

Fish Oil–Containing Lipid Emulsions in Adult Parenteral Nutrition: A Review of the Evidence

Osman Abbasoglu, MD¹; Gil Hardy, PhD²; William Manzanares, MD³; and Alessandro Pontes-Arruda, MD⁴

Journal of Parenteral and Enteral Nutrition
Volume 43 Number 4
May 2019 458–470
© 2017 American Society for Parenteral and Enteral Nutrition
DOI: 10.1177/0148607117721907
wileyonlinelibrary.com

WILEY

Abstract

Background. There is evidence from laboratory and animal studies that fish oil–containing intravenous lipid emulsions (FOC-IVLEs) have a beneficial effect on inflammation and the immune response, suggesting a possible clinical benefit. Clinical studies of FOC-IVLEs have reported mixed results. The aim of this review is to present findings from recent randomized controlled clinical trials and other quality clinical studies investigating the effects of administering intravenous fish oil alone or as part of a multilipid emulsion and to examine the quality of these studies in an objective, evidence-based manner. **Methods.** Studies comparing FOC-IVLEs with other IVLEs in adults were included. Thirty-four clinical studies were evaluated: 19 investigated levels of inflammatory and immune markers as an endpoint; 13 investigated rates of infection or sepsis; 3 investigated clinical outcomes in septic patients; and 29 investigated general clinical outcomes. **Results.** There was conflicting evidence for a beneficial effect of fish oil on levels of inflammatory and immune markers and some evidence that fish oil decreased the rate of postoperative atrial fibrillation. Studies generally reported few statistical differences in clinical outcomes and rates of infection and sepsis with FOC-IVLEs as compared with other IVLEs. The quality of reporting was generally poor, and the presented evidence for comparisons between FOC-IVLEs and other IVLEs was inconclusive or weak. **Conclusions.** There is very little high-quality evidence that FOC-IVLEs have a more beneficial effect than other IVLEs on clinical outcomes in adult patients. (*JPEN J Parenter Enteral Nutr.* 2019;43:458–470)

Keywords

lipid emulsions; fat emulsions; intravenous; fish oils; parenteral nutrition

Intravenous lipid emulsions (IVLEs) are an important component of parenteral nutrition (PN) as a source of essential fatty acids and as an energy source in patients who are unable to tolerate nutrition through other routes. Traditionally, IVLEs for PN were derived from soybean oil (SO).^{1,2}

However, SO is high in ω -6 polyunsaturated long-chain triglycerides (LCTs), and concerns have been expressed that PN with SO may have an immunosuppressive effect. SO may also exacerbate the release of proinflammatory cytokines and prostaglandin 2, thus contributing to an increased risk

From the ¹Division of Nutrition Support, Department of General Surgery, Faculty of Medicine, Hacettepe University, Ankara, Turkey; ²College of Health, Massey University, Auckland, New Zealand; ³Intensive Care Unit, Department of Critical Care, Faculty of Medicine, Universidad de la República, Montevideo, Uruguay; and ⁴Baxter Healthcare Corporation, Deerfield, Illinois, USA.

Linked content: This article is related to a Letter to the Editor by Adolph et al. (<https://onlinelibrary.wiley.com/doi/10.1002/jpen.1047>) and a Letter to the Editor by Abbasoglu et al. (<https://onlinelibrary.wiley.com/doi/10.1002/jpen.1046>)

Financial disclosure: This study was sponsored by Baxter Healthcare, manufacturer/licensee of Clinoleic. Medical writing assistance was provided by Elise Magatova, PhD, and Tania Dickson, PhD, CMPP, of ProScribe–Envision Pharma Group, and was funded by Baxter Healthcare. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

Conflicts of interest: A.P.-A. is an employee and shareholder of Baxter Healthcare. O.A. and G.H. have received financial reimbursement from Baxter Healthcare for consultancy work, advisory boards, and speaking engagements. W.M. has no conflicts of interest to declare. Baxter Healthcare was involved in the study design, data collection, data analysis, preparation of the manuscript, and the decision to submit this study for publication.

Received for publication February 14, 2017; accepted for publication June 30, 2017.

This article originally appeared online on August 9, 2017.

Corresponding Author:

Alessandro Pontes-Arruda, MD, TA Integrated Pharmacy Solutions, Baxter International Inc, One Baxter Parkway, DF5-3E, Deerfield, IL, USA. Email: alessandro_pontes_arruda@baxter.com

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

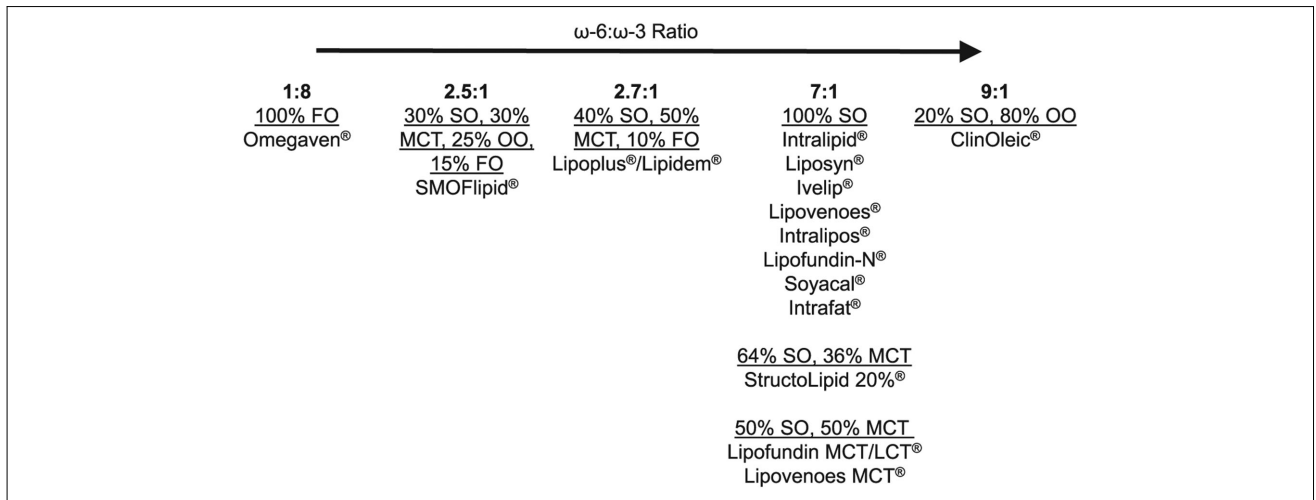


Figure 1. Commercially available intravenous fat emulsion products by ω -3: ω -6 triacylglyceride ratio.⁵ FO, fish oil; LCT, long chain triglycerides; MCT, medium-chain triglycerides; OO, olive oil; SO, soybean oil.

of complications.^{3,4} To address this potential risk, newer IVLEs have been developed to contain lower levels of long-chain ω -6 polyunsaturated fatty acids (PUFAs) to minimize the possible adverse effects associated with LCTs (Figure 1). One strategy in creating these new IVLEs has been to replace a portion of the SO component in an IVLE with medium-chain triglycerides (MCTs) and/or with olive oil (OO) and/or fish oil (FO).⁴ Another strategy has been to use an IVLE supplement derived solely from FO, which is high in ω -3 PUFAs.

