9.2 Composition of Parenteral Nutrition: Type of lipids May 2015

2015 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.*

2015 Discussion: The committee noted that there were 4 new studies (Grau Carmona 2014, Gultekin 2014, Burkhart 2014 and Hall 2014) that used a lipid strategy aimed at reducing the overall omega-6 fatty acid loads (or soybean oil sparing strategy). The trend for a reduction in mortality, and reduced ventilation seen previously was not evident with the inclusion of the data from these new trials. Furthermore the trend for a reduction in ICU length of stay was still associated with significant statistical heterogeneity, weakening this signal. There were emerging signals showing that fish oils IV fish oils/fish oil containing emulsions are associated with a significant reduction in infections and a trend towards a reduction in duration of ventilation. However, the committee expressed concern regarding the clinically important increase in mortality but decrease in infections in one fish oil study (Grau Carmona 2014) and the heterogeneity between trials. The signals for a beneficial effect of Olive oil containing emulsions was not clear (a trend towards increased infections but a significant reduction in duration of ventilation).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 the absent clear signal of benefit but the higher safety rating for alternative lipid emulsions, it was agreed that the recommendation remain unchanged and IV lipids that that reduce the load of omega-6 fatty acids/soybean emulsions should be considered.

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.

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	1 (mortality) 0 (infection)	0 (mortality) 0 (infections) 3 (fish oils)
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	0 (mortality) 2 (infections fish oils)
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	3	3 fish oils
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	3

9.2 Topic: Composition of Parenteral Nutrition: Type of lipids

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

Summary of evidence: There were 10 level 2 studies (Nijveldt 1998, Garnacho-Montero 2002, Iovinelli 2007, Wang 2009, Huschak 2005, Garcia de Lorenzo 2005, Pontes-Arruda 2012, Burkhart 2013, Gultekin 2014 & Hall 2014) and 8 level 1 studies (Lindgren 2001, Grecu 2003, Friesecke 2008, Barbosa 2010, Gupta 2011, Khor 2011, Umperrez 2012 & Grau Carmona 2014) 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. Fourteen studies compared varying strategies of reducing omega-6 fatty acids 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); 5 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, Grau Carmona 2014 & Gultekin 2014) 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 2013 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. Four studies compared supplementation with intravenous fish oil emulsion vs. a control group that received no IV soybean oil, therefore a sensitivity analysis was completed with these studies (Gupta 2011, Khor 2011, Burkhart 2014, Hall 2014).

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 had no effect on mortality (; RR 0.97, 95%CI 0.77, 1.24, p = 0.82, heterogeneity I^2=0%; figure 1.1). When the 3 studies in which the control group received no IV soybean oil were included, the lack of effect on reduction in mortality was still observed (RR 0.91, 95% CI 0.74, 1.11, p=0.35; figure 1.2).

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 no difference in mortality observed (, RR 1.05, 95% CI 0.77, 1.45, p = 0.75, heterogeneity I^2=0%; figure 1.1.2). When Gupta 2011, Burkhart 2014 and Hall 2014 studies were included, this lack of an effect on difference in mortality remained (p=0.46; figure 1.2.2).

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, 1.39, p = 0.62, heterogeneity I^2=0%; figure 1.1.3) was observed.

Infections:

Overall omega-6 fatty acid reducing strategy: When all 6 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 (RR 0.95, 95% CI 0.69, 1.29, p = 0.73, heterogeneity I^2=39%; figure 1.3). As well, no effect was observed when including Hall 2014 (p=0.63; figure 1.4).

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 3 studies of fish oil emulsions vs. LCT or LCT+ MCT in PN fed patients were aggregated, there was a significant effect on reduction of infectious complications in the fish oil group (RR 0.65, 95% CI 0.44, 0.96, p = 0.03, heterogeneity I^2=0%; figure 1.3). When including Hall 2014, a similar effect was seen (p=0.02; figure 1.4.1)
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 an increase in infections in the olive oil group (RR1.23, 95% CI 0.92, 1.63, p=0.16, heterogeneity I^2=0%, p=0.80; figure 1.3.2).

Hospital LOS:
Overall omega-6 fatty acid reducing strategy: When the 5 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 hospital LOS when compared to LCT (WMD -5.99, 95% CI -13.68, 1.69, p = 0.13, heterogeneity I^2=89%; figure 1.5). The same trend was seen when including Khor 2011, Gupta 2011 and Hall 2014 (p=0.12; figure 1.6).
LCT + MCT vs LCT: No studies reported on hospital LOS.
Fish Oils vs LCT or LCT + MCT: When the data from the three studies of fish oil emulsions vs LCT+MCT or LCT that reported on this outcome were aggregated, no effect on hospital LOS was observed (WMD -5.87, 95% CI -15.27, 3.53, p =0.22, heterogeneity I^2= 94%; figure 1.5). A trend towards a reduction in hospital LOS was observed when including Khor 2011, Gupta 2011 and Hall 2014 (p=0.19; figure 1.6.1).
Olive Oils vs LCT+MCT: When the data from the two studies of olive oil emulsions were aggregated, olive oil emulsions had no effect on hospital length of stay (\WMD -6.79, 95% CI -13.68, 1.69, p = 0.13, heterogeneity I^2= 0%; figure 1.5).

ICU 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 (WMD -2.31, 95%CI -5.28, 0.66, p=0.13, heterogeneity I^2=68%, p=0.003; figure 1.7). The same trend was seen when including Khor 2011, Gupta 2011 and Hall 2014 (p=0.13; figure 1.8).
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 1.7.1).
Fish Oils vs LCT or LCT + MCT: When the data from the three studies of fish oil emulsions vs LCT+MCT or LCT 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 1.7.1). As well, no effect was observed on ICU LOS when including Khor 2011, Gupta 2011 and Hall 2014 (p=0.55; figure 1.8.2).
Olive Oils vs LCT+MCT: When the data from the three studies of olive oil emulsions vs LCT+MCT to LCT 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 1.7.3).

