Masterclass Voeding 2019

Is there evidence for specific lipids in (par)enteral nutrition?

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Dr. van Zanten has received honoraria for advisory board meetings, lectures, research and travel expenses from:

- Astellas
- Baxter
- BBraun
- Cardinal Health
- Fresenius Kabi
- Gilead
- Lyric
- Mermaid
- MSD
- Nestlé-Novartis
- Nutricia-Danone
- Pfizer

Other COI:

- ESPEN guidelines committee Critical Care Nutrition for Adults
- ESICM Working Group Gastrointestinal Failure
- NESPEN Executive Team
- Chair Netherlands Sepsis Guideline Working Group Dutch Working Party on Antibiotic Policy Guideline Committee for the Management of Fungal Infections

Lipids are an important

- enteral and parenteral nutrition
- essential fatty acids
- concentrated source of calories
- building blocks for cell membranes

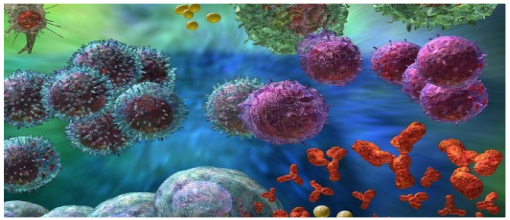
Enteral lipids, focus on fish oil

Which lipid should I choose for my patients?

Omega-3 PUFA	Omega-6 PUFA	Omega-9 MUFA	LCT/MCT

Requires well controlled and clinically relevant trials in select patient populations using relevant dosing

Long Chain Fatty Acids: Many Immune Effects are class effects



	Omega-3 PUFA	Omega-6 PUFA	Omega-9 MUFA	LCT/MCT
Pro-inflammatory Mediators[1-7] Cytokines Adhesion molecules	↓	↑↓	↓	↑
Cellular Immune Functions[3,8-12]	↓	↓	Little Effect	↓

1. James MJ, et al. Am J Clin Nutr. 2000;71(suppl):343S-348S; 2. Oh DY, et al. Cell. 2010;142:687-698; 3. Buenestado A, et al. JPEN J Parenteral Enteral Nutr. 2006;30(4):286-296; 4. Lee JY, et al. J Biol Chem. 2001;276(20):16683-16689; 5. Suzuki M, et al. J Biol Chem. 2013;288(15):10684-10691; 6. Versleijen M, et al. Clin Nutr. 2005;24(5):822-829; 7. Wanten GJA, et al. Eur J Clin Invest. 1999;29(5):357-363; 8. Søyland E. et al. Eur J Clin Invest. 1993;23(2):112-121; 9. Calder PC et al. Clin Nutr. 1994;13(2):69-74; 10. Granato D, et al. JPEN J Parenter Enteral Nutr. 2000;24(2):113-118; 11. Bellinati-Pires R, et al. Barz J Med Biol Res. 1992;25(4):369-373; 12. Tull SP, et al. PLoS Biology. 2009;7(8):e1000177; 13. Vanek WV, et al. Nutr Clin Pract. 2012;27:150–192.

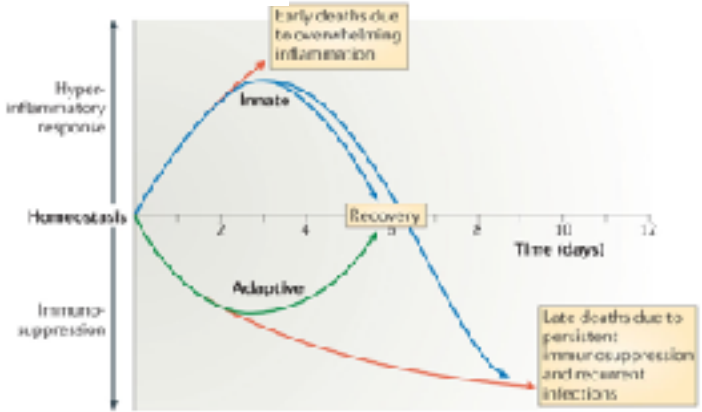
Effects of fish oil

- Long-chain fatty acids from fish oils:
  - EPA (eicosapentaenoic acid)
  - DHA (docosahexaenoic acid)
- EPA and DHA modulate:
  - Synthesis of eicosanoids
  - Activity of the nuclear receptor
  - Nuclear transcription factors
  - Production of resolvins
- EPA and DHA have long been recognized as having anti-inflammatory and immunomodulatory effects

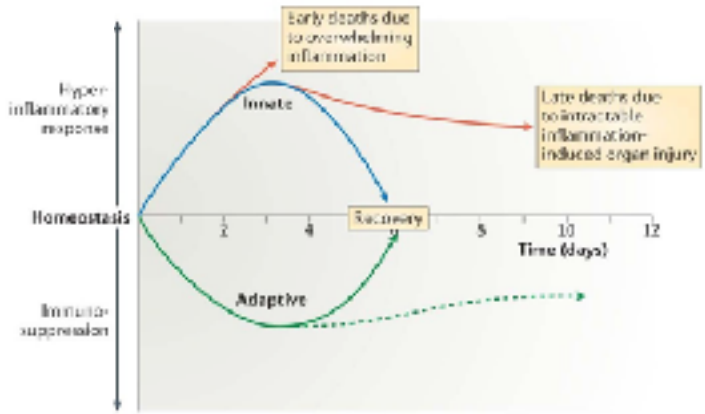
Waitzberg DL, et al. Nutr Clin Pract. 2009;24:487-99.

Persistent inflammatory, immunosuppressed, catabolic syndrome

Theory 1



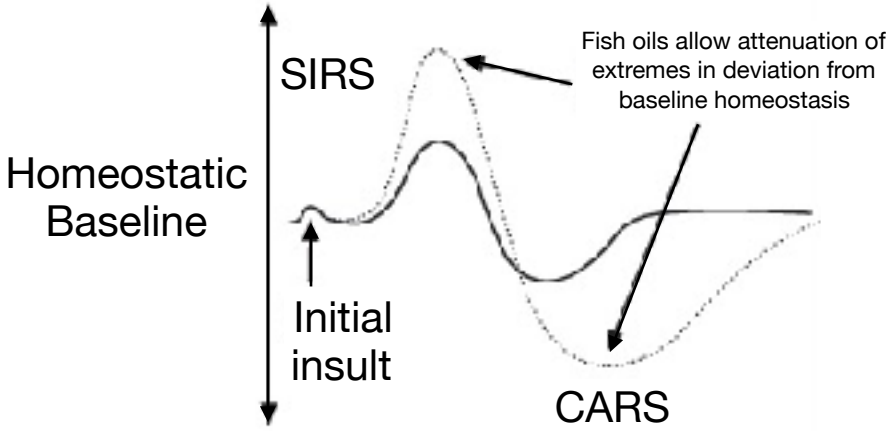
Theory 2



A new phenotype of multiple organ failure

Rosenthal MD, et al. J Adv Nutr Hum Metab 2015; 2: e784.
Hotchkiss R. Nature Reviews Immunology 13, 862–874 (2013)

PICS: A new phenotype of multiple organ failure

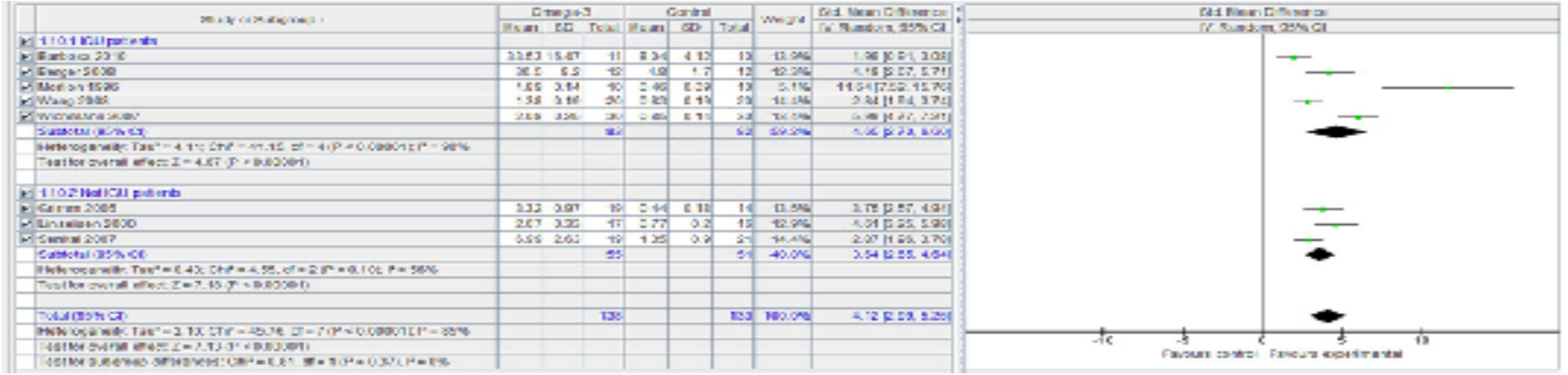


Hypothetical biphasic metabolic/
inflammatory response to trauma

Can fish oil be a double-edged sword and have both anti-inflammatory properties in the SIRS phase and pro-inflammatory properties in the CARS phase?

