Published in final edited form as:

Intensive Care Med. 2013 October ; 39(10): 1683–1694. doi:10.1007/s00134-013-2999-4.

Alternative Lipid Emulsions in the Critically Ill: A Systematic Review of the Evidence

William Manzanares, MD, PhD¹, Rupinder Dhaliwal, RD², Brian Jurewitsch, PharmD³, Renee D. Stapleton, MD, PhD⁴, Khursheed N. Jeejeebhoy, M.D., F.R.C.P.(C), Ph.D³, and Daren K. Heyland, MD, FRCPC, MSc^{2,5}

William Manzanares: wmanzanares@adinet.com.uy; Rupinder Dhaliwal: dhaliwal@KGH.KARI.NET; Brian Jurewitsch: jurewitschb@smh.ca; Renee D. Stapleton: renee.stapleton@uvm.edu; Khursheed N. Jeejeebhoy: khushjeejeebhoy@compuserve.com; Daren K. Heyland: dkh2@queensu.ca

¹Department of Critical Care Medicine, Faculty of Medicine, Universidad de la República (UDEAR), Montevideo, Uruguay

²Clinical Evaluation Research Unit, Kingston General Hospital, Ontario, Canada

³St Michael's Hospital and University of Toronto, Toronto, Ontario, Canada

⁴Division of Pulmonary and Critical Care, Department of Medicine, University of Vermont College of Medicine, Burlington, USA

⁵Department of Medicine, Queen's University Kingston, Ontario-Canada

Abstract

Introduction—Parenteral lipid emulsions (LEs) are commonly rich in long-chain triglycerides (LCT) derived from soybean oil (SO). SO containing emulsions may promote systemic inflammation and therefore may adversely affect clinical outcomes. We hypothesized that alternative oil-based LEs (SO-sparing strategies) may improve clinical outcomes in critically ill adult patients compared to SO emulsion only products. The purpose of this systematic review was to evaluate the effect of parenteral SO-sparing strategies on clinical outcomes in intensive care unit (ICU) patients.

Methods—We searched computerized databases from 1980 to 2013. We included randomized controlled trials (RCTs) conducted in critically ill adult patients that evaluated SO-sparing strategies versus SO-based LEs in the context of parenteral nutrition (PN).

Results—A total of 12 RCTs met inclusion criteria. When the results of these RCTs that were statistically aggregated, SO-sparing strategies were associated with clinically important reductions in mortality (risk ratio RR= 0.83, 95% confidence intervals CI 0.62, 1.11, P = 0.20), in duration of ventilation (weighted mean difference, WMD –2.57, 95% CI –5.51, 0.37, P= 0.09), and in ICU length of stay (WMD –2.31, 95% CI –5.28, 0.66, P= 0.13) but none of these differences were statistically significant. SO-sparing strategies had no effect on infectious complications (RR=1.13, 95% CI 0.87, 1.46, P=0.35).

Correspondence to: D.K. Heyland, MD, FRCPC, MSc., Angada 4, Kingston General Hospital, 76 Stuart Street, Kingston, Ontario K7L 2V7, Canada, Tel.: 1-613-549-6666 ext. 4847; Fax: 1-613-548-2428, dkh2@queensu.ca.

Competing interests

The other authors declare that they have no competing interests.

Conclusion—Alternative oil-based LEs may be associated with clinically important reductions in mortality, duration of ventilation, and ICU LOS but lack of statistical precision precludes any clinical recommendations at this time. Further research is warranted to confirm these potential positive treatment effects.

Keywords

alternative lipid emulsions; soybean oil reducing strategies; critically ill

Introduction

Lipid emulsions (LEs) are an essential constituent of parenteral nutrition (PN) [1] and are considered an important source of energy, essential fatty acids (FA) and vitamins E and K [2,3,4]. However, the current literature suggests that soy-bean oil (SO) and safflower-based LEs which are rich in the ω -6 fatty acid linoleic acid, might promote production of pro-inflammatory prostanooids and leukotrienes resulting in increased oxidative stress and systemic inflammation[5,6] and may be associated with worse clinical outcomes [7].

Over the past three decades, different generations of alternative oil-based LEs have been developed, which could have less proinflammatory effects, less immune suppression, and more antioxidant effects than the standard SO-based LEs [8,9]. These SO-sparing strategies consist of different formulations of SO combined with medium-chain triglycerides (MCTs), olive oil (OO) which contains the ω -9 monounsaturated FA (MUFA) oleic acid, and fish oil (FO) which contains ω -3 FA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The purpose of the current study was to provide an up-to-date systematic review and meta-analysis of all randomized clinical trials (RCTs) of alternative oil-based LEs, compared to SO emulsion products evaluating clinically relevant outcomes in the critically ill.

