4.1b(i) Composition of Enteral Nutrition: Fish Oils, Borage Oils and Antioxidants

There were no new randomized controlled trials since the 2015 update and hence there are no changes to the following summary of evidence.

Question: Does the use of an enteral formula with fish oils, borage oils and antioxidants result in improved clinical outcomes in the critically ill adult patient?

Summary of evidence: There were 3 level 1 and 7 level 2 studies reviewed and 8 of these used Oxepa®, an enteral formula with fish oils, borage oils, antioxidants, vitamin E and C, beta-carotene, taurine & L-carnitine as a continuous formula. One used the components of the Oxepa® formula but administered them as a bolus (Rice 2011). One study used an omega 3 enriched EN formula and gave additional supplemental omega 3 and antioxidants (Hosny 2014). Of the included studies, 7 studies used the special diets as treatments for patients with Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI), one used the special diets prophylactically in multiple trauma/head injury patients (Kagan 2015), one study looked at effects of the fish oil/borage oil formula on the healing of pressure ulcers (Theilla 2011) and one studied septic patients (Hosny 2014).The earlier Moran 2006 study was replaced by the recent Grau-Carmona 2011 study and the earlier Miller 2005 study that was in abstract form was replaced by Elamin 2012. The INTERSEPT study (Pontes-Arruda 2011) was excluded as less than 50% patients were mechanically ventilated.

In the Rice study, participants were also randomized to a separate trial (EDEN study) comparing low vs full enteral nutrition in a 2X2 factorial design in which the control group received significantly more protein. For more for details on the low vs full enteral nutrition, refer to section *3.3 Intentional Underfeeding: Trophic Feeds.* Two studies used a fish oil only supplement; one as a bolus (Stapleton 2011) and another as soft gel capsules (Parish 2014). These studies are covered under the section *4.1(b-ii): Fish Oils.*

Since the delivery of the intervention through bolus vs continuous may affect blood levels (absorption), sensitivity analyses excluding the study that used bolus administration (Rice 2011) were done.

Mortality: When the data from the 9 studies that reported on mortality were aggregated, the use of Oxepa® and/or fish oil supplementation had no effect on mortality (RR 0.91, 95% CI 0.65, 1.27, p=0.58, heterogeneity I^2=49%; figure 1). When a sensitivity analyses was done excluding the Rice 2011 study, the use of fish oil, borage oil and antioxidants was associated with a significant reduction in mortality (RR 0.75, 95% CI 0.59, 0.96, p=0.02, heterogeneity I^2=4%; figure 2).

Infections: Three multicentre studies reported on ventilator associated pneumonia and found no significant differences between the groups (RR 1.07, 95% CI 0.82, 1.69, p=0.63, heterogeneity I^2=0%; figure 3).

LOS and Ventilator days: When the data from the 7 studies were aggregated, the use of Oxepa® /fish oil supplement showed a trend toward a reduction of ICU length of stay (WMB -2.60, 95% CI -5.43, 0.22, p=0.07; figure 4). In two of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses and 1 study reported on ICU free days, showing a significant reduction in ICU free days with the use of fish oil supplementation (Rice 2011, p=0.04). When the data from the 5 studies were aggregated, the use of Oxepa®/fish oil supplementation was associated with a significant reduction in ventilated days (WMD -3.49, 95% CI -6.33, -0.66, p=0.02; figure 5). In three of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses (Grau-Carmona 2011, Elamin 2012, Hosny 2014) and in 2 studies ventilator free days were reported. Rice et al reported a significant reduction in ventilator free days in the fish oil group (p=0.02), Hosny et al saw a trend in reduction of ventilated days (p=0.115) while Elamin et al and Grau-Carmona et al reported no difference in ventilator dependent days (p=0.3 and p=0.4, respectively).

Other complications: The use of Oxepa® was associated with a significant reduction in number of new organ failures in 2 studies (Gadek 1999 p=0.018) (Pontes-Arruda 2006, p< 0.0010), and a significant reduction in MODS score after 28-days in one study (Elamin 2005, p<0.05). However, in another study (Grau-Carmona 2011), the median SOFA score was 9 (IQ range: 7-11) and the number of organ failures was similar in both groups. Kagan 2015 found no difference in the development of new organ failures (p=0.27). In two studies, Oxepa® was associated with an improvement in oxygenation, pulmonary static compliance and resistance (Gadek 1999, Singer 2006). There were no differences in GI events between the groups (p=0.82) in one study (Gadek 1999).

