FINAL DRAFT

4.1 (b) Composition of Enteral Nutrition: Fish oils* January 31st, 2009

Recommendation:

Based on 1 level 1 study and 4 level 2 studies, we recommend the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS).

Discussion:

While the effect size was large, it was noted that the results came from 3 industry sponsored studies with high internal validity and 2 non industry sponsored studies. These results were confirmed in a recent meta-analysis in this population [(1)]. The committee noted that the acquisition costs of this specialty formula are much higher than standard formula and that since the effects of fish oils cannot be distinguished from the effects of borage oil or antioxidants, this recommendation pertains to a combination product and not to fish oils in general. The need for a bronchoscopy to meet the inclusion criteria in one study limits the application of the findings. A closer look at the content of the high fat control formula used in all 3 studies shows a more favourable ratio of omega 3 and omega 6 fatty acids when compared to standard formulas (see Table 2). Based on this, the committee agreed that the benefits of using a product enriched with fish oils, borage oils and antioxidants would potentially be even more pronounced if compared against a standard formula. The committee noted that in the recent Spanish study of septic patients (Moran 2006), there was no evidence of a treatment effect. The recommendation was therefore, not extended to all septic patients without lung injury. We await the results of the EDEN-Omega trial of fish oils, borage oils and antioxidants to strengthen our clinical recommendation [(2)].

(1) Pontes-Arruda A, Demichele S, Seth et al. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data.JPEN 2008(6):596-605.
(2) Early Versus Delayed Enteral Feeding and Omega-3 Fatty Acid/Antioxidant Supplementation for Treating People With Acute Lung Injury or Acute Respiratory Distress Syndrome (The EDEN Omega Study) Clinical Trials registry # NCT00609180 http://clinicaltrials.gov/ct2/show/NCT00609180?term=eden&rank=1

Values	Definition	Score 0, 1, 2 or 3
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	3
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	3
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2
Homogeneity/Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	1
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogeneous patients, diverse practice settings =3.	2
Cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2

Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2

* refers to formula containing fish oils, borage oils and antioxidants

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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 1 level 1 and 4 level 2 studies reviewed that used Oxepa®, an enteral formula with fish oils, borage oils, antioxidants, vit. E, C, beta-carotene, taurine & L-carnitine. Two studies were in abstract form and additional data was obtained from the authors (Moran 2006 and Elamin 2005).

Mortality: When the data from the 5 studies were aggregated, the use of Oxepa® was associated with a significant reduction in 28 day mortality RR =0.67, 95% CI 0.51, 0.87, p=0.003, no heterogeneity present) (figure 1).

Infections: One multicentre study reported on infections and the incidence of newly acquired pneumonia was reported to be significantly lower in the fish oil group (22% vs. 36%, p <0.05, Moran 2006).

LOS and Ventilator days: When the data from the 3 studies were aggregated, the use of Oxepa® was associated with a significant reduction in ICU length of stay (Weighted mean difference WMD -4.48, 95 % CI -6.49, -2.47, p <0.0001, however significant heterogeneity was present (I^2=76%) (figure 2). In two of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses. When the data from the 3 studies were aggregated, the use of Oxepa® was associated with a significant reduction in ventilated days (WMD -4.83, 95% CI -7.96, -1.70, p=0.002, however significant heterogeneity was present (I^2 =88%) (figure 3). In two of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses.

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), a significant reduction in MODS score in one study (Elamin 2005, p <0.05) and a significant reduction in SOFA score in another study (Moran 2006, p< 0.01). 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 Pulmocare (or a standard high fat diet), the use of an enteral formula with fish oil/borage oil and antioxidants is associated with a significant reduction in 28 day mortality in patients with ALI/ARDS.

2) When compared to Pulmocare, the use of an enteral formula with fish oil/borage oil and antioxidants may be associated with a significant reduction in ICU LOS, ventilated days and organ failure in critically ill patients with ALI/ARDS.

