9.2 Composition of Parenteral Nutrition: Type of lipids

May 27th 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.

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.

	Definition	Score (0, 1, 2 or 3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	0
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1
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
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	2
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	2
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	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
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
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	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

9.2 Topic: Composition of Parenteral Nutrition: Type of lipids May 27th 2009

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

Summary of evidence: There were 6 level 2 studies and 4 level 1 studies (Lindgren 2001, Grecu 2003, Wang 2008 and Friesecke 2008) 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. Four studies compared long chain trigylcerides (LCTs) plus medium chain triglycerides (MCT) to a LCT emulsion (Nijveldt 1998, Lindgren 2001, Garnacho-Montero 2002 and Iovinelli 2007; 3 studies compared a fish oil containing emulsion (Omegaven) mixed with LCT or LCT/MCT to a LCT or LCT+MCT mixture (Grecu 2003, Wang 2008, Friesecke 2008) while 2 studies compared an olive oil containing emulsion (Clinoleic) to a LCT + MCT mixture (Garcia de-Lorenzo 2005, Huschak 2005). One study compared two different types of LCT emulsions (Kari 1998) In the Friesecke 2008 study, a mixture of LCT/MCT and fish oils {omega 3 fatty acids} was compared to a LCT/MCT mixture while in the Huschak study, a high lipid/low CHO emulsion mixed with olive oil was compared to a lower fat/higher CHO emulsion mixed with soybean oil.

Mortality: A meta-analysis of the studies of LCT+ MCT vs. LCT showed no difference in mortality between the groups (RR = 0.84, 95 % confidence intervals 0.43-1.61, p = 0.59) (figure 1). Similarly, no difference in mortality was seen between the groups of fish oils containing emulsions vs. LCT or LCT+ MCT (RR 0.76, 95 % CI 0.46, 1.26 , p = 0.29) (figure 2) or between the groups receiving the olive oil containing emulsions vs. LCT + MCT (RR 1.34, 95 %CI 0.47, 3.82, p = 0.59) (figure 3). There were no differences in mortality in the single trial that compared Emulsan to Intralipid (both LCT emulsions).

Infections: 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). When the data from the 3 studies of fish oil emulsions were aggregated, there was no significant effect on infection complications (RR 0.77, 95 % 0.39, 1.49, p =0.43) (figure 4). In the one study of olive oil emulsions (Clinoleic), there were no differences in the number of patients with infections between the two groups (Garcia de Lorenzo 2005) and the other study reported fewer infections in the intervention group (high fat plus Clinoleic) but no data was reported (Huschak 2005).

LOS and Ventilator days: 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, significant heterogeneity was present 78%) (figure 5). Similarly, when the data from the three studies of fish oil emulsions were aggregated, no effect on ICU LOS was observed (WMD -2.15, 95 %CI -10.31, 6.01, p = 0.61, significant heterogeneity was present 77%) (figure 6). When the data from the two studies of olive oil emulsions were aggregated, olive oil emulsions were associated with a significant reduction in ICU length of stay (WMD -7.59, 95 % CI -13.09, -2.09, p= 0.007) (figure 7).

Only one study comparing LCT+MCT to LCT reported duration of ventilation and no significant differences were seen between the two groups (Iovinelli 2007). When the data from the studies of fish oils were aggregated, there was no effect on duration of mechanical ventilation (WMD -1.04, 95 % CI -5.22, 3.14, p = 0.63) (figure 8) however, 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), although significant heterogeneity was present (62%) (figure 9).

Other complications: 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). 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).

Conclusion:

1) LCT+MCT, fish oil containing, olive oil containing emulsions have no effect on mortality or infections in critically ill patients.
2) LCT+MCT, fish oil containing emulsions have no effect on ICU LOS, while olive oil containing emulsions may be associated with a reduction in ICU LOS.
3) LCT+MCT, fish oil containing emulsions have no effect on mechanical ventilation, while olive oil containing emulsions may be associated with a reduction in mechanical ventilation.
4) The use of Emulsan (LCT emulsion) over Intralipid (LCT emulsion) has no effect on clinical outcomes in critically ill patients.