Conclusions:

1) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants administered continuously is associated with a reduction in mortality in patients with ALI/ARDS or sepsis.
2) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants has no effect on infectious complications.
3) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants may be associated with a reduction in ICU LOS.
4) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants is associated with a reduction in ventilator dependent days.

Level 1 study: *if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.*
Level 2 study: *If any one of the above characteristics are unfulfilled.*

Table 1. Randomized studies evaluating enteral formula with fish oils, borage oils and antioxidants in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
				Fish Oils	Standard	Fish Oils	Standard
1)Gadek 1999	ARDS patients from 5 ICUs N=146	C.Random: yes ITT: yes Blinding: yes (13)	Fish oil, borage oil +antioxidants Oxepa ®) vs standard high fat, low CHO (Pulmocare†) Received 9.8 gms/day fish oils (EPA+DHA††)	**28-day** 11/70 (16)	**28-day** 19/76 (25)	NR	NR
2)Singer 2006	ARDS and acute lung injury patients N=100	C.Random: yes ITT: yes Blinding: no (11)	Fish oil, borage oil +antioxidants Oxepa ®) vs standard high fat, low CHO (Pulmocare†)	**28-day** 14/46 (30)	**28-day** 26/49 (53)	NR	NR
3) Pontes-Arruda 2006	Severe sepsis or septic shock patients with ALI from 3 ICUs N=165	C.Random: not sure ITT: yes* Blinding: double (7)	Fish oil, borage oil +antioxidants ((Oxepa ®) vs standard high fat, low CHO (Pulmocare†). Received 7.1 gms/day of fish oils ((EPA+DHA††)	**28-day** 26/83** (31)	**28-day** 38/82** (46)	NR	NR
4) Rice 2011	ALI patients, mechanically ventilated from 44 ICUs N=272	C.Random: yes ITT: yes Blinding: yes (13)	Fish Oil supplement (6.84g EPA, 3.4g DHA, 5.92g GLA) with 5.8 gms protein, Vit C, E, beta-carotene, selenium 120 ms boluses X2 day vs. isovolemic control solution (no EPA/DHA) with 52 gms protein, Both groups receieved EN feeding.	**60-day** 38/143 (27)	**60-day** 21/129 (16)	**VAP** 10/143 (7) **Bacteremia** 16/143 (11)	**VAP** 10/129 (8) **Bacteremia** 14/129 (11)
5) Grau-Carmona 2011	Septic patients with ALI or ARDS N=160	C.Random: no ITT: no Blinding: yes (5)	Fish oil, borage oil + antioxidants (Oxepa ®) 52.5g Pro/L vs. isocaloric, isonitrogenous, high protein formula (Ensure Plus) 66.6g Pro/L isocaloric	**28-day** 11/61 (18)	**28-day** 11/71 (16)	**VAP** 32/61 (53)	**VAP** 34/71 (48)
6) Thiella 2011	ICU patients with pressure ulcers N=40	C.Random: no ITT: yes Blinding: no (5)	Fish oil, borage oil + antioxidants 66.1 gm pro/day (Oxepa ®) vs. Isocaloric/isonitrogenous polymeric formula (Jevity) 65.1 gm pro /day	NR	NR	NR	NR

