ among several prospective, randomized, double-blinded, control studies of an enteral feeding containing eicosapentaenoic acid (EPA) and $\gamma$-linolenic acid (GLA) (solid bar) or a isocaloric, isonitrogenous standard formula (open bar). Data represent means ± SEM. (Data from: Refs. [47,49,51,53].)
The Injured Alveolus

The Injured Alveolus during the Acute Phase

- Protein-rich edema fluid
- Activated neutrophil
- Leukotrienes
- Proteases
- Cellular debris
- IL-6, IL-10
- TNF-α, IL-1
- Alveolar macrophage
- Swollen, injured interstitium

Normal Alveolus

- Alveolar air space
- Type I cell
- Epithelial basement membrane
- Interstitium
- Type II cell
- Alveolar macrophage
- Surfactant layer

N Engl J Med 2000;342(18):1339, fig 3. Adapted with permission. ©2000 Massachusetts Medical Society. All rights reserved.
P Cotogni et al
JPEN 2010 in press

- Alveolar cells A549 FA composition according to lipid exposure
- Effects of LPS challenge on TNF alpha, IL1, IL 6 and IL 10
Table 1. Percentage content of fatty acids in phospholipids of A549 cell membranes

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Baseline</th>
<th>Control</th>
<th>DHA/AA 1:1</th>
<th>DHA/AA 1:2</th>
<th>DHA/AA 1:4</th>
<th>DHA/AA 1:7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C14:0</td>
<td>3.7</td>
<td>7.2</td>
<td>7</td>
<td>6.9</td>
<td>7.4</td>
<td>7.5</td>
</tr>
<tr>
<td>C16:0</td>
<td>31.9</td>
<td>56.5</td>
<td>51.2</td>
<td>52</td>
<td>58.2</td>
<td>59.7</td>
</tr>
<tr>
<td>C16:1</td>
<td>9.6</td>
<td>1.8</td>
<td>1.6</td>
<td>1.9</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>C18:0</td>
<td>16.8</td>
<td>26.6</td>
<td>17.2</td>
<td>18.1</td>
<td>15.2</td>
<td>14.2</td>
</tr>
<tr>
<td>C18:1</td>
<td>27.3</td>
<td>4.3</td>
<td>3.5</td>
<td>3.9</td>
<td>4.8</td>
<td>5</td>
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<tr>
<td>C18:2</td>
<td>2.8</td>
<td>0.5</td>
<td>0.6</td>
<td>0.8</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>C20:4 (AA)</td>
<td>6.2\footnote{5}</td>
<td>0.9\footnote{5}</td>
<td>2.2\footnote{5}</td>
<td>3.5\footnote{5}</td>
<td>4.5\footnote{5}</td>
<td>4.9\footnote{5}</td>
</tr>
<tr>
<td>C22:6 (DHA)</td>
<td>1.7</td>
<td>2.2</td>
<td>16.7*</td>
<td>12.9*</td>
<td>6.3*</td>
<td>4.7*</td>
</tr>
<tr>
<td>ω-3/ω-6 PUFA ratio</td>
<td>1:5</td>
<td>1.6:1</td>
<td>6:1*</td>
<td>3:1*</td>
<td>1:1</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>
Use of eicosapentaenoic acid (EPA) and gamma linolenic acid (GLA) enriched diet in H1N1 influenza A virus-associated acute lung injury: a retrospective study.
ECMO as a referral center
H1N1 associated ARDS: effect of EPA, GLA and antioxidants

8 patients with study diet and 6 with control

<table>
<thead>
<tr>
<th></th>
<th>Study group n= 8</th>
<th>Control Group n= 6</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>26.5</td>
<td>21</td>
<td>0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>4/4</td>
<td>3/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>42 +/- 14</td>
<td>51 +/- 14</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>5M/3F</td>
<td>3M/3F</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>142 ± 92</td>
<td>119 ± 89</td>
<td>NS</td>
</tr>
</tbody>
</table>
PaO2/FIO2 during the first week

- DAY 1: Study = X, Control = X
- DAY 4: Study = X, Control = X
- DAY 7: Study = X, Control = X

* denotes significance.
Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers and clinical outcomes in septic patients: a RC clinical trial VL Barbosa, et al Crit Care 2010

