Intravenous Lipid Emulsion (ILE) in Parenteral Nutrition: Assessing New Options

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Disclosures

Fresenius Kabi, Inc:

- Consultant & Speaker’s Bureau

Baxter Healthcare:

- Consultant

Learning Objectives

Upon completion of this session, the learner will be able to

1. Describe the similarities and differences between ILE formulations.
2. Identify patient populations that would benefit from a non-soybean centered ILE.

FDA Approved ILE

	Intralipid[1,2]	Nutrilipid[3]	Clinolipid[2,4]	Smoflipid[5]
Manufacturer	Fresenius Kabi/Baxter*	B.Braun Medical	Baxter	Fresenius Kabi
Oil Source	Soybean Oil	Soybean Oil	Olive Oil 80% Soybean Oil 20%	Soybean Oil 30% MCT 30% Olive Oil 25% Fish Oil 15%
Fat Composition (%, mean values)[1-6]				
Linoleic	53	53	17.9	19.5
α-Linolenic	7.5	7.5	2.4	2.5
Eicosapentaenoic	0	0	0	2.3
Docosahexaenoic	0	0	0	2.3
α-Tocopherol (mg/L)	38	N/A	32	163-225
Phytosterols (mg/L)[6]	439	311	274	178
ω3 : ω6 ratio	1 : 7	1 : 7	1 : 9	1 : 2.5

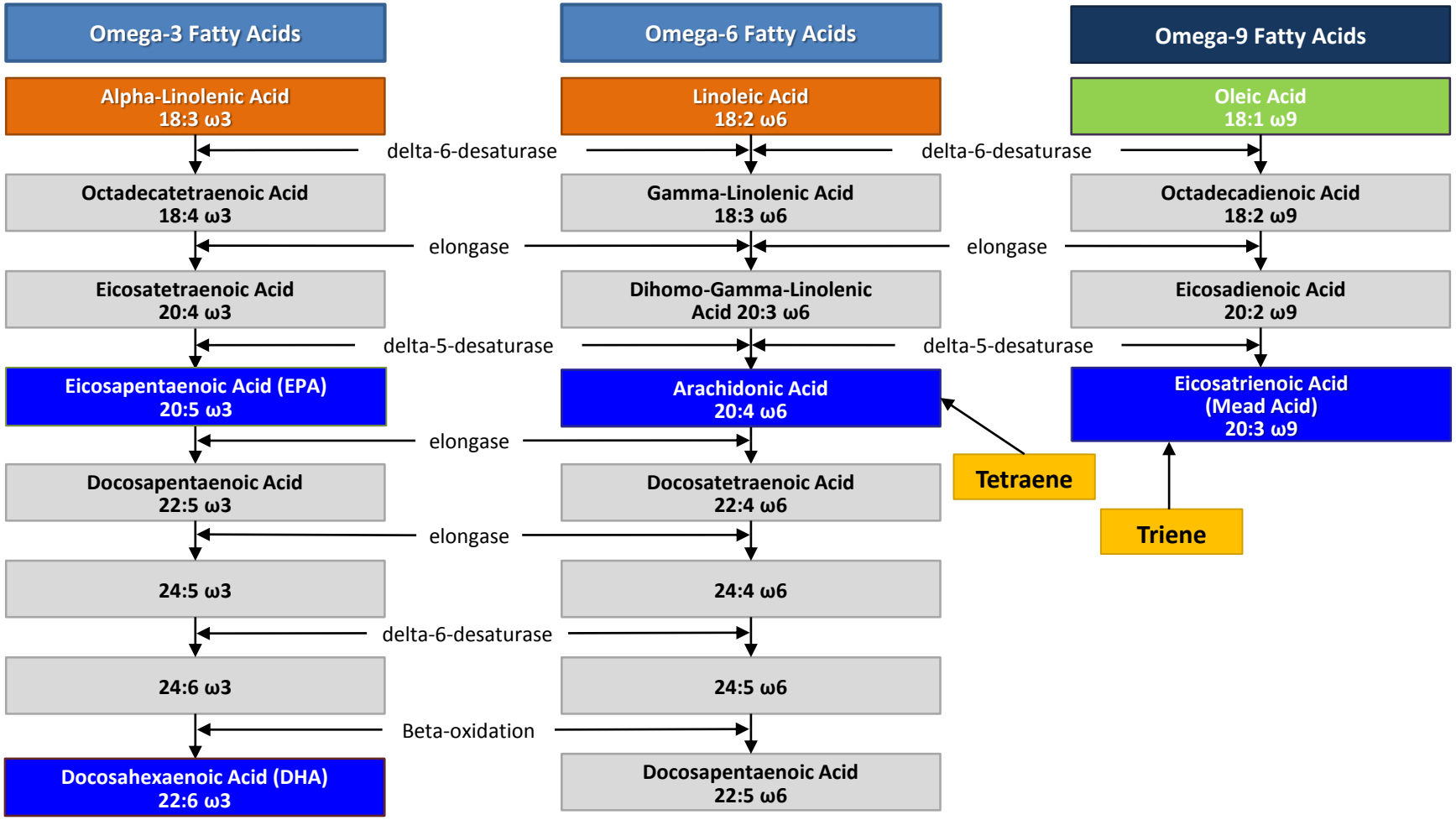
MCT, medium chain triglycerides; N/A, not available
*Distributed

1. Intralipid Prescribing Information, 2015
2. *Vanek VW, et al.* Nutr Clin Pract 2012;27:150-192
3. Nutrilipid Prescribing Information 2014
4. Clinolipid Prescribing Information, 2013
5. Smoflipid Prescribing Information 2016
6. *Xu Z, et al.* Nutrients 2012;4;904-21

Omega-3 polyunsaturated fatty acids produce which of the following?

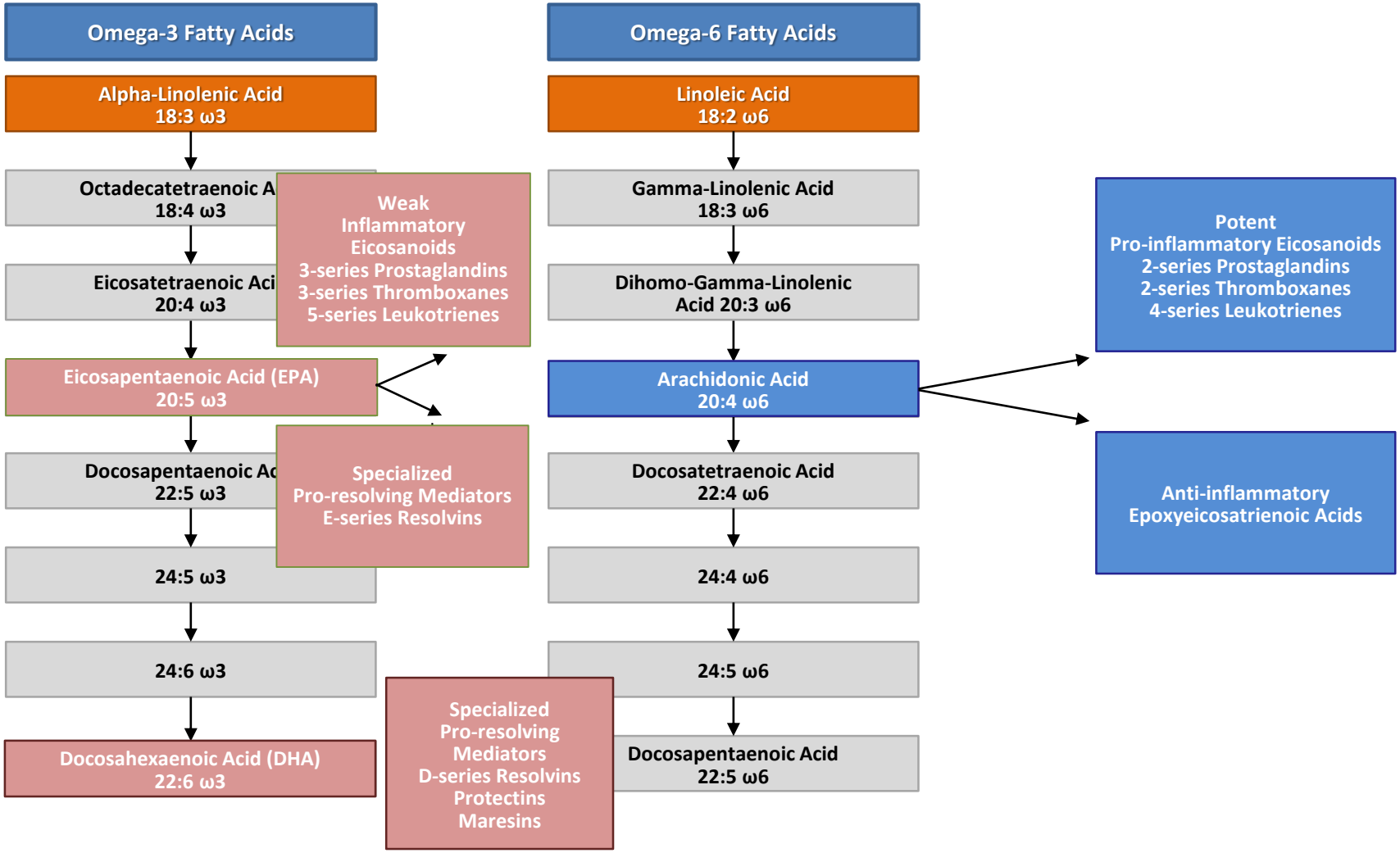
A. Arachidonic acid
B. Thromboxane A2
C. Resolvins E1/D1
D. Leukotriene B4