7) Elamin 2012	ARDS patients from 2 ICUs N = 22	C.Random: yes ITT: no Blinding: double (7)	EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs EN formula of standard high fat vs low CHO (Pulmocare)	**28-day** 0/9 (0)	**28-day** 1/8 (12.5)	NR	NR
8) Hosny 2014	ICU patients with sepsis. Single centre. N=75	C.Random: no ITT: no Blinding: no (7)	High dose omega 3 + antioxidants medications + EN enriched with omega 3s (14.2% of lipid content) vs control group (standard EN, no meds).	**28-day** 8/25 (32)	**28-day** 10/25 (40)	NR	NR
9) Kagan 2015	Multiple trauma or head injury patients from a single ICU N=120	C.Random: yes ITT: yes Blinding: double (10)	EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs EN formula of standard high fat/low CHO (Pulmocare)	**28-day** 8/62 (13)	**28-day** 5/58 (8)	**VAP** 25/62 (40%) **Wound infection** 12/62 **Bacteremia** 14/62 **New organ failure** 31/62	**VAP** 22/58 (38%) **Wound infection** 10/58 **Bacteremia** 3/58 **New organ failure** 23/58
10) Shirai 2015	Mechanically ventilated ICU patients. Single centre. N=46	C.Random: no ITT: yes Blinding: single (11)	EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs isocaloric polymeric formula (Ensure)	**60-day** 3/23 (13)	**60-day** 3/23 (13)	NR	NR

Table 1. Randomized studies evaluating enteral formula with fish oils, borage oils and antioxidants in critically ill patients (continued)

Study	Length of Stay (days)		Duration of Ventilation (days)		Other	
	Fish Oils	Standard	Fish Oils	Standard	Fish Oils	Standard
1) Gadek 1999	**ICU***** 11 ± 7.53 (70) **Hospital***** 27.9 ± 17.57 (70)	**ICU***** 14.8 ± 11.03 (72) **Hospital***** 31.1 ± 13.15 (72)	9.6 ± 7.94 (70)***	13.2 ± 11.88 (72)***	**New Organ Failures** 7/70 (10)	19/76 (25)
2) Singer 2006	**ICU** 13.5 ± 11.8 (46)**	**ICU** 15.6 ± 11.8 (49)**	12.1 ± 11.3 (46)**	14.7 ± 12 (49)**		
3) Pontes-Arruda 2006	**ICU** 17.2 ± 4.9 (55)**	**ICU** 23.4 ± 3.5 (48)**	14.64 ± 4.3 (55)**	22.19 ± 5.1 (48)**	**New Organ Dysfunction** 38%	81%

4) Rice 2011	**ICU Free Days** 14.0 ±10.5	**ICU Free Days** 16.7 ± 9.5	**Ventilator-free Days** 14.0 ±11.1	**Ventilator-free Days** 17.2 ±10.2	**Non-pulmonary Organ Failure-free Days** 12.3 ± 11.1 15.5 ± 11.4
5) Grau-Carmona 2011	**ICU** 16 (11-25)	**ICU** 18 (10-30)	10 (6-14) p=0.4	9 (6-18)	**Nutritional Intake 1 (kcal/day)** 718 (1189-1965) 1599 (1351-1976) p=0.5
6) Thiella 2011	**ICU** 26.1 ± 14.2 (20)	**ICU** 21.2 ± 9.1 (20)	NR	NR	**Change in Pressure Ulcers Scale** 1.5 0.3 p≤0.05
7) Elamin 2012	**ICU** 12.8	**ICU** 17.5	6.7	8.2	**MODS Score at 7 days** Lower in fish oil group (p<0.06) **MODS Score at 28 days** Lower in fish oil group (p<0.05)
8) Hosny 2014	**ICU** 11.6 ± 6.1 (25)	**ICU** 13.9 ± 4.2 (25)	6.7 ± 3.8	10.9 ± 6.3	**Diarrhea** 20% 16%
9) Kagan 2015	**ICU** 19.5 ± 15.3 (62) **Hospital** 33.1 ± 25.7 (62)	**ICU** 16.4 ± 11.3 (58) **Hospital** 27.1 ± 17.3 (58)	17 ± 15.1	13.6 ± 10.7	**New organ failure** 31/62 23/58, p=0.27
10) Shirai 2015	**ICU** Mean, (SE, 95% CI) 17.63 (1.70, 14.30-20.97) SD = 8.15***	**ICU** Mean, (SE, 95% CI) 25.87 (2.6, 20.81-30.94) SD=12.47***	Mean, (SE, 95% CI) 13.61 (1.00, 11.66-15.56) SD=4.80***	Mean, (SE, 95% CI) 17.777 (1.81, 14.21-21.33) SD=8.68***	**Nutritional intake, day 7, kcal/kg/d** 18.78 (18.12-20.21) 19.48 (15.73-20.68) **Nutritional intake, day 14, kcal/kg/d** 24.22 (23.32-25.9) 24.32 (22.67-25.75) **Nutritional intake, day 7, g/kg/d** 0.781 (0.7-0.837) 0.613 (0.529-0.683) **Nutritional intake, day 14, g/kg/d** 0.988 (0.933-1.063) 0.81 (0.749-0.863)