Table 1
Characteristics of the patients in the two treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Fish oil group (n=13)</th>
<th>MCT/LCT group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>54 to 80</td>
<td>32 to 79</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70 ± 2*</td>
<td>57 ± 5</td>
</tr>
<tr>
<td>Sex: male/female (n)</td>
<td>5/8</td>
<td>4/6</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.59 ± 0.1</td>
<td>1.63 ± 0.06</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.3 ± 18.01</td>
<td>76.8 ± 21.28</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9 ± 1.7</td>
<td>28.5 ± 2.6</td>
</tr>
<tr>
<td>Admitted from:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating theatre</td>
<td>9/3/1</td>
<td>6/3/1</td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td>47.5 ± 5</td>
<td>41.6 ± 6.5</td>
</tr>
<tr>
<td>Sequential organ failure assessment score</td>
<td>9.5 ± 0.9</td>
<td>8.9 ± 1.2</td>
</tr>
<tr>
<td>Primary diagnosis:</td>
<td>8/4/1</td>
<td>5/2/3</td>
</tr>
<tr>
<td>Sepsis/Severe sepsis/Septic shock</td>
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<td></td>
</tr>
<tr>
<td>Secondary Diagnosis:</td>
<td>9/1/1/2/0/0</td>
<td>7/0/2/2/2/1</td>
</tr>
<tr>
<td>Cardiovascular/Respiratory/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal/Gastric/Mental/Metabolic (n)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are shown for patients who received parenteral nutrition (n=23)

SAPS - Simplified Acute Physiology Score

*p = 0.019 vs. MCT/LCT
Table 3
Plasma cytokine and eicosanoid concentrations in the two treatment groups at day 1 (pg/ml) and the differences in concentrations between days 6 and 1 (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>Fish oil group</th>
<th>MCT/LCT group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 6 – Day 1</td>
</tr>
<tr>
<td>IL-1β</td>
<td>5.0 ± 3.2</td>
<td>-3.8 ± 3.0*</td>
</tr>
<tr>
<td>IL-6</td>
<td>8181 ± 5723</td>
<td>-4950 ± 6690*</td>
</tr>
<tr>
<td>IL-10</td>
<td>44 ± 8</td>
<td>-29 ± 8*</td>
</tr>
<tr>
<td>TNF-α</td>
<td>18.0 ± 3.1</td>
<td>-8.1 ± 3.6*</td>
</tr>
<tr>
<td>PGE₂</td>
<td>267 ± 126</td>
<td>391 ± 393</td>
</tr>
<tr>
<td>LTB₄</td>
<td>338 ± 88</td>
<td>111 ± 147</td>
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</tbody>
</table>

*P < 0.001 vs MCT/LCT group after adjusting for Day 1 value, or for Day 1 value, age and glucose supply, or for Day 1 value, age, glucose supply and SAPS II at entry.
<table>
<thead>
<tr>
<th></th>
<th>Fish oil group</th>
<th>MCT/LCT group</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Admission</td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>pH</td>
<td>7.27 ± 0.15</td>
<td>7.38 ± 0.11</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.2 ± 1.8</td>
<td>4.0 ± 1.7</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>198 ± 121</td>
<td>138 ± 45</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>78 ± 125</td>
<td>39 ± 7</td>
</tr>
<tr>
<td>PO₂/FiO₂</td>
<td>269 ± 125</td>
<td>248 ± 81</td>
</tr>
</tbody>
</table>

PO₂, Partial pressure of oxygen; PCO₂, Partial pressure of carbon dioxide; FiO₂, Fraction of inspired oxygen.

*p = 0.033 vs. MCT/LCT group at the same timepoint (Student’s t-test with equal variances not assumed; p = 0.016 after adjusting for age and glucose supply; p = 0.027 after adjusting for age, glucose supply and SAPS II at entry);

**p = 0.047 vs. MCT/LCT group at the same timepoint (Student’s t-test with equal variances not assumed; p = NS after adjusting for age and glucose supply or for age, glucose supply and SAPS II at entry).
MORE VENTILATOR-FREE DAYS

\[ p < 0.0001 \]
Loss of muscle mass in ICU patients

Daily UL measurement of upper arm, forearm and thigh for a median of 7 days (N=50).
Admission APACHE II score: 17. Mortality: 28%
Reid et al. 2004; Clin Nutr 23: 273-280
Muscle thickness decreased by an average of 1.6% per day