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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 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: yes (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	CRandom: 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 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) Wang 2008	Severe acute pancreatitis patients in ICU N = 40	C.Random: yes 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 0/20	LCT ICU 2/20 (10)	Omegaven 3/20 (15)	LCT 5/20 (25)
7) Friesecke 2008	Medical ICU patients N= 166	CRandom: yes ITT: yes Blinding: double	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)

Study	Population	Methods (score)	Intervention	Mortality # (%)†		Infections # (%)‡	
Olive oil containing emulsions vs. LCT+MCT							
8) 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)
9) 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)	
LCT vs. LCT							
10) Kari 1998	ICU , severe injury patients N = 20	C.Random: not sure ITT: yes Blinding: no (6)	Two different types of lipids i.e. Emulsan (100% LCT, soybean oil- egg phosphatide) vs Intralipid (100% LCT)	Emulsan 2/10 (20)	Intralipid 2/10 (20)	Emulsan NR	Intralipid NR

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

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

Study	LOS days		Ventilator days		Other	
4) Iovinelli 2007	LCT + MCT NR	LCT NR	LCT + MCT 10.6 ± 3.0 (12)	LCT 13.4 ± 3.5 (12)	LCT + MCT Timebefore weaning 52 ± 36 hrs	LCT 127 ± 73 hrs
Fish oil (ω 3) containing emulsions 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 Patients undergoing reoperation for septic episode 2/28 (7)	LCT 8/26 (31)
6) Wang 2008	Omegaven ICU 21.4 ± 18.8 (20) Hospital 65.2 ± 32.6 (20)	LCT ICU 27.5 ± 25 (20) Hospital 70.5 ± 40.7 (20)	Omegaven NR	LCT NR	Omegaven Duration of CRRT 18 ± 2.3	LCT 26 ± 3.4
7) 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 Urinary Tract Infections 6/83 (7) Catheter-related infections 1/83 (1) Total EN Energy Intake (kcal/kg) 22.2 ± 5.5	LCT+MCT 4/82 (5) 3/83 (4) 21.6 ± 5.6
Olive oil containing emulsions vs. LCT+MCT						
8) Garcia-de-Lorenzo 2005	Clinoleic ICU 32.9 ± 3.2 (11) Hospital 57 ± 4.6 (11)	Lipofundin ICU 41.8 ± 4.9 (11) Hospital 64.9 ± 8.2 (11)	Clinoleic 11.0 ± 3.6 (11)	Lipofundin 13.0 ± 4.9 (11)	Clinoleic Multiple organ dysfunction score 11.0 ± 3.6	Lipofundin 13.0 ± 4.9
9) 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 Total Energy Intake (kcal/kg) 17.9 ± 6.3	Low fat + LCT + MCT 22.3 ± 4.2
LCT vs. LCT						
10) Kari 1998	Emulsan NR	Intralipid NR	Emulsan NR	Intralipid NR	Emulsan NR	Intralipid NR

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

Figure 1. Studies comparing LCT + MCT to LCT

Review: Type of PN lipids
Comparison: 01 LCT + MCT vs. LCT
Outcome: 01 Mortality

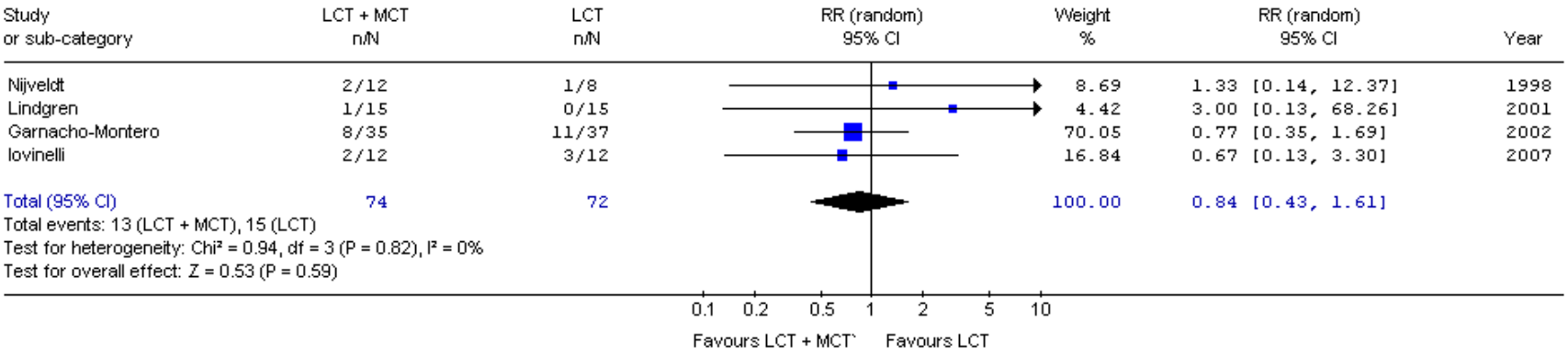


Figure 2. Studies comparing Fish oil containing emulsions to LCT or LCT+MCT

Review: Type of PN lipids
Comparison: 01 Fish oils vs. LCT, LCT/MCT
Outcome: 01 Mortality