† Fat source of Pulmocare varied between the studies: Gadek 1999 study used product that had 97 % corn oil, 3% soy lecithin; Singer 2006 and Pontes-Arruda 2006 used product that had 14 % corn oil, 20% MCT,56 % canola oil.

†† EPA: Eicosapentanoic acid, DHA: docosahexanoic acid

* data on mortality is Intent-to–treat   ** data obtained from authors   ***values computed from mean ± SE to obtain mean ± SD   C.Random: concealed randomization

ITT: intent to treat   # assumed to be hospital mortality unless specified   ‡ refers to the # of patients with infections unless specified

± ( ) : mean ± Standard deviation (number)   NR: not reported

Figure 1. Mortality

Study or Subgroup	Fish Oils Events	Fish Oils Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gadek	11	70	19	76	12.6%	0.63 [0.32, 1.23]	1999
Pontes-Arruda 2006	26	83	38	82	18.9%	0.68 [0.46, 1.00]	2006
Singer	14	46	26	49	16.0%	0.57 [0.34, 0.96]	2006
Rice	38	143	21	129	16.8%	1.63 [1.01, 2.63]	2011
Grau-Carmona	11	61	11	71	10.9%	1.16 [0.54, 2.49]	2011
Elamin	0	9	1	8	1.1%	0.30 [0.01, 6.47]	2012
Hosny	8	25	10	25	11.2%	0.80 [0.38, 1.69]	2014
Kagan	8	62	5	58	7.1%	1.50 [0.52, 4.31]	2015
Shirai	6	23	3	23	5.4%	2.00 [0.57, 7.05]	2015
Total (95% CI)		**522**		**521**	**100.0%**	**0.91 [0.65, 1.27]**	
Total events	122		134				

Heterogeneity: Tau² = 0.11; Chi² = 15.65, df = 8 (P = 0.05); I² = 49%
Test for overall effect: Z = 0.56 (P = 0.58)

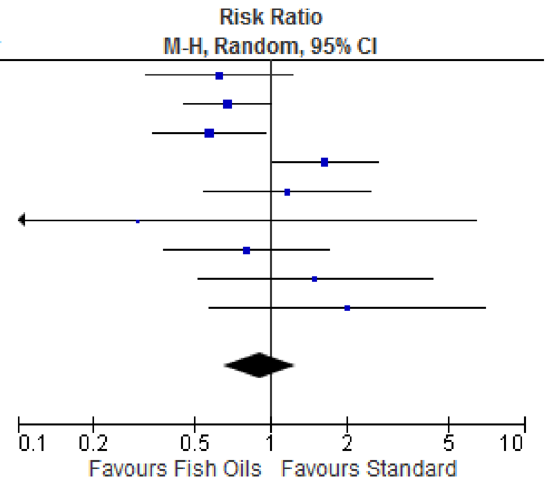

Figure 2. Mortality (without Rice 2011)

Study or Subgroup	Fish Oils Events	Fish Oils Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gadek	11	70	19	76	13.1%	0.63 [0.32, 1.23]	1999
Pontes-Arruda 2006	26	83	38	82	34.7%	0.68 [0.46, 1.00]	2006
Singer	14	46	26	49	21.8%	0.57 [0.34, 0.96]	2006
Grau-Carmona	11	61	11	71	10.1%	1.16 [0.54, 2.49]	2011
Elamin	0	9	1	8	0.6%	0.30 [0.01, 6.47]	2012
Hosny	8	25	10	25	10.6%	0.80 [0.38, 1.69]	2014
Kagan	8	62	5	58	5.3%	1.50 [0.52, 4.31]	2015
Shirai	6	23	3	23	3.8%	2.00 [0.57, 7.05]	2015
Total (95% CI)		**379**		**392**	**100.0%**	**0.75 [0.59, 0.96]**	
Total events	84		113				

