9.2 Composition of Parenteral Nutrition: Type of lipids

March 2013

2013 Recommendation: *When parenteral nutrition with intravenous lipids is indicated, IV lipids that reduce the load of omega-6 fatty acids/soybean oil emulsions should be considered. However, there are insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 fatty acid/soybean oil load in critically ill patients receiving parenteral nutrition.*

2013 Discussion: The committee noted that the weak recommendation for withholding lipids in section 10.2 pertains to soybean emulsion lipids only but if lipids are to be used, this section provides guidelines for the type of lipid to be used. There were 4 new RCTs (Wang 2009, Barbosa 2010, Umperrez 2012 & Pontes-Arruda 2012) and the committee noted that all the trials compared a lipid strategy aimed at reducing the overall omega-6 fatty acid load (or soybean oil sparing strategy) to a soybean emulsion product. The trend towards a reduction in mortality, ICU LOS and duration of ventilation associated with overall omega-6 reducing/soybean sparing lipids was noted, as was the presence of statistical heterogeneity for the ICU LOS data. There are no direct comparisons of the types of lipids (i.e. omega-3, omega-9, or medium chain triglyceride (MCT) emulsions) to each other. Given this, the committee agreed that in the event PN lipids are indicated, lipids that reduce the overall load of omega-6 fatty acids ought to be utilized; however there are no clear signals from the evidence to date regarding what type of omega-6 sparing strategy should be used.

2009 Recommendation: *There are insufficient data to make a recommendation on the type of lipids to be used in critically ill patients receiving parenteral nutrition.*

2009 Discussion: The committee noted the variations in the types of lipids used in these small, single-centered studies and although the interventions aimed at reducing the overall omega 6 fatty acid content, there was too much variability in study design to allow for statistical aggregation of all the studies. When they were grouped by the nature of the experimental lipid, there was a lack of a clear signal towards a benefit in clinical outcomes. Only in two small studies using olive oil emulsions was a reduction in ICU length of stay observed; however, the control groups in both studies were different, the studies were small, and did not show any effect on mortality or other clinical parameter. Given this and the concerns around feasibility, potential safety concerns and cost of the varying lipid emulsions, the committee decided that there was not enough evidence to make a recommendation for one type of lipid emulsion over another.

Semi Quantitative Scoring

	Definition	2009 Score (0,1,2,3)	2013 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	1 (mortality) 0 (infection)
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	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2	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	2
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, heterogenous patients, diverse practice settings =3	1	1
Low 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	1	1
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

9.2 Topic: Composition of Parenteral Nutrition: Type of lipids March 2013

Question: Does the type of lipids in parenteral nutrition affect outcomes in the critically ill adult patient?

Summary of evidence: There were 7 level 2 studies (Nijveldt 1998, Garnacho-Montero 2002, Iovinelli 2007, Wang 2009, Huschak 2005, Garcia de Lorenzo 2005 & Pontes-Arruda 2012) and 5 level 1 studies (Lindgren 2001, Grecu 2003, Friesecke 2008, Barbosa 2010& Umperrez 2012) reviewed. For most of the studies, the focus of the investigation was on surrogate endpoints but the studies were still included because they did report on mortality or infection. All studies compared varying strategies of reducing omega-6 fatty acids (also called) to LCT. Four of these studies compared LCTs plus medium chain triglycerides (MCT) to a LCT emulsion (Nijveldt 1998, Lindgren 2001, Garnacho-Montero 2002 and Iovinelli 2007); 1 study compared LCT + MCT + fish oils emulsion (Lipoplus) to a MCT + LCT emulsion (Barbosa 2010); 3 studies compared a fish oil containing emulsion (Omegaven) mixed with LCT or LCT/MCT to a LCT or LCT+MCT mixture (Grecu 2003, Friesecke 2008, Wang 2009);), while 4 studies compared an olive oil containing emulsion (Clinoleic) to a LCT + MCT mixture (Garcia de-Lorenzo 2005, Huschak 2005, Umperezz 2012 & Pontes-Arruda 2012). One study that compared an outdated long chain triglyceride (LCT) emulsion to another form of LCT (Kari 1998) was removed in the 2012 summary of evidence as it did not involve a soybean oil reducing strategy. The Wang 2008 study was replaced by a later version of the study by the same authors that had more patients i.e. Wang 2009.Two studies compared supplementation with intravenous fish oil emulsion without parenteral nutrition (fed enteral nutrition) and given that the control group had no soybean oil, these studies (Gupta 2011, Khor 2011) were excluded.

