Lipids – An indispensable part of Parenteral Nutrition Therapy

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Our most common worries?

- Mortality, of course
- INFECTIONS
- Multiple Organ Failure
- Leaks (post-op)
Which tools do we have?

- Good clinical practice
  - Surgical technique, understanding the problems, clean/sterile care, etc.
- Antibiotics and other drugs
- Any other tools????
Complications in surgery

% weight loss

20 cases <20%
1 death = 3.5%

18 cases >20%
6 deaths = 33.3%

Studley, 1936

75 years ago, this was clear

Mechanical ileus

Wound ruptures
Pneumonias
Sepsis

Studley, 1936
Assessment of a novel screening score for nutritional risk in predicting complications in gastro-intestinal surgery

608 elektive surgical patients (Zürich, Switzerland)

Prospectively evaluated with ”Nutrition Risk Screening 2002”

”Overall Nutrition Risk incidence” was 14%

Serious complications in patients with increased risk:

54% vs. 15%  p<0.001
Fatty acid-structure

Methyl end

Carboxyl end

Stearic acid
18:0

Oleic acid
18:1n-9

Linoleic acid
18:2n-6

α-linolenic acid
18:3n-3

Essential fatty acids
The lipids are the same today as on the time of Hippocrates and before.

We have been adapted to lipids during the evolution

(as for everything else except poison)
Intralipid
registered
1962

"The question is not whether we should treat malnutrition or not, but how."

Prof. Arvid Wretlind
Soja
Effects:

Essential fatty acids

Energy
### Long chain Soybean

<table>
<thead>
<tr>
<th>Acid</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myristic C14</td>
<td>0.1</td>
</tr>
<tr>
<td>Palmitic C16</td>
<td>11.0</td>
</tr>
<tr>
<td>Stearic C18</td>
<td>4.0</td>
</tr>
<tr>
<td>Oleic C18</td>
<td>23.4</td>
</tr>
<tr>
<td>Linoleic C18</td>
<td>53.2</td>
</tr>
<tr>
<td>Linolenic C18</td>
<td>7.8</td>
</tr>
<tr>
<td>Arachidic C20</td>
<td>0.3</td>
</tr>
</tbody>
</table>
PUFA and

- risk for oxidative stress?

Difficult to evaluate clinically
- many parameters have been used
  and many contradictive results

Isoprostanes, MDA, TBARS, TRAP,
pentane etc
Oxidative stress – not a simple event
PUFA and risk for oxidative stress?

No difference in MDA between Intralipid, Olive oil-emulsion or mothers milk

Cipierre et al, Acta Paediatr 2009

No difference in F2-isoprostanes and TRAP between Intralipid, MCT/LCT or Olive oil-emulsion

Roggero et al, Nutrition 2009
The effect of sepsis on the oxidation of carbohydrate and fat

Glucose oxidation g/m²/h

Fat oxidation g/m²/h

Sepsis score 0 10 20 30

Sepsis score 0 10 20 30
Increased lipid fuel dependence in the critically ill septic patients

Nanni et al, J Trauma 24(1):14-30, 1984
Phosphate & Fatty acids
Female 88 years

Could be your grandma

July-August
Complaining about gases and abdominal distention

Weekend Aug 26-27, anorexia, doesn’t eat much, drinks a little fluids, loose stools, upper abdominal pains

Gets worse during the week and her daughter takes her to ER on Saturday Sept 2nd
Cannot eat
Is she a risk patient?

At admission late afternoon complaining about pain mainly in the upper part of abdomen

A little underhydrated, slightly anemic, nothing special on physical exam, has had a couple of loose stools during the day borderline albumin

To the ward for observation (Saturday evening). Prescribed 5% glucose

Female 88 years
Sunday Sept 3\textsuperscript{rd}

Same problems. Diarrhea
Refuses to eat or drink.
Sent for X-ray – overview of
the abdomen shows signs
of an ileus with an empty
left colon

Suspicion of an obstruction
in the left colon

Discussion with radiologist
on call to get a CT – denied
due to overload of work

Prescribed 5% glucose

Female 88 years
How much energy?
Indirect calorimetry
REE for women

655.0955 + (9.6534 x weight) + (1.8496 x height) - (4.6756 x age)