Methods

Study Identification

We conducted a systematic review of the published literature to identify all relevant clinical trials using a strategy found in Appendix 1. We included studies if they met all the following eligibility criteria:

- a. Study design: randomized controlled trials (RCTs).
- b. Population: critically ill adult patients (>18 years old).
- c. Intervention: parenteral strategies to reduce the overall load of ω -6 FA (alternative ω 6-sparing LEs) versus ω 6 oil-based LEs (LCT in the control group).
- d. Study outcomes: mortality was the primary outcome for this meta-analysis. Secondary outcomes were: intensive care unit (ICU) and hospital LOS, infections, and mechanical ventilation (MV) days. We excluded the clinical studies that reported only biochemical, metabolic, immunologic or nutritional outcomes. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate $\geq$ 5%) to distinguish them from patients

with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5%).

Data Extraction and Risk of Bias Assessment

Two reviewers independently extracted data using a data abstraction form with a scoring system [10]. We scored the methodological quality of individual trials according to key methodological features outlined in the Appendix 2. Disagreement was resolved by consensus between both reviewers. We attempted to contact the authors of included trials and requested missing or unclear information. We designated as a level 1 study if all of the following criteria are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis. A study was considered as level 2 study if any one of the above characteristics was unfulfilled.

Data synthesis

The primary outcome of the systematic review was overall mortality. From all trials, we combined hospital mortality where reported. If hospital mortality was not reported, we used ICU mortality or 28-day mortality. Secondary outcomes included infections, MV days, and ICU LOS. We used definitions of infections as defined by the authors in their original papers. We analyzed data using RevMan 5.1 [11] with a random effect model. We calculated pooled relative risks using the Mantel-Haenszel estimator for dichotomous outcomes and weighted mean differences (WMDs) were estimated by the inverse variance approach for continuous outcomes, with associated 95% CIs. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators [12]. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rucker and colleagues [13]. Statistical heterogeneity was assessed by the I^2 statistic. We considered $P < 0.05$ to be statistically significant and $P < 0.20$ as indicator of trend.

A priori hypotheses testing

Given the different ω -6 FA sparing strategies and the heterogeneity of trial design, we performed pre-specified, hypothesis-generating subgroup analyses to attempt to elucidate potentially more beneficial treatment strategies. We compared the results of trials that provided a) LCTs plus MCT to a LCT emulsion; b) ω -3 oil-based LEs to a LCT or LCT/MCT mixture, and c) ω -9 oil-based LEs to a LCT or LCT + MCT mixture.

Results

Study identification and selection

A total of 52 potentially eligible RCTs were identified. Of these, we excluded 40 trials due to the following reasons: 22 trials [14,15,16,17,18,19,20,21,22,23,24,25,26,27, 28,29,30,31,32, 33,34,35] trials did not include ICU patients (mostly elective surgery and cancer patients), 12 trials [36,37,38,39,40,41,42,43,44,45,46,47] did not evaluate clinically important outcomes; 2 trials [48,49] did not include SO-based LE in the control group; 1 trial [50] compared LCT vs. another LCT emulsion without reduction in SO; 1 trial [51] was conducted in a pediatric population; 1 trial [52] had a short duration of intervention (12 hour of lipid emulsion infusion

during the first day); 1 trial included patients with poisoning and not representative of ICU patients[53]. In the end, 12 RCTs [54,55,56,57,58,59,60,61,62,63,64,65] enrolling a total of 806 patients met the inclusion criteria and were included in this systematic review (see Table 1 and 2). The authors reached 100% agreement for inclusion of relevant trials in this review. The mean methodological score of all trials was 9.8 (6 to 14). Randomization was concealed in 8/12 (67 %) trials, ITT analysis was performed in 11/12 (92 %) trials and 8/12 (67 %) trials were double blinded. There were 5 level 1 studies and 7 level 2 studies.

Meta-Analysis of Primary Outcome

When the results of 12 RCTs [54–65] that evaluated mortality were statistically aggregated, ω -6-sparing strategies were associated with a reduction in mortality that was not statistically significant (risk ratio [RR]= 0.83, 95 % confidence intervals [CI] 0.62, 1.11, $P=0.20$, heterogeneity $I^2=0\%$ see Figure 1).

Secondary Outcomes

Compared to LCT, when the RCTs reporting ventilator days were aggregated [58,60,61,62, 64], overall ω -6 FA-sparing strategies were consistent with a -reduction in duration of MV but differences were not statistically significant (WMD -2.57 , 95% CI -5.51 , 0.37 , $P=0.09$, heterogeneity $I^2=25\%$) (Figure 2). There was a trend towards a reduction in ICU LOS associated with the use of ω -6-sparing strategies when compared to LCT [54,56,58,59,60,61, 62,64] (WMD -2.31 , 95% CI -5.28 , 0.66 , $P=0.13$, $I^2=68\%$, $P<0.003$) (Figure 3). When the data from 5 RCTs [58,60,62,63,65] that reported ICU-acquired infections were aggregated, ω -6-sparing strategy had no effect (RR= 1.13, 95% CI 0.87, 1.46, $P=0.35$, heterogeneity $I^2=0\%$).