Evidence from laboratory studies indicate that ω -3 PUFAs may result in lower inflammatory responses.¹ ω -3 and ω -6 PUFAs have competitive metabolic pathways. The metabolism of linoleic acid, a dominant ω -6 PUFA, produces arachidonic acid (C20:4 n-6), which is further metabolized to products with proinflammatory activity.^{1,6} Therefore, in theory, PN high in ω -6 PUFAs may be detrimental for patients at risk of a pathologic inflammatory response.² In contrast, metabolism of eicosapentaenoic acid (C20:5 n-3) and docosahexaenoic acid (C22:6 n-3), which are the ω -3 PUFAs predominant in FO, may reduce the production of proinflammatory eicosanoids in a dose-dependent way: (1) by directly competing with the metabolism of arachidonic acid^{1,6} and (2) by the nature of eicosapentaenoic acid and docosahexaenoic acid, which are metabolized to products that are less proinflammatory than arachidonic acid. Based on in vitro and animal experiments, the immune and proinflammatory properties of IVLEs rich in linoleic acid, a precursor of arachidonic acid, could have an adverse impact on clinical outcomes (eg, by increasing risk of infection, sepsis, or systemic inflammatory response syndrome [SIRS]).^{2,7}

Despite evidence from in vitro and animal models indicating that ω -3 PUFAs may have a dose-dependent

beneficial effect on inflammatory responses, there have been conflicting reports from meta-analyses and systematic reviews regarding the clinical benefits of using FO-containing (FOC)-IVLEs over other lipids. While well-conducted meta-analyses can be key to demonstrating positive or negative effects, inappropriately conducted meta-analyses can lead to skewed results. Of the meta-analyses and systematic reviews conducted, some have reported a statistically significant clinical benefit for FOC-IVLEs.⁸⁻¹¹ However, 1 meta-analysis included only 6 relatively low-quality trials,¹⁰ and another not only imputed up to 50% of standard deviations not reported by the original trial but did not correct for possible type 1 errors.⁸ Neither of these practices is recommended as good practice by the Cochrane Collaboration.^{12,13} Other reviews have reported either no significant clinical benefits with FOC-IVLEs or an overall poor quality of included studies with considerable heterogeneity, making it likely that any statistical benefit would be insufficient to recommend the use of FO over other IVLEs.¹⁴⁻¹⁷

Given the conflicting results from previous reviews and meta-analyses, we decided to investigate the current published evidence base for the use of FOC-IVLEs for PN. Because of the low quality of most studies and the substantial heterogeneity across studies, it was not feasible to conduct a meta-analysis of the current published evidence base. Therefore, we have instead focused on this qualitative narrative review, which presents the findings from randomized controlled trials (RCTs) and other clinical studies and examines the quality of these studies in an objective, evidence-based manner. We sought to address the following question: Does administering FO alone or as part of a multilipid IVLE improve clinical outcomes?

Methods

Literature Search and Assessment of Study Quality

This qualitative review of the literature on the use of FOC in PN used a comprehensive, preplanned search strategy to locate potentially relevant human clinical studies in English for inclusion. We conducted online searches of MEDLINE and EMBASE (inception to March 16, 2016), using the search terms “fish oil” and “parenteral nutrition.” Articles comparing FOC-IVLEs with other IVLEs with respect to clinical outcomes, infection and inflammation, or immune markers were eligible for inclusion in this review. Articles were excluded if they described results from studies of pediatric and neonatal patients or nonhuman or laboratory studies; if they were based on case studies or case series; if they exclusively used enteral nutrition (EN) in adults; or if they were not written in English. Additional studies were retrieved by searching the reference lists of relevant meta-analyses and systematic reviews.

Study quality was assessed with the Cochrane Collaboration assessment criteria for assessing risk of bias.¹⁸ This tool grades studies as having a low, high, or unknown risk according to the following possible sources of bias:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessments
- Incomplete outcome data
- Selective reporting
- Other biases

Endpoints Assessed

Key endpoints identified for inclusion were the effects of FO on inflammation and immune response, sepsis and infection, mortality, length of hospitalization, length of stay in the intensive care unit (ICU) and other ICU-related or general outcomes, and cardiac surgery outcomes.

Results

Inflammation and Immune Response

Reported results. A total of 19 studies investigated the effect of FOC-IVLEs on markers of inflammation and immune response. Of these, 12 compared an FOC-IVLE with an SO-based IVLE,¹⁹⁻³⁰ 1 with an OO-based IVLE,³¹ 3 with a mixed MCT/LCT IVLE,³²⁻³⁴ 2 with saline,^{35,36} and 1 with a control group in which patients received nutrition chosen at the discretion of the study clinicians.³⁷ None of the included studies compared 100% FOC-IVLE with other FOC-IVLEs. Therefore, for the purposes of this review,

we henceforth simplify the text by referring to all FOC-IVLEs as FO. The inflammatory markers commonly reported in these studies were the proinflammatory cytokines interleukin 1 (IL-1), IL-6, and IL-8; the anti-inflammatory cytokine IL-10; the cell-signaling cytokine tumor necrosis factor alpha (TNF- α); and the ratio of T-cell lymphocytes CD4 and CD8 (cluster of differentiation). A CD4/CD8 ratio >2 is indicative of satisfactory immune status, whereas impairment in CD4 T-cell regeneration and persistent elevation of CD8 T-cell counts, leading to a lower CD4/CD8 ratio, are associated with immunologic dysfunction.

Based on the results of these included studies, there is conflicting evidence for a beneficial effect of FO on the immune response and inflammation in adults. Six studies cited significantly lower levels of IL-6 with FO than with SO,^{19,27,29} MCT/LCT,^{25,33} or saline.³⁶ In contrast, 10 studies found no significant differences in levels of IL-6 with FO vs SO,^{20-22,26} MCT/LCT,^{24,28,32,34} OO,³¹ or control nutrition.³⁷

One study reported significantly lower levels of IL-1 and IL-8 with FO than with MCT/LCT.³³ Another study cited lower levels of IL-1 with FO as compared with SO.²⁷ In contrast, 2 studies found no significant difference in levels of IL-1 vs MCT/LCT.^{24,34} One study indicated higher levels of IL-10 and HLA-DR (human leukocyte antigen–antigen D related) with FO than with SO.³⁰ Another study cited a lower level of IL-10 with FO and no significant difference in HLA-DR.¹⁹ In contrast, 3 studies reported no significant difference in levels of IL-10 with FO than with MCT/LCT^{28,34} or saline.³⁶

Three studies observed significantly lower levels of TNF- α with FO than with MCT/LCT³³ or SO.^{27,29} In contrast, 5 studies found no significant differences in TNF- α levels when compared with placebo,³⁵ SO,^{20,22} MCT/LCT,³⁴ or OO.³¹ Two studies found significantly higher CD4/CD8 ratios in patients using a FO/SO combination vs those using SO alone,^{23,29} whereas another study reported no significant difference for the same endpoint.³⁰ One study found no significant differences in T lymphocytes, CD3, CD4, CD8, and CD4/CD8 ratio between patients using FO and those using SO.²⁷

Importantly, 4 of the 7 studies that recorded differences in inflammatory or immune markers with FO over other IVLEs reported no corresponding differences in clinical outcomes^{19,25,30,33}; 1 additional study did not examine clinical outcomes.²³ However, 1 included study noted a lower rate of postoperative infections with FO vs SO.²⁷ Three studies investigated patients with SIRS, and of these, 2 cited significantly fewer instances of SIRS with FO than with SO.^{20,29} The third study found no difference in outcomes for patients with SIRS in the intent-to-treat population when FO was compared with SO (length of stay in ICU).³²

Study quality. Although significant differences in the levels of some proinflammatory markers were reported in some

studies, it is not possible to determine whether these changes are clinically relevant. None of the studies reported which standard thresholds, if any, were used to assess whether the reported levels of proinflammatory markers were within or outside the clinical reference range for the laboratory in which they were measured.