With 6 kg metabolizable protein in lean body mass:
≈ 100g/day

After 10 days: 16% muscle loss
≈ 1000 g protein ≈ 5 kg lean body mass

REE in 24 patients:
10 patients in positive energy balance: 1.1 % per day
14 patients in negative energy balance: 1.3 % per day
Effect of EPA on muscle
ENTERAL NUTRITION ENRICHED WITH EPA PRESERVES LEAN BODY MASS FOLLOWING EOSOPHAGEAL CANCER SURGERY: RESULTS OF A DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

RYAN ET AL ANN SURG 2009; 249:355-63
IL-10

Median interleukin-10 (pg/ml)

Day

Pre 1 3 7 14 21

IL-8

Median interleukin-8 (pg/ml)

Day

Pre 1 3 7 14 21

TNF-α

Median tumour necrosis factor alpha (pg/ml)

Day

Pre 1 3 7 14 21

Standard Feed

EPA Enriched
Eicosapentaenoic acid preserves diaphragm force generation following endotoxin administration

Critical Care 2010, 14:R35  doi:10.1186/cc8913

Gerald S Supinski (gsupi2@email.uky.edu)
Jonas Vanags (jvanags@students.mcg.edu)
Leigh Ann Callahan (lacall2@email.uky.edu)
Study Design:
- Multicenter
- Prospective
- Randomized
- Double blind
- Placebo controlled

146 adults with ARDS, confirmed by BAL and X-Ray
**EPA+GLA Study Design**

**Baseline**
- Consent obtained
- Randomized
- Double blinded
- BAL
- Feeding tube
- Caloric goal
- Gas exchange (PaO₂/FiO₂)
- Initiate feeding (75% BEE x 1.33)

**Study Day 4**
- BAL
- Gas exchange
- Routine labs
- Clinical outcomes
- EPA+GLA or Control Diet

**Study Day 7**
- BAL
- Protein
- Neutrophil Count
- Inflammatory Mediators
- Ventilator Parameters

ALI / ARDS
P/F = 100-250

Bronchoalveolar Lavage Ceruloplasmin

-25 -20 -15 -10 -5 0 5 10 15 20
Change in BAL Ceruloplasmin (µg/ml) from Baseline

Study Day 4 - Baseline    Study Day 7 - Baseline

Control    Oxepa®

(P = 0.03)

(Pacht et al: Crit Care Med 2003;31:491-500.)
Bronchoalveolar Lavage

IL-8

Change in BALF IL-8 (pg/ml) from Baseline

Study Day 4 - Baseline       Study Day 7 - Baseline

(Pacht et al: Crit Care Med 2003;31:491-500.)
The diagram illustrates the metabolism of fatty acids into eicosanoids.

**n-6 series**
- **18:2** (LA) can undergo **Δ6 desaturation** to form **18:3**.
- **18:3** can be elongated to form **20:3**.
- **20:3** can undergo **Δ5 desaturation** to form **20:4** (AA).
- **20:4** (AA) can be elongated to form **22:4**.
- **22:4** can be elongated to form **24:4**.
- **24:4** can undergo **Δ6 desaturation** to form **24:5**.
- **24:5** can undergo partial β-oxidation to form **22:5** (DPA).

**n-3 series**
- **18:3** (LNA) can undergo **Δ6 desaturation** to form **18:4**.
- **18:4** can be elongated to form **20:4** (EPA).
- **20:4** (EPA) can be elongated to form **22:5**.
- **22:5** can be elongated to form **24:5**.
- **24:5** can undergo **Δ6 desaturation** to form **24:6**.

- **Series 2 eicosanoids (i.e., PGE₂)**
- **Series 4 leukotrienes (i.e., LTB₄)**
- **Series 3 eicosanoids (i.e., PGE₃)**
- **Series 5 leukotrienes (i.e., LTB₅)**

The metabolic pathways are catalyzed by enzymes such as COX (cyclooxygenase) and LOX (lipoxygenase).
Jing X Kang, MD, PhD
Harvard Medical School and Mass. General Hospital

n-6 FA: \[\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH} = \text{CH}\ldots -\text{COOH}\]

\[\downarrow n-3\text{ desaturase}\]

n-3 FA: \[\text{CH}_3\text{-CH}_2\text{-CH} = \text{CH}\text{-CH}_2\text{-CH} = \text{CH}\ldots -\text{COOH}\]
Green Fluorescent Protein

Transgenic cells (in vitro)