Mortality:

Overall omega-6 fatty acid reducing strategy: When all the studies that used an omega-6 fatty acid sparing strategy were aggregated, the use of a lower omega-6 fatty acid strategy was associated with a trend towards a reduction in mortality (RR 0.83, 95% CI 0.62, 1.11, p=0.20), heterogeneity I^2=0%, p=0.96; figure 1.1).

LCT + MCT vs LCT: A meta-analysis of the studies of LCT+ MCT vs. LCT showed no difference in mortality between the groups (RR 0.84, 95 % CI 0.43, 1.61, p=0.59, heterogeneity I^2=0%; figure 1.1.1).

Fish Oils vs LCT or LCT + MCT: With respect to studies of fish oils containing emulsions vs. LCT or LCT+ MCT, there was a trend towards reduction in mortality observed (RR 0.76, 95% CI 0.48, 1.21, p=0.25, heterogeneity I^2=0%; figure 1.1.2).

Olive Oils vs LCT+MCT: No difference between the groups receiving the olive oil containing emulsions vs. LCT + MCT (RR 0.90, 95% CI 0.58, 1.394, p = 0.62, heterogeneity I^2=0%; figure 1.1.3) was observed.

Infections:

Overall omega-6 fatty acid reducing strategy: When all 5 studies that used a LCT (omega-6 fatty acid) sparing strategy were aggregated, the use of a lower LCT emulsion had no effect on infections, when compared to LCT (RR 1.13, 95% CI 0.87, 1.46, p=0.35, heterogeneity I^2=0%, p=0.65; figure 1.2).

LCT + MCT vs LCT: One study comparing LCT + MCT to MCT reported no differences in the incidences of new infections or positive blood cultures between the groups, however no data was reported (level 1 study Nijveldt 1998). In another study, a higher incidence of infections was observed in the intervention group (Lindgren 2001).
Fish Oils vs LCT or LCT + MCT: When the data from the 2 studies of fish oil emulsions in PN fed patients were aggregated, there was no significant effect on infection complications (RR 0.79, 95% CI 0.43, 1.43, p=0.43, heterogeneity I^2=0%, p=0.62; figure 1.2.1).
Olive Oils vs LCT+MCT: When the data from the 3 studies of olive oil emulsions in PN fed patients were aggregated, there was a trend towards in increase in infections (RR1.23, 95% CI 0.92, 1.63, p=0.16, heterogeneity I^2=0%, p=0.80; figure 1.2.2).

LOS:
Overall omega-6 fatty acid reducing strategy: When all the studies that used a LCT (omega-6 fatty acid) sparing strategy were aggregated, the use of a lower LCT emulsion was associated with a trend towards a reduction in ICU LOS when compared to LCT (WMD -2.31, 95%CI -5.28, 0.66, p=0.13, heterogeneity I^2=68%; figure 1.3).
LCT + MCT vs LCT: When the data from the two studies comparing LCT+MCT to LCT were aggregated, there were no differences in ICU LOS between the two groups (WMD -1.46, 95 % CI -5.77, 2.85, p=0.51, heterogeneity I^2=78%; figure 1.3.1).
Fish Oils vs LCT or LCT + MCT: Similarly, when the data from the three studies of fish oil emulsions that reported on this outcome were aggregated, no effect on ICU LOS was observed (WMD -1.13, 95% CI -8.96, 6.69, p=0.78, heterogeneity I^2=78%; figure 1.3.2).
Olive Oils vs LCT+MCT: When the data from the three studies of olive oil emulsions were aggregated, olive oil emulsions had no effect on ICU length of stay (WMD -4.08, 95 % CI -10.97, 2.81, p=0.25, heterogeneity I^2=59%; figure 1.3.3).

Ventilator days:
Overall omega-6 fatty acid reducing strategy: LCT (omega-6 fatty acid) sparing strategies were associated with a trend towards a reduction in duration of ventilation, compared to LCT (WMD -2.57, 95% CI -5.51, -0.378, p =0.09, heterogeneity I^2=25%; figure 1.4).
LCT + MCT vs LCT: Only one study comparing LCT+MCT to LCT reported duration of ventilation and no significant differences were seen between the two groups (Iovinelli 2007).
Fish Oils vs LCT or LCT + MCT: When the data from the three studies of fish oils were aggregated,), there was a trend towards a reduction in the duration of mechanical ventilation (WMD -1.81, 95% CI -3.98, 0.36, p=0.10, heterogeneity I^2= 0%; figure 1.4.1).
Olive Oils vs LCT+MCT: The use of olive oil emulsions was associated with a significant reduction in the duration of mechanical ventilation (WMD -6.47, 95% CI -11.41, -1.53, p=0.01, heterogeneity I^2=0%; figure 1.4.2).