The quality and strength of evidence were low in most studies, and it is not possible to determine whether studies were adequately powered. All studies had small sample sizes and were likely to be underpowered for an assessment of proinflammatory markers (Table 1). Only 2 of 19 studies cited a sample size calculation based on levels of a proinflammatory marker (IL-6). Of these, 1 study recruited a sufficient number of patients, based on the sample size calculation, but found no significant differences in levels of IL-6 between FO and MCT/LCT.³² The investigators in the other study predicted that a sample of 95 was required to demonstrate a statistical effect, but only 38 patients were recruited for their study.³³

The majority of studies did not report statistical methods in sufficient detail to allow for an appropriate quality assessment. In general, most authors poorly described their methodology; therefore, the quality of each study was difficult to determine (Figure 2). Most studies included multiple endpoints, but none used tests to assess or correct for possible effects of multiplicity on significant outcomes. Based on the Cochrane Collaboration Assessment Tool, which ranks quality as high, low, or unknown,¹⁸ 14 of the 18 included studies with an RCT design were classified as having an unknown to high risk of bias (Figure 2).^{20-25,27-31,33-35}

Conclusions. There is insufficient high-quality data investigating inflammatory and immune markers, which has resulted in inconclusive evidence for a beneficial effect of PN with FO on inflammatory and immune markers as compared with other IVLEs (Table 2).

Sepsis and Infection in Adults

Reported results. A total of 11 studies were included comparing the effect of FO and other IVLEs on rates of postsurgical sepsis and infection, with 3 additional studies comparing clinical outcomes in patients who had sepsis at study entry. Of these, 9 compared an FOC-IVLE with a SO-based IVLE,^{19-22,24,26,28-30} 2 with an OO-based IVLE,^{31,38} 3 with a mixed MCT/LCT IVLE,^{30,33,39} and 1 with control nutrition.³⁷ Sepsis and infectious complications were defined by standardized criteria in 4 studies.^{19,20,29,38} One study reported on catheter-associated infections,²¹ 3 studies on infectious events (eg, pneumonia, bacteremia, and abdominal abscesses),^{24,26,30} and 3 studies on infectious complications without providing details.^{22,28,33}

The majority of studies concluded that administering PN with FO does not reduce the risk of postsurgical

sepsis or infection when compared with other IVLEs. One study indicated significantly fewer patients in the ICU with nosocomial infections when parenteral FO was compared with MCT/LCT; however, 50% of the energy contribution from lipids was achieved through EN in this study.⁴⁰ Another study cited significantly fewer infections in adult postsurgical patients with FO vs OO (23.1% vs 78.6%, $P = .007$)³⁸; however, the difference in the percentage of patients with sepsis (the primary endpoint) between the FO and OO groups did not reach significance (7.7% vs 35.7%, $P = .1$). In addition, of the 23 endpoints investigated, the rate of infection was the only endpoint that showed a significant difference. Moreover, no appropriate statistical methods were used to correct for multiple endpoints. In contrast, 10 studies reported no significant differences in infection rates with FO vs other IVLEs.^{19-22,24,28-30,32,33}

Based on the 3 studies that included septic patients at study entry, there was no significant difference in overall mortality with FO over other IVLEs.^{31,37,39} One study investigating markers of brain injury and sepsis-associated delirium found no differences between FO and control nutrition.³⁷ One retrospective study of septic patients cited no differences in relevant inflammatory markers with FO over standard nutrition therapy and no improvement in clinical outcomes.⁴¹

Study quality. In general, the clinical studies were of short duration: 3 studies collected data for 4 weeks,^{21,32,40} whereas the remainder were completed within 5–8 days. Only 2 studies engaged in long-term follow-up to determine the long-term clinical effects of FOC-IVLEs.^{37,40}

The quality and strength of evidence of most studies were low, primarily due to poor reporting of statistical methods. It is not possible to determine whether studies were adequately powered to assess rates of sepsis or infection. Only 2 of the 12 studies investigating rates of sepsis or infection indicated a sample size calculation that was specifically based on sepsis or infection (Figure 2).^{20,38} One of the 3 studies investigating septic patients cited a sample size calculation using an outcome relevant to septic patients ($S100\beta$ level). This study found no differences in markers of sepsis-associated injury or inflammatory mediators between patients receiving FO and those given standard care.³⁷

The included studies generally did not report the study protocol or methods in sufficient detail to allow for an appropriate quality assessment. Most studies measured multiple endpoints, but none reported using a test to assess or correct for possible effects of multiplicity on significant outcomes (Figure 2). When study quality of RCT designs was assessed via the Cochrane Collaboration assessment tool,¹⁸ 10 of the 14 included RCTs were classified as having an unknown or high risk of bias (Figure 2).*

*References 20-22, 24, 28, 30, 31, 33, 38, 39.

Table 1. Findings From Clinical Studies of FO-Containing IVLEs in Adults.