Rosenthal MD, et al. J Adv Nutr Hum Metab 2015; 2

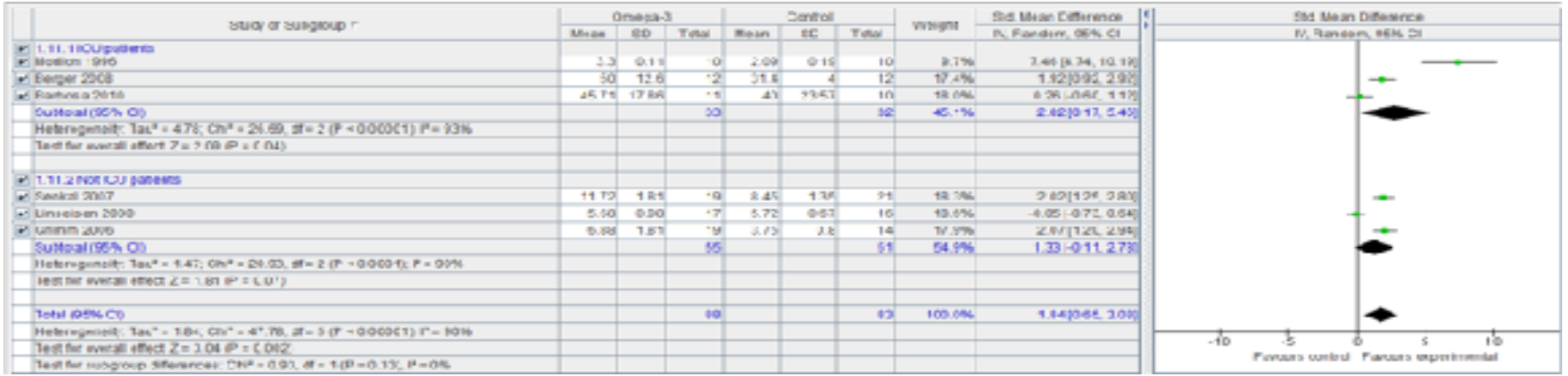
Does fish oil supplementation lead to increased EPA levels? yes



Standard mean difference
4.12 (95% CI 2.99-5.25)

Pradelli, et al. Critical Care 2012,16:R184.

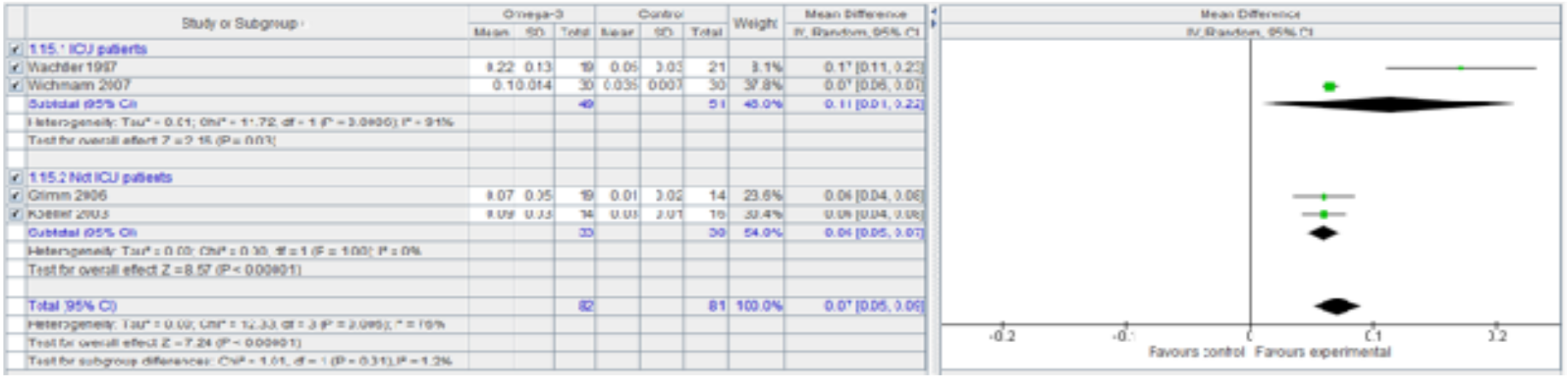
Does fish oil supplementation lead to increased DHA levels? yes



Standard mean difference
1.84 (95% CI 0.65-3.03)

Pradelli, et al. Critical Care 2012;16:R184.

Does EPA and DHA from fish oil lead to reductions in proinflammatory mediators? yes



Significantly greater reduction in IL-6 and a shift in the generation of leukotrienes towards the leukotriene-5 series, as indicated by the significant absolute increase in leukotriene B5 (LTB5), the absolute decrease of LTB4, and the significantly ameliorated LTB5: LBT4 ratio.

Reflects Anti-inflammatory Response

Pradelli, et al. Critical Care 2012;16:R184.

Enteral fish oil in Acute Respiratory Distress Syndrome

Eden Omega trial

Factorial Design Study
Enteral fish oil vs. Placebo (protein)
Trophic vs. Full nutritional support

Study was stopped early for futility after 143 & 129 patients in the n-3 and control groups

Supplement	"Early Full" Fast Ramp Up	"Early Trophic" (10 ml/hr)
N-3 + GLA + Antioxidants (Module delivered as bolus bid)	N=250	N=250
Control Standard EN (480 cal/ 20 g proteins)	N=250	N=250

Rice T. JAMA. 2011;306(14):1574-1581.

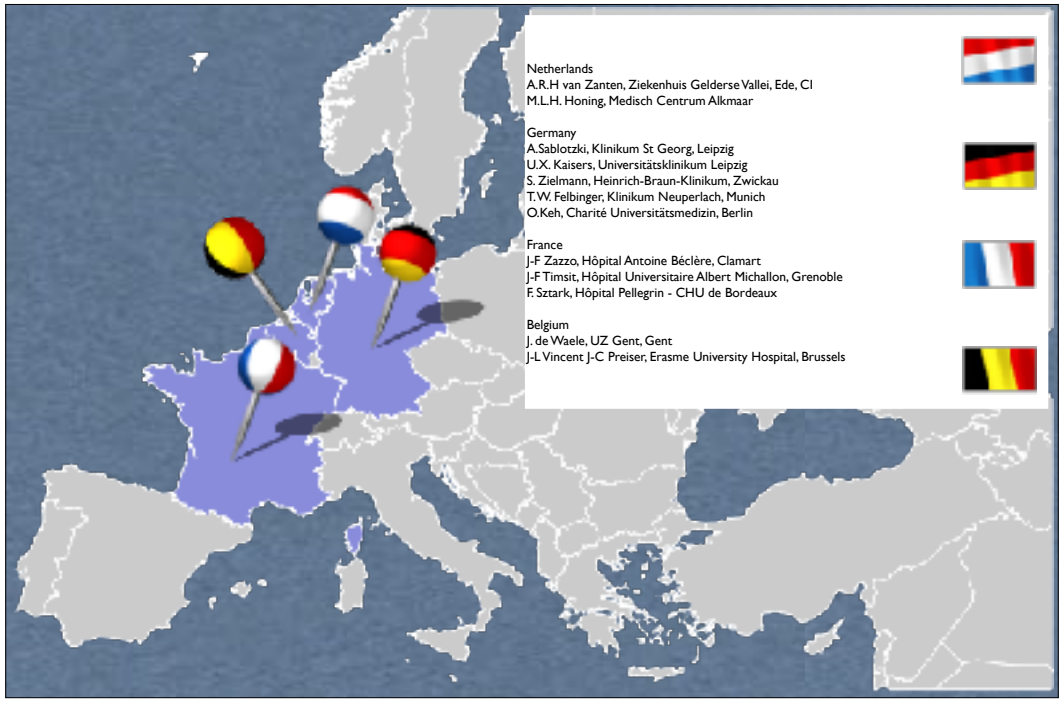
Enteral fish oil in Acute Respiratory Distress Syndrome

Eden Omega trial

Outcome	N-3 (n=143)	Control (n=129)	95% CI Difference	P value
Ventilator free days 28d	14.0 (11.1)	17.2 (10.2)	-3.2 (-5.8 to -0.7)	0.02
Hospital mortality unadjusted	26.6 (19.3-33.8)	16.3 (9.9-22.7)	10.3 (0.7 to 19.9)	0.054
Adjusted mortality	25.1 (9.2-41.0)	17.6 (3.3-31.9)	7.5 (-3.1 to 18.1)	0.11
Days not in ICU 28d	14.0 (10.5)	16.7 (9.5)	-2.7 (-5.1 to -0.3)	0.04
Days without organ failure 28d	12.3 (11.1)	15.5 (11.4)	-3.2 (-5.9 to -0.5)	0.02

Rice T. JAMA. 2011;306(14):1574-1581.

MetaPlus trial



Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Compositions Immune-modulating High Protein and HP control feed

during ICU stay up to maximum of day 28

Nutrients (per 1500 mL)	IMHP	HP
Energy	1920 kcal	1920 kcal
Protein (g) ▪ Cas/ wheat hydr / Ala-Gln ▪ **Glutamine**	112.5 g (23.4 En%) ▪ 41% / 39% / 20% ▪ **30 g**	112.5 g (23.4 En%) ▪ 100 %/0/0 ▪ 9 g
Carbohydrates ▪ Fructose	141 g - (29.3 En%) ▪ 0 g	231 g - (48 En%) ▪ 0 g
Fat ▪ MCT ▪ **EPA – DHA**	96 g (45 En%) ▪ 19.5 g ▪ **7.5 g**	55.5 g (26.3 En%) ▪ 0 g ▪ 0 g
Anti-oxidants ▪ **vitamin C** ▪ **vitamin E (alpha toco)** ▪ **Selenium** ▪ **Zinc**	Above normal values ▪ **690 mg** ▪ **266 mg (400 IU)** ▪ **285 mcg** ▪ **30 mg**	Normal values ▪ 195 mg ▪ 22.5 mg ▪ 112.5 mcg ▪ 22.5 mg
Other Vit / Min./ trace el.	Normal values	Normal values
Fiber	22.5 g (2.3 En%)	22.5 g (2.3 En%)

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Incidence new infections

Primary Outcome Measure	IMHP	HP	P value
	n=152	n=149	
All	**53%**	**52%**	0.961
Medical (IMHP n=54 vs. Protison n=55)	**39%**	**47%**	0.377
Surgical (IMHP n=81 vs. Protison n=75)	**62%**	**51%**	0.164
Trauma (IMHP n=55 vs. Protison n=54)	**58%**	**67%**	0.361

- **% of subjects with at least one infection after start study product, using CDC-infection criteria**
- **No statistical significant differences between IMHP and HP based on Chi square tests.**

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Mortality

	28-days mortality Incidence (%)		
	IMHP	HP	p value
All (n=168)	**20%**	**17%**	0.420
Medical (n=109)	**35%**	**24%**	0.186
Surgical (n=156)	**14%**	**16%**	0.670
Trauma (n=109)	**7%**	**4%**	0.679

	6-months mortality Incidence (%)		
	IMHP	HP	p value
All (n=297)	**35%**	**28%**	0.212
Medical (n=109)	**54%**	**35%**	0.044
Surgical (n=152)	**27%**	**28%**	0.900
Trauma (n=107)	**15%**	**17%**	0.759

Differences between IMHP and HP based on Chi square tests.

Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

6-months mortality Cox hazard model

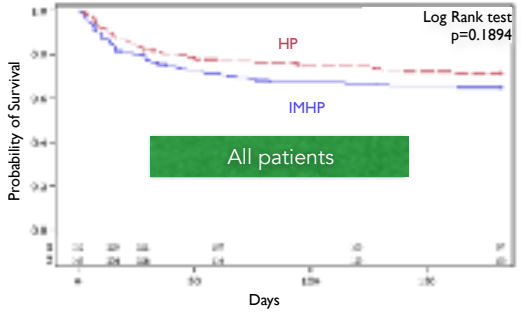
	Hazard Ratio	Lower Limit	Upper Limit	P value
IMHP vs. HP	1.57	1.03	2.39	0.036
Age (70-80 vs. age (>80)	0.47	0.27	0.81	0.006
Age (50-70) vs. age (>80)	0.24	0.14	0.43	<0.001
Age (<50) vs. age (>80)	0.12	0.05	0.27	<0.001
APACHE-II score (unit)	1.05	1.02	1.09	<0.001

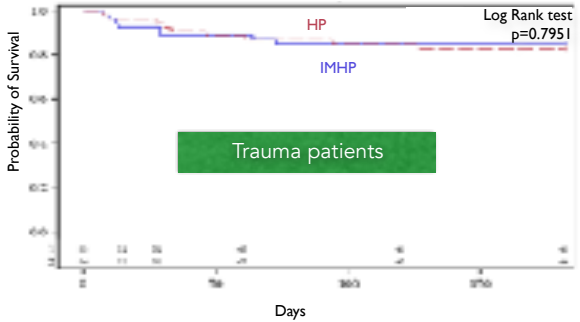
After adjustment for age and APACHE-II score,
risk of death is 57% higher for patients on IMHP versus control feed patients (P=0.036)

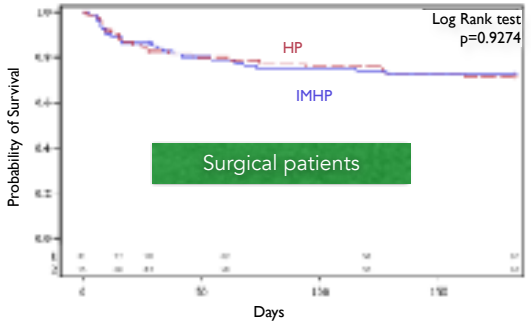
pre-defined covariates: age (≤50, 51-70, 71-80, >80 yrs), sex, BMI, APACHE-II score, adj. pred. mortality, screening SOFA score, baseline glutamine, baseline glucose, type of patient (medical, surgical non trauma, surgical trauma, trauma non surgical), start study product since ICU admission, occurrence of pre-existing infection, and treatment with antibiotics at start of study. The final model was constructed using univariate screening followed by a stepwise variable-selection procedure.

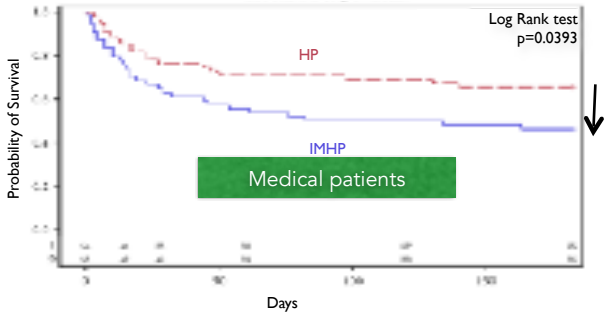
Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

6-months Kaplan-Meier survival MetaPlus trial





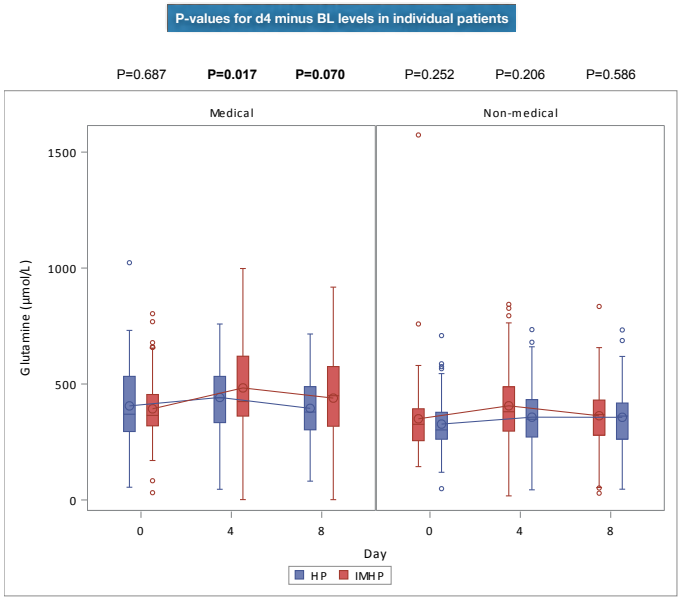




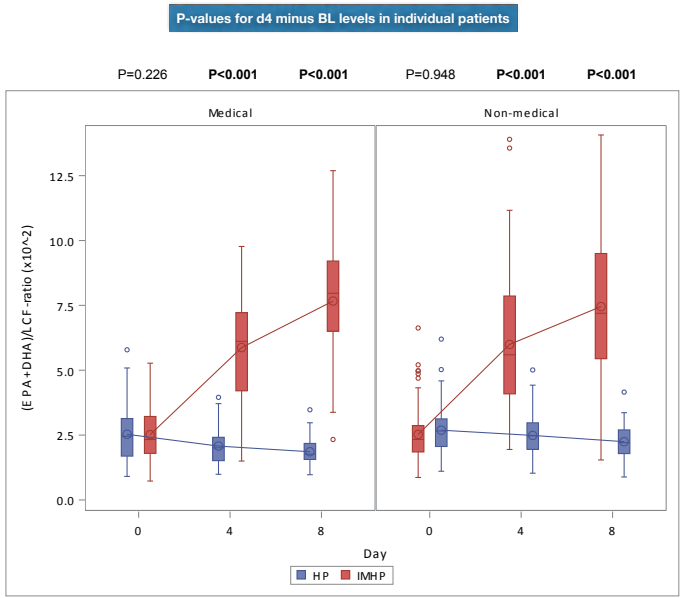
Van Zanten AR et al. JAMA 2014 Aug 6;312(5):514-24.

Does the intervention lead to increased plasma levels?

Proof of concept: MetaPlus post-hoc analysis



Glutamine plasma levels d0, d4 and d8



(EPA+DHA)/LCF-ratio plasma levels d0, d4 and d8

Hofman D, … van Zanten AR. Ann. Intensive Care (2016) 6:119

high (epa+dha)/lcf-ratios on ICU admission are not associated with increased 6-month mortality

	Univariate Analysis			Multivariate Analysis		
Immune-modulating Nutrient	Coef	Std Err	P-value	Coef	Std Err	P-value
Glutamine	0.00119	0.00059	0.046	0.00034	0.00065	0.599
(EPA+DHA)/LCF-ratio	21.17397	9.87606	0.032	-2.08190	10.41535	0.842
Selenium	0.06623	0.16564	0.689	0.11961	0.14465	0.408
Vitamin E	-0.00416	0.01402	0.766	-0.00750	0.01458	0.607
Vitamin C	0.00297	0.00754	0.694	-0.00507	0.00817	0.535
Zinc	0.01189	0.02532	0.639	0.02327	0.02437	0.340

Coef = Coefficient; Std Err = parameter estimate standard regression; (EPA+DHA)/LCP-ratio = (eicosapentaenoicacid+decosahexaenoicacid)/long chain polyunsaturated fatty acid-ratio. The coefficient is the Cox Proportional Hazard Regression Parameter estimate; a positive coefficient indicates a worse prognosis and a negative coefficient indicates a protective effect of the variable on 6-month mortality. Chi-square statistic testing the null hypothesis that the estimate is zero.

Hofman D, ... van Zanten AR. Ann. Intensive Care (2016) 6:119

Are increased levels on d4 and d8 associated with 6-month mortality in medical patients?