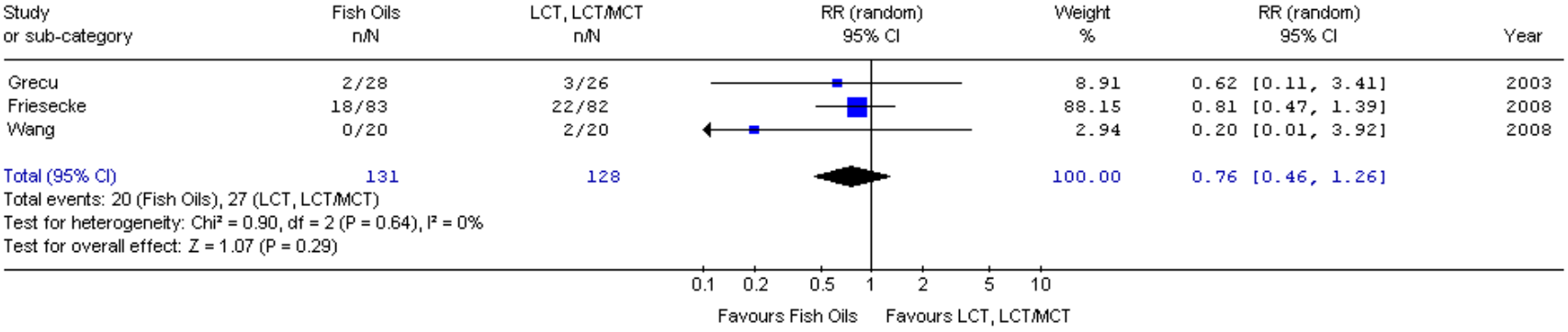


Figure 3. Studies comparing Olive oil containing emulsions vs. LCT+MCT

Review: Type of PN lipids
Comparison: 01 Olive oils vs. LCT/MCT
Outcome: 01 Mortality

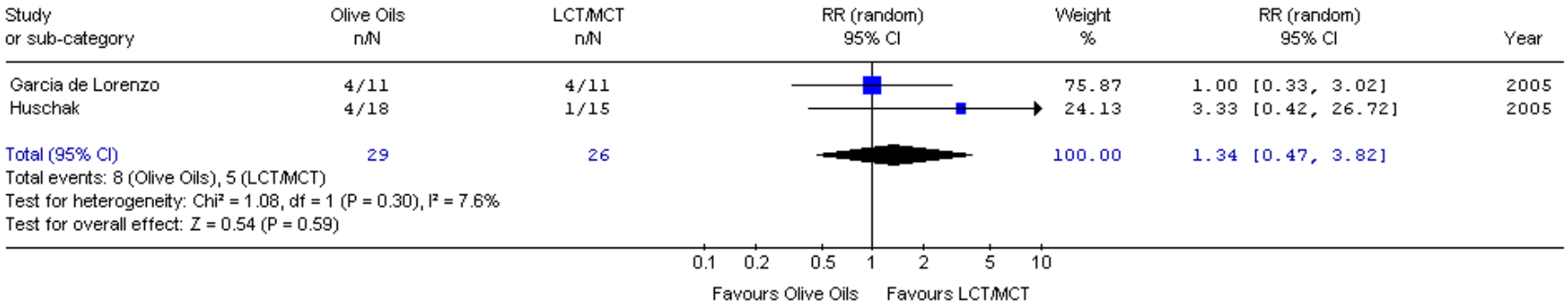


Figure 4. Studies comparing Fish oil containing emulsions to LCT or LCT+MCT

Review: Type of PN lipids
Comparison: 01 Fish Oils vs. LCT, LCT/MCT
Outcome: 02 Infections

