4.1 b.(ii) Composition of Enteral Nutrition: Fish oil supplementation* May 2015

2015 Recommendation: ***There are insufficient data to make a recommendation on the supplementation of fish oils alone in critically ill patients***

2015 Discussion: The committee noted the data from a recent study (Parish 2014) in which fish oils were delivered to patients with ARDS via soft gels which when aggregated with previous study, demonstrated no effect on clinical outcomes. Concerns were also raised about the lack of details of the placebo used in this study. The committee agreed that the data were too sparse to put forward a recommendation for the use of fish oils alone.

2013 Recommendation: ***There are insufficient data to make a recommendation on the supplementation of fish oils alone in critically ill patients***

2013 Discussion: The committee noted the single centre nature of the study and the lack of treatment effect on outcome. The data were considered to sparse to make any treatment recommendations

Semi Quantitative Scoring

Values	Definition	2013 Score (0,1,2,3)	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	**0**	**0**
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	**1**	**1**
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	**3**	**3**
Homogeneity/Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	**n/a**	**3**
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	**2**	**1**
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	**2**	**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**	**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**	**2**
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	**2**	**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**	**2**

*** refers to fish oil supplementation alone (not with borage oil, antioxidants)**

4.1 b.(ii) Composition of Enteral Nutrition: Fish oil supplementation

Question: Does supplementation with fish oils result in improved clinical outcomes in the critically ill adult patient?

Summary of evidence: There was one level 2 study and one level 1 study using a fish oil only supplement as a bolus (Stapleton 2011, Parish 2014) in patients with acute lung injury. There were 8 studies that looked at fish oil, borage oil, antioxidants, and these are covered under section 4.1 b-i Fish Oils, Borage Oil, antioxidants

Mortality: Both studies reported on mortality and no effect was seen with fish oil supplementation (RR 0.98, 95% CI 0.56, 1.74, p=0.95; figure 1).

Infections: In the study by Stapleton et al, there were no differences in the incidence of sepsis between the two groups. Parish et al did not report on infections.

LOS: Both studies reported on ICU LOS and no effect was seen with fish oil supplementation (WMD -2.41, 95% CI -7.05, 2.22, p=0.31; figure 2) and it had no effect on hospital length of stay in the Stapleton et al study (WMD -4.60, 95% CI -12.68, 3.48, p=0.26).

Duration of ventilation: In the Stapleton et al study, fish oil supplementation alone was associated with a trend towards a reduction in duration of mechanical ventilation (WMD -4.30, 95% CI -8.87, 0.27, p=0.07). Parish et al only reported on ventilator free days and found no effect (p=0.304).

Other complications: There were no significant differences in multi-organ dysfunction score between the two groups in the Stapleton et al study.

Conclusions :

1) Fish oil supplementation vs placebo has no effect on mortality or infections in patients with ALI/ARDS.
2) Fish oil supplementation vs placebo has no effect on ICU length of stay or hospital length of stay.
3) Fish oil supplementation vs placebo is associated with a trend towards a reduction in duration of mechanical ventilation.

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 supplementation with fish oils in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%) Fish oil	Mortality # (%) Standard	Infections # (%)‡ Fish oil	Infections # (%)‡ Standard
1) Stapleton 2011	ALI patients (Trauma, sepsis, PNA, shock) from 5 ICUs N=90	C.Random: Yes ITT: Yes Blinding: Yes (12)	Fish Oil (9.75g EPA, 6.75g DHA/day x 14 days as bolus q 6 hrs) vs. 0.9% Saline isonitrogenous diet	**Hospital** 10/41 (22) **60 day** 9/41 (23)	**Hospital** 10/49 (20) **60 day** 12/49 (24)	**Sepsis** 1/41 (2)	**Sepsis** 1/49 (2)
2) Parish 2014	ARDS patients from 2 ICUs N = 58	C.Random: yes ITT: yes Blinding: double (7)	EN formula (not specified) + 6 omega-3 soft gels/day (2 capsules q 8hr; 360 mg EPA and 240 mg DHA per two capsules) vs EN formula (not specified) and placebo (not specified)	**28-day** 7/29 (26)	**28-day** 9/29 (32)	NR	NR

Study	LOS (days)		Ventilator days		Other
1) Stapleton 2011	**ICU** 11.9 ± 10.6 (41) **Hospital** 23.0 ± 18.3 (41) **ICU free days** 12 ± 11 **Hospital free days** 23 ± 19	**ICU** 17.4 ± 14.8 (48) **Hospital** 27.6 ± 20.6 (48) **ICU free days** 11 ± 10 **Hospital free days** 27.5 ± 22	8.6 ± 9.0 (38) **Vent free days** 14.8 ± 10	12.9 ± 12.2 (45) (p=0.07) **Vent free days** 14.0 ± 10	**Nutritional Intake in 1st week** 7362 ± 3800 kcal 7495 ± 3831 kcal
2) Parish 2014	**ICU** 15 ± 3.5 (29)	**ICU** 15.6 ± 4.3 (29)	**Ventilator free days** 6.6±2	**Ventilator free days** 6±2.5	

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	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Stapleton	10	41	10	49	54.4%	1.20 [0.55, 2.59]	2011
Parish	7	29	9	29	45.6%	0.78 [0.33, 1.81]	2014
Total (95% CI)		**70**		**78**	**100.0%**	**0.98 [0.56, 1.74]**	
Total events	17		19				

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

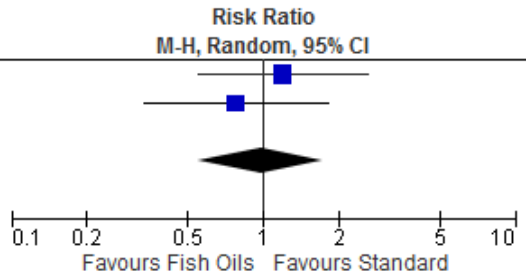

Figure 2. ICU Length of Stay

Study or Subgroup	Fish Oils Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Stapleton	11.9	10.6	41	17.4	14.8	48	37.0%	-5.50 [-10.80, -0.20]	2011
Parish	15	3.5	29	15.6	4.3	29	63.0%	-0.60 [-2.62, 1.42]	2014
Total (95% CI)			**70**			**77**	**100.0%**	**-2.41 [-7.05, 2.22]**	

Heterogeneity: Tau² = 7.82; Chi² = 2.87, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.02 (P = 0.31)