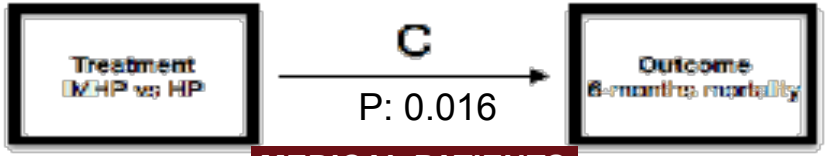
MetaPlus post-hoc analysis: n=301

	Baseline to day 4					Baseline to day 8				
Immunonutrient	**Coef.**	**Std Err**	**Hazard Ratio**	**95% CI of the Hazard Ratio**	**P-value**	**Coef.**	**Std Err**	**Hazard Ratio**	**95% CI of the Hazard Ratio**	**P-value**
Glutamine (µmol/L)	-0,002	0,001	0,998	[0.996, 1.000]	0,111	-0,001	0,001	0,999	[0.996, 1.001]	0,302
(EPA+DHA)/LCF-ratio (x10-2)	0,162	0,070	**1,176**	**[1.023, 1.348]**	**0,021**	0,055	0,053	1,057	[0.949, 1.170]	0,294
Selenium (µmol/L)	0,487	0,457	1.628	[0.644, 3.892]	0,286	-0,551	0,615	0,576	[0.159, 1.776]	0,370
Vit E (µmol/L)	-0,005	0,015	0,995	[0.964, 1.024]	0,758	0,009	0,012	1,009	[0.985, 1.031]	0,446
Vit C (µmol/L)	-0,006	0,011	0,994	[0.971, 1.016]	0,614	-0,001	0,011	0,999	[0.976, 1.020]	0,944
Zinc (µmol/L)	-0,013	0,049	0,988	[0.890, 1.080]	0,799	-0,093	0,064	0,912	[0.794, 1.020]	0,145

Hofman D, … van Zanten AR. Ann. Intensive Care (2016) 6:119

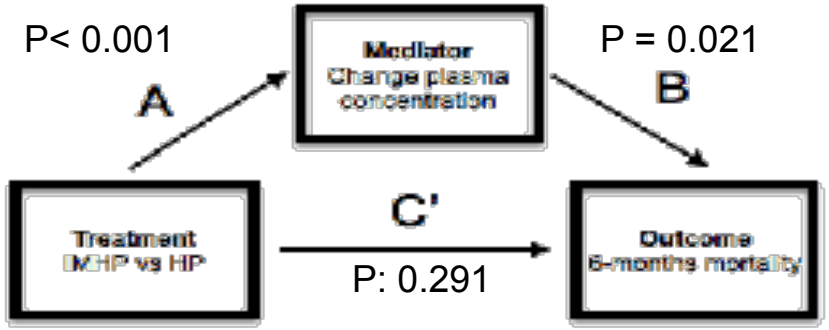
Changes in (epa+dha)/lcf-ratios from admission to d4, are associated with 6-month mortality independent of baseline ratio

MODEL I



MEDICAL PATIENTS

MODEL II



MEDICAL PATIENTS: Significant increase from baseline on day 4 and day 8

MEDICAL PATIENTS: Increase from baseline on day 4 independently associated with increased 6-month mortality irrespective of baseline levels

MEDICAL PATIENTS: When including the interaction term EPA+DHA/LCP-ratio C' is no longer significant

Hofman D, … van Zanten AR. Ann. Intensive Care (2016) 6:119

Nutrition 59 (2019) 56–68

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: A systematic review and meta-analysis

WAC (Kristine) Koekkoek M.D. [a], Vasilianna Panteleon M.Sc. [b], Arthur RH van Zanten M.D., Ph.D. [a,*]

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Data in Brief 21 (2018) 604–615

Contents lists available at ScienceDirect

Data in Brief

journal homepage: www.elsevier.com/locate/dib

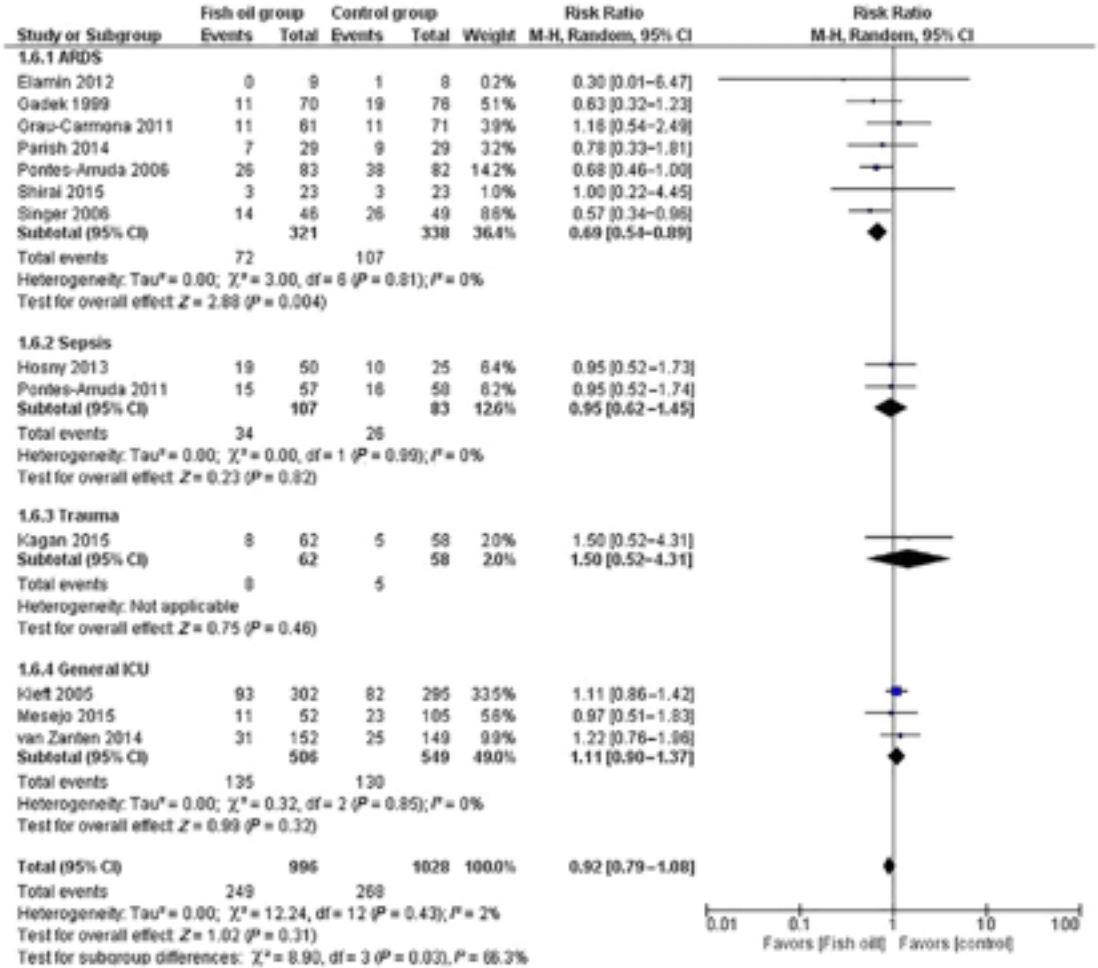
Data Article

Data on effects, tolerability and safety of Omega-3 Fatty Acids in Enteral Nutrition in the Critically ill

24 trials, 3574 ICU patients treated with fish oil EN vs. no fish oil EN

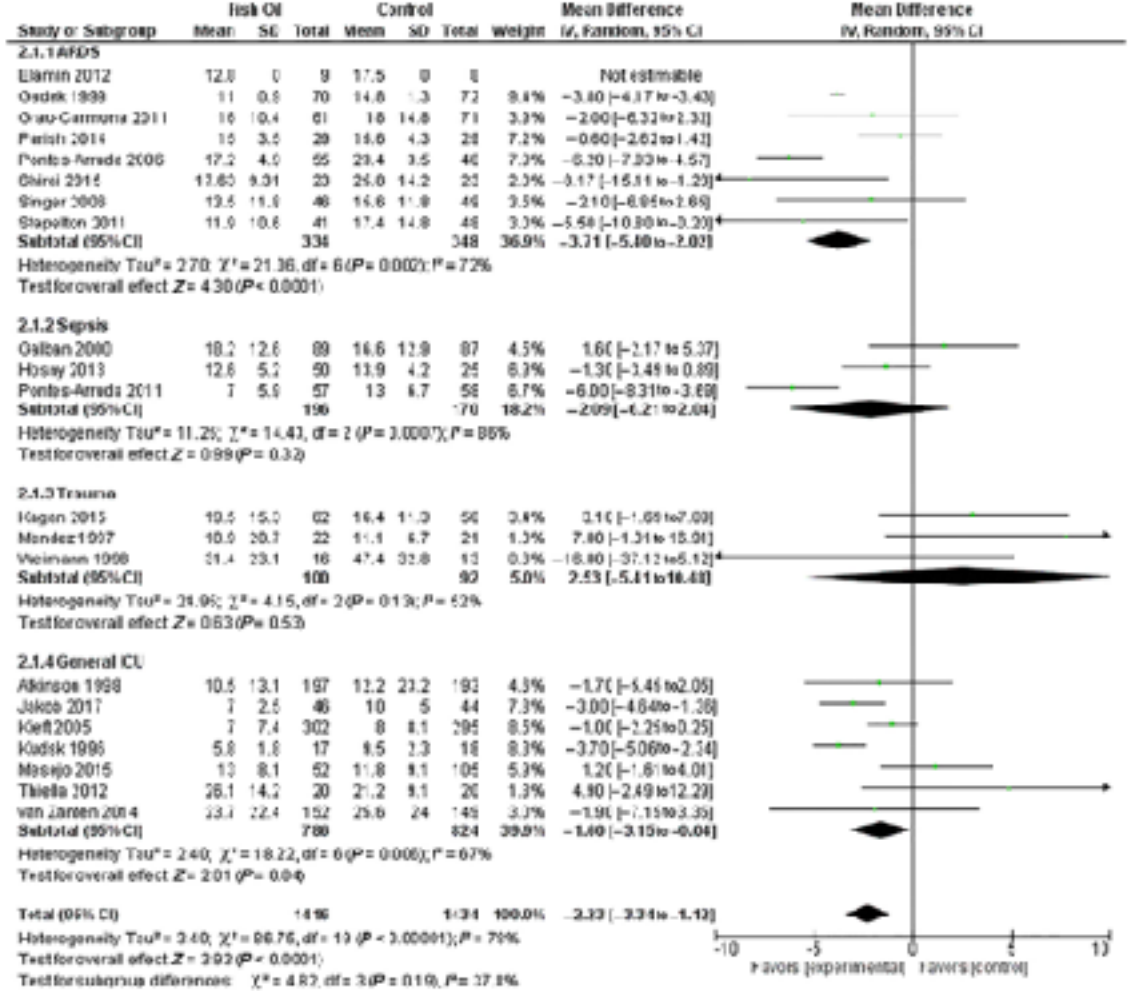
Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615