Other complications:

LCT + MCT vs LCT: A significant improvement in nutritional parameters (i.e. nitrogen balance, retinol binding protein, prealbumin) was observed in the groups receiving LCT + MCT in some of the studies (Garnacho-Montero, Lindgren) and a significant reduction in the time of weaning was seen in one study (Iovinellei 2007).

Fish Oils in PN fed patients vs LCT or LCT + MCT: The use of Omegaven was associated with a reduction in the need for surgery due to a subsequent septic episode when compared to LCT (p=0.010, Grecu 2003). Wang 2009 reported a reduction in the need for surgery for pancreatic necrosis in the group receiving fish oils but this was not statistically different. There was a trend towards a reduction in catheter related blood stream infections in the group receiving fish oils (p=0.10, Friesecke 2008) and better gas exchange (Barbosa 2010).

Olive Oils vs LCT+MCT: The use of olive oil emulsions was associated with better liver function (Garcia de Lorenzo 2005), lower blood sugars & carbon dioxide production (p =0.03 Huschak 2005).

Conclusions:

1) LCT reducing strategies, also known as Soybean oil sparing strategies, are associated with a trend towards reduction in mortality, ICU LOS and duration of ventilation, but have no effect on infections in critically ill adults.
2) LCT + MCT emulsions, compared to LCT, have no effect on mortality or ICU length of stay in critically ill patients.
3) IV fish oils/fish oil containing emulsions, compared to LCT are associated with a trend towards a reduction in duration of ventilation but have no effect on mortality, infections or ICU LOS.
4) Olive Oil containing emulsions, compared to LCT, have no effect on mortality or ICU LOS but are associated with a trend towards increased infections but a significant reduction in duration of 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 is unfulfilled.

Table 1. Randomized studies evaluating type of lipids (PN) in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
Long Chain Triglyceride (LCT) plus Medium Chain Triglycerides (MCT) vs. LCT							
1) Nijveldt 1998	ICU, septic surgical patients, trauma N=20	C.Random: not sure ITT: yes Blinding: double (10)	PN + Lipofundin (50% LCT+ 50% MCT) vs. PN + Intralipid (100% LCT, soybean)	LCT + MCT ICU 2/12 (17)	LCT ICU 1/8 (13)	LCT + MCT NR	LCT NR
2) Lindgren 2001	ICU patients, sepsis, multi-trauma N=30	C.Random: yes ITT: yes Blinding: double (12)	PN + Structolipid (64% LCT + 36% MCT) vs. PN + Intralipid (100% LCT, soybean)	LCT + MCT 1/15 (7)	LCT 0/15 (0)	LCT + MCT 6/15 (40)	LCT 4/15 (27)
3) Garnacho-Montero 2002	Surgical ICU Patients with peritonitis and abdominal sepsis N=72	C.Random: not sure ITT: no Blinding: no (6)	PN + Lipofundin (50% LCT + 50% MCT) vs. PN with Intralipid (100% LCT, soybean) Both groups received PN with 45 % Branched chain amino acids	LCT + MCT ICU 8/35 (23) Hospital 11/35 (31)	LCT ICU 11/37 (30) Hospital 13/37 (35)	LCT + MCT NR	LCT NR
4) Iovinelli 2007	Patients with COPD requiring ventilation N=24	C.Random: yes ITT: yes Blinding: no (7)	PN + Lipofundin (50% LCT + 50% MCT) vs. 100% LCT (100% LCT, soybean). In both received 50% of non-protein calories given as lipids	LCT + MCT ICU 2/12 (17)	LCT ICU 3/12 (25)	LCT + MCT Catheter-related 1/12 (8)	LCT Catheter-related 2/12 (17)
Fish oil (ω 3) containing emulsions in PN fed patients vs. LCT or LCT+MCT							
5) Grecu 2003*	Patients with abdominal sepsis N=54 (15/54 in ICU)	C.Random: yes ITT: yes Blinding: double (12)	PN + Omegaven (10% fish oils) plus LCTs vs. PN with LCT	Omegaven + LCT ICU 2/28 (7)	LCT ICU 3/26 (12)	Omegaven VAP 0/8	LCT VAP 1/7 (14)
6) Friesecke 2008	Medical ICU patients N=166	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipofundin MCT (50% LCT + 50% MCT) + Omegaven (10% fish oil) vs. Lipofundin MCT (50% LCT + 50% MCT)	LCT+MCT+Fish oil 28 day 18/83 (22)	LCT+MCT 28 day 22/82 (27)	LCT+MCT+Fish oil 10/83 (12)	LCT + MCT 11/82 (13)