Heterogeneity: Tau² = 0.01; Chi² = 7.27, df = 7 (P = 0.40); I² = 4%
Test for overall effect: Z = 2.27 (P = 0.02)

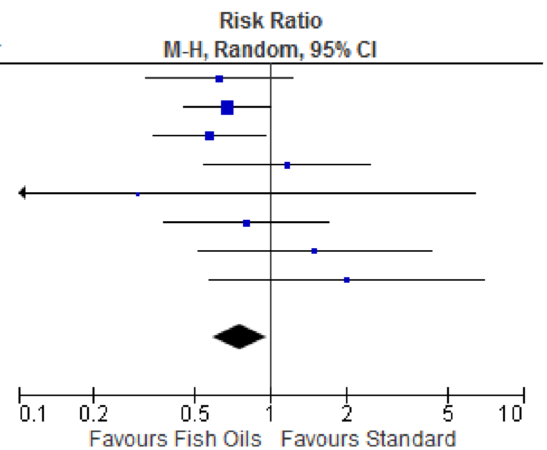

Figure 3. Ventilator Associated Pneumonia

Study or Subgroup	Fish Oils Events	Fish Oils Total	Standard Events	Standard Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grau-Carmona	32	61	34	71	57.4%	1.10 [0.78, 1.54]	2011
Rice	10	143	10	129	9.4%	0.90 [0.39, 2.10]	2011
Kagan	25	62	22	58	33.3%	1.06 [0.68, 1.66]	2015
Total (95% CI)		**266**		**258**	**100.0%**	**1.07 [0.82, 1.38]**	
Total events	67		66				

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

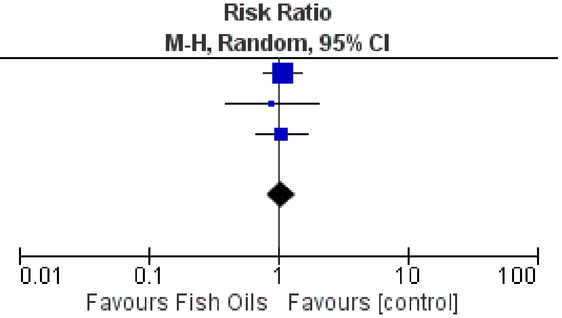

Figure 4. ICU Length of Stay

Study or Subgroup	Fish Oils Mean	Fish Oils SD	Fish Oils Total	Standard Mean	Standard SD	Standard Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gadek	11	7.53	70	14.8	11.03	72	16.9%	-3.80 [-6.90, -0.70]	1999
Pontes-Arruda 2006	17.2	4.9	55	23.4	3.5	48	19.9%	-6.20 [-7.83, -4.57]	2006
Singer	13.5	11.8	46	15.6	11.8	49	13.3%	-2.10 [-6.85, 2.65]	2006
Thiella	26.1	14.2	20	21.2	9.1	20	8.7%	4.90 [-2.49, 12.29]	2011
Hosny	11.6	6.1	25	13.9	4.2	25	17.4%	-2.30 [-5.20, 0.60]	2014
Shirai	17.63	8.15	23	25.87	12.47	23	10.7%	-8.24 [-14.33, -2.15]	2015
Kagan	19.5	15.3	62	16.4	11.3	58	13.2%	3.10 [-1.69, 7.89]	2015
Total (95% CI)			**301**			**295**	**100.0%**	**-2.60 [-5.43, 0.22]**	

Heterogeneity: Tau² = 9.76; Chi² = 24.67, df = 6 (P = 0.0004); I² = 76%
Test for overall effect: Z = 1.81 (P = 0.07)