Subgroup analysis

LCTs plus MCT versus LCT emulsion—Four RCTs [54–57] compared LCTs plus MCT to a LCT emulsion. When statistically aggregated, these studies showed no difference in mortality (RR= 0.84, 95 % CI 0.43, 1.61, $P=0.59$, heterogeneity $I^2=0\%$) (Figure 1). Only one trial [57] compared LCT+MCT to LCT that reported duration of ventilation and no significant differences were seen between the two groups. When the data from the two trials [54,56] that report ICU LOS were aggregated, there were no differences in ICU LOS (WMD -1.46 , 95 % CI -5.77 , 2.85 , $P=0.51$, heterogeneity was present $I^2=78\%$, $P=0.03$) (Figure 3).

Fish oil containing emulsions vs. LCT or LCT +MCT—Four RCTs [61–64] comparing ω -3 oil-based LEs to a LCT or LCT+MCT reported mortality. When these data were aggregated, this strategy was not associated with a reduction in mortality (RR= 0.76, 95% CI 0.48, 1.21, $P=0.25$ heterogeneity $I^2=0\%$) (Figure 1). We found 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 2). There were no differences between the groups in ICU LOS (WMD -1.13 , 95% CI -8.96 , 6.69 , $P=0.78$; heterogeneity $I^2=78\%$, $P=0.01$) (Figure 3) and infections (RR= 0.79, 95% CI 0.43, 1.43, $P=0.43$, heterogeneity $I^2=0\%$).

ω 9 oil-based LEs versus a LCT + MCT mixture—Four RCTs [58,59,64,65] compared a ω -9 oil-based LE to a LCT + MCT mixture. We did not find any difference between the

groups in mortality (RR= 0.90, 95% CI 0.58, 1.39, P=0.62, heterogeneity $I^2=0\%$) (Figure 1), however we found a significant reduction in the duration of MV (WMD -6.47, 95% CI -11.41, -1.53, P= 0.01, heterogeneity $I^2=0\%$) (Figure 2) but no effect on ICU LOS (WMD -4.08, 95% CI -10.97, 2.81, P=0.25, heterogeneity $I^2=59\%$) (Figure 3). When 3 RCTs [58,60,65] that reported on ICU-acquired infections were aggregated, this strategy showed a tendency towards an increase in infections (RR= 1.23, 95% CI 0.92, 1.63, P= 0.16, heterogeneity $I^2=0\%$).

Risk of publication bias—There was no indication that publication bias influenced the observed aggregated results. Funnel plots were created for each study outcome (data not shown) and the tests of asymmetry were not significant for any outcome measure (mortality, P= 0.48; ICU LOS, P= 0.88, and mechanical ventilation days P= 0.78).

Discussion

Our systematic review and meta-analysis is the first in evaluating the overall effects of parenteral ω -6 reducing strategies in the critically ill. When 12 eligible trials were statistically aggregated, we did not find statistically significant effects. However, the magnitude of the potential treatment effect, in terms of a reduction in mortality (relative risk reduction 17%) and reduction in ICU LOS (more than 2 days less), if realized, would be consistent with a large and clinically and economically important difference. The lack of statistical precision is likely due to the small number of studies and the small sample size of each study. Given the heterogeneous population of ICU patients included in this systematic review (sepsis, severe sepsis/septic shock, surgery, trauma, burns, and SIRS), the conclusions of our systematic review could be applied to a broad group of ICU patients. However, given the heterogeneity of alternative LEs, we explored several subgroups to evaluate if the treatment effect was different across different commercial preparations. There are no head-to-head comparisons of these different alternative LEs strategies. Indirectly, by examining the risk ratios of the different alternatives, there does not appear to be any difference in the treatment effects. Therefore, we are unable to define the best ω -6 sparing strategy in the critically ill as available evidence on the differential effects of LEs in ICU patients remains limited after our meta-analysis.

The anti-inflammatory properties of EPA and DHA have been described and exhaustively studied in different experimental and clinical studies [66,67]. Two RCTs included in our systematic review found a significant reduction of the proinflammatory cytokine interleukin 6 and an increase in the HLA-DR expression. However, we were unable to demonstrate any significant effect with FO based LEs rich in EPA and DHA. Recently, two meta-analyses on parenteral FO have been published. Pradelli et al [68] demonstrated that parenteral FO enriched LE were associated with a statistically and clinically significant reduction in infections (P= 0.002) and the LOS, both in the ICU (P= 0.005) and in hospital (P= 0.0005) [68]. Nonetheless, these results cannot be compared with our findings because our meta-analysis included only RCTs evaluating clinical outcomes in the critically ill and excluded RCTs performed in non ICU surgical patients.