Metabolic Pathways of ω3, ω6, ω9



Le HD, et al. **Prostaglandins Leukot Essent Fatty Acids 2009;81:165-170**

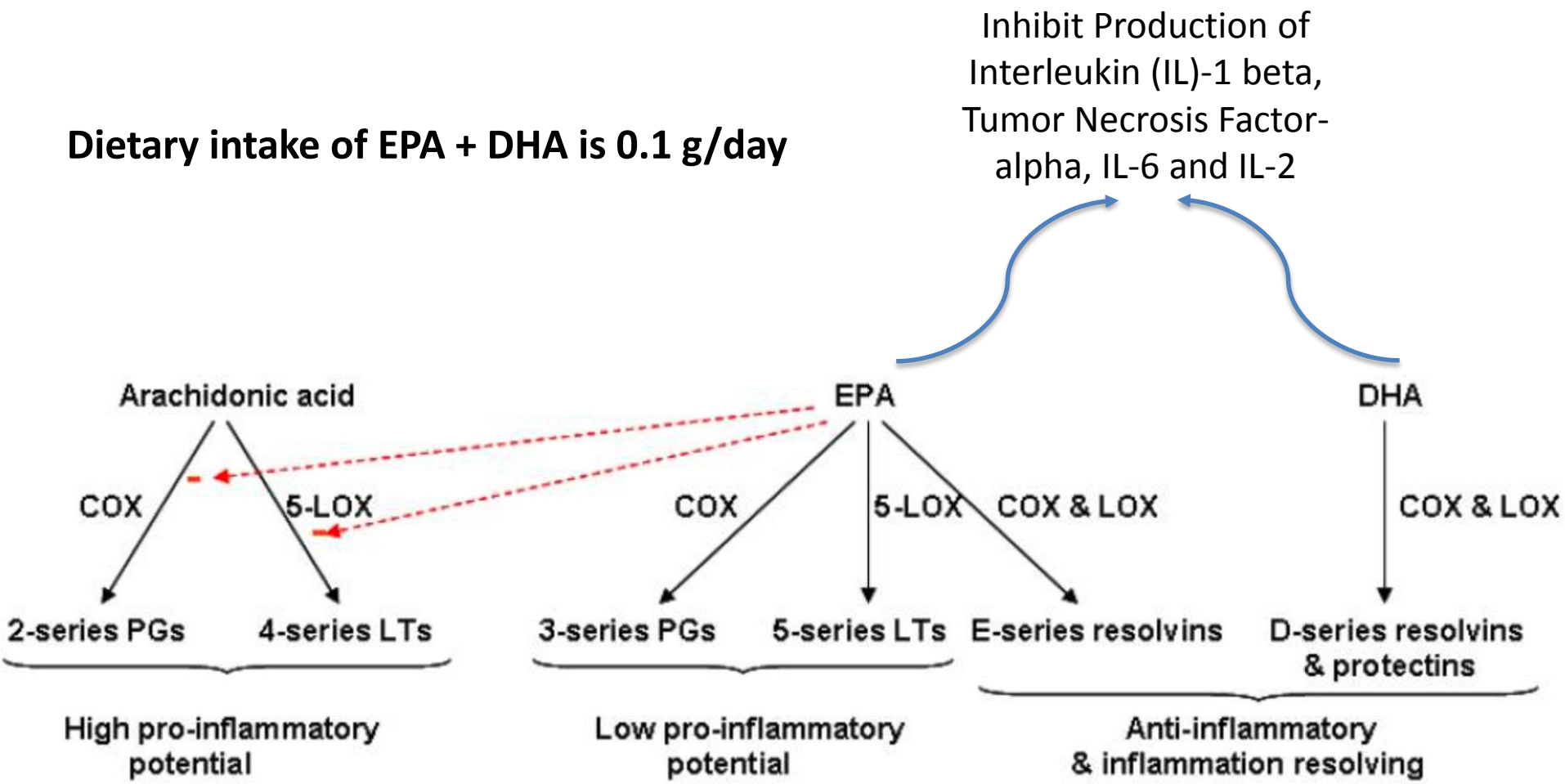
Metabolic Pathways of ω3, ω6, ω9



Le HD, et al. **Prostaglandins Leukot Essent Fatty Acids 2009;81:165-170**

ω3 vs. ω6 Fatty Acids

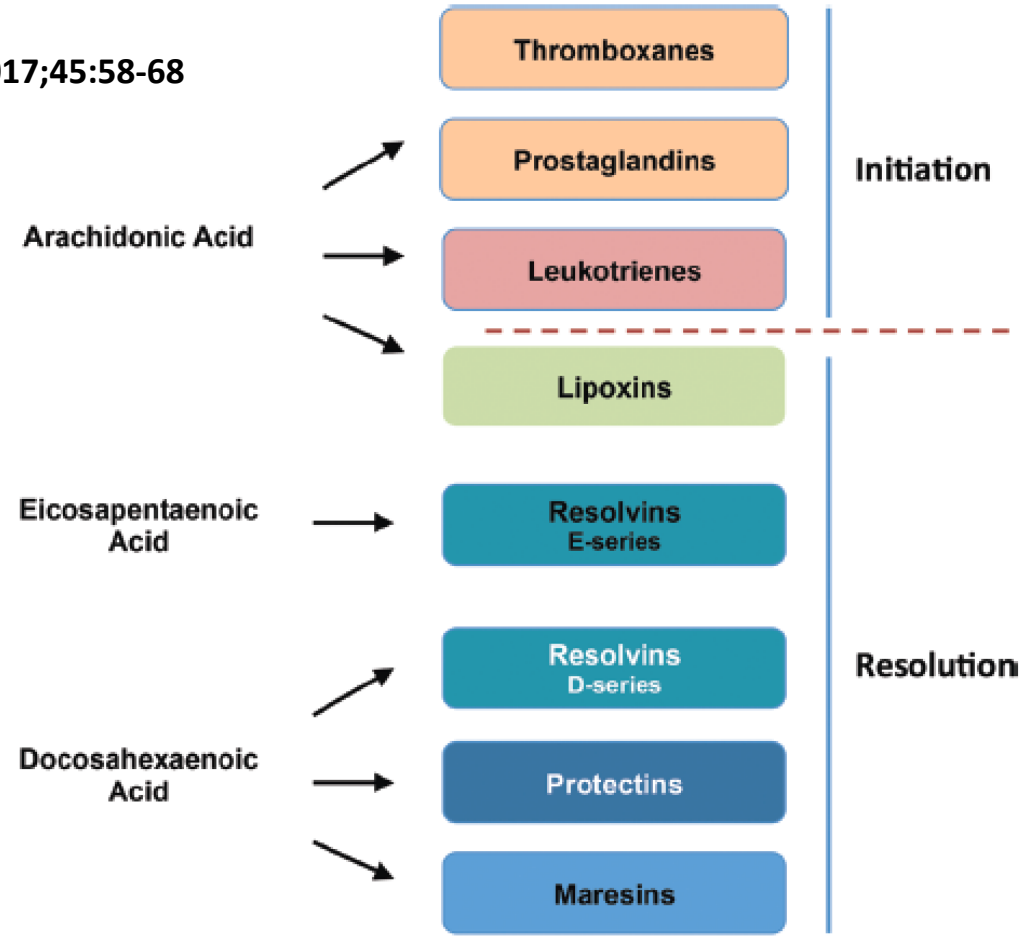
Dietary intake of EPA + DHA is 0.1 g/day



COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene

Calder PC. **Nutrients 2010;2(3):355-74**

Dalli J, et al. Crit Care Med 2017;45:58-68



SPM Anti-Inflammatory and Pro-Resolving Defining Functions	Mediator	SPM Selective Actions
• Accelerate the resolution of acute inflammation • Limit neutrophil infiltration • Promote efferocytosis of apoptotic cells • Enhance microbial killing and clearance • Counter regulation and sequestration of cytokines • Down regulation of prostanoids	RvD1	Enhances cognitive function
	RvD2	Regulates vascular endothelium
	RvD5	Macrophage phagocytosis
	PD1	Neuro-protective
	RvE1	Reduces platelet aggregation

Omega-3 polyunsaturated fatty acids produce which of the following?