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, 0.37, p =0.09, heterogeneity I^2=25%; figure 1.9). A trend was also observed when including Khor 2011 and Gupta 2011 (p=0.10; figure 1.10).

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 vs LCT+MCT or LCT 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 1.9.1). A trend was also observed when including Khor 2011 and Gupta 2011 (p=0.17; figure 1.10.1).

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 1.9.2).

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, have no effect on mortality or infections in critically ill adults but are associated with a trend towards reduction in hospital LOS, ICU LOS and duration of ventilation.
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, vs LCT + MCT or LCT (or vs no IV soybean oil), have no effect on mortality or ICU/hospital LOS but are associated with a significant reduction in infections and a trend towards a reduction in duration of ventilation
4) Olive Oil containing emulsions, compared to LCT, have no effect on mortality or ICU LOS, may be 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
12) Grau Carmona 2014	Medical and surgical pts requiring TPN N=175	C.Random: yes ITT: yes Blinding: double (10)	PN + Lipoplus (50% MCT, 40% LCTs soybean oil, 10% fish oil) vs PN + Lipofundin (50% LCT + 50% MCT)	MCT+LCT+Fish oil ICU 26/81 (32.5) Hospital 6/81 (11.1) 6-month 2/81 (4.3)	MCT+LCT ICU 16/78 (20.5) Hospital 6/78 (9.7) 6-month 2/78 (3.6)	MCT+LCT+Fish oil 17/81 (21)	MCT+LCT 29/78 (37.2)
13) Gultekin 2014	ICU pts needing TPN N=58	C.Random: unknown ITT: other Blinding: double (3)	PN + 100ml/day Omegavan (10% fish oils) plus Clinoleic (80% olive oil, 20% soybean oil) vs PN + Clinoleic. Both groups were prescribed IV lipids to provide 30-40% of total energy requirements.	Omegaven + olive Unspecified 8/16 (50)	Olive Unspecified 7/16 (44)	NR	NR
Fish oil (ω 3) containing IV lipid emulsions in PN, EN or orally fed patients vs. no IV soybean oil							
9) Gupta 2011	ICU patients with suspected ARDS N=61	C.Random: yes ITT: yes Blinding: double (9)	EN (standard diet) + Omegaven 10% (ω3:ω6 ratio was 1:4) vs EN (standard diet)	Omegaven ICU 7/31 (23) Hospital **9/31 (29)**	Standard EN ICU 13/30 (43) Hospital **14/30 (47)**	NR	NR
10) Khor 2011	ICU patients with severe sepsis/septic shock N = 28	C.Random: yes ITT: No Blinding: double (8)	EN and/or oral diet supplementated with 100 ml 10% Omegavan (10g refined fish oil, EPA 12.5-28.2 g/L, DHA 14.4-30.9 g/L) vs. 100 ml 0.9% normal saline + EN and/or oral diet	NR	NR	NR	NR
11) Burkhart 2013	ICU Septic patients N=50	C.Random: unknown ITT: yes Blinding: single (assessor) (8)	2 ml.kg/d Omegavan vs no parenteral fish oils. Both groups received EN and/or PN without added fish oils at the discretion of the clinician.	Omegavan Hospital 13/25 (52)	No Omegavan Hospital 13/25 (52)	NR	NR
14) Hall 2014	ICU Septic patients N=60	C.Random: ? ITT: yes Blinding: no (9)	Omegavan at 0.2 g fish oils /kg/d given at a rate of 0.05 g FO/kg/d vs no fish oils. In both group nutrition was assessed, by those patients requiring it, by the intensivists and dietitians who commenced oral, nasogastric (enteral), or parenteral nutrition as directed by the underlying pathology.	Omegavan Hospital 4/30 (13.3) 28 day 4/30 (13.3)	No Omegavan Hospital 9/30 (30) 28 day 8/30 (26.7)	Omegavan **3/30 (10)**	No Omegavan **5/30 (16.7)**

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).	
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 MCT/LCT All infections 39/103 (38) 35/101 (35) ICU acquired infections 28/103 (27) 23/101 (23) VAP/lower respiratory infections 9/103 (9) 11/101 (11)	
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 Intralipid 29/51 (57) 21/49 (43) Pneumonia 7/51 (14) 5/49 (10)	

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
12) Grau Carmona 2014	MCT+LCT+Fish oil ICU 18.9±15.5 (81) Hospital 41.1±41.0 (81)	MCT+LCT ICU 21.8±20.9 (78)Hospital 42.5±28.5 (78)	MCT+LCT+Fish oil 8.4±6.6 (67)	MCT+LCT 9.2±6.9 (64)	MCT+LCT+ Fish oil MCT+LCT Parenteral lipid intake [(g/kg BW)/d] 1.04 ± 0.12 1.05 ± 0.13 PN kcal 1,737 ± 353 1,782 ± 312
13) Gultekin 2014	Omegaven + olive Hospital 31.6 ± 4,3	Olive Hospital 30.6 ± 4,3	NR	NR	Omegavan + Olive oil Olive oil Kcal/kg/day 27.5±1.5 15.8±1.5 g protein/kg/d 1.3±0.2 1.1±0.1
Fish oil (ω 3) containing IV lipid emulsions in PN, EN or orally fed patients vs. no IV soybean oil					
9) Gupta 2011	Omegaven ICU 15.96 + 7.57 (31) Hospital 21.5+ 13.49 (31)	Standard EN ICU 15.88 + 6.47 (30) Hospital 26.63 + 18.22 (30)	Omegaven 11.78 + 10.63 (31)	6Standard EN 10.71 + 14.55 (30)	
10) Khor 2011	Omegaven ICU 10.3 ± 8.4 (14) Hospital 19.6 ± 7.4 (14)	Saline ICU 8.4 ± 6.5 (13) Hospital 17.5 ± 6.0 (13)	Omegaven 13.0 ± 10.1 (9)	Saline 11.6 ± 9.5 (5)	
11) Burkhart 2013	Omegavan I CU 5 (3-22)	No Omegavan I CU 6 (2-33)	NR	NR	Omegavan no Omegavan Subsyndromal delirium 5 (25) 6(29) Sepsis associated delirium 15 (75) 15 (71)
14) Hall 2014	Omegavan I CU 8.8±7.7 Hospital 26.7+18.2	No Omegavan I CU 12.3±12.4 Hospital 33.5+30.4	NR (reported as free ventilator days)	NR (reported as free ventilator days)	

