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

Question: Does Enteral nutrition (EN) supplemented with fish oils result in improved clinical outcomes in the critically ill adult patient?

Summary of evidence: There were two level 1 and two level 2 studies that studied the effects of fish oil use with enteral nutrition. Three studies provided fish oil supplements as a bolus in addition to EN, two of these were in patients with acute lung injury (Stapleton 2011, Parish 2014), one in septic patients (Ibrahim 2018), and one study used a 50% fish oil EN formula in burn patients (Tihista 2018). 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 4 studies reported on mortality and no effect was seen with fish oil supplementation (RR 0.98, 95% CI 0.71, 1.36. p=0.90, test for heterogeneity I^2 =0%; 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. Similarly, no differences were seen in the rates of urinary tract, respiratory tract, blood or other infections between the fish oil supplemented group and standard EN in the Ibrahim et al study.

LOS: Three studies reported on ICU LOS in mean and standard deviation and fish oil supplementation was associated with a significant reduction (WMD -3.05, 95% CI -5.99, -0.10, p=0.04, test for heterogeneity I^2 =78%; figure 2). Due to the different methods used to report on hospital LOS in three studies (Stapleton 2011, Tihista 20018, Ibrahim 2018), the data could not be aggregated. Stapleton et al reported hospital LOS in mean and standard deviation, and fish oil supplementation had no effect on hospital LOS (p=0.27). Tihista et al found no difference between groups in the median and IQR hospital LOS (p=0.53).

Duration of ventilation: Due to the different methods used to report mechanical ventilation in two studies (Stapleton 2011, Tihista 20018) and the limited number of patients that needed ventilation in one study (Ibrahim 2018), 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) and there was no effect of fish oil supplementation on days of ventilation in the Ibrahim study (p=0.31).

Other: There were no significant differences in multi-organ dysfunction score between the two groups in the Stapleton et al study. Ibrahim et al found a significant reduction in SOFA scores (p=0.03) and organ failure free days (p=0.002) while observing a significant increase in organ dysfunction free days (p=0.001) and hemodynamic failure free days (p=0.002) in the group that received fish oil supplementation compared to standard EN alone. A significant reduction in diarrhea and gastric residual volumes in the fish oil group was reported in one study (Tihista et al 2018).

Conclusions:
In critically ill patients with lung injury, burns or sepsis, EN supplemented with fish oils

1) Has no significant effect on mortality or and no consistent effect on infectious complications.
2) May be associated with a significant reduction in ICU length of stay, however this is limited by heterogeneity. There is no effect on hospital length of stay.
3) May be associated with a reduction in duration of mechanical ventilation but the data are inconclusive.

***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 # (%)		Infections # (%)‡	
				Fish oil	Standard	Fish oil	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
4) Ibrahim 2018	Septic patients who could receive enteral nutrition N=110	C.Random: yes ITT: yes Blinding: double (12)	Standard EN +1000mg fish oil (omega-30 with 180 mg EPA and 120 mg DHA, three times daily started within 6 hrs vs. standard EN Both started within 6 hrs, to receive same rate, 75% target within 72 hrs. Isocaloric, isonitrogenous	**ICU** 16/55 (29.1%) **Hospital** 18/55 (32.7%)	**ICU** 18/55 (32.7%), p=0.27 **Hospital** 20/55 (36.4%), p=0.24	**Urinary tract** 24/55 (43.6%) **Respiratory tract** 11/55 (20%) **Blood infections** 9/55 (16.4%) **Other** 11/55 (20%)	**Urinary tract** 23/55 (41.8%) **Respiratory tract** 13/55 (23/6%) **Blood infections** 10/55 (18.2%) **Other** 9/55 (16.4%)