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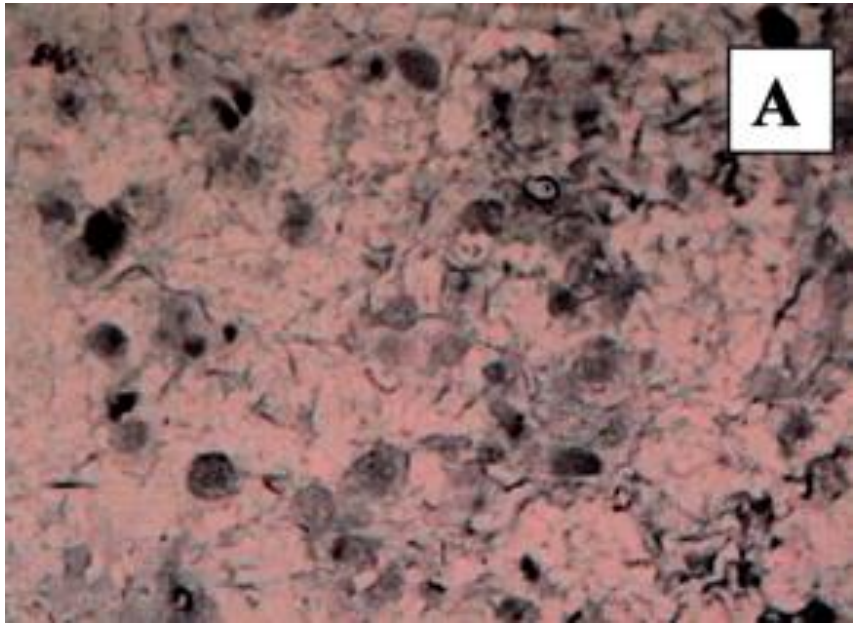
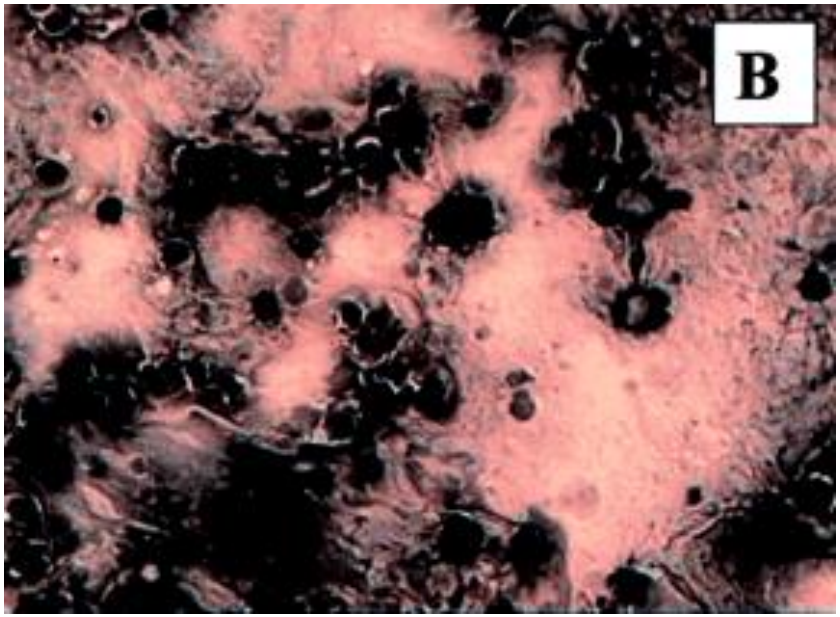
B. Thromboxane A2
C. **Resolvins E1/D1**
D. Leukotriene B4

ILE & ? Fat Embolism Syndrome





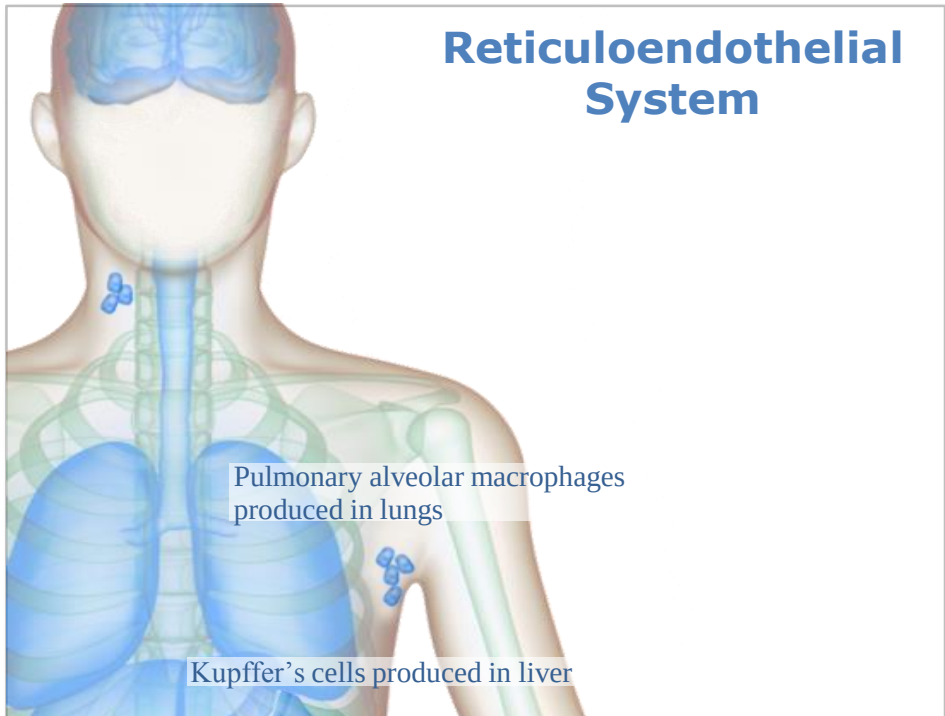
- 20% Lipofundin (50% MCT/50% Soybean) 0.21 g/kg/hr for 1 hr
  - Heterogeneous ICU ARDS group (n=8)
  - PaO_2/FiO_2 decreased from 129 → 95

	ARDS-Lipids Group	
	Before	After
Total cell count, × 10^3/ml	290 ± 50*	320 ± 55
Alveolar macrophages, %	45 ± 5†	39 ± 6
Neutrophils, %	35 ± 4†	45 ± 5‡
Eosinophils, %	8 ± 2	7 ± 3
Lymphocytes, %	12 ± 2	9 ± 3
Sudan Black B staining, %	18 ± 8*	63 ± 16‡

Lekka ME, et al. **Am J Resp Crit Care Med 2004;169:638-44**

ILE in Acute Respiratory Distress Syndrome

- ILE administration may have clinical consequences in severe lung injury or ARDS
  - ↓ diffusion capacity with changes in alveolar capillary membrane
    - Deposition of fat particles in the reticuloendothelial system
- Dosages > 0.1 g/kg/hr will impair oxygenation for the duration of the infusion
  - ↓ PaO_2/FiO_2
- Assess benefits vs. risks
  - Essential fatty acid deficiency



Which of the following is recommended from the published available guidelines for intravenous lipid emulsions?

A. For malnourished critically ill patients the weekly dose should not exceed 50 grams throughout hospitalization
B. Use of lower content of ω6 fatty acids/soybean oil for critically ill patients in the first week
C. Medium chain triglycerides are the preferential fuel for critically ill patients and may be administered alone
D. Use of 100% fish oil has been shown to reduce mortality, ventilator days, and hospital length of stay

Clinical Guidelines

aspen | LEADING THE SCIENCE AND PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

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.)

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McClave SA, et al. JPEN J Parenter Enteral Nutr 2016;40:159-211

When to Use PN in ICU?