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
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)
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

C.Random: concealed randomization
ITT: intent to treat
NR: not reported
MCT: medium chain triglycerides
LCT: long chain triglycerides
† hospital mortality unless specified
‡ number of patients with infections unless specified
* data obtained from author, 8 out of 28 in Omegaven and 7 out of 26 in LCT group were in ICU
**intervention includes high fat low CHO PN plus fish oil
[a] converted Standard Error Mean (SEM) to Standard deviation (SD)

Figure 1.1: Overall Mortality in studies using an omega-6 reducing strategy

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
1.1.1 LCT + MCT vs LCT							
Nijveldt	2	12	1	8	1.2%	1.33 [0.14, 12.37]	1998
Lindgren	1	15	0	15	0.6%	3.00 [0.13, 68.26]	2001
Garnacho-Montero	8	35	11	37	9.3%	0.77 [0.35, 1.69]	2002
Iovinelli	2	12	3	12	2.2%	0.67 [0.13, 3.30]	2007
Subtotal (95% CI)		**74**		**72**	**13.3%**	**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	2.0%	0.62 [0.11, 3.41]	2003
Friesecke	18	83	22	82	19.5%	0.81 [0.47, 1.39]	2008
Wang 2009	0	28	2	28	0.6%	0.20 [0.01, 3.99]	2009
Barbosa	4	13	4	10	4.6%	0.77 [0.25, 2.34]	2010
Gultekin	8	16	7	16	10.5%	1.14 [0.54, 2.40]	2014
Grau-Carmona	26	81	16	78	19.7%	1.56 [0.91, 2.68]	2014
Subtotal (95% CI)		**249**		**240**	**56.9%**	**1.05 [0.77, 1.45]**	
Total events	58		54				
Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 5 (P = 0.43); I² = 0%							
Test for overall effect: Z = 0.31 (P = 0.75)							
1.1.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	4	11	4	11	4.7%	1.00 [0.33, 3.02]	2005
Huschak	4	18	1	15	1.3%	3.33 [0.42, 26.72]	2005
Pontes-Arruda	19	103	21	101	18.5%	0.89 [0.51, 1.55]	2012
Umpierrez	5	51	8	49	5.2%	0.60 [0.21, 1.71]	2012
Subtotal (95% CI)		**183**		**176**	**29.8%**	**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)		**506**		**488**	**100.0%**	**0.97 [0.77, 1.24]**	
Total events	103		103				
Heterogeneity: Tau² = 0.00; Chi² = 8.53, df = 13 (P = 0.81); I² = 0%							
Test for overall effect: Z = 0.23 (P = 0.82)							
Test for subgroup differences: Chi² = 0.58, df = 2 (P = 0.75), I² = 0%							

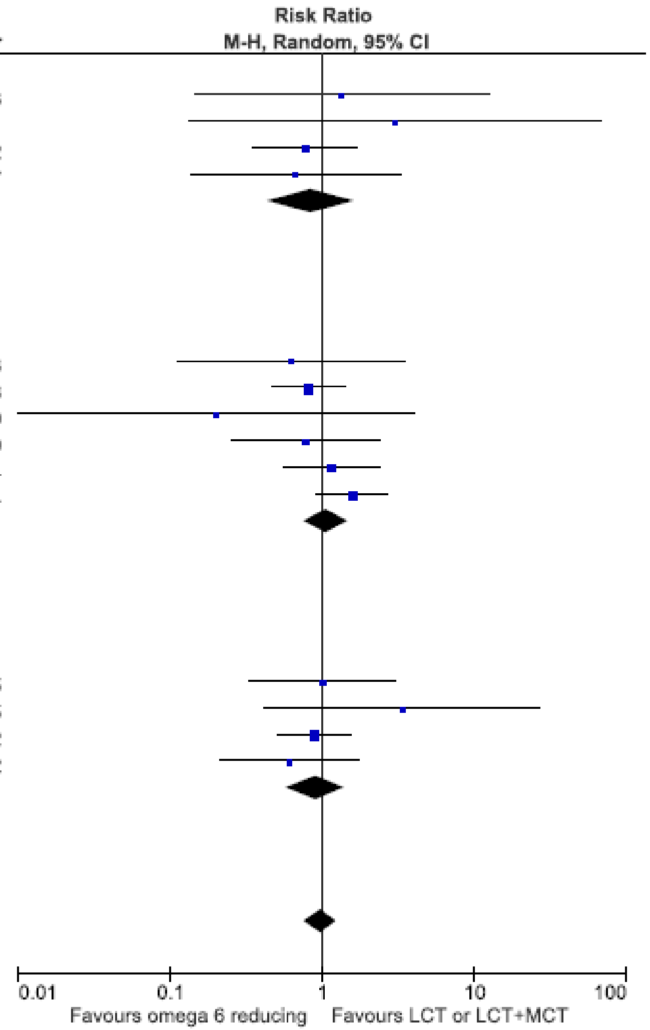

Figure 1.2 Overall Mortality in all studies (includes Gupta, Burkhart & Hall)