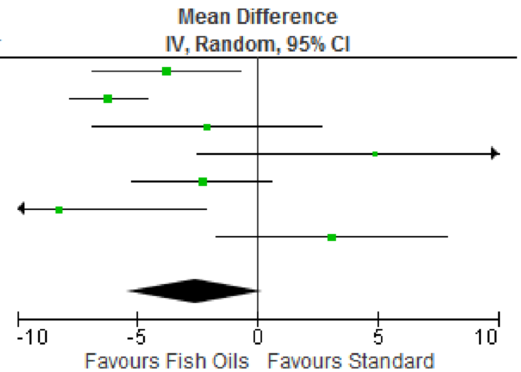

Figure 5. Duration of Ventilation

	Fish Oils			Standard				Mean Difference		Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**	**IV, Random, 95% CI**
Gadek	9.6	7.94	70	13.2	11.88	72	17.3%	-3.60 [-6.92, -0.28]	1999	
Pontes-Arruda 2006	14.64	4.3	55	22.19	5.1	48	20.7%	-7.55 [-9.39, -5.71]	2006	
Singer	12.1	11.3	46	14.7	12	49	14.0%	-2.60 [-7.29, 2.09]	2006	
Hosny	6.7	3.8	25	10.9	6.3	25	18.4%	-4.20 [-7.08, -1.32]	2014	
Shirai	13.61	4.8	23	17.777	8.68	23	15.5%	-4.17 [-8.22, -0.11]	2015	
Kagan	17	15.1	62	13.6	10.7	58	14.1%	3.40 [-1.26, 8.06]	2015	
Total (95% CI)			**281**			**275**	**100.0%**	**-3.49 [-6.33, -0.66]**		

Heterogeneity: Tau² = 9.23; Chi² = 22.04, df = 5 (P = 0.0005); I² = 77%
Test for overall effect: Z = 2.41 (P = 0.02)

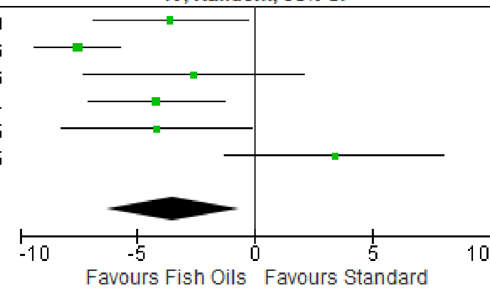

Table 2. Composition of Fish Oil Containing Formulas Compared to Standard

These values represent the version of these products produced for sale in the United States.
Products sold in other countries may have other nutrient values, depending on country specific requirements.

	Oxepa	Pulmocare*	Jevity 1.5	
Cal/ml	1.5	1.5	1.5	
Grams fat/liter	93	93	49.8	
Grams n-3/liter	10.15	4.8	2.4	
Grams alpha-linolenic acid/liter	3.1	4.8	2.4	
Grams EPA/liter	4.6	0	0	
Grams DHA/Liter	2.0	0	0	
Grams n-6/liter	18.4	18.4	13.3	
Grams linoleic acid/liter	14.5	18.4	13.3	
Grams GLA/liter	4.29	0	0	
Grams n-9 per liter	21.7	39	17.2	
Grams oleic acid/liter	21.7	39	17.2	
Grams of MCT oil/liter	23.5 grams (25% of fat blend)	18.6 grams (20% of fat blend)	9.46 grams (19% of fat blend)	**Recommended**
n6:n3 ratio	1.8:1	3.8:1	5.5:1	**2:1 to 4:1**
n3:n6 ratio	0.5:1	0.26:1	0.18:1	
Oil blend ingredients	31.8%Canola oil, 25% MCT oil, 20% fish oil, 20%borage oil, 3.2% soy lecithin	55.8%Canola oil, 20%MCT oil, 14%corn oil, 7%high oleic acid safflower oil, 3.2% soy lecithin	Canola oil, MCT oil and corn oil, soy lecithin	

EPA: Eicosapentanoic acid DHA: docosahexanoic acid GLA: gamma linoleic acid

**Fat source of Pulmocare varied between the studies: Gadek 1999 study used product that had 97 % corn oil, 3% soy lecithin; Singer 2006 and Pontes-Arruda 2006 used product that had 14 % corn oil, 20% MCT,56 % canola oil.*