Koekkoek K, Panteleon V, van Zanten AR. Nutrition 2019;59:56-68



28-day mortality: Benefit in ARDS, not in sepsis, trauma and general ICU populations

Koekkoek K, Panteleon V, van Zanten AR. Nutrition 2019;59:56-68

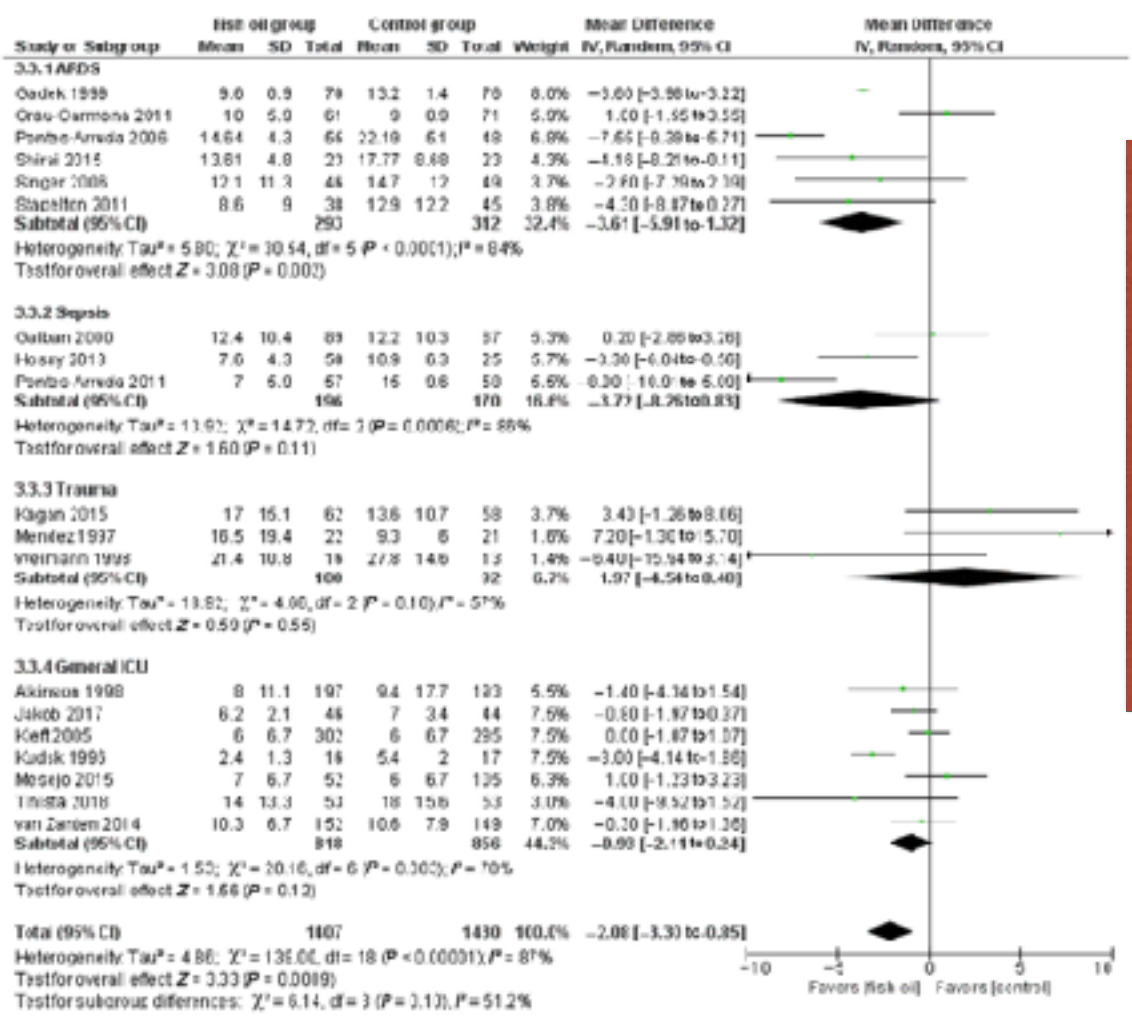


ICU LOS:
reduced in ARDS and general ICU patients, not in sepsis and trauma patients

Significant statistical heterogeneity

Hospital LOS:
No effect, data not show

Koekkoek K, Panteleon V, van Zanten AR. Nutrition 2019;59:56-68

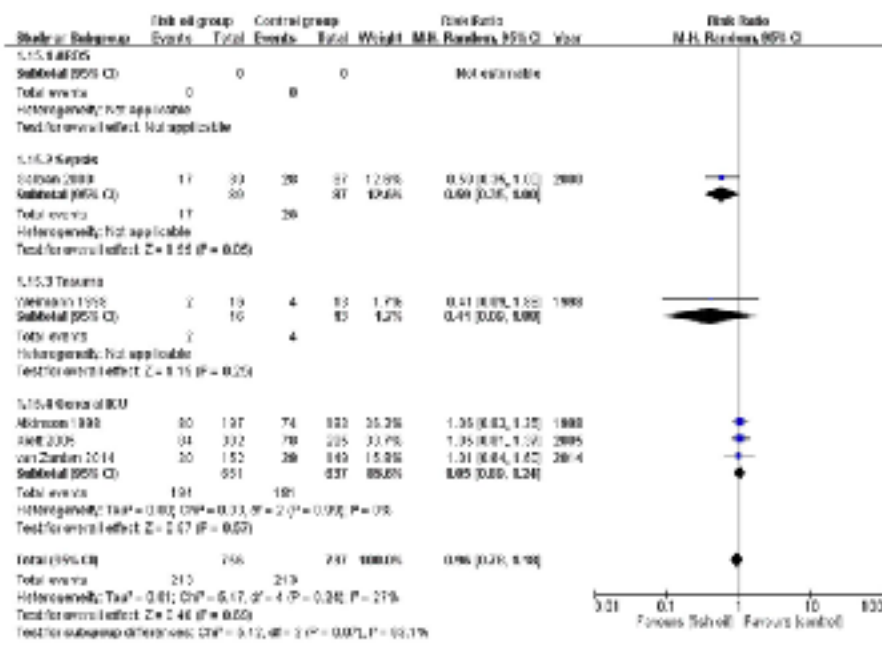


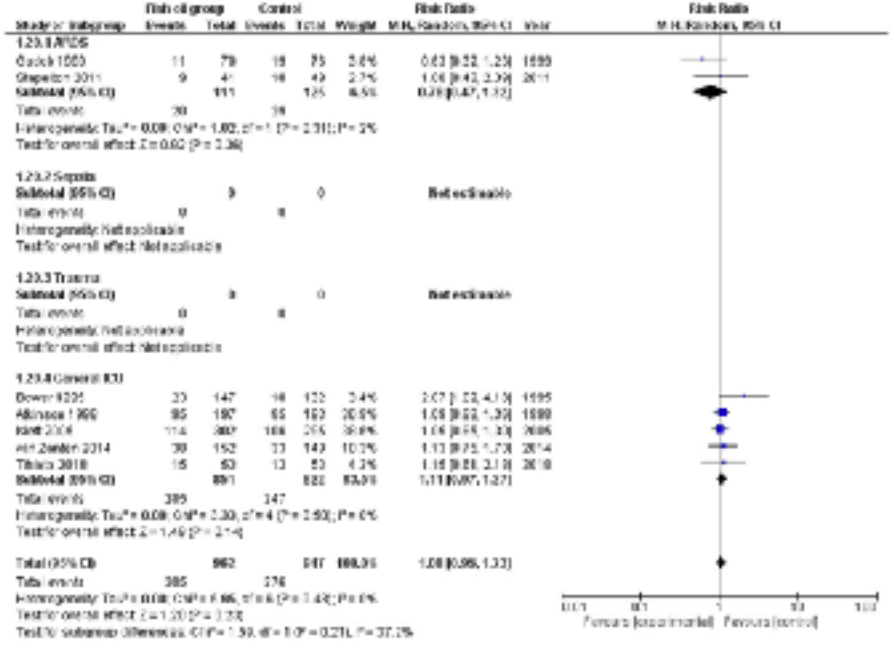
Duration of ventilation: reduced in ARDS patients and not in sepsis, trauma and general ICU patients