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 LCT + MCT vs LCT							
Nijveldt	2	12	1	8	0.9%	1.33 [0.14, 12.37]	1998
Lindgren	1	15	0	15	0.4%	3.00 [0.13, 68.26]	2001
Garnacho-Montero	8	35	11	37	6.9%	0.77 [0.35, 1.69]	2002
Iovinelli	2	12	3	12	1.7%	0.67 [0.13, 3.30]	2007
Subtotal (95% CI)		**74**		**72**	**9.9%**	**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)							
1.2.2 Fish oil containing emulsions vs LCT or LCT + MCT							
Grecu	2	28	3	26	1.5%	0.62 [0.11, 3.41]	2003
Friesecke	18	83	22	82	14.4%	0.81 [0.47, 1.39]	2008
Wang 2009	0	28	2	28	0.5%	0.20 [0.01, 3.99]	2009
Barbosa	4	13	4	10	3.4%	0.77 [0.25, 2.34]	2010
Gupta	7	31	13	30	7.2%	0.52 [0.24, 1.13]	2011
Burkhart	13	25	13	25	15.0%	1.00 [0.59, 1.70]	2014
Hall	4	30	9	30	3.8%	0.44 [0.15, 1.29]	2014
Grau-Carmona	26	81	16	78	14.6%	1.56 [0.91, 2.68]	2014
Gultekin	8	16	7	16	7.7%	1.14 [0.54, 2.40]	2014
Subtotal (95% CI)		**335**		**325**	**68.1%**	**0.90 [0.67, 1.20]**	
Total events	82		89				
Heterogeneity: Tau² = 0.03; Chi² = 9.62, df = 8 (P = 0.29); I² = 17%							
Test for overall effect: Z = 0.74 (P = 0.46)							
1.2.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	4	11	4	11	3.5%	1.00 [0.33, 3.02]	2005
Huschak	4	18	1	15	1.0%	3.33 [0.42, 26.72]	2005
Umpierrez	5	51	8	49	3.9%	0.60 [0.21, 1.71]	2012
Pontes-Arruda	19	103	21	101	13.7%	0.89 [0.51, 1.55]	2012
Subtotal (95% CI)		**183**		**176**	**22.1%**	**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)		**592**		**573**	**100.0%**	**0.91 [0.74, 1.11]**	
Total events	127		138				
Heterogeneity: Tau² = 0.00; Chi² = 12.72, df = 16 (P = 0.69); I² = 0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² = 0%							

Risk Ratio M-H, Random, 95% CI

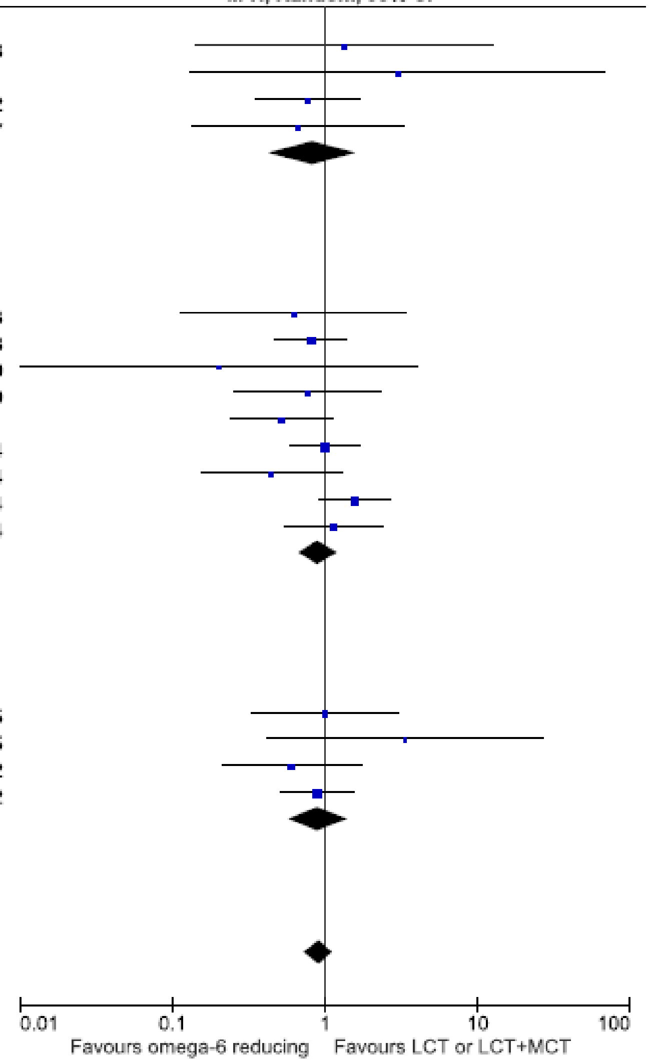

Figure 1.3 Infections in studies using an omega-6 reducing strategy

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
1.3.1 Fish oil containing emulsions vs LCT or LCT + MCT							
Friesecke	10	83	11	82	11.2%	0.90 [0.40, 2.00]	2008
Wang 2009	6	28	9	28	9.5%	0.67 [0.27, 1.62]	2009
Grau-Carmona	17	81	29	78	20.1%	0.56 [0.34, 0.94]	2014
Subtotal (95% CI)		**192**		**188**	**40.9%**	**0.65 [0.44, 0.96]**	
Total events	33		49				
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%							
Test for overall effect: Z = 2.18 (P = 0.03)							
1.3.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	6	11	6	11	12.0%	1.00 [0.47, 2.14]	2005
Umpierrez	29	51	21	49	25.5%	1.33 [0.89, 1.98]	2012
Pontes-Arruda	28	103	23	101	21.6%	1.19 [0.74, 1.93]	2012
Subtotal (95% CI)		**165**		**161**	**59.1%**	**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)		**357**		**349**	**100.0%**	**0.95 [0.69, 1.29]**	
Total events	96		99				
Heterogeneity: Tau² = 0.06; Chi² = 8.17, df = 5 (P = 0.15); I² = 39%							
Test for overall effect: Z = 0.35 (P = 0.73)							
Test for subgroup differences: Chi² = 6.71, df = 1 (P = 0.010), I² = 85.1%							