More recently, Palmer et al [69] concluded that parenteral FO does not improve mortality, infectious complications, and ICU LOS in comparison with standard PN. These results are similar to our findings. However, we found a tendency toward a reduction in mechanical

ventilation days. We believe that this difference was largely due to the difference in the papers included in the different reviews. In fact, Palmer et al [69] have included two papers published by Wang et al in 2008 [28] and 2009 [63]. However, we have decided to include the study published in 2009 [63] and exclude the previous study because it did not include ICU patients and did not report on relevant clinical outcomes. In addition, we excluded two unpublished studies by Liderman et al [70] and Ignatenko et al [71], as both are published as abstracts and we have not had any response from the investigators, which was needed to complete our data abstraction form.

The strength of our meta-analysis includes the fact that we used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, specific criteria for searching and analysis) and have focused on clinically important primary outcomes for ICU patients. The major limitation of our meta-analysis was the small number of trials included which resulted in statistical imprecision. Furthermore, the presence of heterogeneity, both clinical and statistical, weakens any inferences we can make from these data.

In spite of these limitations, we have demonstrated that alternative oil-based LEs in the critically ill could be able to reduce overall mortality, shorten ventilation days and ICU LOS. Further research is warranted and should define the best mixture of lipids, target patient population, best timing, and duration of therapy to optimize the effects on underlying systemic inflammation, immune status, and metabolic processes while at the same time achieving an acceptable safety and tolerance profile.

Acknowledgments

Daren Heyland received speaking honorarium and research grants from Fresenius Kabi and Baxter.

References

1. Vanek VW, Seidner DL, Allen P, Bistran B, Collier S, Gura K, Miles JM, Valentine CJ, Kochevar M. Novel Nutrient Task Force, Intravenous Fat Emulsions Workgroup; and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. Position Paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract*. 2012; 27:150–192. [PubMed: 22378798]
2. Vinnars E, Wilmore D. Jonathan Roads Symposium Papers. History of parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2003; 27:225–231. [PubMed: 12757118]
3. Hippalgaonkar K, Majumdar S, Kansara V. Injectable Lipid Emulsions: advancements, opportunities and challenges. *AAPS Pharm Sci Tech*. 2010; 11:1526–1540.
4. Carpentier YA, Dupont IE. Advances in intravenous lipid emulsions. *World J Surg*. 2000; 24:1493–1497. [PubMed: 11193713]
5. Wanten GJA, Calder P. Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr*. 2007; 85:1171–1184. [PubMed: 17490951]
6. Furukawa K, Yamamori H, Takagi K, Hayashi N, Suzuki R, Nakajima N, Tashiro T. Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition*. 2002; 18:235–240. [PubMed: 11882396]
7. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA*. 1998; 280:2013–2019. [PubMed: 9863853]
8. Bannenberg G, Serhan CN. Specialized pro-resolving lipid mediators in the inflammatory response: an update. *Biochim Biophys Acta*. 2010; 1801:1260–1273. [PubMed: 20708099]

9. Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. *Annu Rev Pathol.* 2008; 3:279–312. [PubMed: 18233953]
10. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA.* 1998; 280:2013–2019. [PubMed: 9863853]
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177–188. [PubMed: 3802833]
12. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21:1539–1558. [PubMed: 12111919]
13. Rucker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Statistics in Medicine.* 2008; 27:746–763. [PubMed: 17592831]
14. Wachtler P, König W, Senkal M, Kemen M, Köller M. Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma.* 1997; 42:191–8. [PubMed: 9042869]
15. Gogos CA, Ginopoulos P, Salsa B, Apostolidou E, Zoumbos NC, Kalfarentzos F. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: a randomized control trial. *Cancer.* 1998; 82:395–402. [PubMed: 9445198]
16. Furukawa K, Tashiro T, Yamamori H, Takagi K, Morishima Y, Sugiura T, Otsubo Y, Hayashi N, Itabashi T, Sano W, Toyoda Y, Nitta H, Nakajima N. Effects of soybean oil emulsion and eicosapentaenoic acid on stress response and immune function after a severely stressful operation. *Ann Surg.* 1999; 229:255–61. [PubMed: 10024108]
17. Linseisen J, Hoffmann J, Lienhard S, Jauch KW, Wolfram G. Antioxidant status of surgical patients receiving TPN with an omega-3-fatty acid-containing lipid emulsion supplemented with alpha-tocopherol. *Clin Nutr.* 2000; 19:177–84. [PubMed: 10895108]
18. Heller AR, Fischer S, Rossel T, Geiger S, Siegert G, Ragaller M, Zimmermann T, Koch T. Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. *Br J Nutr.* 2002; 87 (Suppl 1):S95–101. [PubMed: 11895160]
19. Heller AR, Rössel T, Gottschlich B, Tiebel O, Menschikowski M, Litz RJ, Zimmermann T, Koch T. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. *Int J Cancer.* 2004; 111:611–6. [PubMed: 15239141]
20. Kłęk S, Kulig J, Szczepanik AM, Jedrys J, Kołodziejczyk P. The clinical value of parenteral immunonutrition in surgical patients. *Acta Chir Belg.* 2005; 105:175–9. [PubMed: 15906909]
21. Grimm H, Mertes N, Goeters C, Schlotzer E, Mayer K, Grimminger F, Fürst P. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr.* 2006; 45:55–60. [PubMed: 16041475]
22. Mertes N, Grimm H, Fürst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOF lipid) in surgical patients: a randomized, double-blind, multicenter study. *Ann Nutr Metab.* 2006; 50:253–9. [PubMed: 16508253]
23. Senkal M, Geier B, Hannemann M, Deska T, Linseisen J, Wolfram G, Adolph M. Supplementation of omega-3 fatty acids in parenteral nutrition beneficially alters phospholipid fatty acid pattern. *JPEN J Parenter Enteral Nutr.* 2007; 31:12–7. [PubMed: 17202435]
24. Wendel M, Rössel T, Bergmann S, Otto S, Ragaller M, Zimmermann T, Konopke R, Koch T, Heller AR. Impact of total parenteral nutrition including omega-3 fatty acids on the regulation of plasma lipoproteins and glycemic control after major abdominal surgery. *E-SPEN.* 2007; 2:e103–e110.
25. Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med.* 2007; 35:700–6. [PubMed: 17261965]
26. Berger MM, Tappy L, Revelly JP, Koletzko BV, Geper J, Corpataux JM, Cayeux MC, Chiolero RL. Fish oil after abdominal aorta aneurysm surgery. *Eur J Clin Nutr.* 2008; 62:1116–22. [PubMed: 17538537]
27. Liang B, Wang S, Ye YJ, Yang XD, Wang YL, Qu J, Xie QW, Yin MJ. Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients. *World J Gastroenterol.* 2008; 14:2434–9. [PubMed: 18416476]

28. Wang X, Li W, Li N, Li J. Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *JPEN J Parenter Enteral Nutr.* 2008; 32:236–41. [PubMed: 18443134]
29. Heidt MC, Vician M, Stracke SK, Stadlbauer T, Grebe MT, Boening A, Vogt PR, Erdogan A. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg.* 2009; 57:276–80. [PubMed: 19629889]
30. Piper SN, Schade I, Beschmann R, Maleck W, Boldt J, Rohm KD. Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. *Eur J Anaesthesiol.* 2009; 26:1076–82. [PubMed: 19916246]
31. Puiggròs C, Sánchez J, Chacón P, Sabín P, Roselló J, Bou R, Planas M. Evolution of lipid profile, liver function, and pattern of plasma fatty acids according to the type of lipid emulsion administered in parenteral nutrition in the early postoperative period after digestive surgery. *JPEN J Parenter Enteral Nutr.* 2009; 33:501–12. [PubMed: 19420283]
32. Badía-Tahull MB, Llop-Talaverón JM, Leiva-Badosa E, Biondo S, Farran-Teixidó L, Ramón-Torrell JM, Jódar-Masanes R. A randomised study on the clinical progress of high-risk elective major gastrointestinal surgery patients treated with olive oil-based parenteral nutrition with or without a fish oil supplement. *Br J Nutr.* 2010; 104:737–41. [PubMed: 20350344]
33. Jiang ZM, Wilmore DW, Wang XR, Wei JM, Zhang ZT, Gu ZY, Wang S, Han SM, Jiang H, Yu K. Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. *Br J Surg.* 2010; 97:804–9. [PubMed: 20473991]
34. Han YY, Lai SL, Ko WJ, Chou CH, Lai HS. Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. *Nutr Clin Pract.* 2012; 27:91–8. [PubMed: 22227725]
35. Zhu MW, Tang DN, Hou J, Wei JM, Hua B, Sun JH, Chui HY. Impact of fish oil enriched total parenteral nutrition on elderly patients after colorectal cancer surgery. *Chin Med J.* 2012; 125:178–81. [PubMed: 22340541]
36. Adams S, Yeh YY, Jensen GL. Changes in plasma and erythrocyte fatty acids in patients fed enteral formulas containing different fats. *JPEN J Parenter Enteral Nutr.* 1993; 17:30–4. [PubMed: 8437321]
37. Schauder P, Rohn U, Schafer G, Korff G, Schenk HD. Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. *Br J Nutr.* 2002; 87(Suppl 1):S103–10. [PubMed: 11895146]
38. Koller M, Senkal M, Kemen M, König W, Zumtobel V, Muhr G. Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. *Clin Nutr.* 2003; 22:59–64. [PubMed: 12553951]
39. Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, Grimminger F, Seeger W. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. *J Immunol.* 2003; 171:4837–4843. [PubMed: 14568963]
40. Mayer K, Fegbeutel C, Hattar K, Sibelius U, Krämer HJ, Heuer KU, Temmesfeld-Wollbrück B, Gokorsch S, Grimminger F, Seeger W. Omega-3 vs. omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. *Intensive Care Med.* 2003; 29:1472–1481. [PubMed: 12897994]
41. Mayer K, Gokorsch S, Fegbeutel C, Hattar K, Rosseau S, Walmrath D, Seeger W, Grimminger F. Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. *Am J Respir Crit Care Med.* 2003; 15(167):1321–1328. [PubMed: 12615625]
42. Mayer K, Meyer S, Reinholz-Muhly M, Maus U, Merfels M, Lohmeyer J, Grimminger F, Seeger W. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. *J Immunol.* 2003; 171:4837–43. [PubMed: 14568963]
43. Antébi H, Mansoor O, Ferrier C, Tétégan M, Morvan C, Rangaraj J, Alcindor LG. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr.* 2004; 28:142–8. [PubMed: 15141405]