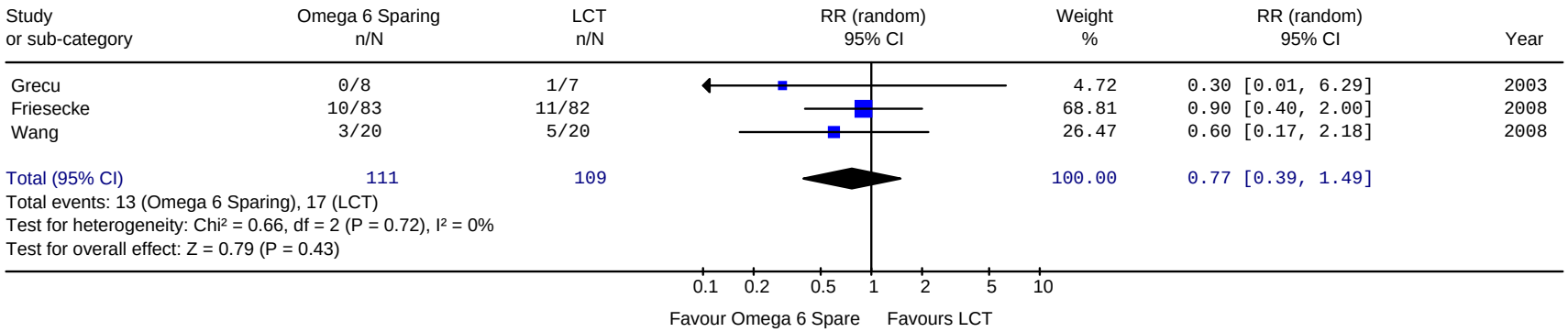


FIGURE 5. Studies comparing LCT + MCT to LCT

Review: Type of PN lipids
Comparison: 01 LCT + MCT vs. LCT
Outcome: 03 ICU LOS

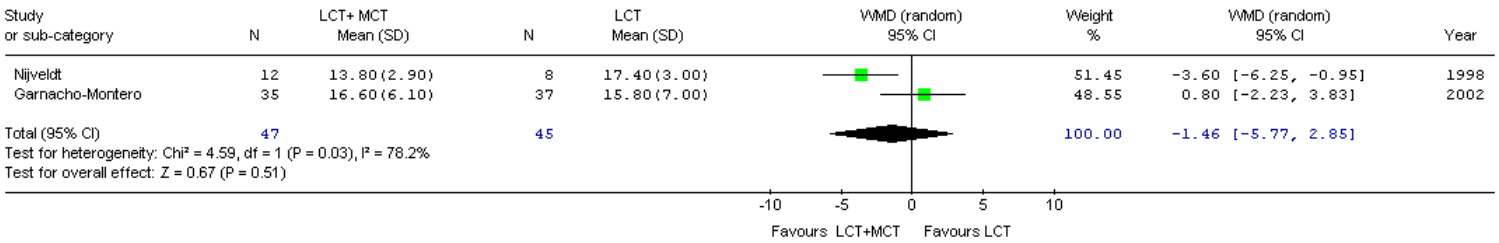


Figure 6. Studies comparing Fish oil containing emulsions to LCT or LCT+MCT

Review: Type of PN lipids
Comparison: 01 Fish oils vs. LCT, LCT/MCT
Outcome: 03 ICU LOS

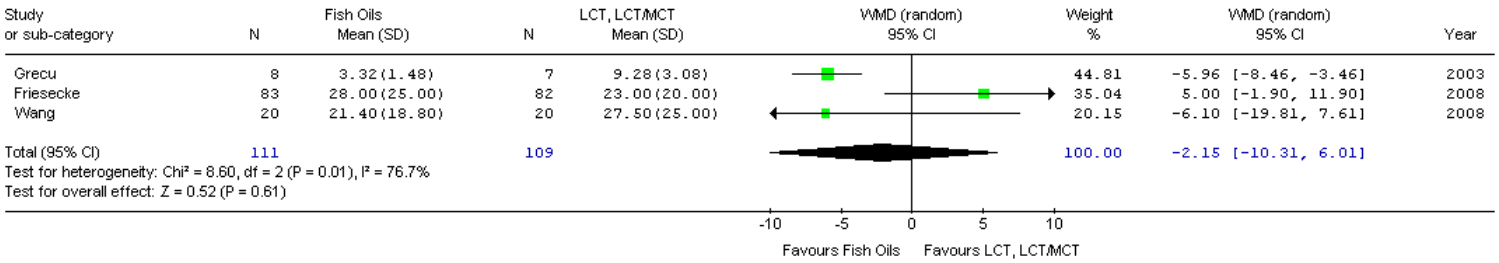


Figure 7. Studies comparing Olive oil containing emulsions vs. LCT+MCT

Review: Type of PN lipids
Comparison: 01 Olive Oil vs. LCT/MCT
Outcome: 03 ICU LOS