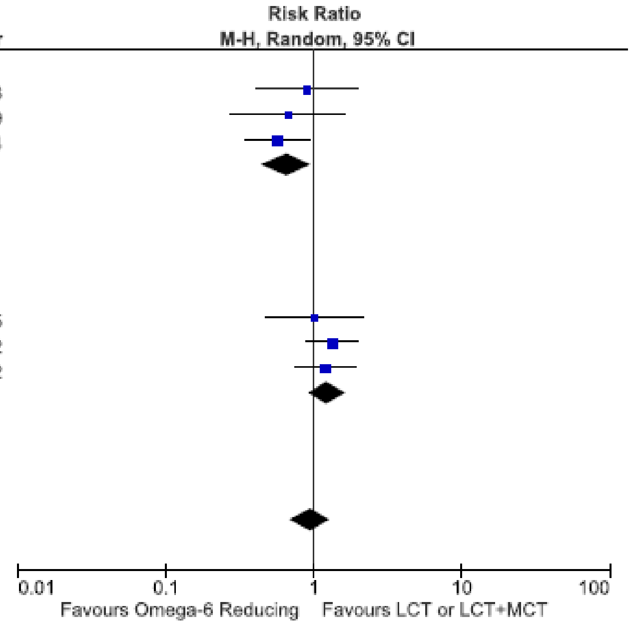

Figure 1.4 Infections in all studies (includes Hall)

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
1.4.1 Fish oil containing emulsions vs LCT or LCT + MCT							
Friesecke	10	83	11	82	10.4%	0.90 [0.40, 2.00]	2008
Wang 2009	6	28	9	28	8.7%	0.67 [0.27, 1.62]	2009
Grau-Carmona	17	81	29	78	19.4%	0.56 [0.34, 0.94]	2014
Hall	3	30	5	30	4.3%	0.60 [0.16, 2.29]	2014
Subtotal (95% CI)		**222**		**218**	**42.8%**	**0.65 [0.44, 0.94]**	
Total events	36		54				
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 2.30 (P = 0.02)							
1.4.3 Olive oil containing emulsions vs LCT or LCT + MCT							
Garcia de Lorenzo	6	11	6	11	11.2%	1.00 [0.47, 2.14]	2005
Umpierrez	29	51	21	49	25.1%	1.33 [0.89, 1.98]	2012
Pontes-Arruda	28	103	23	101	20.9%	1.19 [0.74, 1.93]	2012
Subtotal (95% CI)		**165**		**161**	**57.2%**	**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)		**387**		**379**	**100.0%**	**0.93 [0.70, 1.25]**	
Total events	99		104				
Heterogeneity: Tau² = 0.05; Chi² = 8.70, df = 6 (P = 0.19); I² = 31%							
Test for overall effect: Z = 0.48 (P = 0.63)							
Test for subgroup differences: Chi² = 7.20, df = 1 (P = 0.007), I² = 86.1%							

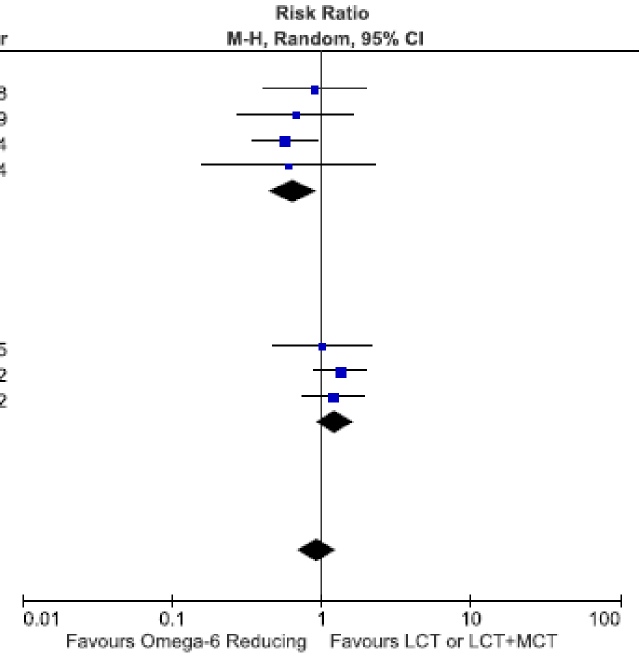

Figure 1.5 Hospital LOS in studies using an omega-6 reducing strategy

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT of LCT+MCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.5.2 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	11.68	2.04	28	20.46	3.27	26	30.1%	-8.78 [-10.25, -7.31]	2003
Barbosa	22	25.2	13	55	50.6	10	3.5%	-33.00 [-67.22, 1.22]	2010
Gultekin	31.6	4.3	16	30.6	4.3	16	28.9%	1.00 [-1.98, 3.98]	2014
Grau-Carmona	41.1	41	81	42.5	28.5	78	17.1%	-1.40 [-12.34, 9.54]	2014
Subtotal (95% CI)			**138**			**130**	**79.6%**	**-4.80 [-12.82, 3.21]**	
Heterogeneity: Tau² = 44.36; Chi² = 36.51, df = 3 (P < 0.00001); I² = 92%									
Test for overall effect: Z = 1.17 (P = 0.24)									
1.5.3 Olive oil containing emulsions vs LCT or LCT + MCT									
Garcia de Lorenzo	57	15.3	11	64.9	27.2	11	9.4%	-7.90 [-26.34, 10.54]	2005
Umpierrez	40.8	36	51	46.7	48	51	11.0%	-5.90 [-22.37, 10.57]	2012
Subtotal (95% CI)			**62**			**62**	**20.4%**	**-6.79 [-19.07, 5.50]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%									
Test for overall effect: Z = 1.08 (P = 0.28)									
Total (95% CI)			**200**			**192**	**100.0%**	**-5.15 [-11.96, 1.67]**	
Heterogeneity: Tau² = 39.55; Chi² = 36.54, df = 5 (P < 0.00001); I² = 86%									
Test for overall effect: Z = 1.48 (P = 0.14)									
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%									