Article	Participants	Groups Analyzed	Main Findings
Lipoplus			
Barbosa (2010) ³⁹	Patients with SIRS or sepsis	Lipoplus (n = 13) MCTs/LCTs (n = 10)	Primary endpoints: Inflammatory markers were different between groups: IL-6 (change day 1 to day 6: FO -4950 ± 6690 pg/mL, MCTs/LCTs -1242 ± 725 pg/mL, <i>P</i> < .001), IL-10 (change day 1 to day 6: FO -29 ± 8 pg/mL, MCTs/LCTs -64 ± 40 pg/mL, <i>P</i> < .001), TNF- α (change day 1 to day 6: FO -8.1 ± 3.6 pg/mL, MCTs/LCTs -9.6 ± 4.9 pg/mL, <i>P</i> < .001) Clinical outcomes similar between groups: duration of stay in ICU (FO 12 ± 4 d, MCTs/LCTs 13 ± 4 d, <i>P</i> = NS), 28-d mortality (FO 4 [31%] participants, MCTs/LCTs 4 [40%] participants, <i>P</i> = NS), duration of mechanical ventilation (FO 10 ± 4 d, MCTs/LCTs 11 ± 4 d, <i>P</i> = NS); length of hospitalization significantly shorter when adjusted for age, glucose supply, and SAPS II score (FO 22 ± 7 d, MCTs/LCTs 55 ± 16 d, <i>P</i> = .038)
Grau-Carmona (2015) ⁴⁰	Patients in ICU	Lipoplus (n = 81) MCTs/LCTs (n = 78)	Primary endpoint: Fewer instances of nosocomial infections with FO (FO 17 [21%] participants, MCTs/LCTs 29 [37.2%] participants, <i>P</i> = .04) Other findings: Clinical outcomes similar between groups (mortality, length of hospitalization, duration of stay in ICU, duration of mechanical ventilation)
Omegaven—Alone			
Berger (2008) ⁴⁵	Patients in ICU after abdominal aortic aneurism surgery	Omegaven (n = 12) MCTs/LCTs (n = 12)	Primary endpoint: No significant differences were noted between groups for glucose kinetics Other findings: Clinical outcomes were similar between groups: significant increases in body temperature were noted in both groups (difference between groups <i>P</i> = NS), length of hospitalization (FO 9 [7–13] d, 10 [8–16] d, <i>P</i> = .19), duration of stay in ICU (FO 24 [19–96] h, MCTs/LCTs 35 [21–143] hours, <i>P</i> = .22)
Berger (2013) ³⁶	Patients undergoing elective cardiac surgery	Omegaven (n = 14) Saline (n = 14)	Primary endpoints: Incorporation of fatty acids into the atrial membrane were consistent with the fatty acid profile of the IVLE Other findings: Clinical outcomes similar between groups: heart rate over 24 h (values NR, <i>P</i> = NS), blood pressure over 24 h (values NR, <i>P</i> = NS), duration of mechanical ventilation (values NR, <i>P</i> = .10), duration of stay in ICU (values NR, <i>P</i> = .118)
Burkhart (2014) ³⁷	Patients with sepsis	Omegaven (n = 25) Control (standard treatment; n = 25)	Primary endpoint: IL-6 over 7 d similar between groups (values NR, <i>P</i> = .654 FO 343 pg/mL, control 409 pg/mL, <i>P</i> = NR) Other findings: Clinical outcomes similar between groups: mortality (FO 13 [52%] participants, control 13 [52%] participants), duration of stay in ICU (FO 5 d, control 6 d, <i>P</i> = NR), and duration of delirium (FO 5 d, control 4 d, <i>P</i> = NR)
de Miranda Torrinhas (2013) ¹⁹	Patients who had undergone elective surgery for the resection of gastric or colon cancer	Omegaven (n = 31) SO (n = 32)	Primary endpoints: Inflammatory markers: IL-6 higher in FO group (FO 0.28 ± 0.14, MCTs/LCTs 0.08 ± 0.20, <i>P</i> < .0001), IL-10 lower in FO group (FO 0.11 ± 0.08, MCTs/LCTs 0.23 ± 0.02, <i>P</i> = .016) Other findings: Clinical outcomes similar between groups: duration of hospitalization (FO 12.0 ± 1.29 d, MCTs/LCTs 11.3 ± 1.14 d, <i>P</i> = .844), infection (FO 6.5%, MCTs/LCTs 15.6%, <i>P</i> = .426)
Gupta (2011) ⁵⁰	Ventilated patients with acute respiratory distress syndrome	Omegaven + enteral standard diet (n = 31) Enteral standard diet (EN; n = 30)	Primary endpoint: Oxygenation and respiratory function (arterial blood gas, ventilatory settings, tidal volume, positive end-expiratory pressure) assessed at days 4, 7, and 14 were not different between groups Other findings: Clinical outcomes similar between groups in patients who survived as well as those who died (all between-group difference <i>P</i> = NS): length of hospitalization surviving patients (FO 21.5 ± 13.5 d, EN 26.6 ± 18.2 d, <i>P</i> = .32), duration of stay in ICU surviving patients (FO 16.0 ± 8.6 d, EN 15.9 ± 8.6 d, <i>P</i> = .97), duration of mechanical ventilation surviving patients (FO 13.9 ± 7.6 d, EN 11.8 ± 6.5 d, <i>P</i> = .37), mortality (FO 7 [23%], 13 [43%], <i>P</i> = .3)
Hall (2015) ⁵¹	Patients with sepsis in ICU	Omegaven (n = 30) Standard care (n = 30)	Primary endpoint: Organ dysfunction defined by the Sequential Organ Failure Assessment score (mean ± SD: FO 1.0 ± 1.5, standard care 2.2 ± 2.2, <i>P</i> = .005) Other findings: Clinical outcomes similar between groups (values for each group NR): duration of mechanical ventilation, mortality, length of stay in ICU, length of hospitalization
Heidt (2009) ⁴³	Patients undergoing cardiac surgery	Omegaven (n = 52) SO (n = 50)	Primary endpoint: Fewer instances of postoperative atrial fibrillation with FO (FO 9 [17.3%] participants, SO 15 [30.6%] participants, <i>P</i> < .05)
Jiang (2010) ²⁰	Patients who have undergone GI cancer surgery	Omegaven (n = 100) SO (n = 103)	Primary endpoint: Rate of postoperative infections and occurrence of SIRS: rates of infection similar between groups (FO 4 [4%] participants, SO 12 [12%] participants, <i>P</i> = .066), rates of SIRS decreased from 13 of 103 to 4 of 100 (<i>P</i> = .039) in the FO group Other findings: Length of hospitalization lower in FO group (FO 15 ± 5 d, SO = 17 ± 8 d, <i>P</i> = .041). Inflammatory markers similar between groups: IL-6 (median change from day 0 to day 8: FO -20.05 pg/mL, SO = -16.7 pg/mL, <i>P</i> = .184), TNF- α (median change from day 0 to day 8: FO -0.19 pg/mL, SO 0.00 pg/L, <i>P</i> = .107)

(continued)

Table 1. (continued)