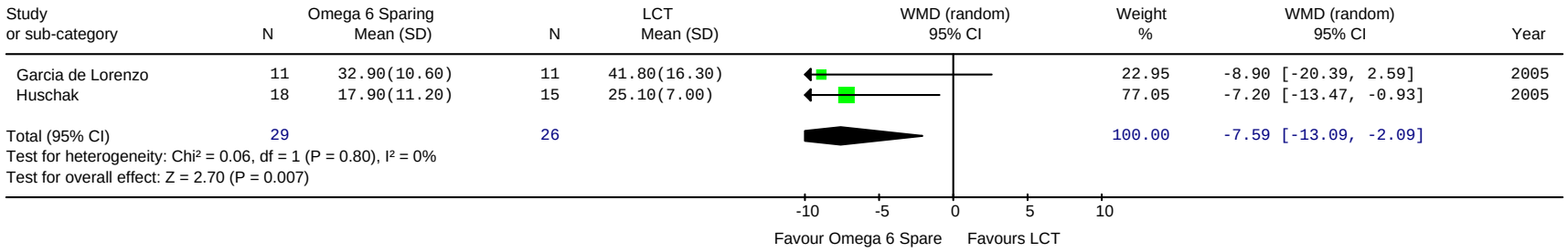


Figure 8. Studies comparing Fish oil containing emulsions to LCT or LCT+MCT

Review: Type of PN lipids
Comparison: 01 Fish Oils vs. LCT/MCT
Outcome: 04 Mechanical Ventilation