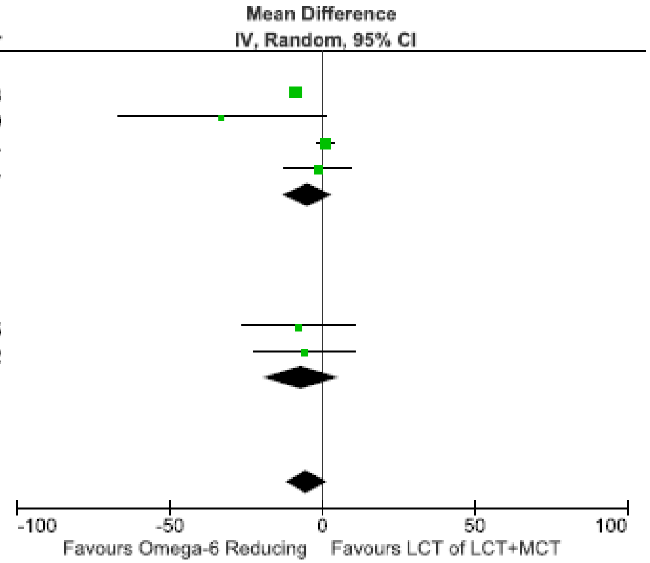

Figure 1.6 Hospital LOS in all studies (includes Khor, Gupta, Hall)

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT of LCT+MCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.6.2 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	11.68	2.04	28	20.46	3.27	26	19.2%	-8.78 [-10.25, -7.31]	2003
Barbosa	22	25.2	13	55	50.6	10	2.0%	-33.00 [-67.22, 1.22]	2010
Gupta	21.5	13.49	31	26.63	18.22	30	13.1%	-5.13 [-13.20, 2.94]	2011
Khor	19.6	7.4	14	17.5	6	13	16.4%	2.10 [-2.97, 7.17]	2011
Hall	26.7	18.2	30	33.5	30.4	30	8.8%	-6.80 [-19.48, 5.88]	2014
Grau-Carmona	41.1	41	81	42.5	28.5	78	10.3%	-1.40 [-12.34, 9.54]	2014
Gultekin	31.6	4.3	16	30.6	4.3	16	18.3%	1.00 [-1.98, 3.98]	2014
Subtotal (95% CI)			**213**			**203**	**88.1%**	**-3.71 [-9.31, 1.88]**	
Heterogeneity: Tau² = 37.40; Chi² = 47.79, df = 6 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 1.30 (P = 0.19)									
1.6.3 Olive oil containing emulsions vs LCT or LCT + MCT									
Garcia de Lorenzo	57	15.3	11	64.9	27.2	11	5.5%	-7.90 [-26.34, 10.54]	2005
Umpierrez	40.8	36	51	46.7	48	51	6.4%	-5.90 [-22.37, 10.57]	2012
Subtotal (95% CI)			**62**			**62**	**11.9%**	**-6.79 [-19.07, 5.50]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%									
Test for overall effect: Z = 1.08 (P = 0.28)									
Total (95% CI)			**275**			**265**	**100.0%**	**-4.04 [-9.13, 1.04]**	
Heterogeneity: Tau² = 34.43; Chi² = 47.83, df = 8 (P < 0.00001); I² = 83%									
Test for overall effect: Z = 1.56 (P = 0.12)									
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%									

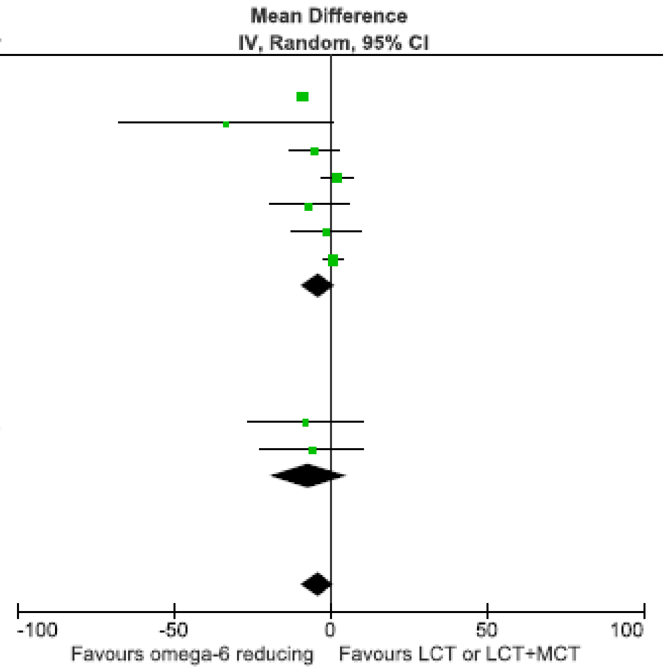

Figure 1.7 ICU LOS in studies using an omega-6 reducing strategy

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT of LCT+MCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.7.1 LCT + MCT vs LCT									
Nijveldt	13.8	2.9	12	17.4	3	8	17.6%	-3.60 [-6.25, -0.95]	1998
Garnacho-Montero	16.6	6.1	35	15.8	7	37	16.7%	0.80 [-2.23, 3.83]	2002
Subtotal (95% CI)			**47**			**45**	**34.3%**	**-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)									
1.7.2 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	3.32	1.48	8	9.28	3.08	7	17.9%	-5.96 [-8.46, -3.46]	2003
Friesecke	28	25	83	23	20	82	8.8%	5.00 [-1.90, 11.90]	2008
Barbosa	12	14.4	13	13	12.6	10	4.6%	-1.00 [-12.06, 10.06]	2010
Grau-Carmona	18.9	15.5	81	21.8	20.9	78	10.7%	-2.90 [-8.64, 2.84]	2014
Subtotal (95% CI)			**185**			**177**	**42.0%**	**-1.93 [-7.02, 3.16]**	
Heterogeneity: Tau² = 16.83; Chi² = 9.23, df = 3 (P = 0.03); I² = 68%									
Test for overall effect: Z = 0.74 (P = 0.46)									
1.7.3 Olive oil containing emulsions vs LCT or LCT + MCT									
Garcia de Lorenzo	32.9	10.6	11	41.8	16.3	11	4.3%	-8.90 [-20.39, 2.59]	2005
Huschak	17.9	11.2	18	25.1	7	15	9.8%	-7.20 [-13.47, -0.93]	2005
Umpierrez	17	18	51	15.2	14	49	9.7%	1.80 [-4.51, 8.11]	2012
Subtotal (95% CI)			**80**			**75**	**23.8%**	**-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)			**312**			**297**	**100.0%**	**-2.40 [-5.06, 0.27]**	
Heterogeneity: Tau² = 8.71; Chi² = 21.87, df = 8 (P = 0.005); I² = 63%									
Test for overall effect: Z = 1.76 (P = 0.08)									
Test for subgroup differences: Chi² = 0.40, df = 2 (P = 0.82), I² = 0%									