- For low nutrition risk patients, exclusive PN should be withheld over the first 7 days after ICU admission even if volitional intake & early EN not feasible (Very Low)
- For high nutrition risk or severely malnourished patients when EN is not feasible, initiate exclusive PN as soon as possible after ICU admission
- Supplemental PN be considered after 7–10 days if unable to meet > 60% of energy/protein EN needs

McClave SA, et al. **JPEN J Parenter Enteral Nutr 2016;40:159-211**

Feeding Recommendations

- If utilizing PN:
  - Hypocaloric dosing ($\leq$ 20 kcal/kg/day or 80% of estimated energy needs) with adequate protein ($\geq$ 1.2 g/kg/day) initially over the 1st week of ICU admission (Low)
  - Withholding or limiting soybean oil-based fat emulsion (ILE) during the 1st week following initiation of PN to 100 g/week (often divided into 2 doses/week) if concern for essential fatty acid deficiency (Very Low)
  - Consider use of alternative ILE over soybean oil-based ILE if available
  - Terminate PN when $\geq$ 60% of target energy requirements are being delivered by EN

McClave SA, et al. **JPEN J Parenter Enteral Nutr 2016;40:159-211**

Fat-free PN in ICU (No Soybean-Based ILE)

57 trauma patients
Study Duration: 10 days

Control PN (w/ILE)
(n=30, Mean Age 33 ± 10 yrs)
28 kcal/kg/day non-protein kcal
(~24% from IVFE)
1.6 g/kg/day protein

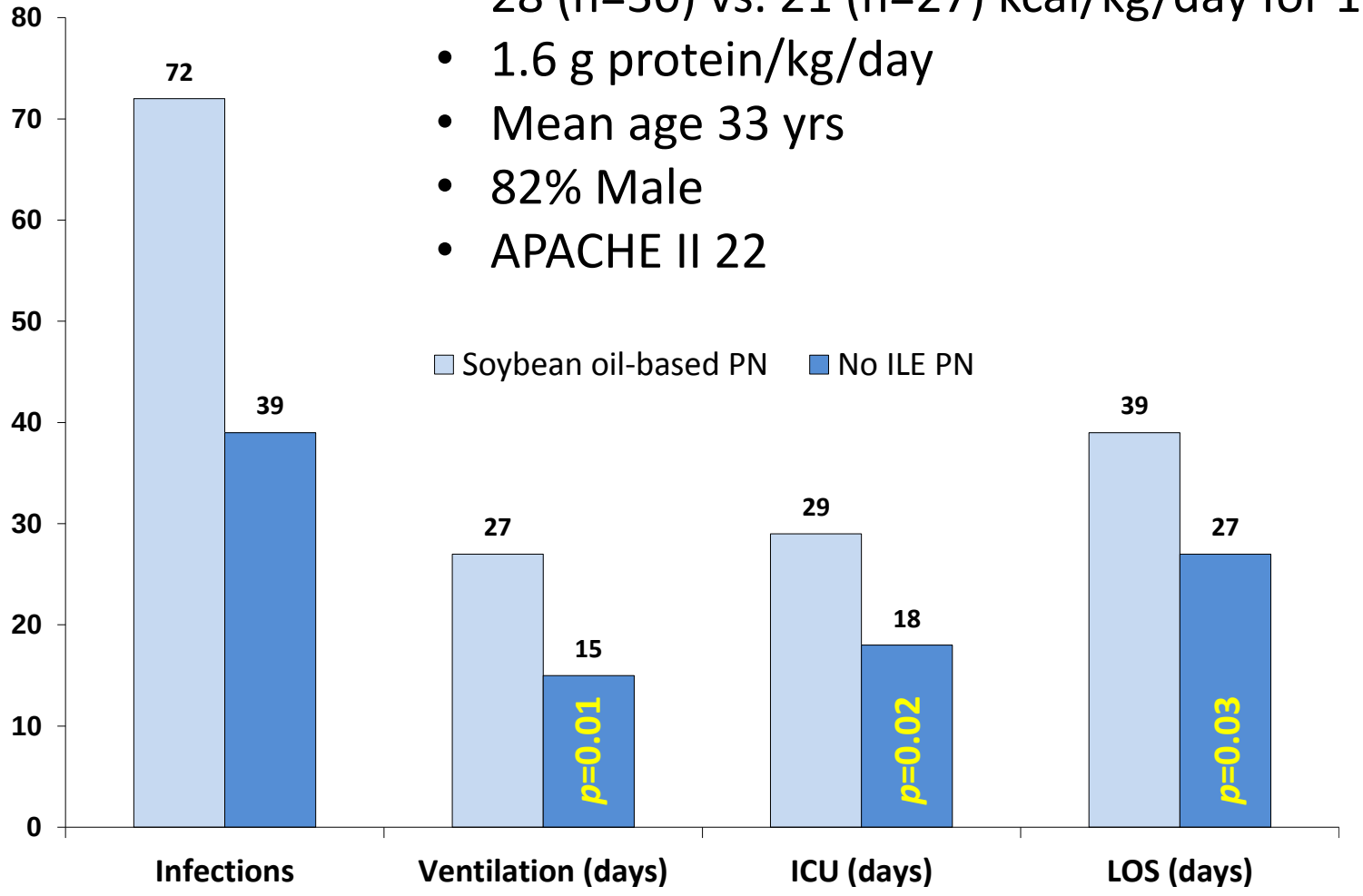
Hypocaloric PN (w/o ILE)
(n=27, Mean Age 32 ± 9 yrs)
21 kcal/kg/day non-protein kcal
1.6 g/kg/day protein

IVFE: Intralipid 10% or 20% infused over 10-12 hours daily

Battistella FD, et al. J Trauma 1997;43:52-58

Fat-free PN in ICU (No Soybean-Based ILE)

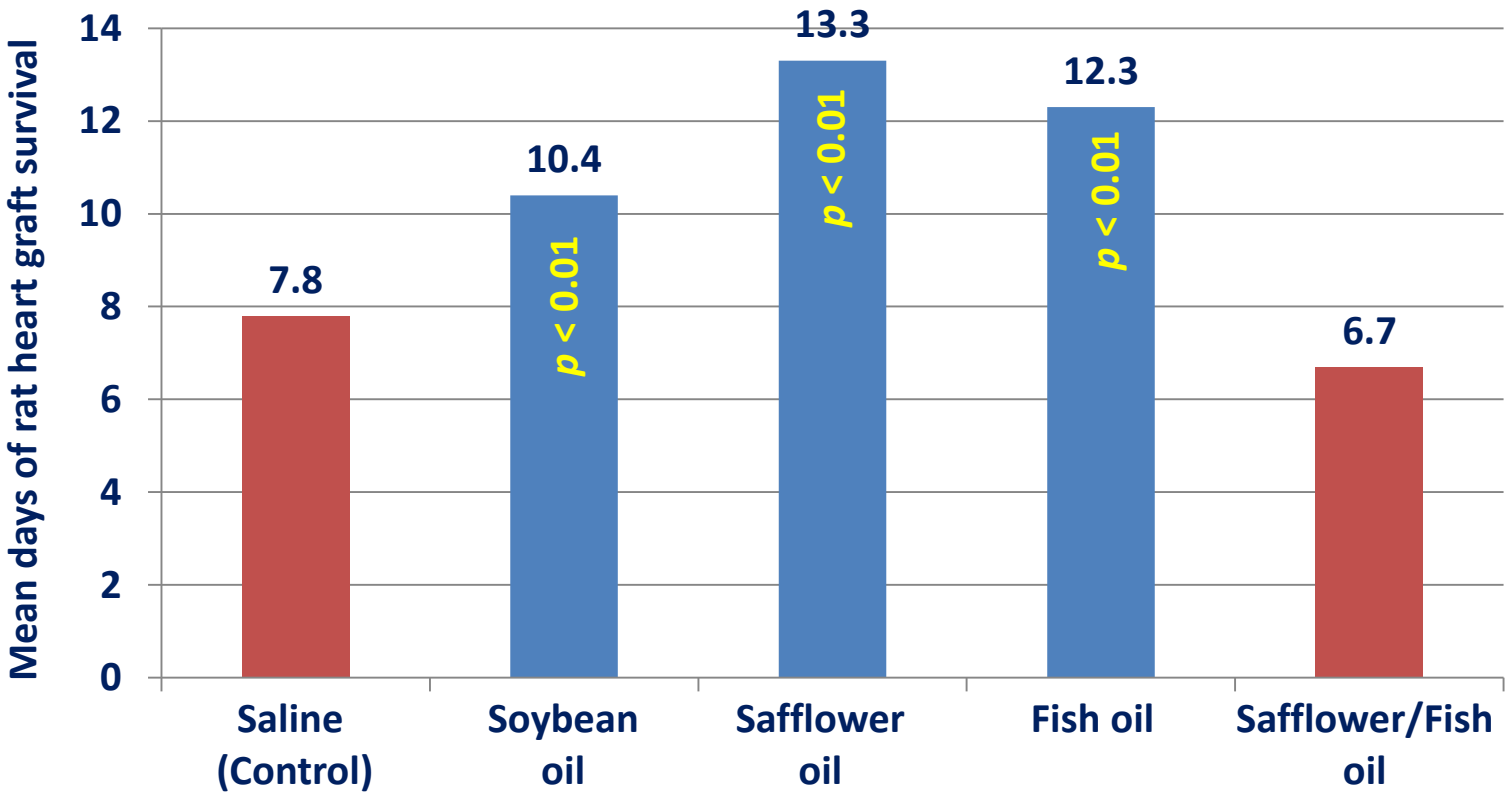
- 28 (n=30) vs. 21 (n=27) kcal/kg/day for 10 days
- 1.6 g protein/kg/day
- Mean age 33 yrs
- 82% Male
- APACHE II 22



Battistella FD, et al. J Trauma 1997;43:52-8

Immunoregulation by ILE

Reduced ω-6:ω-3 ratio (Approximately 2:1) has no immunosuppressive effects



Grimm H, et al. JPEN J Parenter Enteral Nutr 1994;18:417-21

Which of the following is recommended from the published available guidelines for intravenous lipid emulsions?