44. Tappy L, Berger MM, Schwarz JM, Schneider P, Kim S, Revely JP, Chioléro R. Metabolic effects of parenteral nutrition enriched with n-3 polyunsaturated fatty acids in critically ill patients. *Clin Nutr.* 2006; 25:588–95. [PubMed: 16697496]
45. Piper SN, Schade I, Beschmann RB, Maleck WH, Boldt J, Röhm KD. Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. *Eur J Anaesthesiol.* 2009; 26:1076–82. [PubMed: 19916246]
46. Xiong J, Zhu S, Zhou Y, Wu H, Wang C. Regulation of omega-3 fish oil emulsion on the SIRS during the initial stage of severe acute pancreatitis. *J Huazhong Univ Sci Technolog Med Sci.* 2009; 29:35–8. [PubMed: 19224159]
47. Sungurtekin H, De irmençi S, Sungurtekin U, Oguz BE, Sabir N, Kaptanoglu B. Comparison of the effects of different intravenous fat emulsions in patients with systemic inflammatory response syndrome and sepsis. *Nutr Clin Pract.* 2011; 26:665–71. [PubMed: 22205554]
48. Khor BS, Liaw SJ, Shih HC, Wang LS. Randomized, double blind, placebo-controlled trial of fish-oil-based lipid emulsion infusion for treatment of critically ill patients with severe sepsis. *Asian J Surg.* 2011; 34:1–10. [PubMed: 21515206]
49. Gupta A, Govil D, Bhatnagar S, Gupta S, Goyal J, Patel S, Baweja H. Efficacy and safety of parenteral omega-3 fatty acids in ventilated patients with acute lung injury. *Indian J Crit Care Med.* 2011; 15:108–113. [PubMed: 21814375]
50. Kari A, Hersio K, Takala J, Penttilä I. Comparison of two long-chain triglyceride fat emulsions in parenteral nutrition of critically ill patients. *Current Therap Res.* 1989; 45:1077–1087.
51. Larsen BM, Goonewardene LA, Joffe AR, Van Aerde JE, Field CJ, Olstad DL, Clandinin MT. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: A randomized, controlled trial. *Clin Nutr.* 2012; 31:322–329. [PubMed: 22136963]
52. Sabater J, Masclans JP, Sacanell J, Chacon P, Sabin P, Planas M. Effects on hemodynamics and gas exchange of omega-3 fatty acid-enriched lipid emulsion in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. *Lipids Health Dis.* 2008; 7:39. [PubMed: 18947396]
53. Taftachi F, Sanaei-Zadeh H, Sepehrian B, Zamani N. Lipid emulsion improves Glasgow coma scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning--a randomized controlled trial. *Eur Rev Med Pharmacol Sci.* 2012; 16(Suppl 1):38–42. [PubMed: 22582483]
54. Nijveldt RJ, Tan AM, Prins HA, de Jong D, van Rij GL, Wesdorp RI, van Leeuwen PA. Use of a mixture of medium-chain triglycerides and longchain triglycerides versus long-chain triglycerides in critically ill surgical patients: a randomized prospective double-blind study. *Clin Nutr.* 1998; 17:23–9. [PubMed: 10205311]
55. Lindgren BF, Ruokonen E, Magnusson-Borg K, Takala J. Nitrogen sparing effect of structured triglycerides containing both medium-and long-chain fatty acids in critically ill patients; a double blind randomized controlled trial. *Clin Nutr.* 2001; 20:43–48. [PubMed: 11161543]
56. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, García-Garmendia JL, Jiménez-Jiménez LM, Garnacho-Montero MC, Barrero-Almodóvar A. Clinical and metabolic effects of two lipid emulsions on the parenteral nutrition of septic patients. *Nutrition.* 2002; 18:134–138. [PubMed: 11844644]
57. Iovinelli G, Marinangeli F, Ciccone A, Ciccozzi A, Leonardi M, Paladini A, Varrassi G. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs. medium chain triglycerides. *Minerva Anesthesiol.* 2007; 73:65–76. [PubMed: 17115015]
58. García-de-Lorenzo A, Denia R, Atlan P, Martínez-Ratero S, Le Brun A, Evard D, Bereziat G. Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion v. medium/long-chain triacylglycerols. *Br J Nutr.* 2005; 94:221–230. [PubMed: 16115356]
59. Huschak G, Zur Nieden K, Hoell T, Riemann D, Mast H, Stuttmann R. Olive oil based nutrition in multiple trauma patients: a pilot study. *Intensive Care Med.* 2005; 31:1202–1208. [PubMed: 16132897]

60. Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP, Peng L, Morris T, Luo M, Garcia H, Thomas C, Newton CA, Ziegler TR. A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. *Crit Care Med*. 2012; 40:1792–1798. [PubMed: 22488002]
61. Grecu I, Mirea L, Grintescu I. Parenteral fish oil supplementation in patients with abdominal sepsis. *Clin Nutr*. 2003 abstract.
62. Friesecke S, Lotze C, Köhler J, Heinrich A, Felix SB, Abel P. Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. *Intensive Care Med*. 2008; 34:1411–1420. [PubMed: 18357434]
63. Wang X, Li W, Zhang F, Pan L, Li N, Li J. Fish oil-supplemented parenteral nutrition in severe acute pancreatitis patients and effects on immune function and infectious risk: a randomized controlled trial. *Inflammation*. 2009; 32:304–309. [PubMed: 19568921]
64. Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC. Effects of fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care*. 2010; 14:R5. [PubMed: 20085628]
65. Pontes-Arruda A, Dos Santos MC, Martins LF, González ER, Kliger RG, Maia M, Magnan GB. EPICOS Study Group. Influence of parenteral nutrition delivery system on the development of bloodstream infections in critically ill patients: an international, multicenter, prospective, open-label, controlled study--EPICOS study. *JPEN J Parenter Enteral Nutr*. 2012; 36:574–586. [PubMed: 22269899]
66. Singer P, Shapiro H, Theilla M, Anbar R, Singer J, Cohen J. Antiinflammatory properties of omega-3 fatty acids in critical illness: novel mechanisms and an integrative perspective. *Intensive Care Med*. 2008; 34:1580–1592. [PubMed: 18461305]
67. Calder PC. Long-chain n-3 fatty acids and inflammation: potential application in surgical and trauma patients. *Braz J Med Biol Res*. 2003; 36:433–446. [PubMed: 12700820]
68. Pradelli I, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care*. 2012; 16:R184. [PubMed: 23036226]
69. Palmer AJ, Ho CKM, Ajibola O, Avenell A. The role of ω -3 fatty acid supplemented parenteral nutrition in critical illness in adults: a systematic review and meta-analysis. *Crit Care Med*. 2013; 41:307–316. [PubMed: 23128380]
70. Leiderman I, Malkova O, Levit A. Omega 3 enriched lipid emulsion decreases APACHE II and SOFA scores values in abdominal sepsis patients. *Clin Nutr Suppl*. 2010; 5:30.
71. Ignatenko O, Yaroshetskiy A, Masolitin S, Protsenko D, Gelfand B. Fish oil treatment in severe trauma patients. *Intensive Care Med*. 2010; 36:S316.

Appendix 1

“omega-6 sparing”, “omega-6 reducing”, “alternative fat emulsions”, “fish oil lipid emulsions”, “omega-3”, “omega 9”, “olive oil lipid emulsions”, “medium chain triglycerides (MCT) lipid emulsions”, “randomized,” “blind,” “clinical trial,” “nutritional support”, “parenteral nutrition”, “lipid emulsions”, “critical illness” and “critically ill”.

Appendix 2: Methodological Quality Assessment

We scored the methodological quality of individual trials considering the following key features of high-quality studies: a) extent to which randomization was concealed, b) blinding, c) analysis was based on the intention-to-treat (ITT) principle, d) comparability of groups at baseline, e) extent of follow-up, f) description of treatment protocol and co-interventions, and g) definition of clinical outcomes. Each individual study was scored from 0 to 14.

Figure 1.

Overall effect on Mortality of LCT (Omega-6 reducing strategy) vs. LCT

Abbreviations: LCT: long chain triglycerides; MCT: medium chain triglycerides; 95% CI: 95% confidence intervals

Figure 2.

Overall effect on ventilation days of Omega 6 reducing strategy vs. LCT

Abbreviations: LCT: long chain triglycerides; 95% CI: 95% confidence intervals; SD: standard deviation

Figure 3.