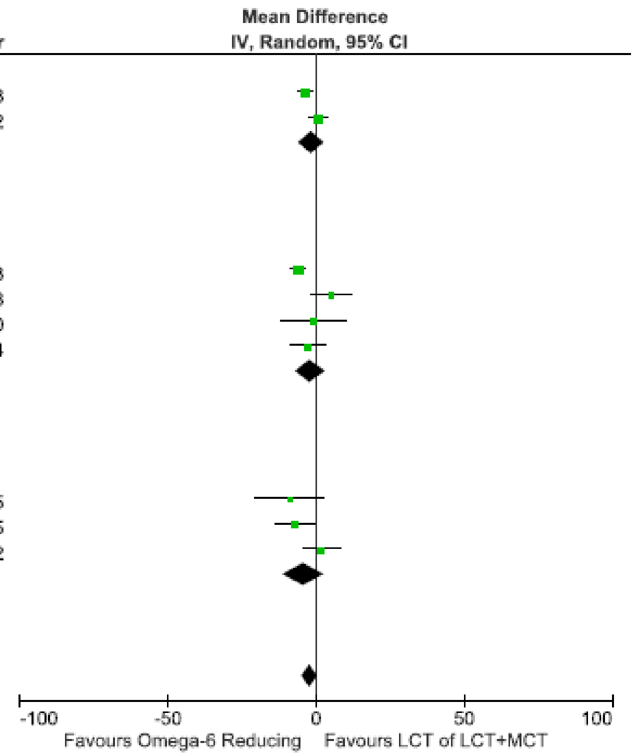

Figure 1.8 ICU LOS in all studies (includes Khor, Gupta, Hall)

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT or LCT+MCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.8.1 LCT + MCT vs LCT									
Nijveldt	13.8	2.9	12	17.4	3	8	13.2%	-3.60 [-6.25, -0.95]	1998
Garnacho-Montero	16.6	6.1	35	15.8	7	37	12.5%	0.80 [-2.23, 3.83]	2002
Subtotal (95% CI)			**47**			**45**	**25.7%**	**-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)									
1.8.2 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	3.32	1.48	8	9.28	3.08	7	13.5%	-5.96 [-8.46, -3.46]	2003
Friesecke	28	25	83	23	20	82	6.1%	5.00 [-1.90, 11.90]	2008
Barbosa	12	14.4	13	13	12.6	10	3.1%	-1.00 [-12.06, 10.06]	2010
Khor	10.3	8.4	14	8.4	6.5	13	7.7%	1.90 [-3.74, 7.54]	2011
Gupta	15.96	7.57	31	15.88	6.47	30	11.4%	0.08 [-3.45, 3.61]	2011
Hall	8.8	7.7	30	12.3	12.4	30	8.4%	-3.50 [-8.72, 1.72]	2014
Grau-Carmona	18.9	15.5	81	21.8	20.9	78	7.6%	-2.90 [-8.64, 2.84]	2014
Subtotal (95% CI)			**260**			**250**	**57.8%**	**-1.42 [-4.53, 1.69]**	
Heterogeneity: Tau² = 10.03; Chi² = 16.42, df = 6 (P = 0.01); I² = 63%									
Test for overall effect: Z = 0.89 (P = 0.37)									
1.8.3 Olive oil containing emulsions vs LCT or LCT + MCT									
Huschak	17.9	11.2	18	25.1	7	15	6.8%	-7.20 [-13.47, -0.93]	2005
Garcia de Lorenzo	32.9	10.6	11	41.8	16.3	11	2.9%	-8.90 [-20.39, 2.59]	2005
Umpierrez	17	18	51	15.2	14	49	6.8%	1.80 [-4.51, 8.11]	2012
Subtotal (95% CI)			**80**			**75**	**16.5%**	**-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)			**387**			**370**	**100.0%**	**-1.89 [-4.03, 0.25]**	
Heterogeneity: Tau² = 7.17; Chi² = 26.84, df = 11 (P = 0.005); I² = 59%									
Test for overall effect: Z = 1.73 (P = 0.08)									
Test for subgroup differences: Chi² = 0.50, df = 2 (P = 0.78), I² = 0%									

