OMEGA 3 & SEPSIS SYNDROM

Prävention und Therapie
Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (and often more), and increasing in incidence.
Biphasic Cytokine Response in Sepsis

Omega 3 & Sepsis Syndrom: Prävention

> Allgemein Chirurgie
Effects of a Metabolic Optimized Fast Track Concept (MOFA)

- **Pre-OP day**
  - 10g FO within 1hr
  - Provide Extra Drink 200ml
  - 500 ml HES 130

- **OP day**
  - Provide Extra Drink 200ml
  - 500 ml HES 130
  - for 48 h: 0,2 g FO/kg/d
  - Thoracic epidural catheter (both groups)
  - Tight glucose control

BfArM Gesch Z: 61-3910-4031476  EUDraCT Nr: 2005-004814-33

Heller A, Infection 2011 Suppl.2 Abstract
Effects of a Metabolic Optimized Fast Track Concept (MOFA)

Inflammation

- **Colon**
  - WBC [Gpt/l] (±95%CI)
  - Control: $P=0.024$ GLM
  - MOFA: $R^2$ Cubic $=0.361$

- **Liver**
  - IL-6/IL-10 Ratio (±95%CI)
  - Control: $P=0.028$ GLM
  - MOFA: $R^2$ Cubic $=0.265$
Effects of a Metabolic Optimized Fast Track Concept (MOFA)

Severity of Illness SAPS II
Methods:
The patients (n = 63) received pre-operative peripheral infusion (0.2 g fat/kg body weight/d) of FOLE (Omegaven®) or control lipid emulsion (MCT/LCT; Lipovenos MCT®) for 3 days. Post-operative concentrations of inflammatory mediators, leukocyte functions, surface molecules, infections, and length of intensive care unit (ICU) and hospital stay were measured.
Conclusion:

Short-term pre-operative infusion of FO alone improves the post-operative immune response of gastrointestinal cancer patients without significantly changing post-operative infections or length of ICU and hospital stay.

Elderly and/or malnourished patients receiving MCT/LCT had a significant higher variation in the length of ICU stay than those receiving FO (15.76 vs. 2.42 for FO patients, p = 0.016),
Omega 3 & Sepsis Syndrom: Prävention

> Herz Chirurgie
Methods:
Thirty-two infants (40 ± 2.3 weeks gestational age; 10.6 days at time of surgery) undergoing open-heart surgery with cardiopulmonary bypass were randomized to receive an intravenous lipid emulsion with (treatment) or without (control) eicosapentaenoic and docosahexaenoic acid in this prospective, randomized, double-blind, controlled trial.
**Conclusion:**

Infants who received an intravenous lipid emulsion containing EPA, DHA and MCT before and after open-heart surgery had reduced plasma TNF-α concentrations compared to infants who received a standard soybean oil lipid emulsion.

In general there was a reduction in inflammatory cytokines with variable effects on anti-inflammatory cytokines.
Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial\textsuperscript{1-3}

Mette M Berger, Frederik Delodder, Lucas Liaudet, Piergiorgio Tozzi, Juerg Schlaepfer, Rene L Chiolero, and Luc Tappy

**Design:**
A prospective randomized controlled trial was conducted in cardiac surgery patients who received 3 infusions of 0.2 g/kg FO emulsion or saline (control) 12 and 2 h before and immediately after surgery. Blood samples (7 time points) and an atrial biopsy (during surgery) were obtained to assess the membrane incorporation of PUFAs.

Conclusions:

Perioperative FO infusions significantly increased PUFA concentrations in platelet and atrial tissue membranes within 12 h of the first FO administration and decreased biological and clinical signs of inflammation.

These results suggest that perioperative FO may be beneficial in elective cardiac surgery with CPB.
Omega 3 & Sepsis Syndrom: Therapie

>> enterales Omega 3
Enteral nutrition with eicosapentaenoic acid, γ-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT Study

Graph showing the development of individual system failures.
Kaplan-Meier survival curves graphed for 28-day all-cause mortality.