Article	Participants	Groups Analyzed	Main Findings
Khor (2011) ³⁵	Patients with severe sepsis in ICU	Omegaven (n = 14) Saline (n = 13)	Primary endpoint: Clinical severity: day 7 APACHE II, APACHE III, and SAPS II scores were higher in the FO group (APACHE II: FO 12.9 ± 6.7, saline 7.3 ± 5.1, <i>P</i> = .03; APACHE III: FO 48.3 ± 28.9, saline 28.5 ± 16.3, <i>P</i> = .028; SAPS II: FO 29.3 ± 14.3, saline 15.9 ± 10.8, <i>P</i> = .019) Other findings: Clinical outcomes similar between groups: length of hospitalization (FO 19.6 d, saline 17.5 d, <i>P</i> = .299), duration of stay in ICU (FO 10.3 d, saline 8.4 d, <i>P</i> = .573) Inflammatory markers were similar between groups: TNF-α (FO 3.5 ± 9.2 pg/mL, saline 4.2 ± 4.7 pg/mL, <i>P</i> = .295)
Kolesnikov (2015) ⁴⁹	Patients with coronary artery disease	Omegaven (n = 33) Control (n = 40)	Primary endpoint: Fewer instances of postoperative atrial fibrillation with FO (FO 3 [9.1%] participants, control 13 [32.5%] participants, <i>P</i> < .01)
Lomivorotov (2014) ⁴⁷	Patients with coronary artery disease	Omegaven (n = 17) Placebo (n = 18)	Primary endpoint: Atrial fibrillation was similar between groups (values NR)
Wohlmut (2010) ⁴¹	Patients with septic shock due to abdominal infection	Omegaven + enteral/parenteral standard care (n = 29) Enteral/parenteral standard care (n = 29)	Primary endpoint: Organ failure rates were similar between groups: median organ failures (FO 2 organs, SOC 2 organs, <i>P</i> = .54) Other findings: Clinical outcomes similar between groups: ICU length of stay (FO 6 d, SOC 8 d, <i>P</i> = .59), infections (pneumonia FO 2 [6.9%] participants, SOC 2 [6.9%] participants, <i>P</i> = 1; urinary tract infection FO 1 [3.4%] participants, SOC 1 [3.4%] participants, <i>P</i> = 1; catheter-related bloodstream infection FO 1 [3.4%] participants, SOC 0 participants, <i>P</i> = 1), mortality (FO 11 [37.9%] participants, SOC 10 [34.5%] participants, <i>P</i> = 1)
Omegaven + other IVLE			
Badia-Tahull (2010) ³⁸	Patients who have undergone elective GI surgery	Omegaven + SO/OO (n = 13) SO/OO (n = 14)	Primary endpoint: Rates of infection lower in FO group (FO 3 [23.1%] participants, SO/OO 11 [78.6%] participants, <i>P</i> = .007) Other findings: Clinical outcomes were similar between groups: length of hospitalization (FO 15 d, SO/OO 16 d, <i>P</i> = NS), sepsis (FO 1 [7.7%] participants, SO/OO 5 [35.7%] participants, <i>P</i> = NS), mortality (FO 1 [7.7%] participants, SO/OO 2 [14.3%] participants, <i>P</i> = NS)
Friesecke (2008) ³²	Patients in ICU	Omegaven + MCTs/LCTs (n = 83) MCTs/LCTs (n = 82)	Primary endpoint: Inflammatory outcomes similar between groups (data not shown) Other findings: Clinical outcomes similar between groups: length of hospitalization (FO 28 ± 25 d; MCTs/LCTs 23 ± 20 d; <i>P</i> = .35), duration of mechanical ventilation (FO 22.8 ± 22.9 d; MCTs/LCTs 20.5 ± 19.0 d; <i>P</i> = .67), infection (pneumonia: FO 4 [5%] participants; MCTs/LCTs 5 [6%] participants; <i>P</i> = .84; catheter-related blood infections: FO 1 [1%] participant; MCTs/LCTs 3 [4%] participants; <i>P</i> = .10), mortality (at 28 d: FO 18 [22%] participants, MCTs/LCTs 22 [27%] participants, <i>P</i> = .44)
Gultekin (2014) ³¹	Patients with sepsis	Omegaven + SO/OO (n = 16) SO/OO (n = 16)	Primary endpoint: Inflammatory markers showed no significant differences between groups in baseline and final IL-6 and TNF-α levels; FO vs SO/OO not compared Other findings: Clinical outcomes similar between groups: mortality (FO 79 [43.8%] participants, SO/OO 8 [50%] participants, <i>P</i> = NS), length of hospitalization (FO 31.6 ± 4.3 d, SO/OO 30.6 ± 4.3 d, <i>P</i> = NS), duration of total PN (FO 23.7 ± 3.8 d, SO/OO 19.1 ± 4.0, <i>P</i> = NS)
Han (2012) ³³	Patients in surgical ICU after major surgery	Omegaven + MCTs/LCTs (n = 18) MCTs/LCTs (n = 12)	Primary endpoint: None defined Other findings: Rates of infection similar between groups (FO 27.8%, MCTs/LCTs 41.7%, <i>P</i> = NS). Inflammatory markers—significant differences were reported, but no values for the individual markers were provided: IL-1 (<i>P</i> < .001), IL-6 (<i>P</i> = .0185), and TNF-α (<i>P</i> = .023) lower in FO group
Heller (2006) ⁵²	Patients admitted to hospital	Omegaven + SO (all; n = 661)	Primary endpoint: Mortality was decreased with FO >0.1 to ≤0.20 g/kg/d vs FO <0.05 g/kg/d (<i>P</i> < .05) Other findings: Reduced length of hospitalization and stay in ICU with FO ≥0.05 g/kg/d vs FO <0.05 g/kg/d (<i>P</i> < .001)
Liang (2008) ²²	Patients with colon or rectal cancer undergoing radical resection	Omegaven + SO (n = 20) SO (n = 21)	Primary endpoint: Not defined. Other findings: Clinical outcomes similar between groups (length of hospitalization, infection, mortality); IL-6 similar between groups; TNF-α similar between groups
Sungurtekin (2011) ³⁴	Patients with SIRS or sepsis	Omegaven (sepsis; n = 10) MCTs/LCTs (sepsis; n = 10) Omegaven (SIRS; n = 10) MCTs/LCTs (SIRS; n = 10)	Primary endpoint: Inflammatory markers were similar between SIRS groups; in the sepsis groups, day 10 IL-1 and IL-6 levels were significantly higher than normal levels in both groups (IL-1: FO 5.0 ± 0.0, MCTs/LCTs 8.00 ± 3.36, <i>P</i> < .006; IL-6: FO 31.58 ± 36.44, MCTs/LCTs 392.53 ± 526.30, <i>P</i> < .002)
Tsekos (2004) ⁴⁶	Patients undergoing major abdominal surgery	Omegaven + MCTs/LCTs (postoperative; n = 86) Omegaven + MCTs/LCTs (preoperative and postoperative; n = 53) MCTs/LCTs (n = 110)	Primary endpoint: Reduced mortality with FO when given preoperatively and postoperatively (FO 3%, MCTs/LCTs 15%, <i>P</i> = .02)

(continued)

Table 1. (continued)