7) Wang 2009	Severe acute pancreatitis patients in ICU N=56	C.Random: no ITT: yes Blinding: double (11)	PN + Omegaven (10% fish oils) plus Lipovenos (LCTs, soybean oil) (ω3:ω6 ratio was 1:4) vs. PN with Lipovenos (LCTs, soybean oil). Both received same amounts of lipids (1 gm/kg/day)	Omegaven ICU 0/28 (0)	LCT ICU 2/28 (7)	Omegaven 6/28 (21)	LCT 9/28 (32)
8) Barbosa 2010	ICU patients with SIRS or sepsis requiring PN N=25	C.Random: yes ITT: yes Blinding: single (10)	PN + Lipolus (50% MCT, 40% LCTs soybean oil, 10% fish oil) vs. Nutriflex LipidSpecial (50% MCT, 50% LCT, soybean oil). Both received same amounts of lipids (~1 gm/kg/day)	MCT+LCT+Fish oil 5 day 2/13 (15) 28 day 4/13 (31)	MCT+LCT 5 day 1/10 (10) 28 day 4/10 (40)	MCT+LCT+Fish oil NR	MCT+LCT NR
Olive oil containing emulsions vs. LCT or LCT+MCT							
9) Garcia-de-Lorenzo 2005	Severe burn patients, burn severity index ≥ 7, TBSA > 30 % N=22	C.Random: not sure ITT: yes Blinding: double (10)	PN with ClinOleic 20% (80% olive oil, 20% soybean oil, (63% ω9, 37% ω6= restricted linoleic acid {ω6} content) vs. Lipofundin (50% LCT+ 50% MCT).	Clinoleic ICU 4/11 (36)	Lipofundin ICU 4/11 (36)	Clinoleic 6/11 (55)	Lipofundin 6/11 (55)
10) Huschak 2005**	ICU trauma patients N=33	CRandom: yes ITT: yes Blinding: None (7)	PN high fat (lipid:glucose 75:25) + Clinoleic (80% olive oil, 20% soybean oil) + EN Glucerrna (lipid:glucose 60:40) vs. PN high carbohydrate (lipid: glucose 37:63) + Lipofundin (50% LCT + 50% MCT) + EN Fresubin HP Energy (lipid:glucose 44:56)	High fat + Clinoleic ICU 4/18 (22)	Low fat + LCT + MCT ICU 1/15 (7)	High fat + Clinoleic Low fat +LCT+MCT Data not reported. Text indicates that infections were less frequent in high fat group (intervention group).	
11) Umperrez 2012	Medical surgical ICU pts post op (88% emergency surgeries) N=100	C.Random: yes ITT: yes Blinding: double (14)	PN with ClinOleic 20% (80% olive oil, 20% soybean oil, ω6:ω3=9:1) vs Intralipid (100% soybean oil, ω6:ω3=7:1)	Clinoleic Hospital 5/51 (10)	Intralipid Hospital 8/49 (16)	Clinoleic 29/51 (57) Pneumonia 7/51 (14)	Intralipid 21/49 (43) 5/49 (10)
12) Pontes-Arruda 2012	ICU pts requiring PN from 8 ICUs and 3 countries N=204	C.Random: yes ITT: yes Blinding: no (9)	PN with ClinOleic (n=103) vs PN with a MCT/LCT based IVLE (n=101)	ClinOleic ICU 19/103 (24) 28-day 24/103 (27)	MCT/LCT ICU 21/101 (21) 28-day 26/101 (26)	ClinOleic All infections 39/103 (38) ICU acquired infections 28/103 (27) VAP/lower respiratory infections 9/103 (9)	MCT/LCT 35/101 (35) 23/101 (23) 11/101 (11)

Table 1. continued Randomized studies evaluating type of lipids (PN) in critically ill patients (continued)