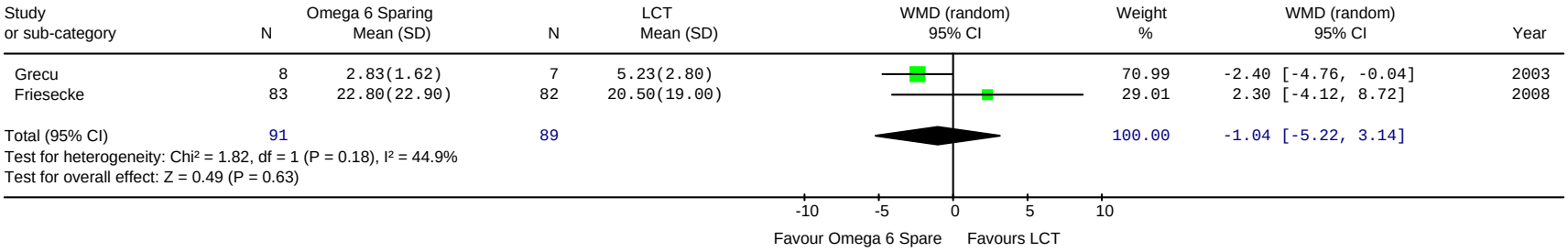
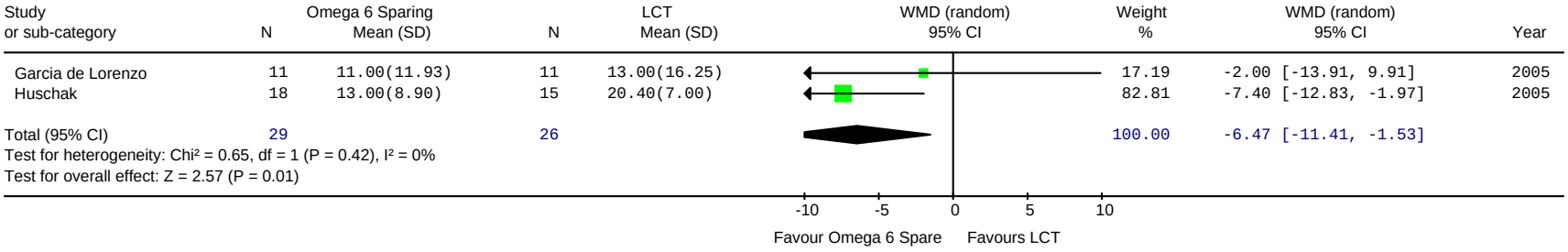
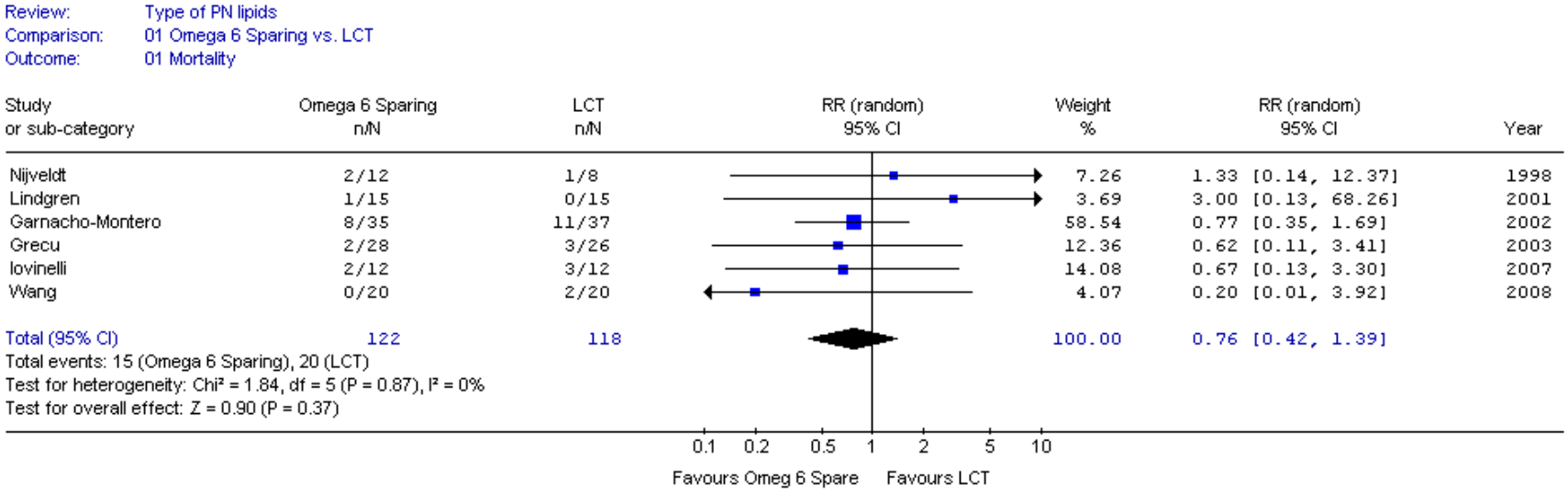


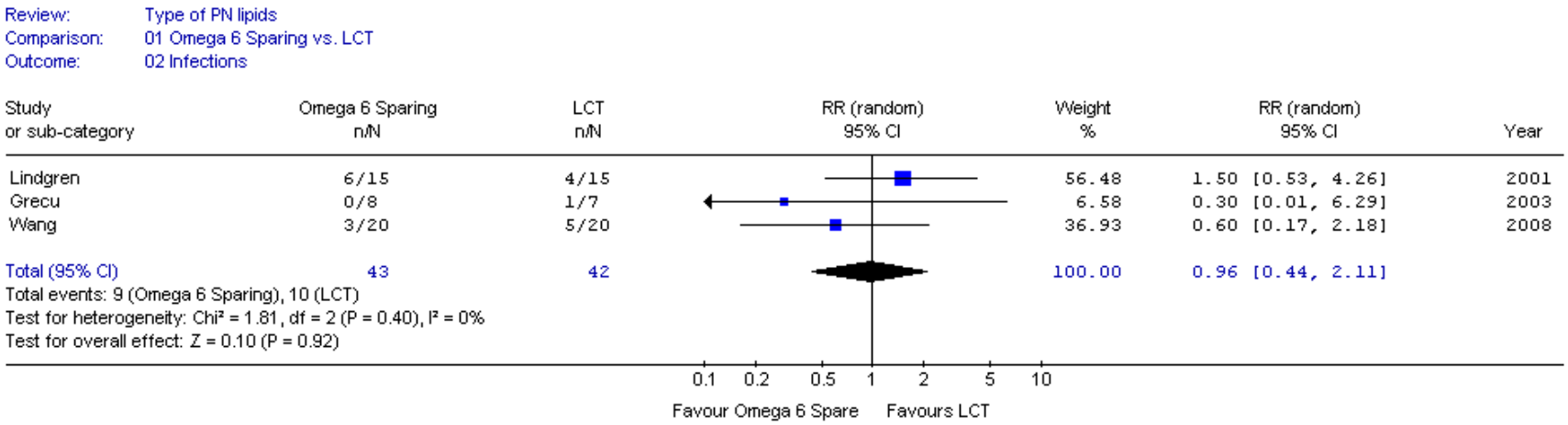
Figure 9. Studies comparing Olive oil containing emulsions vs. LCT+MCT change