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B. Use of lower content of ω6 fatty acids/soybean oil for critically ill patients in the first week

C. Medium chain triglycerides are the preferential fuel for critically ill patients and may be administered alone

D. Use of 100% fish oil has been shown to reduce mortality, ventilator days, and hospital length of stay

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes, MB BS, MD(Res) (Co-chair)[1]; Laura E. Evans, MD, MSc, FCCM (Co-chair)[2]; Waleed Alhazzani, MD, MSc, FRCPC (methodology chair)[3]; Mitchell M. Levy, MD, MCCM[4]; Massimo Antonelli, MD[5]; Ricard Ferrer, MD, PhD[6]; Anand Kumar, MD, FCCM[7];

Rhodes A, et al. **Crit Care Med 2017;45:486-552**

International Guidelines for Management of Severe Sepsis & Septic Shock: 2016

- Recommend against the administration of early PN alone or PN in combination with EN (but rather initiate early EN) in critically ill patients with sepsis or septic shock who can be fed enterally (strong recommendation, moderate quality of evidence)

- Recommend against the administration of PN alone or in combination with EN (but rather to initiate IV glucose and advance EN as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence)

Rhodes A, et al. **Crit Care Med 2017;45:486-552**

International Guidelines for Management of Severe Sepsis & Septic Shock: 2016

- Recommend against the use of ω3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock (strong recommendation, low quality of evidence)
- Recommend against the use of the following to treat sepsis and septic shock:
  - IV selenium (strong recommendation, moderate quality of evidence)
  - Arginine (weak recommendation, low quality of evidence)
  - Glutamine (strong recommendation, moderate quality of evidence)
- No recommendation about the use of carnitine for sepsis and septic shock

Rhodes A, et al. **Crit Care Med 2017;45:486-552**

What Do Clinical Guidelines Say?

American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) position paper[1]:

"Alternative oil-based ILEs are safe and effective alternatives to soybean oil ILEs for a source of energy and essential FAs and may have potential biochemical and/or clinical benefits"

Canadian Critical Care Nutrition guidelines[2]:

"When PN with IV lipids is indicated, IV lipids that reduce the load of ω-6 fatty acids/ soybean oil emulsions should be considered"

ESPEN guidelines for critically ill patients[3]:

- "Lipids should be an integral part of PN for energy to ensure essential fatty acid provision in long-term intensive care unit patients"
- "This may include fish oil-enriched and olive oil-based lipid emulsions"

ESPEN guidelines for surgical patients[4]:

- "Postoperative PN including omega-3-fatty acids should be considered only in patients who cannot be adequately fed enterally"

1. Vanek VW, et al. *Nutr Clin Pract.* 2012;27:150-192; 2. Dhaliwal R. *Nutr Clin Pract*. 2014;29(1):29-43; 3. Singer P, et al. *Clin Nutr.* 2009; 28:387-400; 4. Weimann A, et al. *Clin Nutr.* 2017; 36:623-650.

Soybean oil-based ILE vs. Alternative ILE

- International Nutrition Survey over 4 separate years (2007, 2008, 2009, 2011) in observational study of ICU practices (n = 451)
  - ICU for minimum of 72 hours & mechanical ventilation within 48 hours of admission
  - Requiring PN for minimum of 5 days
    - Provided ~1409 kcal/day

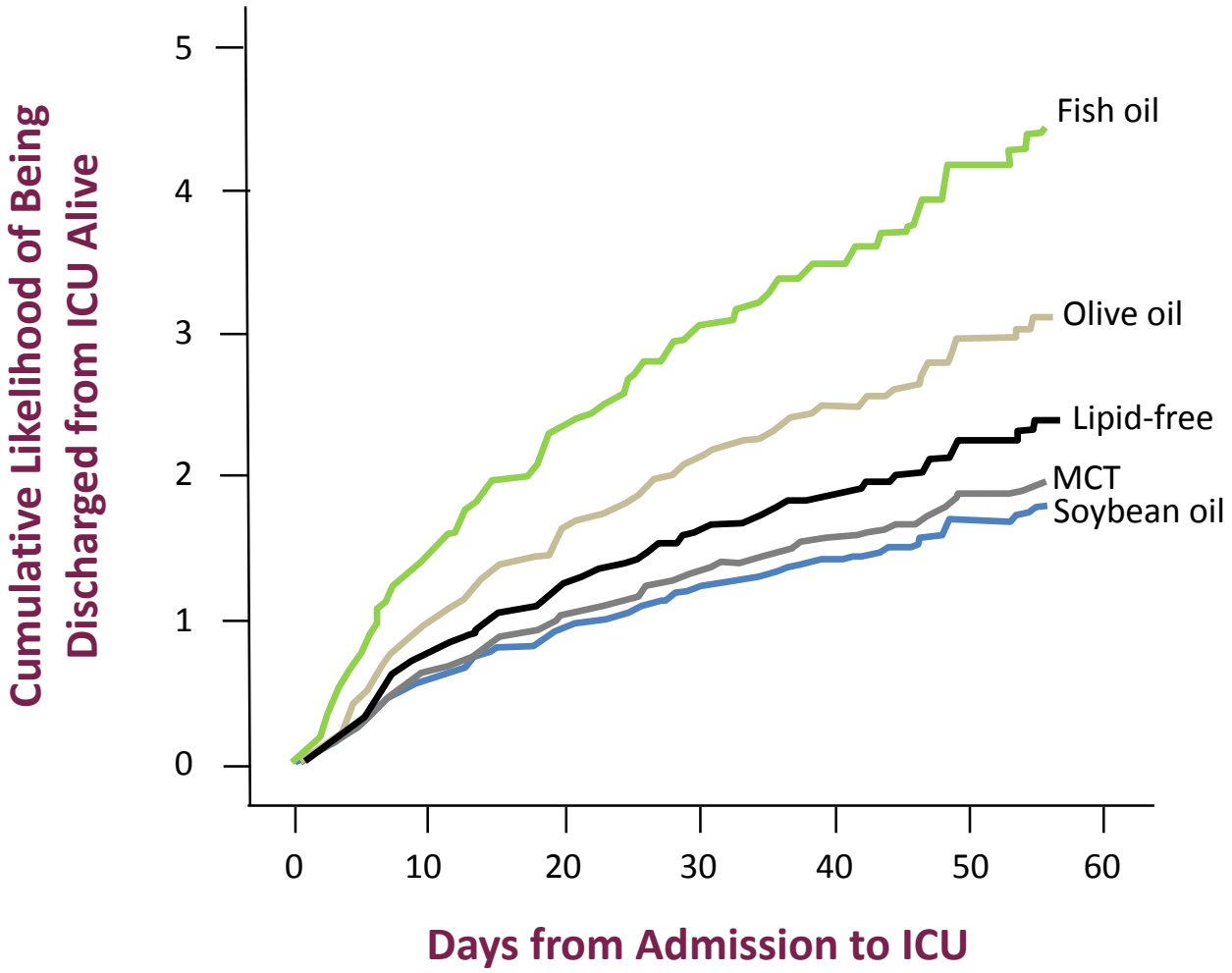
- Mean age ~64 yrs
- 62% male
- 68% surgical
- APACHE II ~22
  - 16% no lipid emulsion
  - 49% soybean oil-based
  - 14% medium-chain triglyceride-based
  - 16% olive oil-based
  - 4% fish oil-based

Clinical Outcomes	Soybean Oil (n = 223)	Lipid Free (n = 70)	MCT Oil (n = 65)	Olive Oil (n = 74)	Fish Oil (n = 19)
Mechanical Ventilation Duration (d)*	4.9 (2.6-16)	8.7 (4.4-16.8)	5.3 (2.9-10.6)	5 (2.4-10.5)	5 (2.9-10.9)
ICU Length of Stay (LOS, d)*	10.9 (7.1-22.2)	11 (6.7-21.8)	9.6 (6.8-21.4)	7.9 (5.9-15.8)	7 (4.7-13.1)
Hospital LOS*	28.1 (17.1-54.6)	27.7 (12.9-60.1)	31.9	22.1 (15.8-48.5)	14.1
Mortality within 60 days	63 (28.3%)	13 (18.6%)	20 (30.8%)	11 (14.9%)	2 (10.5%)

* Median (interquartile range)

Edmunds CE, et al. **Crit Care Med 2014;42:1168-77**

Soybean oil-based ILE vs. Alternative ILE



Edmunds CE, et al. **Crit Care Med 2014;42:1168-77**

Can ILE Composition Impact Outcome?