REE for men

66.4730 + (13.7516 x weight) + (5.0033 x height) - (6.7550 x age)
The eyeball method
AND RARELY MORE THAN 2000 kcal
Different combinations of glucose and fat…

…all works as long as no overfeeding with any component

Remember: Too much glucose is harmful and tumor cells prefer glucose as substrate
Increasing glucose intake during total parenteral nutrition increases norepinephrine excretion in trauma and sepsis

Before (with 5% dextrose)

After 4-6 days

50:50 Lipid:glucose
100% glucose

n.s.  p<0.01
Hyperglycemia is a major threat against a good outcome.

How to control it?

- Avoid too much glucose
- Use insulin
- Dual, physiological energy (glucose + lipids)
- Control stress = control glucose intolerance
Monday Sept 4th

Ordinary staff on duty

Nutrition?

Yes, she receives a bag with **Kabiven 1000 kcal**
(bw 49 kg – has lost approx. 3 kg the last 2-3 weeks)

i.e. approx 20 kcal/kg

Peripheral vein
Malnutrition Increases Postoperative Complications
Subjective Global Assessment (SGA)


Infections (%)  LOS (Days)  P<0.005 (infections)  P<0.0001 (LOS)

SGA A  SGA B  SGA C
Effects:

Essential fatty acids
Balance n6/n3
Immune-functions
Cardio-vasc function
Fish oil

- the content depends on the fish

- high content of
  Eicosapentanoic acid (EPA)
  \( \text{C}20:5 \text{ n-3} \)
  and
  Docosahexanoic acid (DHA)
  \( \text{C}22:6 \text{ n-3} \)
Energy-beta oxidation

Cell membranes

Elongation
Essential fatty acids

Linoleic acid
C18:2 n-6

DHGLA
C20:3 n-6

Arachidonic acid
C20:4 n-6

alpha-Linolenic acid
C18:3 n-3

Eicosatetraenoic acid
C20:4 n-3

Eicosapentanoic acid
C20:5 n-3 (EPA)

Docosahexanoic acid
C22:6 n-3 (DHA)

Pro-inflammatorv

Tromboxanes
Prostaglandines
Leucotriens

Moderating inflammation

PG2

Resolvins

Cell membranes

36
Omega-3 fatty acids improve the diagnosis-related clinical outcome

- Prospective multicenter open study
- 661 patients from 82 German hospitals
- PN $\geq 3$ d (8.7±7.5 d)- inclusive FO
- Major abdominal surgery 255, abdominal sepsis 276,
  (non-abd sepsis 16, multi-trauma 59, severe head injury 18 and 37 with “other” diagnoses)
- Age 63, BMI 25, LOS hosp 29 d, LOS ICU 12.5 d
  SAPS II 32.2 ± 13.6 with expected mortality 18.9%
Figure 1. Dose-related length of stay (mean and SD): black columns in hospital, white columns in intensive care unit (ICU). Between-group comparisons are age, Simplified Acute Physiology Score (SAPS) II, and mortality adjusted in covariance analysis ($p < .001$). Significant differences from Tukey’s post hoc multiple-comparison cofactor analysis of variance with covariates age, SAPS II, daily calorie intake, and survival as indicated: ICU stay ($p < .001$); hospital stay ($p < .001$).
FO dose and need of antibiotics

Figure 2. Antibiotic demand in percentage of patients in dose-related subgroups (absolute number of patients given in lower part of column). Significant differences from Tukey’s post hoc multiple-comparison cofactor analysis of variance with covariates age, Simplified Acute Physiology Score II, and daily calorie intake, as indicated: ★★★p < .001; ★★p = .01; ★p < .05.