Review: Type of PN lipids
Comparison: 01 Olive Oils vs. LCT/MCT
Outcome: 04 Mechanical Ventilation

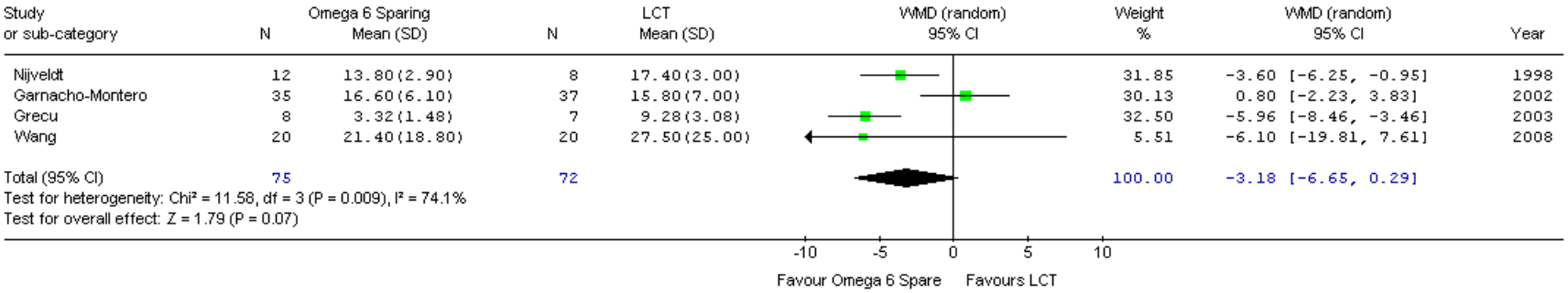


Overall Omega 6 fatty acid Sparing Strategy (all studies of lower LCT {omega 6 fatty acids} load vs. LCT)

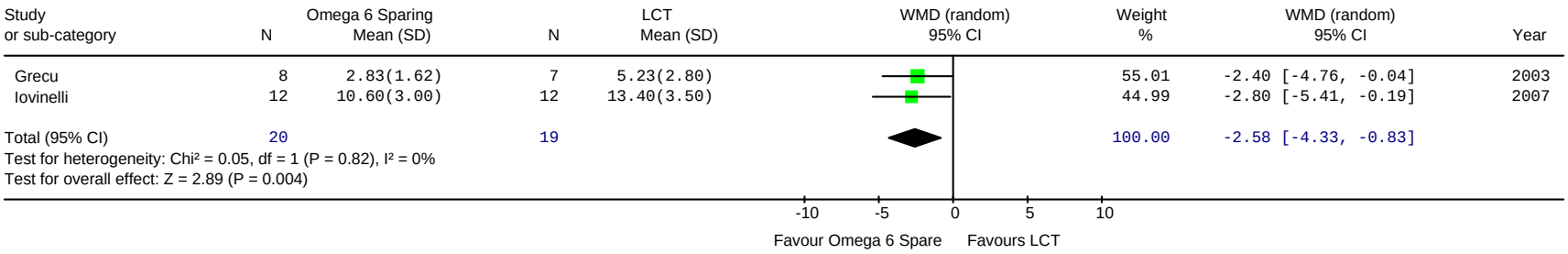




Review: Type of PN lipids
Comparison: 01 Omega 6 Sparing vs. LCT
Outcome: 03 ICU LOS



Review: Type of PN lipids
Comparison: 01 Omega 6 Sparing vs. LCT
Outcome: 04 Mechanical Ventilation



TOPIC: 9.2 Composition of PN: Type of lipids

Article inclusion log

Criteria for study selection

Type of study: RCT or Meta-analysis
Population: critically ill ventilated patients (no elective surgery patients)
Intervention: TPN
Outcomes: mortality, LOS, QOL, functional recovery, complications, cost. Exclude studies with only biochemical, metabolic or nutritional outcomes.