Transgenic animals (in vivo)

fat-1

Shuttle vector

Adenoviral plasmid

pAd-Track-CMV

pAdEasy-1

pAd-YFG
Omega 6
Omega 3
<table>
<thead>
<tr>
<th>Mol % of total Fatty acids</th>
<th>Control</th>
<th>Fat-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-6 Polyunsaturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:2n-6</td>
<td>14.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20:2n-6</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20:3n-6</td>
<td>1.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>20:4n-6</td>
<td>15.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>22:4n-6</td>
<td>4.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>22:5n-6</td>
<td>0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total</td>
<td>36.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>n-3 Polyunsaturates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:3n-3</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>20:4n-3</td>
<td>0.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>20:5n-3</td>
<td>0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>22:5n-3</td>
<td>1.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>22:6n-3</td>
<td>1.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Total</td>
<td>2.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>n-6/n-3 Ratio</td>
<td>14.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.8&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>
Free FA Content

Arachidonic Acid

EPA

DHA
Improvement in BAL

Leukocytes

Protein

Compliance
### Study name

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
<th>Relative weight</th>
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<tbody>
<tr>
<td>Pontes-Arruda et al, 2006</td>
<td>0.143 0.058 0.353 -4.213 0.0000</td>
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<tr>
<td>Gadek et al, 1999</td>
<td>0.223 0.067 0.742 -2.445 0.0145</td>
<td>36.15</td>
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<tr>
<td>Fixed effects</td>
<td>0.167 0.081 0.345 -4.837 0.0000</td>
<td></td>
<td></td>
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</tbody>
</table>

83% LESS ORGAN FAILURES

p < 0.0001

MORE ICU-FREE DAYS

p < 0.0001

---

### More ICU-Free Days

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Relative weight</th>
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<tbody>
<tr>
<td>Pontes-Arruda et al, 2006</td>
<td>0.845</td>
<td>0.206</td>
<td>0.042</td>
<td>0.441</td>
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<td>4.100</td>
<td>0.0000</td>
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<tr>
<td>Singer et al, 2006</td>
<td>0.19</td>
<td>0.206</td>
<td>0.042</td>
<td>-0.206</td>
<td>0.601</td>
<td>0.960</td>
<td>0.3368</td>
<td>33.29</td>
</tr>
<tr>
<td>Gadek et al, 1999</td>
<td>0.482</td>
<td>0.205</td>
<td>0.042</td>
<td>0.080</td>
<td>0.884</td>
<td>2.349</td>
<td>0.0188</td>
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<tr>
<td>Fixed effects</td>
<td>0.508</td>
<td>0.119</td>
<td>0.014</td>
<td>0.275</td>
<td>0.740</td>
<td>4.276</td>
<td>0.0000</td>
<td>33.52</td>
</tr>
</tbody>
</table>

---

Macrophage Cell

Inflammatory Insult

Lung- and other critical organs

EPA → AA

Cell Membrane

Amplifying Loop

Cytokines
IL-8
TNF-α

NFκB
IκB

Nucleus
mRNA
DNA

NFκB Binding

© bo 1/9/03
Chronic Inflammation

Classic Leukotrienes
Prostaglandins

Pro-inflammatory Mediators

Resolution

Resolvins [Rv]
Protectins [PD]
Lipoxins [LX]
Aspirin-triggered Lipoxins [ATL]

Pro-Resolution Programs "New Terrain"

Resolution of Acute Inflammation

Host Defense

Injury/trauma
Microbial infection
Chemical stimuli

Acute Inflammation

Neutrophil

Pro-inflammatory Mediators

Resolvins [Rv]
Protectins [PD]
Lipoxins [LX]
Aspirin-triggered Lipoxins [ATL]

Resolution

Pro-Resolution Programs "New Terrain"
“... in addition to serving as agonists to stop and reduce neutrophil infiltration to inflamed tissues, pro-resolution molecules promote the uptake and clearance of apoptotic cells and microorganisms by macrophages in inflamed sites”
Resolvins

**EPA: E series**

**E1:**
- reduces inflammation
- increased when taking aspirin and/or EPA

**E2:**
- reduces neutrophil infiltration

**DHA: D series**

**17R:**
- produced in the presence of aspirin: aspirin-triggered resolvin D1

**17S:**
- resolvins D1-D4

17R and 17S resolvins control inflammation resolution, including in neural tissue
Chemokines, Chemokine Receptors, and macrophages in Inflammation
Heart rate variability and fatty acid content of blood cell membranes: a dose response study with n-3 fatty acids