Article	Participants	Groups Analyzed	Main Findings
Wang (2008) ²⁶	Patients with severe acute pancreatitis	Omegaven + SO (n = 20) SO (n = 20)	Primary endpoint: Inflammatory markers were similar between groups (values NR) Other findings: Clinical outcomes were similar between groups: SIRS (FO 4 [20%] participants, SO 9 [45%], <i>P</i> = NS), infections (FO 3 [15%] participants, SO 5 [25%] participants, <i>P</i> = NS), length of hospitalization (FO 65.2 ± 7.3 d, SO 70.5 ± 9.1 d, <i>P</i> = NS)
Wang (2009) ³⁰	Patients with severe acute pancreatitis	Omegaven + SO (n = 28) SO (n = 28)	Primary endpoint: Inflammatory markers (IL-10 and HLA-DR expression): HLA-DR higher in FO group (<i>P</i> = .01), IL-10 higher in FO group (<i>P</i> = .04) Other findings: Clinical outcomes were similar between groups: infection (FO 6 [21%] participants, SO 9 [32%] participants, <i>P</i> = .20), rate of surgery (FO 3 [11%], SO 6 [21%], <i>P</i> = NS), mortality (FO 0 [0%], SO 1 [4%], <i>P</i> = NR). Inflammatory markers: CD4+/CD8+ similar between groups (values NR, <i>P</i> = .38)
Wei (2014) ²⁷	Patients who have undergone gastric surgery	Omegaven + SO (n = 26) SO (n = 20)	Primary endpoint: Levels of IL-1 (FO 302.32 ± 37.61, SO 332.61 ± 35.34, <i>P</i> = .011), IL-6 (FO 14.35 ± 45.95, SO 48.25 ± 67.49, <i>P</i> = .007), and TNF-α (FO 12.05 ± 60.31, SO 53.56 ± 75.23, <i>P</i> = .005) lower in FO group; other immunologic indicators similar between groups
Zhu (2012) ²⁹	Patients who have undergone major abdominal surgery	Omegaven + SO (n = 29) SO (n = 28)	Primary endpoint: Infectious complications were similar between groups (FO 4 [14%], SO 8 [29%], <i>P</i> = NS); duration of SIRS was shorter in FO group (FO 12 ± 4 d, SO 15 ± 6 d, <i>P</i> < .05); inflammatory markers were lower in FO group: IL-6 (FO 18.2 ± 7.6 pg/mL, SO 23.7 ± 8.2 pg/mL, <i>P</i> < .05), TNF-α (FO 5.7 ± 2.8 pg/mL, SO 7.8 ± 3.2 pg/mL, <i>P</i> < .05); CD4+/CD8+ was lower in FO group (FO 1.3 ± 0.8, SO 0.9 ± 1.4, <i>P</i> < .05) Other findings: Length of hospitalization lower (FO 12 ± 4 d, SO 15 ± 6 d, <i>P</i> < .05)
SMOFLipid			
Grimm (2006) ⁴²	Patients who have undergone major abdominal surgery	SMOFLipid (n = 19) SO (n = 14)	Primary endpoint: Laboratory measures showed no significant differences between groups Other findings: Reduced length of hospitalization with FO (SMOF 13.4 ± 2.0 d; SO 20.4 ± 10.0 d; <i>P</i> < .05)
Klek (2013) ²¹	Patients unable to sustain oral/enteral food intake for at least 4 wk	SMOFLipid (n = 34) SO (n = 39)	Primary endpoint: Adverse events and safety: rates of infection similar between groups (during treatment: SMOF 6 [17.6%] participants, SO 7 [17.9%] participants; follow-up period: SMOF 0 [0.0%] participants, SO 2 [5.1%] participants) Other findings: IL-6 similar between groups (change from baseline: SMOF 0.5 ± 18.4, SO -0.7 ± 6.3, <i>P</i> = .66)
Ma (2012) ²⁴	Patients who have undergone elective GI surgery	SMOFLipid (n = 20) SO (n = 20)	Primary endpoint: None identified Other findings: Clinical outcomes similar between groups (overall: SMOF vs SO, <i>P</i> = .687), length of hospitalization (SMOF 12.2 ± 6.2 d; SO 10.4 ± 2.7 d; <i>P</i> = .687), postoperative complications (anastomosis leaks: SMOF 1 participant, SO 0 participants; postoperative ileus: SMOF 1 participant, SO 1 participant), infection (pneumonia: SMOF 0 participants, SO 0 participants; bacteremia: SMOF 0 participants, SO 0 participants; abdominal abscess: SMOF 2 participants, SO 1 participant). Inflammatory markers were similar between groups: IL-1 (day 6: SMOF 2.22 ± 4.76 pg/mL, SO 2.5 ± 5.35 pg/mL, <i>P</i> = .866), IL-6, and TNF-α
Mertes (2006) ⁴⁴	Patients who have undergone elective abdominal or thoracic surgery	SMOFLipid (n = 99) SO (n = 100)	Primary endpoint: Serum lipid values (phospholipids, total cholesterol, triglycerides) Other findings: Clinical outcomes similar between groups: length of stay (SMOF 17.6 d, SO 18.3 d, <i>P</i> = NR), mortality (SMOF 3 [2.4%] participants, SO 4 [3.3%] participants, <i>P</i> = NR)
Metry (2014) ²⁵	Patients in ICU after major abdominal surgery	SMOFLipid (n = 41) SO (n = 42)	Primary endpoint: IL-6 lower in FO group (day 7: SMOF 1986 ± 1021, SO 4137 ± 3435, <i>P</i> < .01; no units reported) Other findings: Clinical outcomes similar between groups: length of hospitalization (SMOF = 15.7 ± 11.4 d, Intralipid = 19.4 ± 12.6 d, <i>P</i> = NS), duration of stay in ICU (SMOF 10.4 ± 6.2 d, SO 11.7 ± 7.2 d, <i>P</i> = NS), duration of mechanical ventilation (SMOF 6.5 ± 5.1 d, SO 7.2 ± 4.3 d, <i>P</i> = NS), mortality (1 wk: SMOF 2 [4.7%] participants, SO 3 [7.3%] participants, <i>P</i> = NS; 1 mo: SMOF 3 [7.1%] participants, SO 3 [7.3%] participants, <i>P</i> = NS)
Wu (2014) ²⁸	Patients who have undergone GI surgery	SMOFLipid (n = 20) SO (n = 15)	Primary endpoints: Clinical outcomes similar between groups: length of hospitalization (FO 17.45 ± 4.80 d, SO 19.62 ± 5.59 d, <i>P</i> = .19), mortality (values NR), infection (values NR), IL-10 (change from day 1 to day 6: FO -1.84 ± 4.79, SO -2.74 ± 5.21, <i>P</i> = .845), IL-6 (change from day 1 to day 6: FO -29.37 ± 34.07, SO -36.54 ± 55.74, <i>P</i> = .813), and TNF-α (change from day 1 to day 6: FO 0.69 ± 1.96, SO 0.35 ± 4.38, <i>P</i> = .551) similar between groups

(continued)

Table 1. (continued)

Article	Participants	Groups Analyzed	Main Findings
Various FO-supplemented IVLEs			
Edmunds (2014) ⁴⁸	Patients in ICU	FO (n = 19) OO (n = 74) MCTs (n = 65) SO (n = 223) Lipid-free (n = 70; reference)	Primary endpoints: Significant between-group differences were noted for duration of stay in ICU (FO 7.0 d, OO 7.9 d, MCT 9.6 d, SO 10.9 d, lipid-free 11.0 d, $P < .001$), duration of mechanical ventilation (FO 5.0 d, OO 5.0 d, MCT 5.3 d, SO 4.9 d, lipid-free 8.7 d, $P = .023$), and mortality (FO 2 [10.5%] participants, OO 11 [14.9%] participants, MCT 20 [30.8%] participants, SO 63 [28.3%] participants, lipid-free 13 [18.6%] participants, $P = .034$). No significant difference among treatment groups was noted for length of hospitalization (FO 14.1 d, OO 22.1 d, MCT 31.9 d, SO 28.1 d, lipid-free 27.7 d, $P = .108$) Cox analysis revealed that when compared with lipid-free, FO was associated with significantly higher discharge from ICU alive (hazard ratio = 1.84, $P = .046$) but not discharge from the hospital alive or termination of mechanical ventilation alive
Long (2013) ²³	Patients who have undergone esophageal surgery	FO/SO (n = 30) SO (n = 30)	Primary endpoint: Immune markers were higher in FO group: CD4+/CD8+ (values NR, $P = .012$)

APACHE, Acute Physiology and Chronic Health Evaluation; CD, cluster of differentiation; EN, enteral nutrition; FO, fish oil; GI, gastrointestinal; HLA-DR, human leukocyte antigen–antigen D related; ICU, intensive care unit; IL, interleukin; IVLE, intravenous lipid emulsion; LCTs, long-chain triglycerides; MCTs, medium-chain triglycerides; NR, not reported; NS, not significant; OO, olive oil; PN, parenteral nutrition; SAPS II, Simplified Acute Physiology Score; SIRS, systemic inflammatory response syndrome; SO, soybean oil; SOC, standard of care; TNF- α , tumor necrosis factor alpha.