Study	LOS days		Ventilator days		Other
Long Chain Triglyceride (LCT) plus Medium Chain Triglycerides (MCT) vs. LCT					
1) Nijveldt 1998	LCT + MCT 13.8 ± 2.9 (12)	LCT 17.4 ± 3.0 (8)	LCT + MCT NR	LCT NR	NR
2) Lindgren 2001	LCT + MCT NR	LCT NR	LCT + MCT NR	LCT NR	LCT + MCT LCT Adverse effects 5/15 (33) 4/15 (27) Nitrogen balance at day 3 2.6 ± 5.6 gms -11.7 ± 4.8 gms
3) Garnacho-Montero 2002	LCT + MCT ICU 16.6 ± 6.1 (35)	LCT ICU 15.8 ± 7 (37)	LCT + MCT NR	LCT NR	LCT + MCT LCT Retinol binding protein 1.7 ± 1 0.8 ± 0.6 Nitrogen balance 14.2 ± 2.9 11.6 ± 4
4) Iovinelli 2007	LCT + MCT NR	LCT NR	LCT + MCT 10.6 ± 3.0 (12)	LCT 13.4 ± 3.5 (12)	LCT + MCT LCT Time before weaning 52 ± 36 hrs 127 ± 73 hrs
Fish oil (ω 3) containing emulsions in PN fed patients vs. LCT or LCT+MCT					
5) Grecu 2003*	Omegaven ICU 3.32 ± 1.48 (8) Hospital 11.68 ± 2.04 (28)	LCT ICU 9.28 ± 3.08 (7) Hospital 20.46 ± 3.27 (26)	Omegaven 2.83 ± 1.62 (8)	LCT 5.23 ± 2.80 (7)	Omegaven LCT Patients undergoing reoperation for septic episode 2/28 (7) 8/26 (31)
6) Friesecke 2008	Fish oil ICU 28 ± 25 (83)	LCT ICU 23 ± 20 (82)	LCT + MCT + Fish oil 22.8 ± 22.9 (83)	LCT + MCT 20.5 ± 19.0 (82)	LCT + MCT + Fish oils LCT+MCT Urinary Tract Infections 6/83 (7) 4/82 (5) Catheter-related infections 1/83 (1) 3/83 (4) Total EN Energy Intake (kcal/kg) 22.2 ± 5.5 21.6 ± 5.6

7) Wang 2009	NR	NR	NR	NR	Omegaven LCT Surgery of infected pancreatic necrosis 3/28 (11) 6/28 (21)
8) Barbosa 2010	MCT+LCT+Fish oil ICU 12 ± 14.4[a] (13) Hospital 22 ± 25.2[a] (13)	MCT+LCT ICU 13 ± 12.6 [a] (10) Hospital 55 ± 50 [a].6 (10)	MCT+LCT+Fish oil 10 ± 14.4 (13)	MCT+LCT 11 ± 12.64 (10)	MCT+LCT+ Fish oil MCT+LCT 2057± 418 kcals 1857 ± 255 kcals
Olive oil containing emulsions vs. LCT or LCT+MCT					
9) Garcia-de-Lorenzo 2005	Clinoleic ICU 32.9 ± 10.6[a] (11) Hospital 57 ± 15.3 [a] (11)	Lipofundin ICU 41.8 ± 16.3[a] (11) Hospital 64.9 ± 27.2 [a] (11)	Clinoleic 11.0 ± 11.93[a] (11)	Lipofundin 13.0 ± 16.25[a](11)	Clinoleic Lipofundin Multiple organ dysfunction score 11.0 ± 3.6 13.0 ± 4.9
10) Huschak 2005**	High fat + Clinoleic ICU 17.9 ± 11.2 (18)	Low fat + LCT + MCT ICU 25.1 ± 7.0 (15)	High fat + Clinoleic 13.0 ± 8.9 (18)	Low fat + LCT + MCT 20.4 ± 7.0 (15)	High fat + Clinoleic Low fat + LCT + MCT Total Energy Intake (kcal/kg) 17.9 ± 6.3 22.3 ± 4.2
11) Umperrez 2012	Clinoleic ICU 17 ± 18 (51) Hospital 40.8 ± 36 (51)	Intralipid ICU 15.2 ± 14 (49) Hospital 46.7 ± 48 (51)	Clinoleic NR	Intralipid NR	Clinoleic Intralipid Total Energy Intake (kcal/kg) 22 ± 6 22 ± 5
12) Pontes-Arruda 2013	Clinoleic ICU 12 (7-17) Hospital 21 (15-25)	MCT/LCT ICU 11 (5-14) Hospital 18 (13-23)	NA	NA	Clinoleic MCT/LCT Nutritional Intake Lipids (g/day) 66 (61-73) 61 (54-67) Days on PN 12 (8-15) 11 (7-15) Dextrose (g/day) 288 (275-303) 281 (273-301) AAs (g/day) 87 (84-90) 87 (83-92)