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) **Ventilator free days** 14.8 ± 10	12.9 ± 12.2 (45) (p=0.07) **Ventilator 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
4) Ibrahim 2018	**ICU** 12.36 ±2.34 **Post ICU length of stay** 13.44 ± 2.46	**ICU** 16.56 ±4.9, p=0.019 **Post ICU length of stay** 14.73 ±3.45, p=0.32	5.32 ± 1.66 (n=5)	6.37 ± 2.36 (n=6), p=0.31	**ICU stay SOFA score, mean,SD** 6.10±1.6 8.89±1.8, p=0.03 **Organ failure free days, median (IQR)** 11(4-11) 4(0-10), p=0.002 **Organ dysfunction-free days, median (IQR)** 9(1-11) 2(0-8), p=0.001 **Hemodynamic failure free days, median (IQR)** 12(8-13) 8(5-10), p=0.002

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	17.8%	1.20 [0.55, 2.59]	2011
Parish	7	29	9	29	14.9%	0.78 [0.33, 1.81]	2014
Tihista	15	47	13	45	27.5%	1.10 [0.59, 2.05]	2018
Ibrahim	18	55	20	55	39.8%	0.90 [0.54, 1.51]	2018
Total (95% CI)		**172**		**178**	**100.0%**	**0.98 [0.71, 1.36]**	
Total events	50		52				

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)

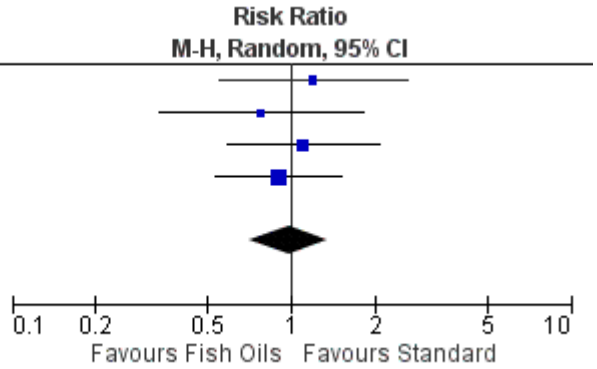
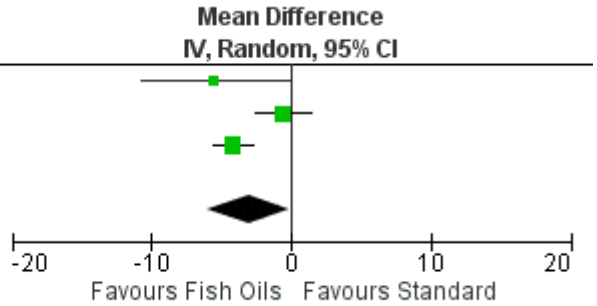


Figure 2. ICU Length of Stay

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	18.7%	-5.50 [-10.80, -0.20]	2011
Parish	15	3.5	29	15.6	4.3	29	38.7%	-0.60 [-2.62, 1.42]	2014
Ibrahim	12.36	2.34	55	16.56	4.9	55	42.6%	-4.20 [-5.64, -2.76]	2018
Total (95% CI)			**125**			**132**	**100.0%**	**-3.05 [-5.99, -0.10]**	

Heterogeneity: Tau² = 4.77; Chi² = 8.94, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 2.03 (P = 0.04)



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Included Studies

1. Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, Akhtar SR, Ruzinski JT, Caldwell E, Curtis JR, Heyland DK, Watkins TR, Parsons PE, Martin JM, Wurfel MM, Hallstrand TS, Sims KA, Neff MJ. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. Crit Care Med. 2011 Jul;39(7):1655-62.
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4. Ibrahim ES. Enteral nutrition with omega-3 fatty acids in critically ill septic patients: A randomized double-blinded study. Saudi J Anaesth. 2018 Oct-Dec;12(4):529-534. doi: 10.4103/sja.SJA_50_18. PMID: 30429732; PMCID: PMC6180704.

Excluded Studies	Reasons
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.	Not critically ill patients
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.	Systematic Review
Chen H, Wang W, Hong Y, Zhang H, Hong C, Liu X. Single-blinded, randomized, and controlled clinical trial evaluating the effects of Omega-3 fatty acids among septic patients with intestinal dysfunction: A pilot study. Exp Ther Med. 2017;14(2):1505-1511. doi:10.3892/etm.2017.4680	See 9.2 PN Composition: Type of Lipids
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.	Systematic Review