Study Design	Purpose	Summary of Findings
• Meta-analysis • Sample: elective surgical and ICU patients • 13 ICU studies (n=762) • 10 surgery studies (n=740)	• Clinical efficacy and safety of ω3 PUFA-enriched ILE compared to standard (non-enriched) ILE	• Mortality rate: no difference • Infection rate: significant reduction in ω3 ILE surgical pts, not ICU patients • LOS: significant reduction in ω3 ILE group for both ICU and surgical patients • Lung gas exchange: significant increase in ω3 ILE groups

Pradelli L, et al. **Crit Care 2012;16:R184**

Can ILE Composition Impact Outcome?

Study Design	Purpose	Summary of Findings

• Meta-analysis
• Sample: Major surgical patients receiving for 5-7 days post-op
• 21 studies (n=1487)
	• Clinical efficacy and safety of ω3 PUFA-enriched ILE compared to standard (non-enriched) ILE	• Mortality rate: no difference
		  • Odds Ratio (OR) = 1.5 (95% Confidence Interval (CI) 0.54-4.19, p = 0.44)
		• Infection rate: significant reduction in ω3 ILE group
		  • OR = 0.53 (95% CI 0.35-0.81, p = 0.003)
		• LOS: significant reduction in ω3 ILE group by mean of -2.14 days
		  • 95% CI -3.02 to -1.27 days, p < 0.001)

Li N, et al. **Clin Nutr 2014;33:226-39**

Fish Oil-containing ILE

- Meta-analysis of 10 randomized clinical trials (n=733)
  - Effects of fish oil-containing ILE in EN and PN for critically ill adults

Clinical Outcome	Effect	95% Confidence Intervals	*p* value
Mortality	RR 0.90	0.67 – 1.20	0.46
Duration of Ventilation	WMD -1.14	-2.67 – 0.38	0.14
Hospital Length of Stay	WMD -3.71	-9.31 – 1.88	0.19
ICU Length of Stay	WMD -1.42	-4.53 – 1.69	0.37
Infections	RR 0.64	0.44 – 0.92	**0.02**

Risk ratio = RR; weighted mean difference = WMD.

Manzanares W, et al. **Crit Care 2015;19:167**

Fish Oil-containing ILE

Study or Subgroup	Fish Oils Events	Fish Oils Total	LCT or LCT+MCT Events	LCT or LCT+MCT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
5.15.1 PN based trials							
Grecu	0	8	1	7	1.5%	0.30 [0.01, 6.29]	2003
Friesecke	10	83	11	82	21.4%	0.90 [0.40, 2.00]	2008
Wang 2009	6	28	9	28	17.3%	0.67 [0.27, 1.62]	2009
Grau-Carmona	17	81	29	78	52.3%	0.56 [0.34, 0.94]	2014
Subtotal (95% CI)		**200**		**195**	**92.4%**	**0.64 [0.44, 0.94]**	
Total events	33		50				
Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 3 (P = 0.76); I² = 0%							
Test for overall effect: Z = 2.26 (P = 0.02)							
5.15.2 EN based trials							
Hall	3	30	5	30	7.6%	0.60 [0.16, 2.29]	2014
Subtotal (95% CI)		**30**		**30**	**7.6%**	**0.60 [0.16, 2.29]**	
Total events	3		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.75 (P = 0.45)							
Total (95% CI)		**230**		**225**	**100.0%**	**0.64 [0.44, 0.92]**	
Total events	36		55				
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 4 (P = 0.88); I² = 0%							
Test for overall effect: Z = 2.38 (P = 0.02)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%							

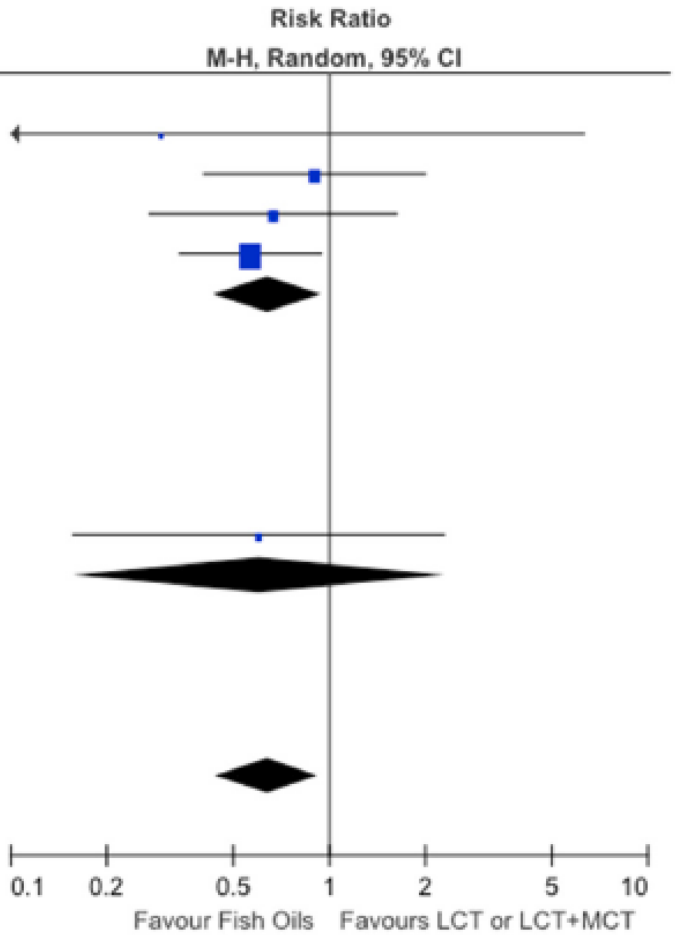


Figure 3 Effects on infections of parenteral fish oil containing emulsions (n =5). CI, Confidence interval; EN, Enteral nutrition; LCT, Long-chain triglycerides; MCT, Medium-chain triglycerides; M-H, Mantel-Haenszel test; PN, Parenteral nutrition.