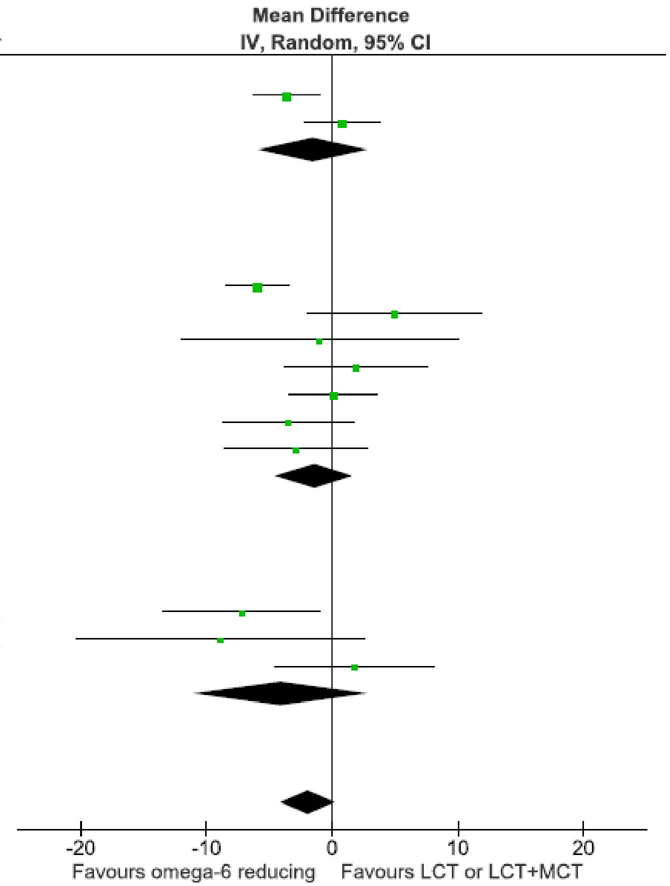

Figure 1.9 Ventilator Days in studies using an omega-6 reducing strategy

Study or Subgroup	Omega-6 Reducing Mean	SD	Total	LCT of LCT+MCT Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.9.1 Fish oil containing emulsions vs LCT or LCT + MCT									
Grecu	2.83	1.62	8	5.23	2.8	7	36.4%	-2.40 [-4.76, -0.04]	2003
Friesecke	22.8	22.9	83	20.5	19	82	8.8%	2.30 [-4.12, 8.72]	2008
Barbosa	10	14.4	13	11	12.64	10	3.2%	-1.00 [-12.07, 10.07]	2010
Grau-Carmona	8.4	6.6	67	9.2	6.9	64	37.1%	-0.80 [-3.11, 1.51]	2014
Subtotal (95% CI)			**171**			**163**	**85.5%**	**-1.34 [-2.92, 0.25]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 3 (P = 0.53); I² = 0%									
Test for overall effect: Z = 1.65 (P = 0.10)									
1.9.2 Olive oil containing emulsions vs LCT or LCT + MCT									
Huschak	13	8.9	18	20.4	7	15	11.7%	-7.40 [-12.83, -1.97]	2005
Garcia de Lorenzo	11	11.93	11	13	16.25	11	2.8%	-2.00 [-13.91, 9.91]	2005
Subtotal (95% CI)			**29**			**26**	**14.5%**	**-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)			**200**			**189**	**100.0%**	**-1.92 [-3.96, 0.11]**	

Heterogeneity: Tau² = 1.51; Chi² = 6.64, df = 5 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Chi² = 3.77, df = 1 (P = 0.05), I² = 73.5%

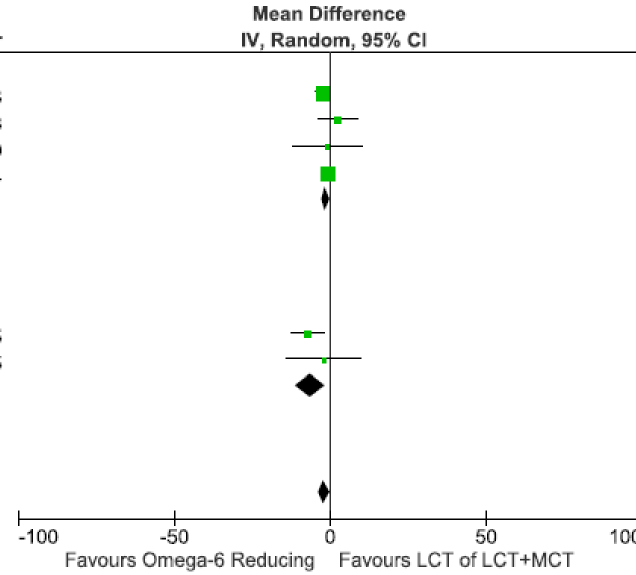

Figure 1.10 Ventilator Days in all studies (includes Khor, Gupta)

	Omega-6 Reducing			LCT or LCT+MCT				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.10.1 Fish oil containing emulsions vs LCT or LCT + MCT										
Grecu	2.83	1.62	8	5.23	2.8	7	35.6%	-2.40 [-4.76, -0.04]	2003	
Friesecke	22.8	22.9	83	20.5	19	82	6.3%	2.30 [-4.12, 8.72]	2008	
Barbosa	10	14.4	13	11	12.64	10	2.2%	-1.00 [-12.07, 10.07]	2010	
Khor	13	10.1	9	11.6	9.5	5	2.4%	1.40 [-9.22, 12.02]	2011	
Gupta	11.78	10.63	31	10.71	14.55	30	6.3%	1.07 [-5.34, 7.48]	2011	
Grau-Carmona	8.4	6.6	67	9.2	6.9	64	36.6%	-0.80 [-3.11, 1.51]	2014	
Subtotal (95% CI)			**211**			**198**	**89.4%**	**-1.14 [-2.67, 0.38]**		
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 5 (P = 0.71); I² = 0%										
Test for overall effect: Z = 1.48 (P = 0.14)										
1.10.2 Olive oil containing emulsions vs LCT or LCT + MCT										
Garcia de Lorenzo	11	11.93	11	13	16.25	11	1.9%	-2.00 [-13.91, 9.91]	2005	
Huschak	13	8.9	18	20.4	7	15	8.7%	-7.40 [-12.83, -1.97]	2005	
Subtotal (95% CI)			**29**			**26**	**10.6%**	**-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)			**240**			**224**	**100.0%**	**-1.60 [-3.26, 0.05]**		
Heterogeneity: Tau² = 0.56; Chi² = 7.70, df = 7 (P = 0.36); I² = 9%										
Test for overall effect: Z = 1.90 (P = 0.06)										
Test for subgroup differences: Chi² = 4.08, df = 1 (P = 0.04), I² = 75.5%