References

Included Articles

1. Gadek JE, DeMichele SJ, Karlstad MD et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Critical Care Medicine 1999;27:1409-20.
2. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006 Sep;34(9):2325-33.
3. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006 Apr;34(4):1033-8.
4. Grau-Carmona T, Morán-García V, García-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, López-Martínez J, González-Fernández C, Montejo-González JC, Blesa-Malpica A, Albert-Bonamusa I, Bonet-Saris A, Herrero-Meseguer JI, Mesejo A, Acosta J. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. Clin Nutr. 2011 Oct;30(5):578-84. Epub 2011 Apr 6. PubMed PMID: 21474219.
5. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P; NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA. 2011 Oct 12;306(14):1574-81. Epub 2011 Oct 5. Erratum in: JAMA. 2012 Feb 8;307(6):563. PubMed PMID: 21976613.
6. Theilla M, Schwartz B, Zimra Y, Shapiro H, Anbar R, Rabizadeh E, Cohen J, Singer P. Br J Nutr. 2012 Apr;107(7):1056-61. doi: 10.1017/S0007114511004004. Epub 2011 Nov 1. PMID: 22040465
7. Elamin EM, Miller AC, Ziad S (2012) Immune Enteral Nutrition Can Improve Outcomes in Medical-Surgical Patients with ARDS: A Prospective Randomized Controlled Trial. J Nutrition Disorder Ther 2(2):109.
8. Hosney M, Nahes R, Ali S, Elshafei SA, Khaled H. Impact of oral omega-3 fatty acids supplementation in early sepsis on clinical outcome and immunomodulation Author links open overlay panel. The Egyptian Journal of Crit Car Med. 2013:1(3);119-126.
9. Kagan I, Cohen J, Stein M, Bendavid I, Pinsker D, Silva V, Theilla M, Anbar R, Lev S, Grinev M, Singer P. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. Intensive Care Med. 2015 Mar;41(3):460-9.
10. Shirai K, Yoshida S, Matsumaru N, Toyoda I, Ogura S. Efect of enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with sepsis-induced acute respiratory distress syndrome. J Intensive Care. 2015;3(1):24

Excluded Articles

#	Reason	Citation
1	Elective surgery/cancer pts	Pironi L, Belluzzi A, Gionchetti P, Ruggeri E, Boschi S, Guarnieri C, Caliceti U, Cenacchi V, Barbara L, Miglioli M. Possible role of the structural lipids in artificial nutrition: comparison of al inoleic acid-based with an oleic acid-based enteral formula in humans. Clinical Nutrition 1993;12(S1):S91-S96
2	Surgery pts	Maachi K, Berthoux P, Burgard G, Alamartine E, Berthoux F. Results of a 1-year randomized controlled trial with omega-3 fatty acid fish oil in renal transplantation under triple immunosuppressive therapy. Transplant Proc. 1995 Feb;27(1):846-9.
3	Elective surgery/cancer pts	Kenler AS, Swails WS, Driscoll DF, DeMichele SJ, Daley B, Babineau TJ, Peterson MB, Bistrian BR. Early enteral feeding in postsurgical cancer patients. Fish oil structured lipid-based polymeric formula versus a standard polymeric formula. Ann Surg. 1996 Mar;223(3):316-33.
4	Elective surgery pts	Wachter P, Konig W, Senkal M, Kemen M, Koller M. Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. J Trauma 1997;42(4):191-8.
5	Not ventilated, No clinical outcomes	Bernier J, Jobin N, Emptoz-Bonneton A, Pugeat MM, Garrel DR. Decreased corticosteroid-binding globulin in burn patients: relationship with interleukin-6 and fat in nutritional support. Crit Care Med. 1998 Mar;26(3):452-60.
6	Elective surgery pts	Alivizatos S, Adamopoulos S, Zorbalas A, Felekis D. Tolerance of early, postoperative nasojejunal immunonutrition in patients undergoing elective gastrointestinal surgery. Nut Clin Prac 2001;16(2):p115 (Abstract # N0011)
7	Surgery pts	Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative administration of n-3 fatty acids. Br J Nutr 2002 Jan;87 Suppl 1:S89.94.
8	No clinical outcomes	Mayer K, Gokorsch S, Fegbeutel C, Hattar K, Rosseau S, Walmrath D, Seeger W, Grimminger F. Parenteral nutritional with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med 2003 May;167(10):1321-8.
9	Not ICU pts	Nelson JL, DeMichele SJ, Pacht ER, Wennberg AK; Enteral Nutrition in ARDS Study Group. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants on antioxidant status in patients with acute respiratory distress syndrome. JPEN J Parenter Enteral Nutr. 2003 Mar-Apr;27(2):98-104.
10	Subset of patients from the Gadek 1999 study	Pacht ER, DeMichele SJ, Nelson JL, Hart J, Wennberg AK, Gadek JE. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid, and antoxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. Crit Care Med 2003 Feb;31(2):491-500.
11	Not ICU pts	Lasztity N, Hamvas J, Biró L, Németh E, Marosvölgyi T, Decsi T, Pap A, Antal M. Effect of enterally administered n-3 polyunsaturated fatty acids in acute pancreatitis--a prospective randomized clinical trial. Clin Nutr. 2005 Apr;24(2):198-205.
12	Abstract, replaced with Grau Carmona 2011	Moran V, Grau T, de Lorenzo AC, Lopez J, Gonzalez C, Montejo JC, Blesa A, Albert I, Bonet A, Herrero I. Effect of an enteral feeding with eicosapentaenoic and gamma-linoleic acids on the outcome of mechanically ventilated critically ill septic patients. Crit Care Med 2006 Dec;34(12 Abstract supplement):A70