Mortality reduction from 18.9%-12% (p<0.001)

Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion

A double-blinded PRCTrial in 44 postoperative patients (22 + 22)

- receiving either a lipid emulsion with n-3 fish oil (SMOFlipid) or an olive-soybean oil LCT-emulsion
- 5 days treatment
- NPE 60 % glucose / 40 % lipid emulsion
- 25 kcal / kg / day - 24h infusion
Changes in triglycerides

- **Olive-soybean oil**
- **n-3 fish oil LE (SMOFlipid)**

Data points:
- **Before**: 100 mg/dl
- **Day 2**: 150 mg/dl
- **Day 5**: 200 mg/dl

*Significant change at Day 5 compared to Before and Day 2.
Aspartate-aminotransferase concentrations

* < 0.05 vs. other Group

Data points

Before
D2
D5

Olive-soybean oil
n-3 fish oil LE
Alanin-aminotransferase concentrations

- Olive-soybean oil
- n-3 fish oil LE

* < 0.05 vs. other Group

Data points
Olive-soybean oil
n-3 fish oil LE

α-GST- concentrations (µg/L)

* < 0,05 vs. other Group

Data points
n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta analysis
Pradelli L et al. Critical Care 2012, 16:R184

23 RCTrials studies (1502 patients – 762 admitted to ICU)

Randomized to Standard TPN (with lipids) or EPA/DHA supplemented TPN

No difference in mortality – relative low underlying mortality risk

Non-outcome benefits:

• Improved lung gas exchange
• Reduced inflammatory markers
• Improved liver function tests
  • Better anti-oxidant status
Pradelli et al 2012
Meta analysis

Figure 1 Infection rate: random effects meta-analysis and forest plot. Squares represent individual study mean of the effect measure, diamonds represent its pooled estimates.

Significant reduction in infectious rate, especially in the NON-ICU patients
**Figure 2** Hospital length of stay: random effects meta-analysis and forest plot. Squares represent individual study mean of the effect measure, diamonds represent its pooled estimates.

**Significant reduction in Hospital LOS both in ICU and Non-ICU patients**
**Figure 3** 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.

**Significant reduction in LOS in ICU patients**
Parenteral fish oil improves outcome in patients with Parenteral Nutrition-Associated Liver Injury

42 children with SBS and developed cholestasis during LCT-containing TPN
Changed to Omegaven vs.
49 with SBS on LCT

<table>
<thead>
<tr>
<th>LCT; n=49</th>
<th>Omegaven; n=42</th>
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</thead>
<tbody>
<tr>
<td><strong>Dead</strong></td>
<td>P = 0.005</td>
</tr>
<tr>
<td><strong>Hyper-TG weeks</strong></td>
<td>P = 0.0003</td>
</tr>
<tr>
<td><strong>Transplanted</strong></td>
<td>P = 0.005</td>
</tr>
</tbody>
</table>
Parenteral fish oil improves outcome in patients with Parenteral Nutrition-Associated liver injury


42 children w SBS
3 dead + 1 transplanted
OMEGAVEN

49 children w SBS
12 dead + 6 transplanted
LCT (Liposyn, Intralipid)

Omegaven: 1 g/kg/d

LCT: 1-4 g/kg/d
Monday Sept 4th

Ordinary staff on duty

Nutrition?

Yes, she receives a bag with Kabiven 1000 kcal (bw 49 kg – has lost approx. 3 kg the last 2-3 weeks) i.e. approx 20 kcal/kg

Peripheral vein

But a candidate for complications

Addition of Omega-3 fish oil (and Glutamine) + all micronutrients
Tuesday Sept 5th

Finally we get a colon exam on X-ray, shows a complete obstruction of the colon (flex. lienalis)

Nutrition?

Yes, she gets it, and planning for surgery on Wednesday the 6th

i.e. 2 days of pre-op nutrition
Cachexia

• There is no definition available describing what cachexia really is.

• Multifactorial and multidimensional events.

• The events will however lead to a REDUCTION IN FOOD INTAKE and METABOLIC ABNORMALITIES.

The patient’s journey

Mild to Moderate to Severe
• Some patients are hypermetabolic, other are hypometabolic. A patient is also hypermetabolic in the beginning and will later during the journey turn into a hypometabolic state.

• First loss of fat tissue, closely followed by a loss of muscle protein.

