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 were two level 2 studies and one level 1 study looking at fish oil use with enteral nutrition. Two studies provided fish oil supplements as a bolus in addition to EN (Stapleton 2011, Parish 2014) in patients with acute lung injury and one study (Tihista 2018) used a 50% fish oil EN formula in burn patients. There were 10 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: All 3 studies reported on mortality and no effect was seen with fish oil supplementation (RR 1.04, 95% CI 0.68, 1.58, p=0.87; 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. Tihista et al found a significant reduction in sepsis and septic shock in the fish oil group (p=0.03) but no difference in pneumonia between the groups.

LOS: Two studies reported on ICU LOS in mean and standard deviation and no effect was seen with fish oil supplementation (WMD -2.41, 95% CI -7.05, 2.22, p=0.31; figure 2). Due to the different methods used to report on hospital LOS in two studies (Stapleton 2011, Tihista 20018), the data could not be aggregated. Stapleton et al reported on hospital LOS in mean and standard deviation, and fish oil supplementation had no effect on hospital LOS (p=0.27). Tihista et al reported on hospital LOS in median and IQR and found no difference between groups (p=0.53).

Duration of ventilation: Due to the different methods used to report mechanical ventilation in two studies (Stapleton 2011, Tihista 20018), the data could not be aggregated. In the Stapleton et al study, fish oil supplementation alone was associated with a trend towards a reduction in duration of mechanical ventilation (p=0.07). Tihista et al also reported a trend in the reduction of mechanical ventilation duration in the fish oil group (p=0.16). Parish et al only reported on ventilator free days and found no effect (p=0.30).

Other complications: There were no significant differences in multi-organ dysfunction score between the two groups in the Stapleton et al study. Tihista et al found a significant reduction in diarrhea and gastric residual volumes in the fish oil group.

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 may be associated with 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
3) Tihista 2018	Burn patients (TBSA >15%) with inhalation injury, single centre N=106	C.Random: no ITT: no Blinding: double (9)	Low fat diet (20 g/L) with 50% of fat from fish oil 50% sunflower oil vs standard low fat diet (20 g/L) from 100% sunflower oil. Isonitrogenous diet.	Hospital 15/47 (32)	Hospital 13/45 (29)	Pneumonia 15/47 Sepsis and shock 7/47	Pneumonia 20/45 Sepsis and shock 15/45

Table 1. Randomized studies supplementation with fish oils in critically ill patients (continued)

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	NR

3) Tihista 2018	Hospital 52 (Q1 29 – Q3 78) P=0.53	Hospital 51 (Q1 36 – Q3 72)	14 (Q1 10 – Q3 28) P=0.16	18 (Q1 11 – Q3 32)	Constipation 45/47 40/45 Diarrhea 2/47 7/45, P=0.06 High Gastric Residuals 4/47 15/45, P=0.003 Kcal/kg/d week 1 16±4 17±3 g protein/kg/d week 1 0.8±0.2 0.8±0.15 Omega 3 g/day week 1 4.38±0.75 0.37±0.05 Kcal/kg/d week 2 23±5 24±6 g protein/kg/d week 2 1.11±0.32 1.21±0.23 Omega 3 g/day week 2 6.38±1.08 0.52±0.07

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

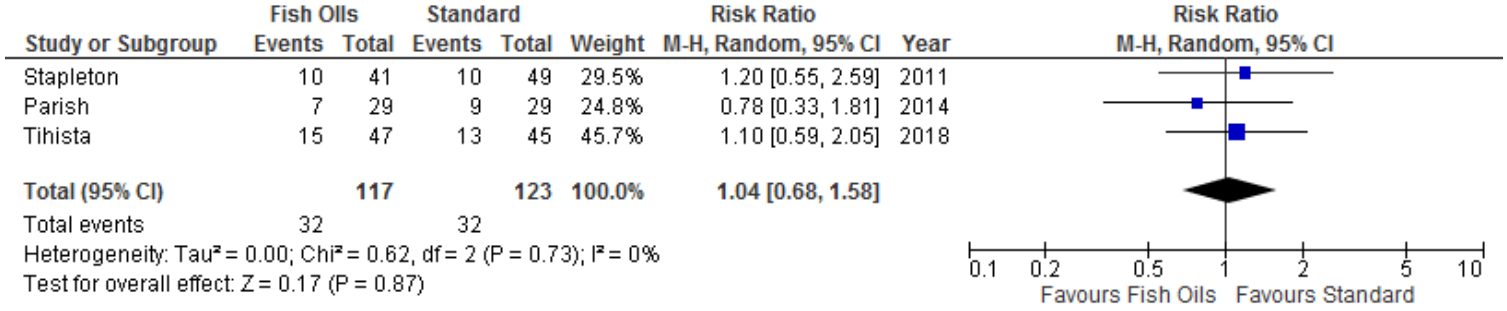

Figure 2. ICU Length of Stay

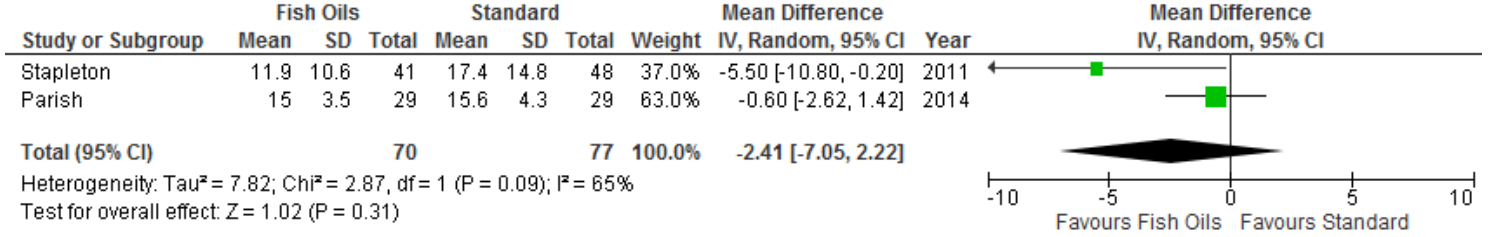

Table 2. Excluded Articles

#	Reason excluded	Reference
1	Not critically ill pts	Jakobsen LH, Wirth R, Smoliner C, Klebach M, Hofman Z, Kondrup J. Gastrointestinal tolerance and plasma status of carotenoids, EPA and DHA with a fiber-enriched tube feed in hospitalized patients initiated on tube nutrition: Randomized controlled trial. Clin Nutr. 2017 Apr;36(2):380-388.
2	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.
3	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.