Manzanares W, et al. **Crit Care 2015;19:167**

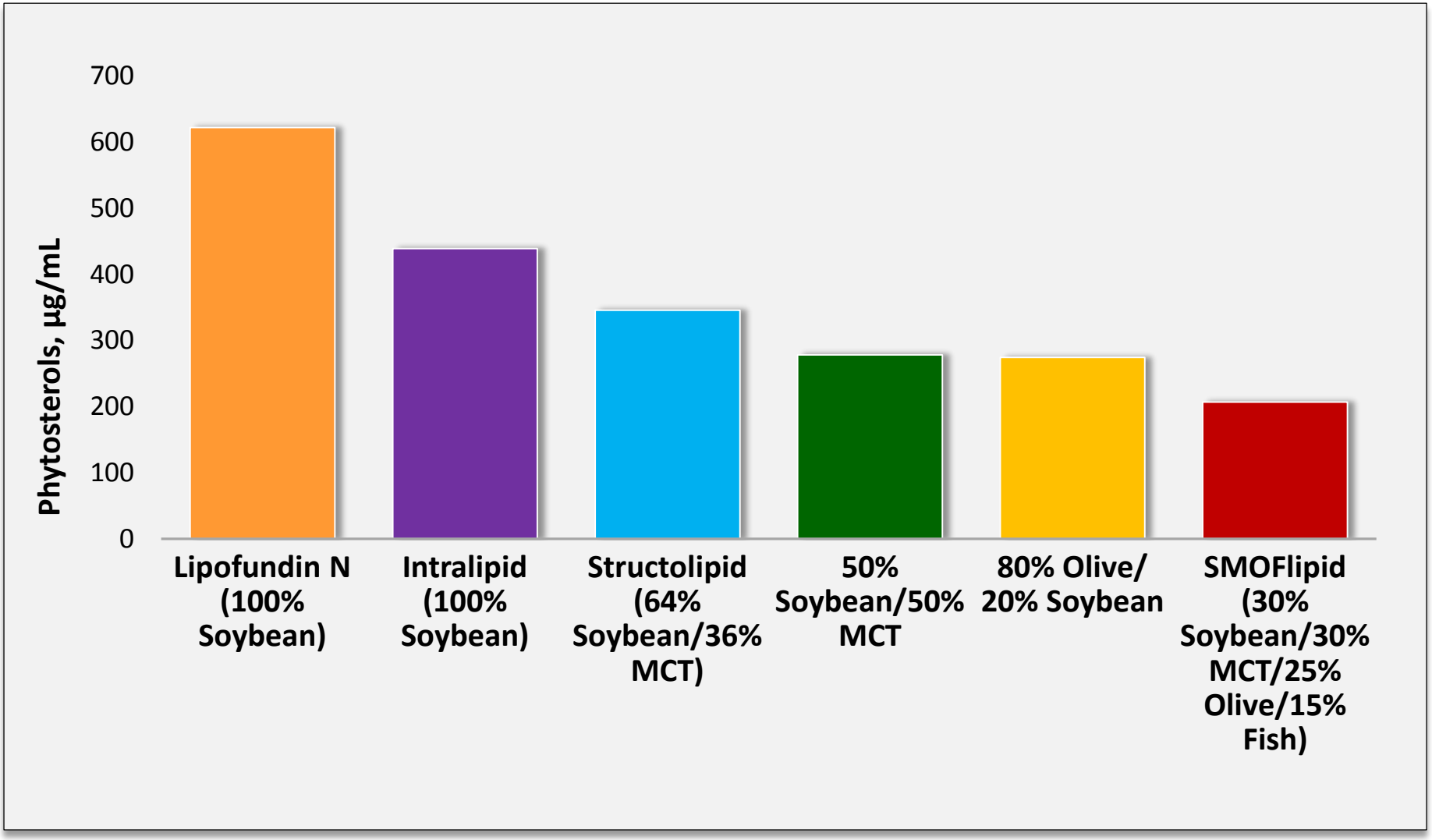
ICU Lipids Study: MCT/Soybean/Fish vs. MCT/Soybean Oil-based PN

- Prospective, double-blind, randomized, multicenter controlled trial in 17 Spanish surgical/medical ICUs (*4.4% of pts screened*)
  - Requiring 3-in-1 PN for at least 5 days & APACHE II ≥ 13
    - Study ILE (n=81): 50% MCT / 40% Soybean / 10% Fish Oil
    - Control ILE (n=78): 50% MCT / 50% Soybean Oil
  - Mean age 61 yrs, 73% male, APACHE II 21
  - 52% surgical & 48% medical
    - 46% sepsis, 29% septic shock, 12% pancreatitis*, 17% trauma, 9% cancer
  - PN provided for 9 days:
    - 1.4 g Protein/kg/day with 1737 (*Study*) vs. 1782 (*Control*) kcal/day
      - 1 g/kg/day as lipid emulsion
  - Prevalence of nosocomial infection: 21% vs. 37.2% (p=0.038)
  - ICU mortality: 32.5% vs. 20.5% (p=0.106)

* p=0.049

Grau-Carmona T, et al. **Crit Care Med 2015;43:31-9**

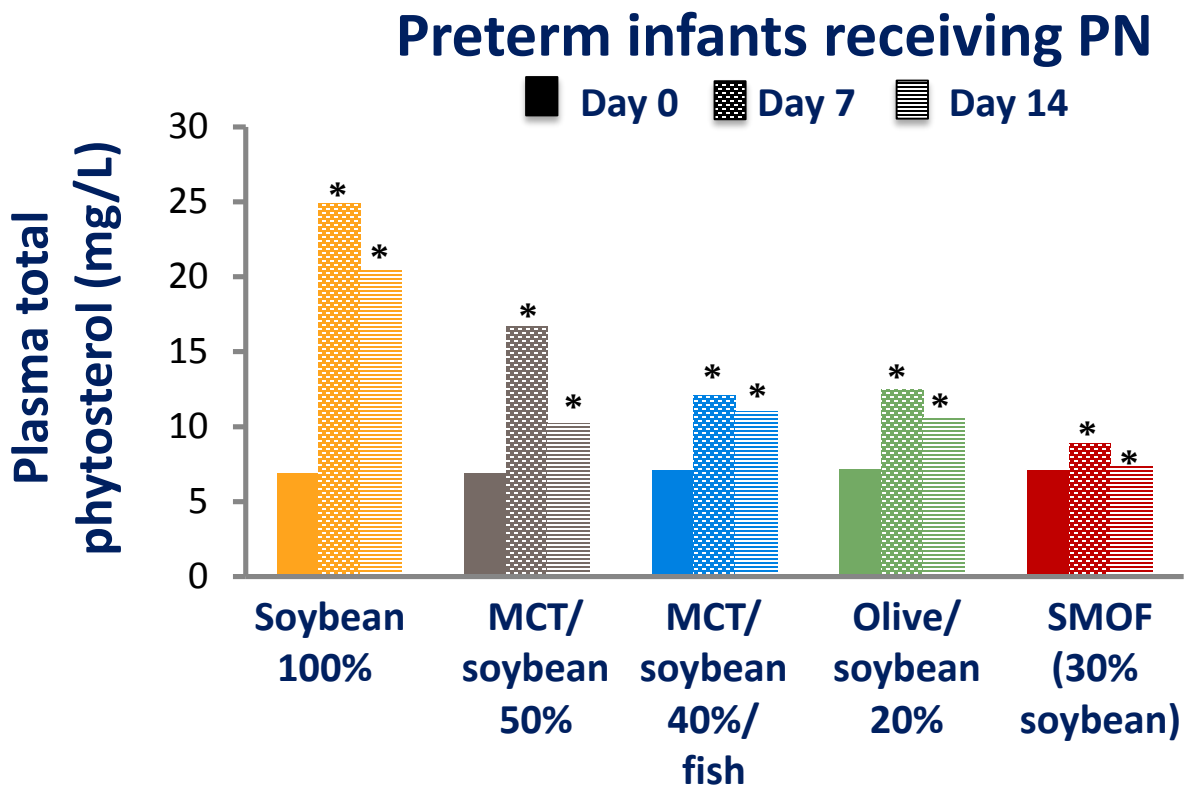
ILE and Phytosterol Content



Xu Z, et al. Nutrients 2012;4:904-921

Phytosterol Intake & Plasma Phytosterol

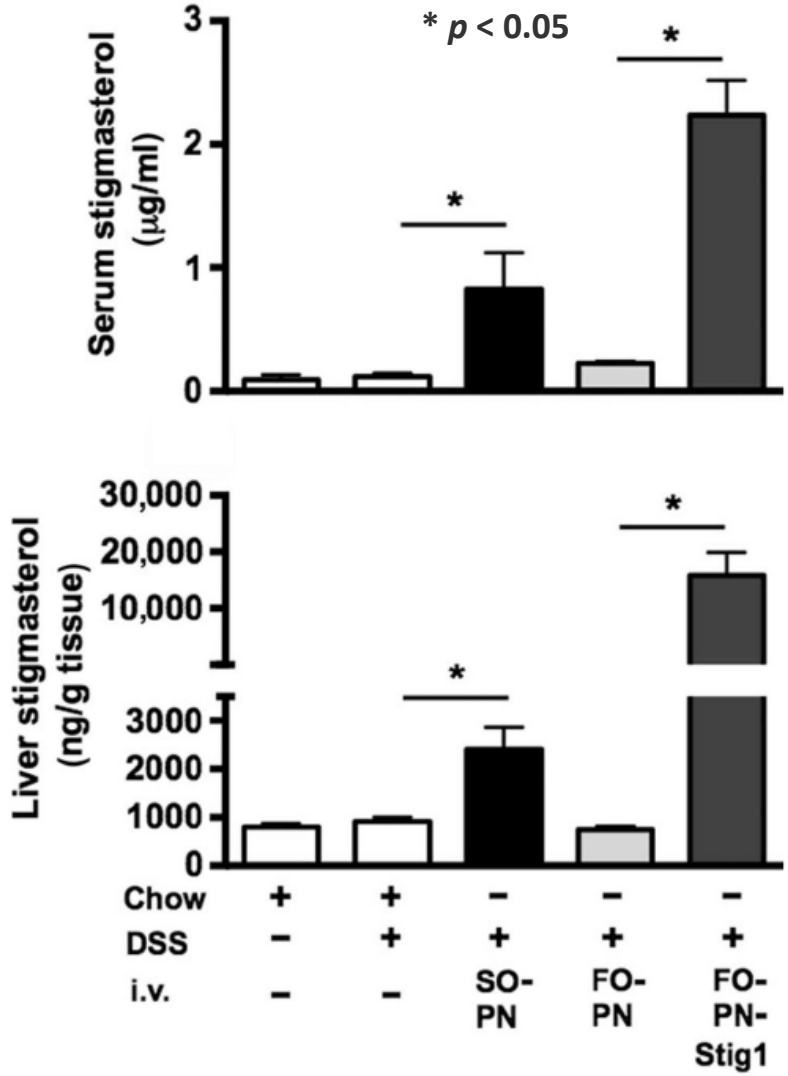
* - Significantly different from others on same day, $p < 0.05$