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 oil and antioxidants in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%) Fish oil	Mortality # (%) Standard	Infections # (%)‡ Fish oil	Infections # (%)‡ 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) Miller 2005 unpublished	ARDS patients from 2 ICUs N = 16	C.Random: not sure ITT: no Blinding: double (7)	Fish oil, borage oil +antioxidants (Oxepa ®) vs standard high fat, low CHO ((Pulmocare†)	28 day 1/8 (13)	28 day 5/8 (63)	NR	NR
3)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
4) 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
5) Moran 2006	Sepsis/Shock patients from 20 ICUs N = 198	C.Random: not sure ITT: no Blinding: no (5)	Fish oil, borage oil + antioxidants vs. isocaloric, isonitrogenous, high protein formula	28 day** 11/61 (18)	28 day** 11/71 (16)	32/61 (53)** pneumonia 10/45 (22)	34/71 (48)** pneumonia 20 /56 (36)

Study	LOS days		Ventilator days		Other
1) Gadek 1999	Fish oil 11± 0.9 (70) ICU 27.9 ± 2.1 (70) hospital	Standard 14.8 ± 1.3 (72) ICU 31.1 ± 2.4 (72) hospital	Fish oil 9.6 ± 0.9 (70)	Standard 13.2 ± 1.4 (72)	Fish oil Standard New organ failures 7/70 (10) 19/76 (25)
2) Miller 2005 unpublished	Fish oil 12.8	Standard 17.5	Fish oil Ventilator Free Days 6.7	Standard Ventilator Free Days 8.2	Fish oil Standard MODS score at 28 days Lower in fish oil group (p <0.05)
3) Singer 2006	Fish oil 13.5 ± 11.8 (46)**	Standard 15.6 ± 11.8 (49)** ICU	Fish oil 12.1 ± 11.3 (46)**	Standard 14.7 ± 12 (49)**	Fish oil Standard NR NR
4) Pontes-Arruda 2006	Fish oil Standard 17.2 ± 4.9 (55)** 23.4 ± 3.5 (48)** ICU		Fish oil Standard 14.64 ± 4.3 (55)** 22.19 ± 5.1 (48)**		Fish oil Standard New organ dysfunction 38 % 81%
5) Moran 2006	Fish oil 16 (11-25)**	Standard 18 (10-30)**	Fish oil 10 (6-14)**	Standard 9 (6-18)**	Fish oil Standard Final SOFA score 5 8

† 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

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

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.

Figure 1.

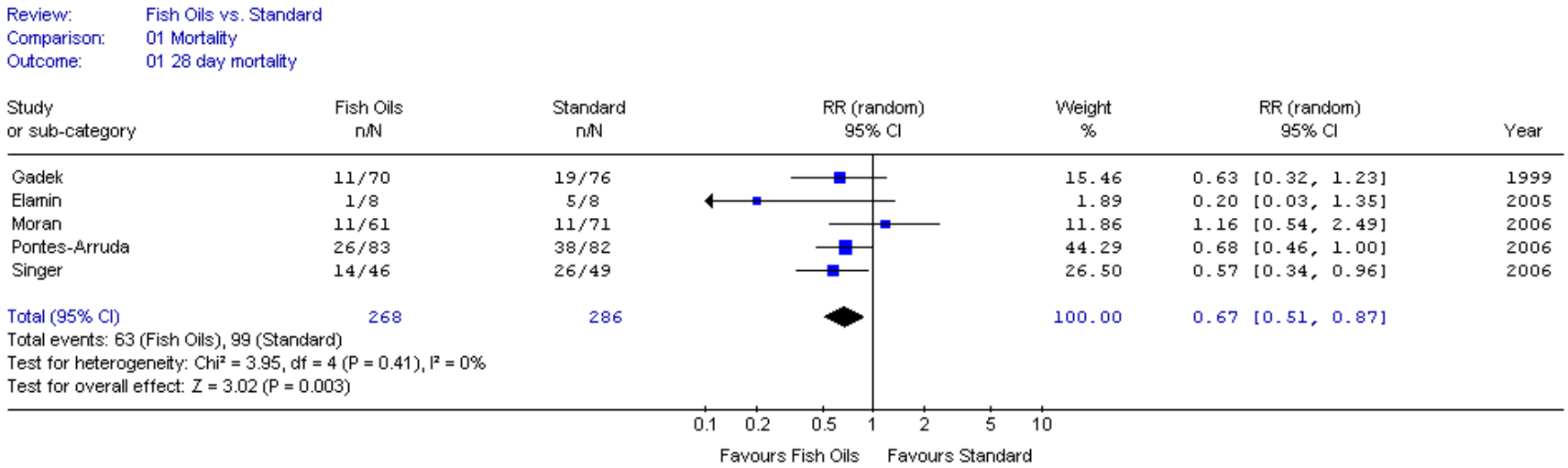


Figure 2.