C.Random: concealed randomization
ITT: intent to treat
NR: not reported
* data obtained from author, 8 out of 28 in Omegaven and 7 out of 26 in LCT group were in ICU
[a] converted Standard Error Mean (SEM) to Standard deviation (SD)

MCT: medium chain triglycerides
LCT: long chain triglycerides

† hospital mortality unless specified
‡ number of patients with infections unless specified
**intervention includes high fat low CHO PN plus fish oil

Figure 1.1. Overall Effect of Varying Lipids on Mortality

	Omega-6 Reducing		LCT			Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
1.1.1 LCT + MCT vs LCT							
Nijveldt	2	12	1	8	1.7%	1.33 [0.14, 12.37]	1998
Lindgren	1	15	0	15	0.8%	3.00 [0.13, 68.26]	2001
Garnacho-Montero	8	35	11	37	13.4%	0.77 [0.35, 1.69]	2002
Iovinelli	2	12	3	12	3.2%	0.67 [0.13, 3.30]	2007
Subtotal (95% CI)		**74**		**72**	**19.1%**	**0.84 [0.43, 1.61]**	
Total events	13		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 0.53 (P = 0.59)							
1.1.2 Fish oil containing emulsions vs LCT or LCT + MCT							
Grecu	2	28	3	26	2.8%	0.62 [0.11, 3.41]	2003
Friesecke	18	83	22	82	27.9%	0.81 [0.47, 1.39]	2008
Wang 2009	0	28	2	28	0.9%	0.20 [0.01, 3.99]	2009
Barbosa	4	13	4	10	6.6%	0.77 [0.25, 2.34]	2010
Subtotal (95% CI)		**152**		**146**	**38.3%**	**0.76 [0.48, 1.21]**	
Total events	24		31				
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 3 (P = 0.83); I² = 0%							
Test for overall effect: Z = 1.16 (P = 0.25)							
1.1.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	4	11	4	11	6.7%	1.00 [0.33, 3.02]	2005
Huschak	4	18	1	15	1.9%	3.33 [0.42, 26.72]	2005
Pontes-Arruda 2012	19	103	21	101	26.5%	0.89 [0.51, 1.55]	2012
Umperrez	5	51	8	49	7.5%	0.60 [0.21, 1.71]	2012
Subtotal (95% CI)		**183**		**176**	**42.7%**	**0.90 [0.58, 1.39]**	
Total events	32		34				
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 3 (P = 0.54); I² = 0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Total (95% CI)		**409**		**394**	**100.0%**	**0.83 [0.62, 1.11]**	
Total events	69		80				
Heterogeneity: Tau² = 0.00; Chi² = 4.19, df = 11 (P = 0.96); I² = 0%							
Test for overall effect: Z = 1.27 (P = 0.20)							
Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%							