Single-center, parallel-group trial in preterm infants with birth weight 500-1249 g who received PN from the first hour of life (50% of energy intake from PN & 50% from enteral route). Neonates were randomized to one of five ILE: soybean oil (n=30), soybean oil/MCT (n=30), soybean oil/MCT/fish oil (n=27), olive oil/soybean oil (n=29) and soybean/MCT/olive oil/fish oil (n=28)

Savini S, et al. Am J Clin Nutr 2013;98:312-8

Stigmasterol in PN-Associated Liver Disease (Mice)

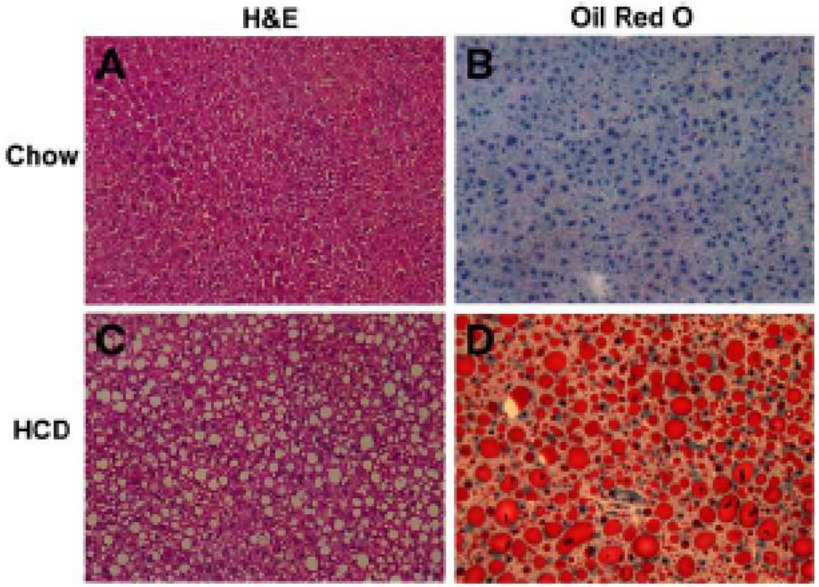


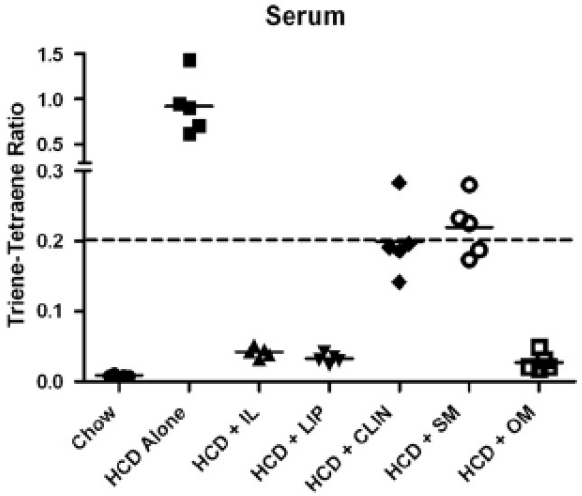
- Stigmasterol is one of the three major phytosterols present in soybean oil ILE
  - Promotes cholestasis by inhibiting nuclear receptor FXR, thereby reducing hepatocyte expression of genes including bile salt export pump, a determinant of bile secretion
- Fish oil-based ILE has no phytosterols
  - Similar effects to a no lipid PN on preventing cholestasis or liver injury
- Adding Stigmasterol to Fish oil-based ILE
  - Produced cholestasis and liver injury
  - Serum Stigmasterol concentration correlated with severity of cholestasis

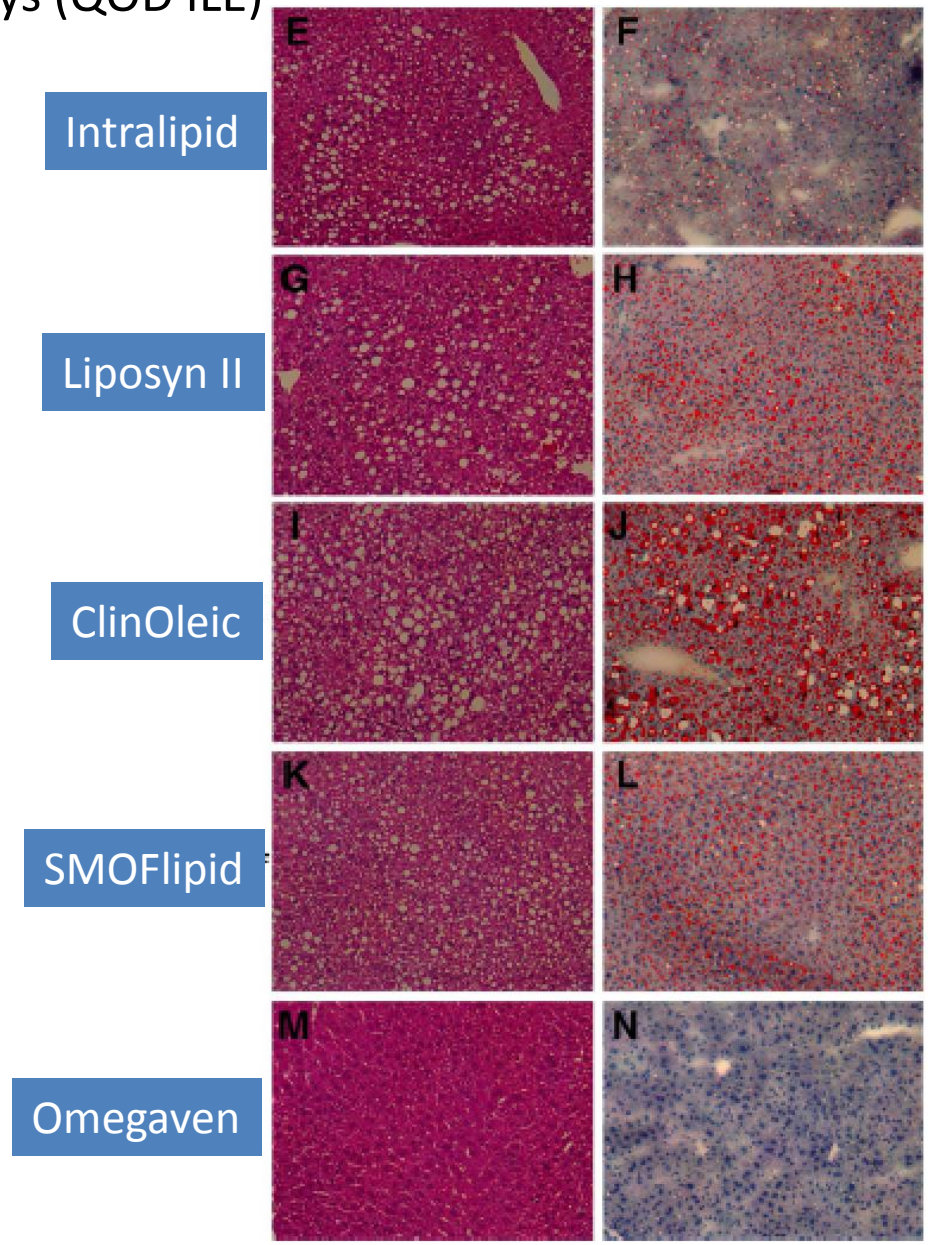
El Kasmi KC, et al. Sci Transl Med 2013;5:206a137

Mouse Liver Architecture and ILE Content

HCD = high carbohydrate diet for 19 days (QOD ILE)







Meisel JA, et al. J Pediatr Surg 2011;46:666-73

Summary

- Lipids are essential in the human diet and can be particularly influential in critically ill patients with evidence of malnutrition
- ω6 fatty acids have pro-inflammatory effects
- ω3 fatty acids have anti-inflammatory effects
- Biological effects of fatty acids are dose dependent
- Guidelines and systematic reviews currently recommend limiting ω6 saturated and polyunsaturated fatty acids
- Composition of commercially-available IVLE varies and provides differing combinations of fatty acid types
- High phytosterol content may be a factor in the development of PN-associated liver disease