Pontes-Arruda et al. Critical Care 2011, 15:R144
Enteral Omega-3 Fatty Acid, $\gamma$-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

**Context**  The omega-3 (n-3) fatty acids docosahexaenoic acid and eicosapentaenoic acid, along with $\gamma$-linolenic acid and antioxidants, may modulate systemic inflammatory response and improve oxygenation and outcomes in patients with acute lung injury.

**Objective**  To determine if dietary supplementation of these substances to patients with acute lung injury would increase ventilator-free days to study day 28.

**Design, Setting, and Participants**  The OMEGA study, a randomized, double-blind, placebo-controlled, multicenter trial conducted from January 2, 2008, through February 21, 2009. Participants were 272 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. All participants had complete follow-up.

**Interventions**  Twice-daily enteral supplementation of n-3 fatty acids, $\gamma$-linolenic acid, and antioxidants compared with an isocaloric control. Enteral nutrition, directed by a protocol, was delivered separately from the study supplement.

**Main Outcome Measure**  Ventilator-free days to study day 28.
Proportion curves of 60-day hospital survival and unassisted breathing

CONCLUSIONS

This study suggests that twice-daily enteral supplementation of n-3 fatty acids, GLA, and antioxidants change plasma levels of n-3 fatty acids but do not improve clinical outcomes or biomarkers of systemic inflammation in patients with ALI and in fact may be harmful.

Rice TW, JAMA (2011): 1574-1581
Omega 3 & Sepsis Syndrom: Therapie

>> parenterale Omega 3
Setting:
Twelve-bed medical ICU of a university hospital.

Patients:
A total of 166 consecutive patients anticipated to need parenteral nutrition for more than 6 days. Patients were stratified for the presence of systemic inflammatory response syndrome (SIRS) at baseline (115 SIRS, 51 non-SIRS).

Conclusion
In comparison to standard parenteral nutrition with MCT/LCT lipids, supplementation with fish oil to modify the n-3/n-6 PUFA ratio to 1:2 did not change parameters of inflammation or clinical outcome in unselected critically ill medical patients.

Comment:

This study was planned to detect a faster reduction in biomarkers modeled after the time course in postoperative patients; however, the authors failed to prove a significant reduction in both groups.

A possible explanation may be that they started to use the lipid emulsions after the initial inflammatory process was already terminated.
Adding Fish Oil to IV May Speed Sepsis Recovery
Jan. 20

By Robert Preidt

HealthDay

TUESDAY, Jan. 19 (HealthDay News) -- Adding fish oil to intravenous solutions proved beneficial for intensive care patients with the potentially lethal blood infection known as sepsis, a new study finds.

The study, published Jan. 19 in the journal Critical Care, compared 13 patients who received fish oil in the normal IV nutrient solution given to patients with sepsis, and 10 patients who received traditional solutions. The patients who received the fish oil had lower levels of inflammatory chemicals in their blood, achieved better lung function, and had a shorter hospital stay.

"This is the first study of this particular fish oil solution in septic patients in the ICU. The positive results are important since they indicate that the use of such an emulsion in this group of patients will improve clinical outcomes, in comparison with the standard mix," researcher Philip Calder, of the University of Southampton in England, said in a news release.
Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial

Methods: Twenty-five consecutive patients diagnosed with a septic syndrome and predicted to require parenteral nutrition were randomly assigned to receive either a MCT/LCT lipid emulsion or 50%MCT/40%LCT/10% fish oil lipid emulsion from days 2 to 5 after admission to ICU.

<table>
<thead>
<tr>
<th>Gas Exchange</th>
<th>Fish Oil group</th>
<th>MCT/LCT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio PaO2/FiO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>2.69 ± 1.25</td>
<td>2.62 ± 1.32</td>
</tr>
<tr>
<td>Day 1</td>
<td>2.48 ± 0.81</td>
<td>2.52 ± 1.25</td>
</tr>
<tr>
<td>Day 2</td>
<td>2.53 ± 1.02</td>
<td>2.99 ± 0.8</td>
</tr>
</tbody>
</table>
| Day 6        | 3.31 ± 0.71    | 2.45 ± 1.07   | \( p = 0.04 \)
Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial

Methods: Twenty-five consecutive patients diagnosed with a septic syndrome and predicted to require parenteral nutrition were randomly assigned to receive either a MCT/LCT lipid emulsion or 50%MCT/40%LCT/10% fish oil lipid emulsion from days 2 to 5 after admission to ICU.