Overall effect on ICU LOS of Omega 6 reducing strategy vs. LCT

Abbreviations: LCT: long chain triglycerides; MCT: medium chain triglycerides; 95% CI: 95% confidence intervals; SD: standard deviation

Table 1

Randomized clinical trial 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							
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
Lindgren 2001	ICU patients, sepsis, multitrauma 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)
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
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 in PN fed patients vs. LCT or LCT+MCT							
Greco 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)
Friesecke 2008	Medical ICU patients N= 166	CRandom: 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 + FO 28 day 18/83 (22)	LCT+MCT 28 day 22/82 (27)	LCT+ MCT+ FO 10/83 (12)	LCT + MCT 11/82 (13)

Study	Population	Methods (score)	Intervention	Mortality # (%) [†]		Infections # (%) [‡]	
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) (0.3:0.6 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)
Barbosa 2010	ICU patients with SIRS or sepsis requiring PN N=25	CRandom: yes ITT: yes Blinding: single (10)	PN + Lipoplus (50% MCT, 40% LCT's soybean oil, 10% FOI) vs. Nutriflex LipidSpecial (50% MCT, 50% LCT, soybean oil). Both received same amounts of lipids (~1 gm/kg/day)	MCT+LCT+FO 5 day 2/13 (15) 28 day 4/13 (31)	MCT+LCT 5 day 1/10 (10) 28 day 4/10 (40)	MCT+LCT+FO NA	MCT+LCT NA
Olive oil containing emulsions vs. LCT or LCT+MCT							
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)
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 Glucerna (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.	

Study	Population	Methods (score)	Intervention	Mortality # (%) [‡]		Infections # (%) [‡]	
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)	Intralipid 21/49 (43)
				Pneumonia			
				7/51 (14)		5/49 (10)	
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)	

Abbreviations: ARDS: acute respiratory distress syndrome; C: Random: concealed randomization; DHA: docosahexaenoic acid; EN: enteral nutrition; EPA: eicosapentaenoic acid; C: Random: concealed randomization; EN: enteral nutrition; FO: fish oil; ICU: intensive care unit; ITT: intention to treat; IV: intravenous; LCT: long chain triglycerides; MCT: medium chain triglycerides; N: number of patients; NA: non attributable; NR: non referred; PN: parenteral nutrition; SIRS: systemic inflammatory response syndrome; VAP: ventilator associated pneumonia; ω-3: omega 3; ω-6: omega 6; ω-9: omega 9.

[‡] 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 carbohydrates PN plus fish oil;

^a converted Standard Error Mean (SEM) to Standard deviation (SD)

Table 2

Outcomes of included trials on omega 9 reducing strategies lipid emulsions

Study	LOS days	Ventilator days	Other
Long Chain Triglyceride (LCT) plus Medium Chain Triglycerides (MCT) vs. LCT			
Nijveldt 1998	LCT + MCT 13.8 ± 2.9 (12)	LCT 17.4 ± 3.0 (8)	LCT + MCT NR
Lindgren 2001	LCT + MCT NR	LCT NR	LCT NR
Adverse effects			
			5/15 (33)
			4/15 (27)
Nitrogen balance at day 3			
			2.6 ± 5.6 gms
			-11.7 ± 4.8 gms
Garnacho-Montero 2002	LCT + MCT ICU 16.6 ± 6.1 (35)	LCT ICU 15.8 ± 7 (37)	LCT + MCT NR
Retinol binding protein			
			1.7 ± 1
			0.8 ± 0.6
Nitrogen balance			
			14.2 ± 2.9
			11.6 ± 4
Iovinelli 2007	LCT + MCT NR	LCT NR	LCT + MCT NR
Time before weaning			
			52 ± 36 hrs
			127 ± 73 hrs
Fish oil (ω 3) containing emulsions in PN fed patients vs. LCT or LCT+MCT			
Greco 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 NR
Patients undergoing reoperation for septic episode			
			2/28 (7)
			8/26 (31)
Friessecke 2008	FO ICU 28 ± 25 (83)	LCT ICU 23 ± 20 (82)	LCT + MCT + FO NR
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

Study	LOS days		Ventilator days		Other	
Wang 2009	NA	NA	NA	NA	Omegaven	LCT
Surgery of infected pancreatic necrosis						
					3/28 (11)	6/28 (21)
Barbosa 2010	MCT+LCT+FO 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+FO 10 ± 14.4 (13)	MCT+LCT 11 ± 12.64 (10)	MCT+LCT+FO 2057 ± 418 kcal	MCT+LCT 1857 ± 255 kcal
Olive oil containing emulsions vs. LCT or LCT+MCT						
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
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
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
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)

Abbreviations: EN: enteral nutrition; FO: fish oil; ICU: intensive care unit; LCT: long chain triglycerides; LOS: length of stay; MCT: medium chain triglycerides; NA: non attributable; NR: not reported; PN: parenteral nutrition;

[†] hospital mortality unless specified;

[‡] number of patients with infections unless specified;

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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 carbohydrates PN plus fish oil;
converted Standard Error Mean (SEM) to Standard deviation (SD)
p