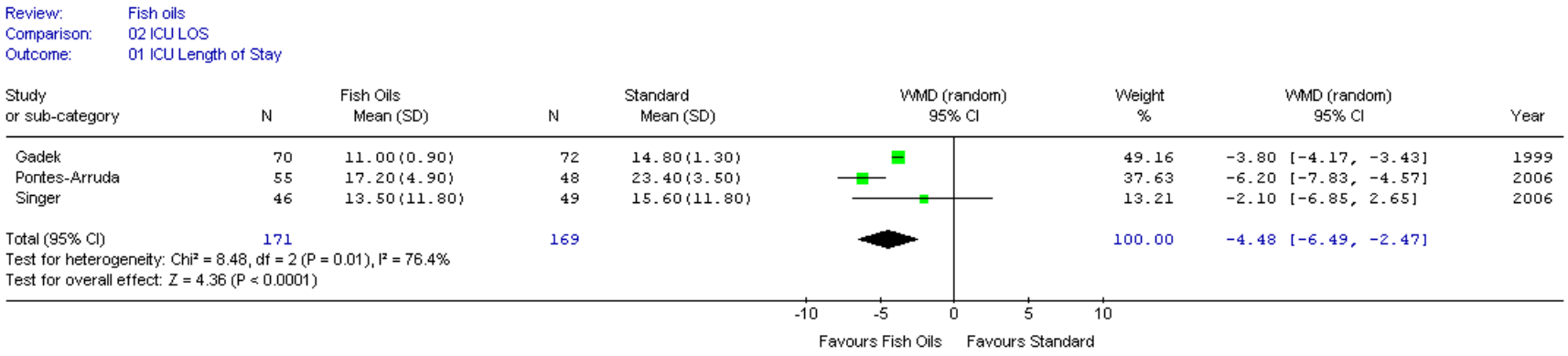
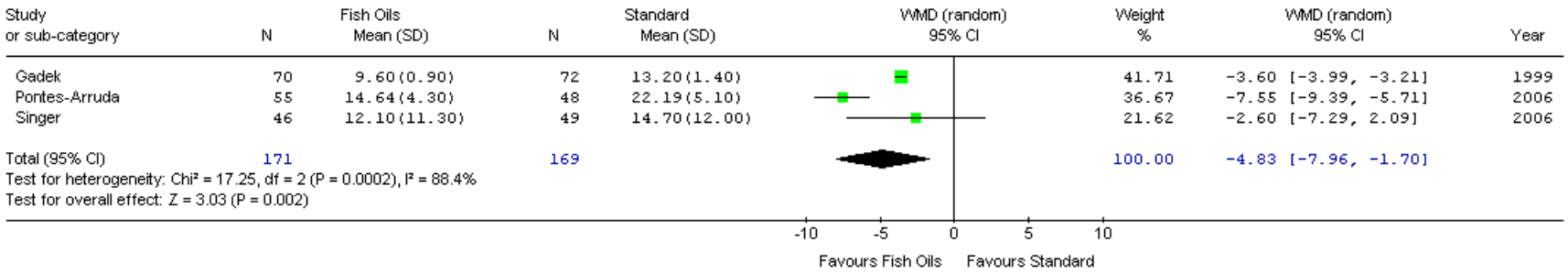


Figure 3.

Review: Fish oils
Comparison: 03 Ventilator Days
Outcome: 01 Ventilator Days



TOPIC: 4.1 (b) Composition of EN: fish oils

Article inclusion log
Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill, ventilated patients (no elective surgery patients)
Intervention: EN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

	Author	Journal	I	E	Why Rejected
1	Pironi	Clinical Nutrition 1993		√	Elective surgery/cancer pts
2	Maachi	Transplantation Proceedings 1995		√	Surgery pts
3	Kenler	Annals of Surgery 1996		√	Elective surgery/cancer pts
4	Wachtler	J Trauma 1997		√	Elective surgery pts
5	Bernier	Crit Care Med 1998		√	Not ventilated, No clinical outcomes
6	Gadek	Crit Care Med 1999	√		
7	Weiss	Br J Nutr 2002		√	Surgery patients
8	Mayer	Am J Resp Care 2003		√	No clinical outcomes
9	Nelson	JPEN 2003		√	Not ICU pts
10	Pacht	Crit Care Med 2003		√	Subset of patients from the Gadek 1999 study
11	Miller	Unpublished data 2005	√		
12	Moran	Crit Care med 2006	√		
13	Singer	Crit Care Med 2006	√		
14	Pontes-Arruda	Crit Care Med 2006	√		

I = included, E = excluded

** For complete fish oils reference list refer to PN lipids section (9.2)

Reference List

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3. 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.

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5. 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. 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.

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10. 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. Miller AC, Ziad S. Efficacy of enteral nutrition with EPA, GLA and antioxidants in patients with ARDS and MODS: a prospective multi-center randomized controlled trial. Unpublished data, see reference folder

12. 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

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14. 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.