Conclusions. The majority of comparative investigations fail to demonstrate any differences in rates of sepsis or infection after administration of PN with FO as compared with other IVLEs. In addition, current evidence suggests no difference in rates of mortality or brain injury in patients with sepsis at study entry when FO is compared with other IVLEs. Consequently, based on the poor quality of reporting, it is not possible to determine whether the observed lack of differences between FO and other IVLEs is conclusive.

General Clinical Outcomes in Adults

Reported results. A total of 29 studies were included comparing FOC-IVLEs with other IVLEs with respect to clinical outcomes in adults. Of these, 13 compared an FOC-IVLE with a SO-based IVLE,^{19-22,24-26,28-30,42-44} 6 with MCT/LCT,^{32,33,39,40,45,46} 2 with OO,^{31,38} 3 with placebo or saline,^{35,36,47} and 1 with various control emulsions.⁴⁸ Three studies included a comparison group that received no intravenous therapy control,⁴⁹⁻⁵¹ and 1 study supplemented all patients with FO.⁵²

Mortality. Only a few of the included RCTs that incorporated mortality as an outcome measure reliably reported a significant difference with FO vs other IVLEs. One prospective observational study indicated increased survival with doses of FO >0.1 and ≤ 0.2 g/kg/d as compared with doses of FO <0.1 and >0.2 g/kg/d.⁵² One retrospective observational study cited a reduced rate of mortality when FO was administered preoperatively or postoperatively as compared with MCT/LCT.⁴⁶ In contrast, 15 studies reported no significant difference in the mortality of patients receiving FOC-IVLEs vs other IVLEs or placebo.[†] It is

important to note that underlying rates of mortality were low in most studies; therefore, it is likely that the included studies had insufficient power to identify an effect of FO on mortality.

Length of hospitalization. Twenty-two studies reported results for length of hospitalization; of these, 17 indicated no significant differences between FOC-IVLE and other lipid emulsions, placebo, or other control. Three studies cited a shorter length of hospitalization with FO than with SO.^{20,29,42} One study reported a reduced length of hospitalization with FO than with MCT/LCT, which was significant after adjusting for age, glucose supply, and Simplified Acute Physiology Score II.³⁹ Finally, 1 study cited a significantly reduced length of hospitalization with FO >0.05 g/kg/d ($P < .001$).⁵² In contrast, 16 studies found no significant difference in hospitalization with FO than with OO,^{31,38} placebo,^{35,50} MCT/LCT,^{32,40,45} SO,^{19,24-26,28,30,44} or other control.^{41,51} One study reported no significant difference among treatment groups (FO, SO, OO, MCT, and lipid-free) but did not directly report individual significance values between FO and the other treatment groups.⁴⁸

Length of stay in ICU and other ICU-related or general outcomes. A total of 14 studies reported no significant differences in length of stay in the ICU, duration of mechanical ventilation, or days of parenteral support between FOC-IVLEs and OO, SO, MCT/LCT,[‡] EN/PN,^{35,36,47} or placebo.⁵¹ In contrast, 1 observational study cited a significantly faster discharge rate from ICU for patients who received FO when compared with those who received

[†]References 22, 24, 25, 28-33, 38-40, 44, 50, 51.

[‡]References 19, 23, 25, 31, 32, 38-40, 45, 50.

	Level of Evidence ⁵⁷	Minimization of Bias ⁵¹				Statistical Methods	
		Random Sequence Generation	Allocation and Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessments	Reported Endpoint Basis for Sample Size Calculation	Test for Multiplicity
Badia-Tahull et al (2010)	II	Green	Yellow	Green	Yellow	Green	Yellow
Barbosa et al (2010)	II	Yellow	Red	Red	Red	Yellow	Yellow
Berger et al (2008)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Green
Berger et al (2013)	II	Green	Green	Green	Green	Yellow	Yellow
Burkhart et al (2014)	II	Green	Green	Green	Green	Green	Yellow
de Miranda Torrinhas et al (2013)	II	Green	Green	Green	Green	Green	Yellow
Edmunds (2014)	III-1	Gray	Gray	Gray	Gray	Gray	Gray
Friesecke et al (2008)	II	Green	Green	Green	Green	Green	Green
Grau-Carmona et al (2015)	II	Green	Green	Green	Green	Yellow	Yellow
Grimm et al (2006)	II	Yellow	Yellow	Green	Yellow	Yellow	Green
Gultekin et al (2014)	II	Yellow	Yellow	Green	Yellow	Yellow	Yellow
Gupta et al (2011)	II	Green	Green	Yellow	Yellow	Yellow	Yellow
Hall et al (2015)	II	Green	Yellow	Red	Red	Yellow	Yellow
Han et al (2012)	II	Green	Green	Yellow	Yellow	Green	Yellow
Heidt et al (2009)	II	Yellow	Yellow	Yellow	Yellow	Green	Yellow
Heller et al (2006)	III-2	Gray	Gray	Gray	Gray	Gray	Gray
Jiang et al (2010)	II	Green	Yellow	Red	Red	Green	Yellow
Khor et al (2011)	II	Green	Green	Green	Yellow	Yellow	Yellow
Klek et al (2013)	II	Red	Yellow	Green	Yellow	Yellow	Yellow
Kolesnikov et al (2015)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Liang et al (2008)	II	Green	Green	Green	Green	Yellow	Yellow
Lomivorotov et al (2014)	II	Green	Green	Green	Green	Green	Green
Long (2013)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Ma et al (2012)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Mertes et al (2006)	II	Green	Yellow	Green	Yellow	Green	Green
Metry et al (2014)	II	Green	Green	Green	Yellow	Yellow	Yellow
Sungurtekin (2011)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Tsekos et al (2004)	III-3	Gray	Gray	Gray	Gray	Gray	Gray
Wang et al (2008)	II	Green	Green	Green	Yellow	Yellow	Yellow
Wang et al (2009)	II	Yellow	Yellow	Green	Yellow	Yellow	Yellow
Wei et al (2014)	II	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Wohlmuth et al (2010)	III-3	Gray	Gray	Gray	Gray	Gray	Gray
Wu et al (2014)	II	Green	Yellow	Yellow	Yellow	Yellow	Yellow
Zhu et al (2012)	II	Green	Yellow	Green	Green	Yellow	Yellow

Figure 2. Assessment of quality of included studies. Red, high risk; yellow, unknown risk / not reported; green, low risk; gray, not available.

Table 2. Potential Effects of FO-Containing IVLEs in Clinical Studies.