Results: Length of Hospital Stay

<table>
<thead>
<tr>
<th></th>
<th>Length of Stay</th>
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<tbody>
<tr>
<td>MCT / LCT</td>
<td>55 ± 16 days</td>
</tr>
</tbody>
</table>
| 50% MCT / 40% LCT / 10% Fish Oil | 22 ± 7 days   | p = 0.05

Barbosa VM et al, Critical Care (2010) 14: R5
Methods:
Forty severe acute pancreatitis / parenteral nutrition for 5 days in a double-blind manner. PN with identical amounts of amino acids (1.25 g/kg/d), glucose (3 g/kg/d), and fat (1 g/kg/d) but different lipid compositions: the control group received a soybean oil emulsion and the ω-3 FA group was supplemented with 0.15 - 0.2 g/kg/d fish oil.

Conclusion
PN supplemented with ω-3 FAs diminishes the hyperinflammatory response by the EPA increase and the proinflammatory cytokine decrease in severe acute pancreatitis. This, together with improved respiratory function and shortened CRRT time, suggests that the systemic response to pancreatic and organ injury is attenuated.


<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>ω-3 Fatty Acids Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS ratio</td>
<td>9/20</td>
<td>4/20</td>
</tr>
<tr>
<td>ARDS ratio</td>
<td>5/20</td>
<td>4/20</td>
</tr>
<tr>
<td>Infectious complication, n</td>
<td>5/20</td>
<td>3/20</td>
</tr>
<tr>
<td>Renal dysfunction, n</td>
<td>2/20</td>
<td>1/20</td>
</tr>
<tr>
<td>CRRT days</td>
<td>26 ± 3.4</td>
<td>18 ± 2.3¹β</td>
</tr>
<tr>
<td>ICU days</td>
<td>27.5 ± 5.6</td>
<td>21.4 ± 4.2</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>70.5 ± 9.1</td>
<td>65.2 ± 7.3</td>
</tr>
</tbody>
</table>

**Table 4.** Effects of Treatment on Primary Outcome

1. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

2. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

3. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

4. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

5. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

6. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

7. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

8. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

9. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis

10. Comparison of the Chinese and Western approaches to parenteral nutrition in acute pancreatitis
Omega-3 in the treatment of sepsis syndrome

>> Metaanalyses
n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis

Lorenzo Pradelli1*, Konstantin Mayer2, Maurizio Muscaritoli3 and Axel R Heller4

The Role of ω-3 Fatty Acid Supplemented Parenteral Nutrition in Critical Illness in Adults: A Systematic Review and Meta-Analysis

Andrew J. Palmer, MB ChB, BSc2; Clement K. M. Ho, MBBS, PhD, FRCPath3; Olawunmi Ajibola, MSc4; Alison Avenell, MD, MBBS, FRCP, FRCPath

Parenteral Fish Oil Lipid Emulsions in the Critically Ill: A Systematic Review and Meta-Analysis

William Manzanares, MD, PhD; Rupinder Dhaliwal, RD; Brian Jurewitsch, PharmD; Renee D. Stapleton, MD, PhD; Khursheed N. Jeejeebhoy, MD, FRCP(C), PhD; and Daren K. Heyland, MD, FRCP, MSc
n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis

Lorenzo Pradelli\textsuperscript{1*}, Konstantin Mayer\textsuperscript{2}, Maurizio Muscaritoli\textsuperscript{3} and Axel R Heller\textsuperscript{4}
Infection rate

Random effects meta-analysis and forest plot. Squares represent individual study mean of the effect measure, diamonds represent its pooled estimates.

n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis

Lorenzo Pradelli¹, Konstantin Mayer², Maurizio Muscaritoli¹ and Axel R Heller³

ICU Length of Stay

Random effects meta-analysis and forest plot. Squares represent individual study mean of the effect measure, diamonds represent its pooled estimates.