Significant statistical heterogeneity

Koekkoek K, Panteleon V, van Zanten AR. Nutrition 2019;59:56-68

Enteral fish oil and ICU and hospital mortality



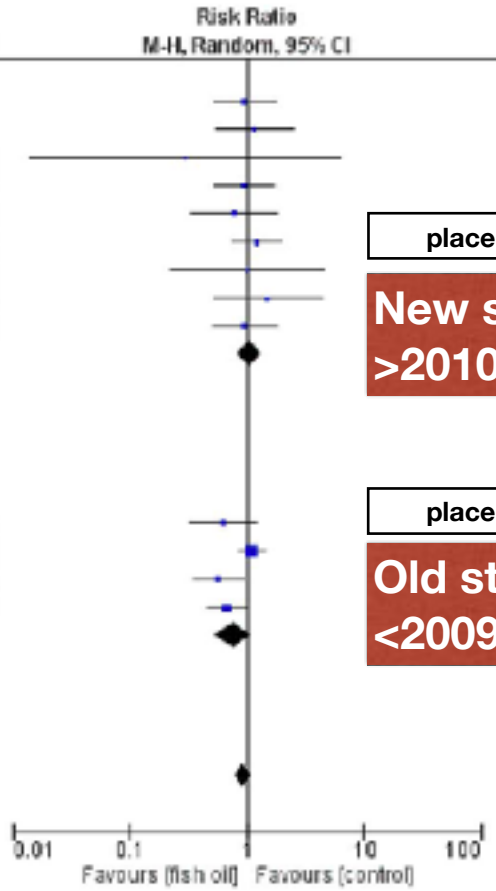


No effect in any subgroup nor combined

Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615

28-day mortality

Study or Subgroup	Fish oil group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.8.1 New studies (2010-2015)							
Pontes-Arruda 2011	15	57	16	59	6.2%	0.95 [0.52, 1.74]	2011
Grau-Carmona 2011	11	61	11	71	3.9%	1.16 [0.54, 2.49]	2011
Ellamin 2012	0	9	1	8	0.2%	0.30 [0.01, 6.47]	2012
Hoeny 2013	19	50	10	25	6.4%	0.95 [0.52, 1.73]	2013
Parish 2014	7	29	9	28	3.2%	0.78 [0.33, 1.81]	2014
van Zanten 2014	31	152	25	149	9.9%	1.22 [0.76, 1.96]	2014
Shirai 2015	3	23	3	23	1.0%	1.00 [0.22, 4.46]	2015
Kagan 2015	8	62	5	58	2.0%	1.50 [0.52, 4.31]	2015
Mesejo 2015	11	52	23	105	5.8%	0.97 [0.51, 1.83]	2015
Subtotal (95% CI)		495		526	38.5%	1.04 [0.81, 1.32]	
Total events	105		103				
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 8 (P = 0.97); I² = 0%							
Test for overall effect: Z = 0.30 (P = 0.76)							
1.8.2 Old studies (1999-2009)							
Gadek 1999	11	70	19	76	5.1%	0.63 [0.32, 1.23]	1999
Klett 2005	93	302	82	295	33.5%	1.11 [0.86, 1.42]	2005
Singer 2006	14	46	26	49	8.8%	0.57 [0.34, 0.96]	2006
Pontes-Arruda 2006	26	83	38	82	14.2%	0.68 [0.46, 1.00]	2006
Subtotal (95% CI)		501		502	61.5%	0.76 [0.53, 1.09]	
Total events	144		165				
Heterogeneity: Tau² = 0.08; Chi² = 8.64, df = 3 (P = 0.03); I² = 65%							
Test for overall effect: Z = 1.49 (P = 0.14)							
Total (95% CI)		996		1028	100.0%	0.92 [0.79, 1.08]	
Total events	249		268				
Heterogeneity: Tau² = 0.00; Chi² = 12.24, df = 12 (P = 0.43); I² = 2%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi² = 1.98, df = 1 (P = 0.16), I² = 49.4%							



placebo mortality 19.6%

New studies >2010 no effect

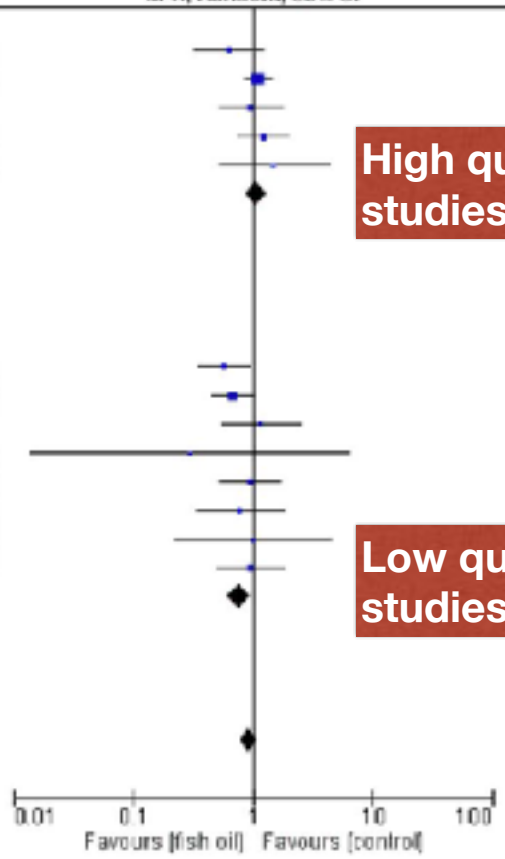
placebo mortality 32.9%

Old studies <2009 trend

Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615

28-day mortality

Study or Subgroup	Fish oil group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.7.1 Level I studies (score: 9-14)							
Gadek 1999	11	70	19	76	5.1%	0.63 [0.32, 1.23]	1999
Kieft 2005	93	302	82	295	33.5%	1.11 [0.86, 1.42]	2005
Pontes-Arruda 2011	15	57	16	58	6.2%	0.95 [0.52, 1.74]	2011
van Zanten 2014	31	152	25	149	9.9%	1.22 [0.76, 1.96]	2014
Kagan 2015	8	62	5	58	2.0%	1.50 [0.52, 4.31]	2015
Subtotal (95% CI)		**643**		**636**	**56.8%**	**1.07 [0.88, 1.30]**	
Total events	158		147				
Heterogeneity: Tau² = 0.00; Chi² = 3.31, df = 4 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
1.7.2 Level II studies (score: 0-8)							
Singer 2006	14	46	26	49	8.6%	0.57 [0.34, 0.96]	2006
Pontes-Arruda 2006	26	83	38	82	14.2%	0.68 [0.46, 1.00]	2006
Grau-Carmona 2011	11	61	11	71	3.9%	1.16 [0.54, 2.49]	2011
Elamin 2012	0	9	1	8	0.2%	0.30 [0.01, 6.47]	2012
Hosny 2013	19	50	10	25	6.4%	0.95 [0.52, 1.73]	2013
Parish 2014	7	29	9	29	3.2%	0.78 [0.33, 1.81]	2014
Shirai 2015	3	23	3	23	1.0%	1.00 [0.22, 4.45]	2015
Mesejo 2015	11	52	23	105	5.6%	0.97 [0.51, 1.83]	2015
Subtotal (95% CI)		**353**		**392**	**43.2%**	**0.77 [0.61, 0.96]**	
Total events	91		121				
Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 7 (P = 0.75); I² = 0%							
Test for overall effect: Z = 2.28 (P = 0.02)							
Total (95% CI)		**996**		**1028**	**100.0%**	**0.92 [0.79, 1.08]**	
Total events	249		268				
Heterogeneity: Tau² = 0.00; Chi² = 12.24, df = 12 (P = 0.43); I² = 2%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi² = 4.64, df = 1 (P = 0.03), I² = 78.4%							



High quality studies no effect

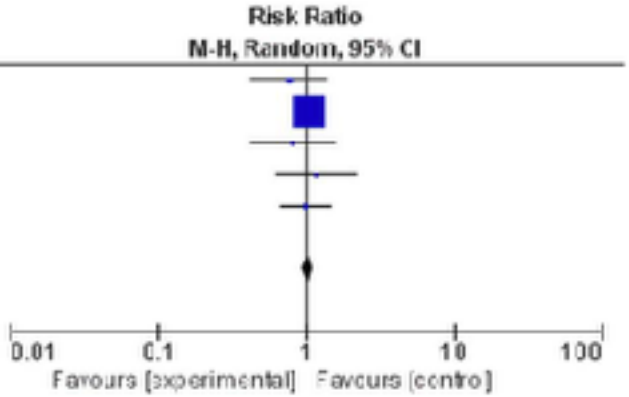
Low quality studies effect

Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615

Adverse event EN fish oil vs control

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gadek 1999	15	70	21	76	2.0%	0.78 [0.44, 1.38]
Kieft 2005	240	302	223	296	90.0%	1.05 [0.96, 1.15]
Pontes-Arruda 2006	13	55	14	48	1.5%	0.81 [0.42, 1.55]
Stapleton 2011	14	41	14	48	1.3%	1.17 [0.63, 2.16]
van Zanten 2014	39	152	38	149	4.5%	1.01 [0.68, 1.48]
Total (95% CI)		**620**		**616**	**100.0%**	**1.04 [0.96, 1.13]**
Total events	321		310			

Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)



No difference in reported adverse events

Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615

ASPEN/SCCM 2016 Guidelines enteral fish oil

- Question: Should EN formulas with fish oils (FOs), borage oil, and antioxidants be used in patients with ALI or ARDS?

- E3. We cannot make a recommendation at this time regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (eg, omega-3 FOs, borage oil) and antioxidants in patients with ARDS and severe ALI, given conflicting data.

- [Quality of Evidence: Low to Very Low]

McClave SA, et al. JPEN J Parenter Enteral Nutr. 2016 Feb;40(2):159-211.

ESPEN ICU guideline 2018

Recommendation 30

High doses of omega-3-enriched EN formula should not be given by bolus administration.

Grade of recommendation: B – strong consensus (91 % agreement)

Recommendation 31

EN enriched with omega-3 FA within nutritional doses can be administered.

Grade of recommendation: 0 – strong consensus (95 % agreement)

Recommendation 32

High doses omega-3 enriched enteral formulas should not be given on a routine basis.

Grade of recommendation: B – consensus (90 % agreement)

Singer P, …van Zanten AR, ..Bischoff SC et al. Clin Nutr. 2019;38(1):48-79

What did this meta-analysis learn us?

- Enteral fish oil supplementation cannot be recommended in general
- Signal of mortality reduction in ARDS based on older studies
- Shorter ICU LOS (only) in ARDS and general ICU patients, does not translate into shorter HLOS
- Shorter duration of mechanical ventilation in ARDS (heterogeneity)
- EN fish oil can be considered in ARDS, but effect is small and probably not clinically relevant.