• Non-muscle protein is preserved at this time.
Gluconeogenesis from 1 kg skeletal muscle

1/3 is dry weight
i.e.
333 g protein
1 g protein ≈ 4 kcal

4 × 333 = 1300 kcal
When the body has lost up to 30% of the weight, the loss of non-muscle protein accelerates.

- Studies from different centers have shown that patients who are running into cachexia have a food intake less than 1500 kcal/day.

- Energy expenditure in these patients are around 1700 kcal/day.

This means that every calory they are taking in is used to try to survive, not to improve function. In other words, without intervention, every day is a step closer to death due to malnutrition. QoL is at the same time decreasing.
Wednesday Sept 6th

To OR

Epidural before anesthesia

Surgery:

Leftsided hemicolecctiony
Some technical problems
Bled approx. 300 ml
Primary anastomosis
decided possible

Nutrition ?
Wednesday Sept 6th

To OR

Epidural before anesthesia

Surgery:

Leftsided hemicolecotomy
Bled approx. 300 ml
Primary anastomosis decided possible

Nutrition?

We didn’t
Thursday Sept 7th

Doing well

Nutrition?

Yes, she gets:

SmofKabiven 1000 kcal
Dipetiven
Fat- & water soluble vitamins
Trace elements (and glutamine)

Plus small amounts of sip-water for well-being.

Ng-tube out

Still a little bit risky
Different combinations…

…to meet the estimated requirements
Early energy supply decreases ICU and hospital mortality: A multicenter study in cohort of 1209 pts
Pichard et al. ESPEN congress 2008

1209 patients >4 days in ICU (14 German ICUs)
EARLY or LATE start of nutrition

<table>
<thead>
<tr>
<th>Kcal/3 days</th>
<th>Early n=374</th>
<th>Late n=835</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2,732 ± 1136</td>
<td>499 ± 458</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU-mortality</td>
<td>13,4 %</td>
<td>18,6 %</td>
<td>0.026</td>
</tr>
<tr>
<td>Hospital-mort.</td>
<td>18,7 %</td>
<td>24,2 %</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Early nutritional support reduces the mortality rate in Critically ill patients suffering from abdominal sepsis with a high APACHE II score
Millan-Lopez et al. ESPEN congress 2008

137 ICU-patients in 4 groups:

<table>
<thead>
<tr>
<th>Mortality</th>
<th></th>
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<tbody>
<tr>
<td>Early PN (&lt; 48 hours)</td>
<td>29.1 %</td>
</tr>
<tr>
<td>Late PN &amp; EN (&gt;48 hours)</td>
<td>23.5 %</td>
</tr>
<tr>
<td>Early PN &amp; EN (&lt;48 hours)</td>
<td>14.0 %</td>
</tr>
<tr>
<td>Late PN (&gt;48 tim)</td>
<td>80.0 %</td>
</tr>
</tbody>
</table>
PO Day 2

Friday Sept 8th

Nutrition?

Same PN

plus fluids to drink, like broth, juice, tea etc
PO Day 3

Saturday Sept 9th

Nutrition:

Same SmofKabiven with all additives

Plus soups and a sandwich orally
PO Day 4

Sunday Sept 10th

Eating but needs support with parenteral Kabiven with all additives

The picture is taken during the morning rounds after being prescribed to free food access in combination with PN support for one day more

Went home on PO Day 8 after adjustment of the social situation
Malnutrition Increases Postoperative Complications
Subjective Global Assessment (SGA)

Summary of lipids

• Lipids have been, is, and will always be a physiological part of our nutrition

• There is no scientific rationale for excluding lipids as a natural part of nutrition (except intolerance)

• More lipids and less glucose to starve cancer cells

• n-3 fish oil have properties we should use in the best interest of our patients:
  - better TG-control
  - better liver control
  - less infections
  - shorter LOS in ICU and hospital
Summary (2):

- There are differences between the oils
- They have different effects, from ZERO to MUCH
- Soybean oil = LCT, without comparison the most well documented
- A balanced composition is the future
  …there is no reason why we should not use the knowledge we vi have got
The lipids are the same today as on the time of Hippocrates and before

We have been adapted to lipids during the evolution
(as for everything else except poison)

There is no support behind the idea to exclude lipids as a part of TPN
The End