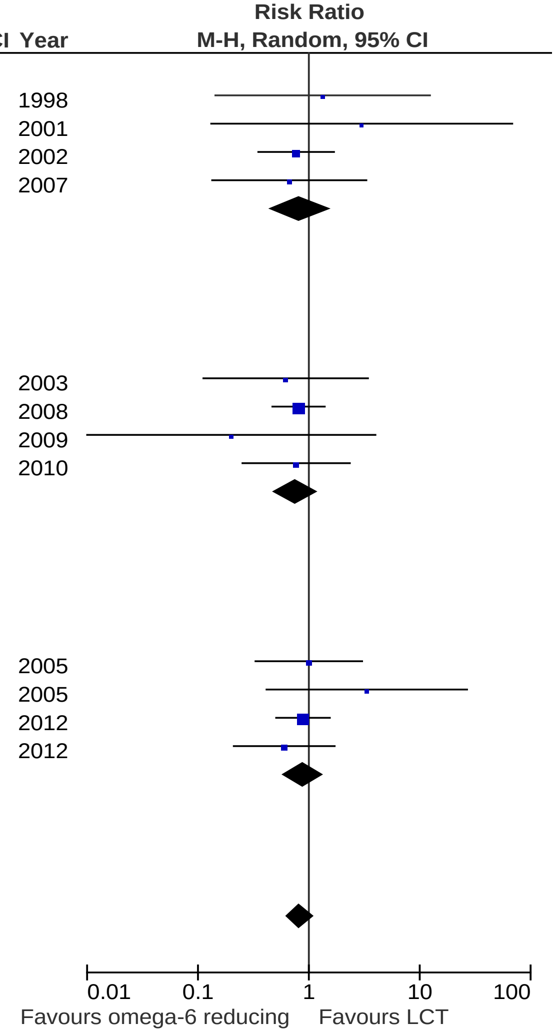

Figure 1.2. Overall Effect of Varying Lipids on Infections

Study or Subgroup	Omega-6 Reducing Events	Omega-6 Reducing Total	LCT or LCT+MCT Events	LCT or LCT+MCT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Fish oil containing emulsions vs LCT or LCT + MCT							
Friesecke	10	83	11	82	10.3%	0.90 [0.40, 2.00]	2008
Wang 2009	6	28	9	28	8.4%	0.67 [0.27, 1.62]	2009
Subtotal (95% CI)		**111**		**110**	**18.7%**	**0.79 [0.43, 1.43]**	
Total events	16		20				
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%							
Test for overall effect: Z = 0.79 (P = 0.43)							
1.2.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	6	11	6	11	11.4%	1.00 [0.47, 2.14]	2005
Pontes-Arruda 2012	28	103	23	101	28.9%	1.19 [0.74, 1.93]	2012
Umperrez	29	51	21	49	41.0%	1.33 [0.89, 1.98]	2012
Subtotal (95% CI)		**165**		**161**	**81.3%**	**1.23 [0.92, 1.63]**	
Total events	63		50				
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.80); I² = 0%							
Test for overall effect: Z = 1.41 (P = 0.16)							
Total (95% CI)		**276**		**271**	**100.0%**	**1.13 [0.87, 1.46]**	
Total events	79		70				
Heterogeneity: Tau² = 0.00; Chi² = 2.46, df = 4 (P = 0.65); I² = 0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.19), I² = 43.0%							

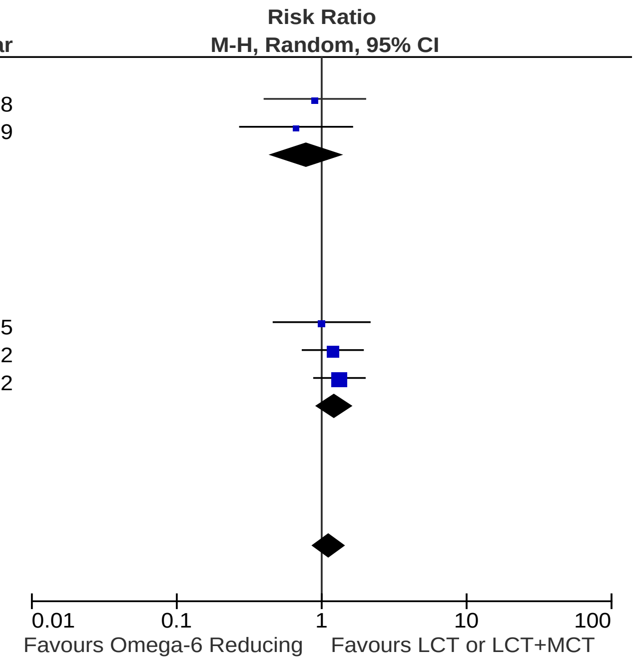

Figure 1.3. Overall Effect of Varying Lipids on ICU LOS

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.3.1 LCT + MCT vs LCT									
Nijveldt	13.8	2.9	12	17.4	3	8	19.1%	-3.60 [-6.25, -0.95]	1998
Garnacho-Montero	16.6	6.1	35	15.8	7	37	18.3%	0.80 [-2.23, 3.83]	2002
Subtotal (95% CI)			**47**			**45**	**37.4%**	**-1.46 [-5.77, 2.85]**	
Heterogeneity: Tau² = 7.57; Chi² = 4.59, df = 1 (P = 0.03); I² = 78%									
Test for overall effect: Z = 0.67 (P = 0.51)									
1.3.2 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	3.32	1.48	8	9.28	3.08	7	19.4%	-5.96 [-8.46, -3.46]	2003
Friesecke	28	25	83	23	20	82	10.2%	5.00 [-1.90, 11.90]	2008
Barbosa	12	14.4	13	13	12.6	10	5.5%	-1.00 [-12.06, 10.06]	2010
Subtotal (95% CI)			**104**			**99**	**35.1%**	**-1.13 [-8.96, 6.69]**	
Heterogeneity: Tau² = 35.46; Chi² = 8.97, df = 2 (P = 0.01); I² = 78%									
Test for overall effect: Z = 0.28 (P = 0.78)									
1.3.3 Olive oil containing emulsions vs LCT or LCT + MCT									
Garcia de Lorenzo	32.9	10.6	11	41.8	16.3	11	5.2%	-8.90 [-20.39, 2.59]	2005
Huschak	17.9	11.2	18	25.1	7	15	11.2%	-7.20 [-13.47, -0.93]	2005
Umperrez	17	18	51	15.2	14	49	11.2%	1.80 [-4.51, 8.11]	2012
Subtotal (95% CI)			**80**			**75**	**27.6%**	**-4.08 [-10.97, 2.81]**	
Heterogeneity: Tau² = 21.46; Chi² = 4.90, df = 2 (P = 0.09); I² = 59%									
Test for overall effect: Z = 1.16 (P = 0.25)									
Total (95% CI)			**231**			**219**	**100.0%**	**-2.31 [-5.28, 0.66]**	
Heterogeneity: Tau² = 10.21; Chi² = 21.87, df = 7 (P = 0.003); I² = 68%									
Test for overall effect: Z = 1.53 (P = 0.13)									
Test for subgroup differences: Chi² = 0.46, df = 2 (P = 0.80), I² = 0%									