Koekkoek K, Panteleon V, van Zanten AR. Data Brief. 2018;21:604-615
Koekkoek K, Panteleon V, van Zanten AR. Nutrition 2019;59:56-68

Parenteral lipids

Recent meta-analysis EN vs PN

Elke et al. Critical Care (2016) 20:117
DOI 10.1186/s13054-016-1298-1

Critical Care

RESEARCH Open Access

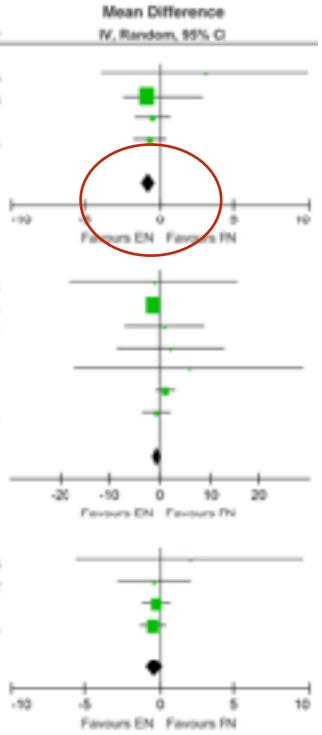
Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials

Gunnar Elke[1], Arthur R. H. van Zanten[2], Margot Lemieux[3], Michele McCall[4], Khursheed N. Jeejeebhoy[5], Matthias Kott[1], Xuran Jiang[3], Andrew G. Day[3] and Daren K. Heyland[3*]

Elke G, Van Zanten AR et al. Crit Care 2016;20:117

EN versus PN: LOS, duration ventilation

Study or Subgroup	EN Mean	EN SD	EN Total	PN Mean	PN SD	PN Total	Weight	Mean Difference IV, Random, 95% CI	Year
ICU LOS									
Adams	13	11	19	10	10	17	0.4%	3.00 [-3.16, 9.16]	1986
Peterson	3.7	0.8	21	4.6	1	25	68.6%	-0.90 [-1.42, -0.38]	1988
Chen	9.09	2.35	49	9.6	3.06	49	14.0%	-0.51 [-1.66, 0.64]	2011
Harvey	11.3	12.5	1197	12	13.5	1190	17.0%	-0.70 [-1.14, 0.34]	2014
Total (95% CI)	26.8		1286			1281	100.0%	-0.80 [-1.25, -0.37]	
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 3 (P = 0.66); I² = 0%									
Test for overall effect: Z = 3.62 (P = 0.0003)									
Hospital LOS									
Adams	30	21	19	31	29	17	0.3%	-1.00 [-17.71, 15.71]	1986
Peterson	13.2	16	21	14.6	1.9	21	62.8%	-1.40 [-2.46, -0.34]	1988
Kudsk	20.5	199	51	19.6	18.8	45	1.4%	0.90 [-6.65, 8.65]	1992
Borzotta	39	231	28	36.9	14	21	0.8%	2.10 [-8.34, 12.54]	1994
Woodcock	33.2	43	16	27.3	18.7	18	0.2%	5.90 [-16.81, 28.67]	2001
Chen	23.32	56	49	22.24	3.27	49	23.6%	1.08 [-0.14, 2.90]	2011
Harvey	26.8	332	1186	27.5	33.9	1185	11.0%	-0.70 [-3.40, 2.00]	2014
Total (95% CI)			1379			1356	100.0%	-0.67 [-1.17, 0.24]	
Heterogeneity: Tau² = 0.05; Chi² = 6.12, df = 6 (P = 0.41); I² = 2%									
Test for overall effect: Z = 1.44 (P = 0.15)									
Mechanical ventilation									
Adams	12	11	17	10	10	13	0.6%	2.00 [-5.14, 9.54]	1986
Kudsk	2.8	4.9	51	3.2	6.7	45	6.2%	-0.40 [-2.77, 1.97]	1992
Chen	7.95	2.11	49	8.23	2.42	49	43.4%	-0.28 [-1.18, 0.62]	2011
Harvey	8.2	9.3	1197	8.7	11.5	1189	49.8%	-0.50 [-1.14, 0.34]	2014
Total (95% CI)			1314			1296	100.0%	-0.38 [-0.98, 0.21]	
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%									
Test for overall effect: Z = 1.27 (P = 0.21)									



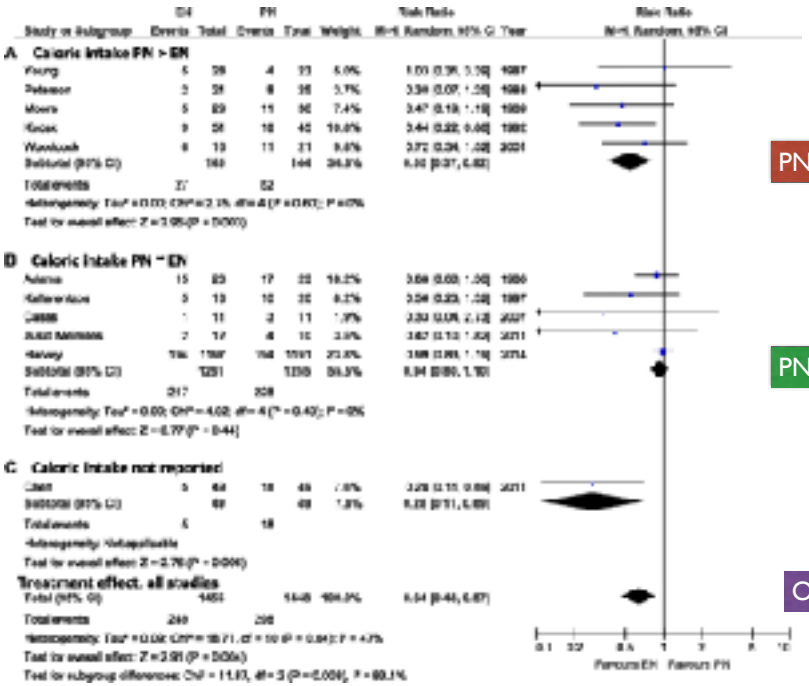
Reduction ICU LOS EN vs PN

No Reduction HLOS EN vs PN

No Reduction
Duration Mechanical Ventilation

Elke G, Van Zanten AR et al. Crit Care 2016;20:117

Enteral versus parenteral nutrition in critically ill patients: and updated systematic review and meta-analysis of randomized controlled trials



PN caloric intake > EN caloric intake

PN caloric intake = EN caloric intake

Overall EN less infections than PN

Only more infections in PN trials when caloric dose in PN group is higher

Elke G, Van Zanten AR... Heyland DK. Crit Care 2016;20:117

Clinical Nutrition 37 (2018) 1–18

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group☆

Philip C. Calder [a, b, *], Michael Adolph [c], Nicolaas E. Deutz [d], Teodoro Grau [e], Jacqueline K. Innes [a], Stanislaw Klek [f], Shaul Lev [g], Konstantin Mayer [h], Adina T. Michael-Titus [i], Lorenzo Pradelli [j], Mark Puder [k], Hester Vlaardingerbroek [l], Pierre Singer [g]

Fatty acids of importance in parenteral nutrition

Fatty acid	Shorthand nomenclature	Oil source
Caprylic acid	8:0	Coconut oil or palm kernel oil
Capric acid	10:0	Coconut oil or palm kernel oil
Lauric acid	12:0	Coconut oil or palm kernel oil
Myristic acid	14:0	
Palmitic acid	16:0	
Oleic acid	18:1n-9	Olive oil
Linoleic acid	18:2n-6	Vegetable seed oils e.g. soybean oil
α-Linolenic acid	18:3n-3	Vegetable seed oils e.g. soybean oil
Eicosapentaenoic acid	20:5n-3	Fish oil
Docosahexaenoic acid	22:6n-3	Fish oil

P.C. Calder et al. / Clinical Nutrition 37 (2018) 1e18

Typical fatty acid compositions (% of total) of commercially available lipid emulsions for use in parenteral nutrition.

	Intralipid®	Lipofundin® MCT/LCT	Structolipid®	Omegaven®	ClinOleic®	Lipoplus® (also known as Lipidem®)	SMOFlipid®
Oil source	100% soybean	50% MCT + 50% soybean	36% MCT + 64% soybean	100% fish[c]	80% olive + 20% soybean	50% MCT + 40% soybean + 10% fish[c]	30% MCT + 30% soybean + 25% olive + 15% fish[c]
SFA	15	58	46	21	14	49	37
MUFA[a]	24	11	14	23	64	14	33
PUFA	61	31	40	56	22	37	30
n-3 PUFA	8	4	5	48	3	10	7
ALA	8	4	5	1	3	4	2
EPA				20		3.5	3
DHA				19		2.5	2
n-6 PUFA[b]	53	27	35	5	19	27	23

Information taken from [203 205].

SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

[a] Mainly oleic acid.

[b] Mainly linoleic acid.

[c] The fatty acid composition of fish oil is more variable than that of vegetable oils so that the precise contribution of different fatty acids may differ in different batches. Note that the fish oil used in Lipolus® is more concentrated in EPA and DHA than that used in SMOFlipid® so that 10% fish oil in Lipoplus® provides more EPA and DHA than 15% fish oil in SMOFlipid®.

Typical fatty acid compositions (% of total) of commercially available lipid emulsions for use in parenteral nutrition.