Included articles

LCT + MCT vs. LCT

	Author	Journal	I	E	Why rejected
1	Nijveldt	Clinical Nutrition 1998	√		
2	Lindgren	Clinical Nutrition 2001	√		
3	Garnacho-Montero	Nutrition 2002	√		
4	Iovinelli	Minerva Anestesiol. 2007	√		

Fish Oil containing emulsions

	Author	Journal	I	E	Why rejected
5	Grecu	Clinical Nutrition 2003 (abstract)	√		
6	Wang	JPEN 2008	√		
7	Friesecke	Intensive Care Med 2008	√		

Olive Oil containing emulsions

	Author	Journal	I	E	Why rejected
8	Garcia-de-Lorenzo	Br J Nutr 2005	√		
9	Huschak	Intensive Care Med 2005	√		

LCT vs. LCT

	Author	Journal	I	E	Why rejected
10	Kari	Current Therap. Research 1998	√		

EXCLUDED

	Author	Journal	I	E	Why rejected
1	Hutchison	Clinical Nutrition, 1984		√	Cancer patients
2	Gazzaniga	Surgery, Gynecology & Obstetrics,1985		√	Unclear if randomized yet elective surgery pts
3	Calon	Infusiontherap., 1990		√	No clinical outcomes
4	Diboune	JPEN, Journal of Parenteral and Enteral Nutrition, 1992		√	No clinical outcomes
5	Adams	JPEN, Journal of Parenteral and Enteral Nutrition, 1993		√	No clinical outcomes
6	Jarnberg	Current Therap Research, 1991		√	No clinical outcomes
7	Ball	Intensive Care Med, 1993		√	No clinical outcomes
8	Chassard	CCMedicine 1994		√	No clinical outcomes
9	Jeevandam	Nutrition 1995		√	No clinical outcomes
10	Wachtler	J Trauma, 1997		√	Elective surgery pts
11	Hailer	Ann Nutr Metab, 1998		√	Elective surgery pts
12	Kalfarentzos	Clinical Nutrition 1998		√	No clinical outcomes
13	Masclans	Intensive Care Med, 1998		√	No clinical outcomes
14	Chambrier	Nutrition, 1998		√	Elective surgery pts
15	Gogos	Cancer, 1998		√	Cancer pts
16	Furukawa	Annals of Surgery, 1999		√	Cancer pts
17	Planas	Int. Care Med, 1999		√	No clinical outcomes
18	Kuse	Transpl. Int., 2002		√	Elective surgery patients
19	Manuel-y-Keenoy	European J Clin Nutr, 2002		√	No clinical outcomes, not ICU patients
20	Garcia-de-Lorenzo	JPEN, 2003		√	No clinical outcomes
21	Grau	Nutr Hosp., 2003		√	Elective surgery or emergency surgery pts
22	Mayer (a)	Intensive Care Med., 2003		√	No clinical outcomes
23	Mayer (b)	Am J Respir Crit Care Med, 2003		√	No clinical outcomes
24	Antebi	JPEN, 2004		√	No clinical outcomes
25	Heller	Int J Cancer, 2004		√	Elective surgery & cancer pts
26	Chen	Kaohsiung J Med Sci, 2005		√	Cancer pts
27	Klek	Acta Chir Belg, 2005		√	Surgical pts
28	Grimm	Eur J Nutr, 2006		√	Surgical pts
29	Mertes	Ann Nutr Metab, 2006		√	Surgical pts
30	Tappy	Clin Nutr., 2006		√	No clinical outcomes
31	Wichmann	Crit Care Med, 2007		√	Elective surgery pts
32	Senkal	JPEN, 2007		√	Elective surgery pts
33	Berger	Eur J Clin Nutr, 2008		√	Elective surgery pts
34	Liang	World J Gastroenterol, 2008		√	Cancer patients
35	Wang	JPEN, 2008		√	Not ICU, No clinical outcomes

I = included, E = excluded

References

LCT + MCT vs. LCT

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