Christensen JH et al, Am J Clin Nutr 1999; 70:331
IV fish oil blunting response to endotoxin in healthy volunteers
Pluess et al ICM 2007; 33:789

2 groups of 8 volunteers randomized
2 doses of FO (.5 g/kg) 48 and 24 h before LPS.
EPA DHA in platelets were increased after FO.
Fever was lower in FO
FO: lower plasma NE, ACTH and cortisol
TNF was lower
FO: increased temperature is blunted
epinephrine: no significant difference FO vs. control
norepinephrine: * = p<0.05 FO vs. control

- ▲ FO + LPS
- △ FO + placebo
- ● control + LPS
- ○ control + placebo

\[ p = 0.08 \]
ACTH and Cortisol
epinephrine: no significant difference FO vs. control
norepinephrine: * = p<0.05 FO vs. control
- FO + LPS
- FO + placebo
- control + LPS
- control + placebo

p=0.08

(B)
Effect of an enteral nutrition enriched in EPA and GLA and antioxidants on the outcome of mechanically ventilated septic critically ill Patients.

Grau et al CCM 2009 abstract
Outcome

- No change in PaO₂/FIO₂
- No change in ICU mortality
- No change in organ failure or total infection rate
- Decrease in LOS in the ICU from 18 to 16 days \((p<0.02)\)
- Decrease in pneumonia rate from 56 to 30 \((p<0.07)\)
- Control diet (Ensure HN) is different from the previous studies (Pulmocare), APACH E 19, mortality 16% for ARDS SOFA 9
ARDS Network study

- PRCT administrating EPA, GLA and antioxidants as supplements in a bolus way during continuous enteral feeding
- Stopped after including 300 patients
- Inconclusive, futile?
- Appeared not to influence the membrane composition!!! No absorption
Brainstorming Activity

1. Generate ideas
2. Use games and exercises to "warm up" your creative thinking
3. When ideas slow down, try another exercise to generate fresh ideas
4. Breaking into smaller groups may be helpful

- Use a computer to capture every comment/idea (in Microsoft PowerPoint, of course, using Meeting Minder)

---

**Dihomo-Gamma Linolenic Acid**

- **Control**
- **EPA+GLA**

* p<.001

**Eicosapentaenoic Acid**

- **Control**
- **EPA+GLA**

* p<.001

**Eicosapentaenoic/Arachidonic**

- **Control**
- **EPA+GLA**

* p<.001

---

*Figure 4: Mean ± SE plasma phospholipid fatty acid levels of dihomo-ω-3 linolenic acid, eicosapentaenoic acid, and eicosapentaenoic/ω-6 arachidonic acid during a 7-day study period.*
Ubiquitous effect
Improves oxygenation
Decrease in LOV and LOS
Reversal of protein catabolism
Improves resolution of the inflammation
Modulates Cytokine response
Improves resolution of the inflammation
Effect on CNS
N-3 FA in the ICU: the conclusions

- Recommended in ARDS/ALI (level A)
- Modulates response to stress
- More investigations in sepsis
<*)\)))-{ + GLA
Thank you
Immunomodulation by n-6 versus n-3 -rich lipid emulsions in murine acute lung injury: role of PAF receptor
Schaeffer B et al. CCM 2007; 35:544

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>SO</th>
<th>FO</th>
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<tbody>
<tr>
<td>C14:0</td>
<td></td>
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<td>C16:0</td>
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<td>8.2</td>
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<tr>
<td>C18:0</td>
<td>5.0</td>
<td>2.4</td>
</tr>
<tr>
<td>C18:1n-9</td>
<td>24.1</td>
<td>12.3</td>
</tr>
<tr>
<td>C18:2n-6</td>
<td>52.2</td>
<td>3.7</td>
</tr>
<tr>
<td>C18:3n-3</td>
<td>8.2</td>
<td>1.3</td>
</tr>
<tr>
<td>C20:4n-6</td>
<td></td>
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</tr>
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<tr>
<td>C22:6n-3</td>
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<td>16.5</td>
</tr>
<tr>
<td>Others</td>
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</table>

The SO-based emulsion (Lipoven) and the FO-based lipid emulsion (Omegaven) were manufactured with identical techniques and additives. Repetitive gas chromatographic controls of
Wild mice, PAF (−/−) and PAF treated
Macrophage inflammatory proteins in BAL

- Wild
- PAF (-/-)
Alveolar TNF alpha