- MCTs and OO appear to be safer and better tolerated than pure SO.
- FO-enriched EN and PN well tolerated and confers clinical benefits, particularly in surgical ICU patients, due to anti-inflammatory and immune-modulating effects.
- FO-enriched nutrition, particularly perioperatively, to reduce complications and ICU LOS and HLOS in surgical ICU patients, and IFALD associated with SO-based LEs.
- Evidence for FO-based nutrition in non-surgical ICU patients is less clear

P.C. Calder et al. / Clinical Nutrition 37 (2018) 1e18

Clinical Nutrition xxx (2017) 1–7

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Opinion paper

Intravenous fish oil in critically ill and surgical patients – Historical remarks and critical appraisal

K. Georg Kreymann [a,*], Daren K. Heyland [b], Geraldine de Heer [a], Gunnar Elke [c]

[a] Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Germany
[b] Department of Critical Care Medicine, Queen's University, Kingston, Ontario, Canada
[c] Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Germany

No exact fish oil doses, product ranges

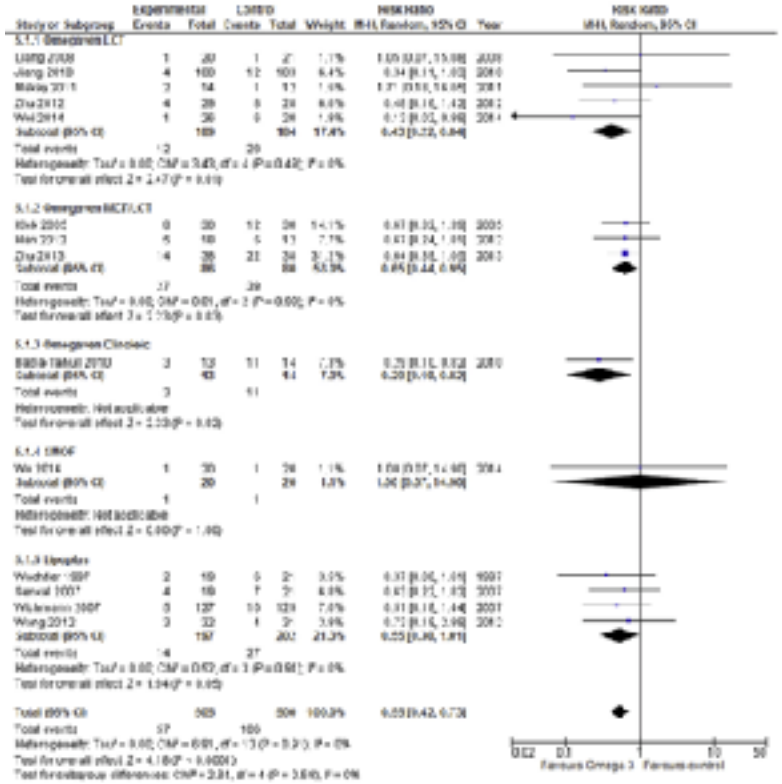
		Omegaven® 10%		SMOF® 20%		Lipoplus® 20%	
Soybean oil	g/100 ml			6		8	
Medium-chain triglycerides	g/100 ml			6		10	
Olive oil	g/100 ml			5			
Fish oil	g/100 ml	10		3		2	
		Min	Max	Min	Max	Min	Max
EPA	g/100 ml	1.25	2.82	0.20	0.70		
DHA	g/100 ml	1.44	3.09	0.20	0.70		
Sum	g/100 ml	**2.69**	**5.91**	**0.40**	**1.40**	**0.86**	**1.72**
		Min	Max	Min	Max	Min	Max
EPA	(g/10 g FO)	1,25	2,82	0,67	2,33		
DHA	(g/10 g FO)	1,44	3,09	0,67	2,33		
Sum	(g/10 g FO)	**2.69**	**5.91**	**1.34**	**4.66**	**4.3**	**8.6**

EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, FO = fish oil, Min = Minimum, Max = Maximum.
References [16–19].

Kreymann KG et al. Clinical Nutrition xxx (2017) 1-7

FO admixtures or FO-supplemented emulsions and infections in surgical patients with malignancies

Less infections

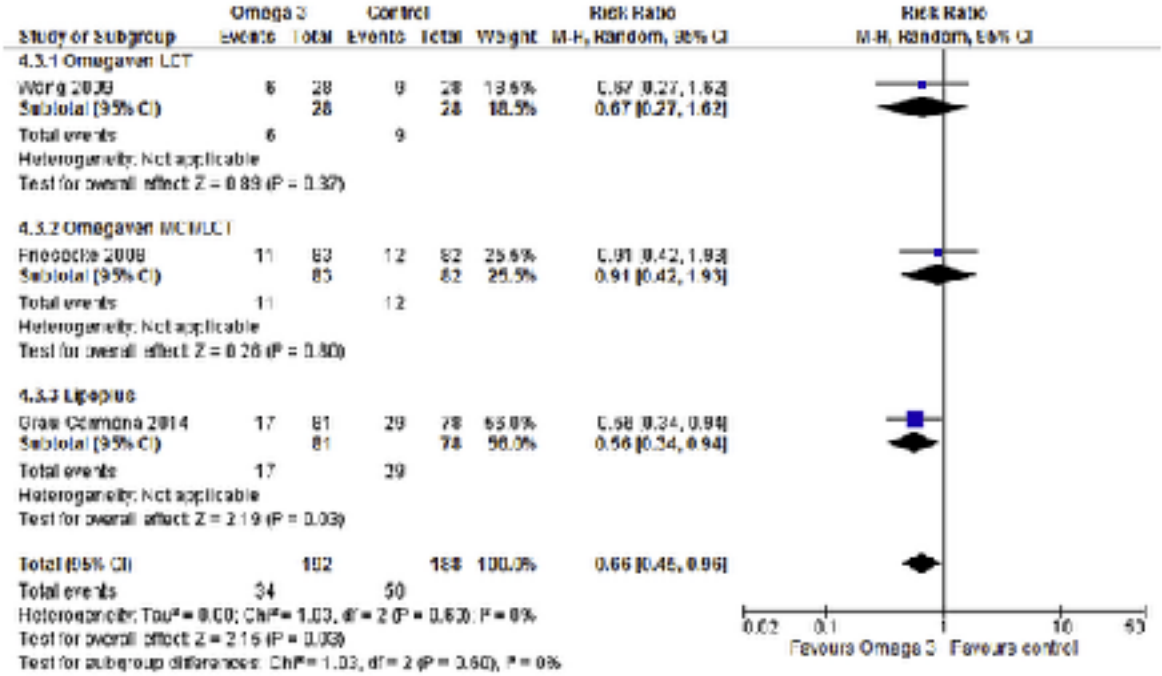


Product specific metaanalysis did not reveal any differences between the products, neither in infections rates nor in ICU or hospital length of stay.

Kreymann KG et al. Clinical Nutrition xxx (2017) 1-7

FO admixtures or FO-supplemented emulsions on infection rates in critically ill patients.

Slight reduction in infections



Kreymann KG et al. Clinical Nutrition xxx (2017) 1-7

Clinical Nutrition 38 (2019) 387–400

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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]

- **Does the addition of EPA and DHA to lipid emulsions have an effect on inflammatory processes, morbidity or mortality?**

- **Recommendation: Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes (Grade B). Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. (Grade B).**

9 years old is it still true?

Journal of Parenteral and Enteral Nutrition
Volume 40 Number 2
February 2016 159–211

DOI: 10.1177/0148607115621863
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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.)

Stephen A. McClave, MD[1*]; Beth E. Taylor, RD, DCN[2*]; Robert G. Martindale, MD, PhD[3]; Malissa M. Warren, RD[4]; Debbie R. Johnson, RN, MS[5]; Carol Braunschweig, RD, PhD[6]; Mary S. McCarthy, RN, PhD[7]; Evangelia Davanos, PharmD[8]; Todd W. Rice, MD, MSc[9]; Gail A. Cresci, RD, PhD[10]; Jane M. Gervasio, PharmD[11]; Gordon S. Sacks, PharmD[12]; Pamela R. Roberts, MD[13]; Charlene Compher, RD, PhD[14]; and the Society of Critical Care Medicine[†] and the American Society for Parenteral and Enteral Nutrition[†]

ASPEN GUIDELINES 2016

- Question: Should soy-based IV fat emulsions (IVFEs) be provided in the first week of ICU stay? Is there an advantage to using alternative IVFEs (ie, medium-chain triglycerides [MCTs], olive oil [OO], FO, mixture of oils) over traditional soybean oil (SO)–based lipid emulsions in critically ill adult patients?

- **H3a. We suggest withholding or limiting SO-based IVFE during the first week following initiation of PN in the critically ill patient to a maximum of 100 g/wk (often divided into 2 doses/wk) if there is concern for essential fatty acid deficiency.**

- [Quality of Evidence: Very Low]

- **H3b Alternative IVFEs may provide outcome benefit over soy-based IVFEs; however, we cannot make a recommendation at this time due to lack of availability of these products in the United States. When these alternative IVFEs (SMOF [soybean oil, MCT, olive oil, and fish oil emulsion], MCT, OO, and FO) become available in the United States, based on expert opinion, we suggest that their use be considered in the critically ill patient who is an appropriate candidate for PN.**

ESPEN guidelines 2019

Recommendation 24
The administration of intravenous lipid emulsions should be generally a part of PN. Grade of recommendation: GPP- strong consensus (100 % agreement)

Recommendation 25
Intravenous lipid (including non-nutritional lipid sources) should not exceed 1.5 g lipids / kg /day and should be adapted to individual tolerance.
Grade of recommendation: GPP – strong consensus (100% agreement)

Recommendation 33
Parenteral lipid emulsions enriched with EPA + DHA (Fish oil dose 0.1-0.2 g/kg/d) can be provided in patients receiving PN.
Grade of recommendation: 0 – strong consensus (100 % agreement)

Conclusions

- Timing of energy, protein and probably lipids is important during critical illness, do not overfeed
- No relevant benefit of enteral fish oil supplementation, earlier effect came from older low-quality studies and even recent large studies show harm of enteral fish oil
- IV Omega-6 lipids (and propofol high/long) should be avoided
- Fish-oil as IVLE is beneficial in perioperative surgical patients, less evidence in other critically ill patients, no clear difference in outcome of various products
- FO confers immune-depressant effects, consider whether you want that
- Olive-oil based lipids confer most immune-neutral profile, can be used in various conditions.