13	No clinical outcomes	Theilla M, Singer P, Cohen J, Dekeyser F. A diet enriched in eicosapentanoic acid, gamma-linolenic acid and antioxidants in the prevention of new pressure ulcer formation in critically ill patients with acute lung injury: A randomized, prospective, controlled study. Clin Nutr. 2007 Dec;26(6):752-7. Epub 2007 Oct 22.
14	Elective surgery pts	Ryan AM, Reynolds JV, Healy L, Byrne M, Moore J, Brannelly N, McHugh A, McCormack D, Flood P. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. Ann Surg. 2009 Mar;249(3):355-63.
15	Not ICU pts	Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, Gottwik M, Steinbeck G, Del Castillo U, Sack R, Worth H, Katus H, Spitzer W, Sabin G, Senges J; OMEGA Study Group. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. Circulation. 2010 Nov 23;122(21):2152-9. Epub 2010 Nov 8.
16	Not ICU pts	Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. Circ Arrhythm Electrophysiol. 2010 Feb;3(1):46-53. Epub 2009 Dec 30.
17	Elective surgery pts	Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JR, Gibson RA, Cleland LG, Sullivan TR, James MJ, Young GD. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. Am J Cardiol. 2011 Sep 15;108(6):851-6. Epub 2011 Jul 15.
18	Not mechanically ventilated pts	Pontes-Arruda A, Martins LF, de Lima SM, Isola AM, Toledo D, Rezende E, Maia M, Magnan GB; Investigating Nutritional Therapy with EPA, GLA and Antioxidants Role in Sepsis Treatment (INTERSEPT) Study Group. 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. Crit Care. 2011 Jun 9;15(3):R144.
19	Meta-analysis	van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA, Brouwer IA, van Leeuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. Am J Clin Nutr. 2011 Nov;94(5):1248-65. Epub 2011 Sep 21.
20	Duplicate of Theilla 2011	Theilla M, Schwartz B, Cohen J, Shapiro H, Anbar R, Singer P. Impact of a nutritional formula enriched in fish oil and micronutrients on pressure ulcers in critical care patients. American Journal of Critical Care. 2012;21(4):e102-9.
21	Meta analyses	Wan X, Gao X, Bi J, Tian F, Wang X. Use of n-3 PUFAs can decrease the mortality in patients with systemic inflammatory response syndrome: a systematic review and meta-analysis. Lipids Health Dis. 2015 Mar 31;14:23.
22	Meta analyses	Lu C, Sharma S, McIntyre L, Rhodes A, Evans L, Almenawer S, Leduc L, Angus DC, Alhazzani W. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. Ann Intensive Care. 2017 Dec;7(1):58.