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Andrew J. Palmer, MB ChB, BSc; Clement K. M. Ho, MBBS, PhD, FRCPa; Olawunmi Ajibola, MSc; Alison Avenell, MD, MBBS, FRCP, FRCPath

Impact of ω-3 fatty acid supplemented parenteral nutrition on new infections.
MH = Mantel-Haenszel; CI = confidence interval;

The Role of ω-3 Fatty Acid Supplemented Parenteral Nutrition in Critical Illness in Adults: A Systematic Review and Meta-Analysis

Andrew J. Palmer, MB ChB, BSc; Clement K. M. Ho, MBBS, PhD, FRCP, FRCPath; Obinna Ajibola, MSc; Alison Ayres, MD, MBBS, FRCP, FRCPed

Figure 4. Impact of ω-3 fatty acid supplemented parenteral nutrition on length of intensive therapy unit stay. IV = inverse variance; CI = confidence interval.

Figure 5. Impact of ω-3 fatty acid supplemented parenteral nutrition on length of hospital stay. IV = inverse variance; CI = confidence interval.

ICULIP - Influence of Two Lipid Emulsions in the Nosocomial Infection in Critical Patients

Purpose  This study aims to analyse the effect of two total parenteral nutrition diets with lipid emulsions of different compositions on the incidence of nosocomial infection in critical ill patients.

One diet will contain an 20% MCT/LCT emulsion (50:50 ratio) and the other will comprise an 20% MCT/LCT/fish oil emulsion (50:40:10 ratio).

Methods  prospective, multicenter, randomized, comparative, double-blind clinical trial

Patients  78 for group MCT/LCT (Lipofundina®) and 81 for group MCT/LCT/fish oil (Lipoplus®)

Inclusion Criteria  Patients who were expected to require TPN as metabolic nutritional support for at least 5 days since they cannot be fed by enteral or oral route or patients who receive enteral nutrition and do not achieve 75% of energy requirements 3 days after introduction of nutrition.

Grau T et al, ClinicalTrials.gov Identifier: NCT00396461
Evaluation of Two Different Types of Lipid Emulsions Used for TPN in Critically Ill Patients and their Influence on Nosocomial Infection: ICULIP Study

Conclusions:

There was a statistically significant decrease in the cumulative incidence of nosocomial infection in the study group with MCT/LCT/FO over control. The control patients have a risk of nosocomial infection 1.8 times higher than the group treated with MCT/LCT/FO.
Relationship among infection, LPS, PUFAs, eicosanoids, cytokines, ROS and sepsis and septic shock

- Disruption of Gut Barrier Function & Absorption of endotoxin (LPS)
  - ↑ Prostaglandins, thromboxanes and leukotrienes

- Activation of phospholipase A₂
  - Release of PUFAs
  - ↓ Lipoxins, resolvins, protectins, maresins, nitrolipsids

- Activation of Neutrophils, T cells and Macrophages
  - Failure to eliminate pathogens and Excess TNF-α, IL-6, MIF, HMGB1, ROS, NO production

- Hypoglycemia, Hypotension and ↓ Tissue perfusion, ↑ Tissue damage

- Sepsis and Septic Shock
Omega-3 in der Behandlung des Sepsis Syndroms

>> Wir haben nach wie vor widersprüchliche Daten!
Zusammenfassung

1. Die beobachteten Unterschiede in den Daten verschiedener Studien sind am ehesten mit der komplexen Natur des Stoffwechsels der mehrfach ungesättigten Fettsäuren (PUFAs) sowie deren Interaktionen mit Cytokinen, freien Radikalen und NO zu erklären.

2. Da die mehrfach ungesättigten Fettsäuren (PUFAs) Präkursoren sind für sowohl pro- als auch anti-inflammatorische Produkte, die ihrerseits einen modulierenden Einfluss haben auf die Bildung und Aktivität von Cytokinen, freien Radikalen und NO, führt die gesteigerte Bildung von pro-inflammatorischen Produkten wahrscheinlich zu einem ungünstigen Outcome, wogegen die Synthese anti-inflammatorischer Produkte vermutlich einen eher benefizienlen Einfluss in der Sepsis oder anderer kritischer Situationen haben wird.