Mean Difference IV, Random, 95% CI

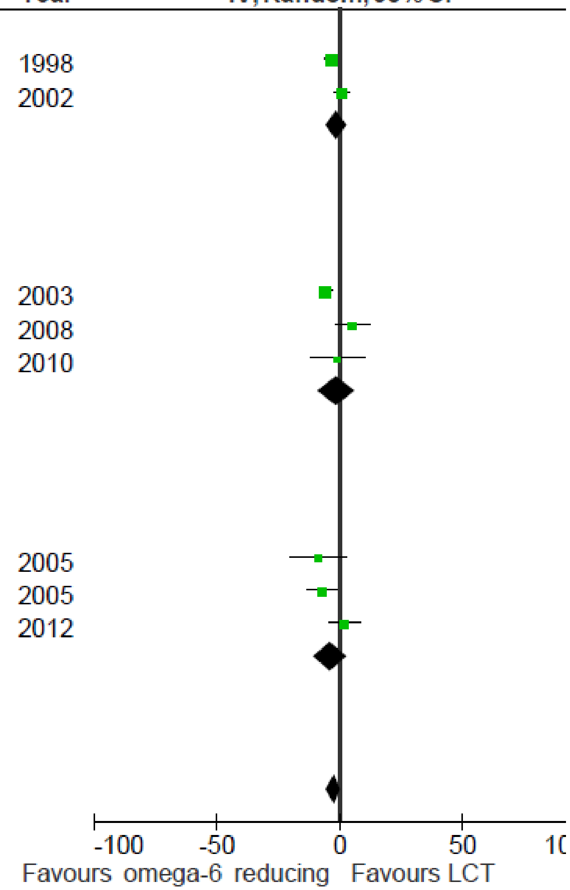

Figure 1.4. Overall Effect of Varying Lipids on Mechanical Ventilation

	Omega-6 Reducing			LCT				Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
1.4.1 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	2.83	1.62	8	5.23	2.8	7	50.5%	-2.40 [-4.76, -0.04]	2003
Friesecke	22.8	22.9	83	20.5	19	82	16.4%	2.30 [-4.12, 8.72]	2008
Barbosa	10	14.4	13	11	12.64	10	6.4%	-1.00 [-12.07, 10.07]	2010
Subtotal (95% CI)			**104**			**99**	**73.3%**	**-1.81 [-3.98, 0.36]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 2 (P = 0.40); I² = 0%									
Test for overall effect: Z = 1.63 (P = 0.10)									
1.4.2 Olive oil containing emulsions vs LCT or LCT + MCT									
Garcia de Lorenzo	11	11.93	11	13	16.25	11	5.6%	-2.00 [-13.91, 9.91]	2005
Huschak	13	8.9	18	20.4	7	15	21.1%	-7.40 [-12.83, -1.97]	2005
Subtotal (95% CI)			**29**			**26**	**26.7%**	**-6.47 [-11.41, -1.53]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%									
Test for overall effect: Z = 2.57 (P = 0.01)									
Total (95% CI)			**133**			**125**	**100.0%**	**-2.57 [-5.51, 0.37]**	
Heterogeneity: Tau² = 3.00; Chi² = 5.36, df = 4 (P = 0.25); I² = 25%									
Test for overall effect: Z = 1.72 (P = 0.09)									
Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.2%