Effect of FO	Studies Reporting a Significant Effect	Studies Measuring Outcome
Inflammatory and Immune Markers		
↑ CD4/CD8	2 studies Omegaven ²⁹	3 studies Omegaven ^{27,29}
↓ IL-1	SO/FO formulation ²³ 2 studies Omegaven ^{27,33}	Custom SO/FO formulation ²³ 4 studies Omegaven ^{27,33,34} SMOFLipid ²⁴
↓ IL-10	1 study Omegaven ¹⁹	5 studies ^a Omegaven ^{19,30,34,36} SMOFLipid ²⁸
↓ IL-6	6 studies Omegaven ^{19,27,29,33,36} SMOFLipid ²⁵	16 studies Omegaven ^{19,20,22,26,27,29,31-34,36,37} SMOFLipid ^{21,24,25,28}
↓ IL-8	1 study Omegaven ³³	1 study Omegaven ³³
↓ TNF- α	3 studies Omegaven ^{27,29,33}	8 studies Omegaven ^{20,22,27,29,31,33-35}
↑ HLA-DR	1 study Omegaven ³⁰	2 studies Omegaven ^{19,30}
Clinical Outcomes		
↓ Days of mechanical ventilation	None	7 studies Omegaven ^{32,36,47} SMOFLipid ^{25,50} ^b Lipoplus ^{39,40}
↓ Days of PN	None	2 studies Omegaven ^{31,38}
↓ Infection	2 studies Omegaven ³⁸ Lipoplus ⁴⁰	12 studies Omegaven ^{19,20,22,29,30,32,33,38} SMOFLipid ^{21,24,28} ^b Lipoplus ⁴⁰
↓ Length of hospitalization	6 studies Omegaven ^{20,29,52} SMOFLipid ^{42,44} Lipoplus ³⁹	22 studies ^c Omegaven ^{19,20,26,29-32,35,38,41,45,50-52} ^d SMOFLipid ^{24,25,28,42,44} ^b Lipoplus ^{39,40} ^e Various ⁴⁸
↓ Length of stay in ICU	1 study Omegaven ⁵²	12 studies ^c Omegaven ^{19,32,35,36,47,51,52} SMOFLipid ²⁵ ^b Lipoplus ^{39,40,45} ^e Various ⁴⁸
↓ Medical costs	None	2 studies Omegaven ^{20,29}
↓ Mortality	3 studies Omegaven ^{46,52} Various ⁴⁸	18 studies ^{c,e} Omegaven ^{22,29-33,38,46,50-52} SMOFLipid ^{24,25,28,44} ^{b,d} Lipoplus ^{39,40} ^f Various ⁴⁸
↓ Mortality in septic patients	None	3 studies Omegaven ^{31,37} Lipoplus ³⁹
↓ Postsurgical outcomes in cardiac patients	2 studies Omegaven ^{43,49}	4 studies Omegaven ^{36,43,47,49}
↓ SIRS	2 studies Omegaven ^{20,29}	2 studies Omegaven ^{20,29}

CD, cluster of differentiation; FO, fish oil; HLA-DR, human leukocyte antigen-antigen D related; ICU, intensive care unit; IL, interleukin; IVLE, intravenous lipid emulsion; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; SO, soybean oil; TNF- α , tumor necrosis factor alpha.

^aWang et al³⁰ reported a significantly higher level of IL-10.

^bGrau-Carmona et al⁴⁰ allowed participants to receive up to 50% of lipids from enteral nutrition.

^cTsekos et al⁴⁶ conducted an observational study.

^dMertes et al⁴⁴ did not report statistical comparisons.

^eHeller et al⁵² did not include a control group that did not receive FO. Comparisons were made among doses of FO, and this was an observational study.

^fOnly 4.2% of participants in the Edmunds et al⁴⁸ study received FO, and this was an observational study.

lipid-free PN. However, only 4.2% (19 of 451) of patients in this study actually received FO.⁴⁸ One dose-response study observed that doses of FO >0.05 g/kg/d were associated with a reduced duration of stay in ICU.⁵² In addition, 2 studies investigated the effect of FO on total medical costs but reported no significant difference in cost between FO-containing PN and SO-based PN.^{20,29}

Cardiac surgery outcomes. Four studies investigated clinical outcomes in patients who were given infusions of FO before cardiac surgery to prevent postoperative complications.^{36,43,47,49} Two of these studies reported no significant differences between treatment arms in general postsurgical clinical outcomes.^{36,47} Two studies cited a beneficial effect of FO on postoperative atrial fibrillation,^{43,49} but 1 study reported no significant improvement.⁴⁷ Of the 2 studies that cited a beneficial effect on atrial fibrillation, 1 did not incorporate a control group treated with an alternative IVLE.⁴⁹

Quality of studies. The quality and strength of evidence for most of the included studies were low, and it is generally not possible to determine whether studies were adequately powered. Most studies had small sample sizes and were likely to be underpowered for an assessment of general clinical outcomes (Table 1). In addition, only 3 of 29 included studies reported a sample size calculation based on 1 of the clinical outcomes investigated.

Most studies did not publish the full study protocol or methodologies in sufficient detail to allow for an appropriate quality assessment. Multiple endpoints were cited in most studies, but only 5 of 29 studies used appropriate tests to assess or correct for possible effects of multiplicity on significant outcomes.^{32,42,44,45,47} When the quality of RCTs was assessed with the Cochrane Collaboration assessment tool,¹⁸ 21 of 27 included RCTs were classified as having an unknown or high risk of bias (Figure 2).[§]

Conclusion. The majority of current published evidence suggests no significant differences in general clinical outcomes, such as length of hospitalization and length of stay in ICU, duration of mechanical ventilation, or mortality, after administration of PN with FO as compared with other IVLEs. Notwithstanding, there is a small amount of low-quality evidence to suggest that FO may have a beneficial effect on postoperative atrial fibrillation (Table 2). Overall, given the poor quality of reporting in the included studies, it is not possible to determine whether the observed lack of differences between FO and other IVLEs is conclusive.

Discussion and Conclusions

The findings from this qualitative narrative review do not demonstrate that FO or FOC-IVLE significantly improves

any of the clinical outcomes assessed. There is very little high-quality published evidence that FOC-IVLE has a beneficial effect on clinical outcomes. Although there was some evidence of a positive effect for FO on inflammatory and immune markers, these findings did not translate to improved clinical outcomes. The majority of studies reported little difference in mortality, length of hospitalization, ICU-based clinical outcomes, postoperative complications, or rates of infection and sepsis with FOC-IVLEs as compared with other IVLEs. Most findings were weak and inconclusive, and the published evidence from these studies was poorly reported. These serious quality deficiencies limit the interpretation of the research data and assessment of the applicability of the findings to clinical practice.

A major impression from this review of all adult RCTs was the overall inferior quality of reporting of clinical studies in the field. The absence of published details on study protocols, methodology, and statistical methods means that it was not possible to accurately assess study quality. However, it is likely that most included studies were underpowered and used inappropriate statistical methods. We submit that this variable quality on the collection and interpretation of individual clinical data is a major contributor to the conflicting reports from meta-analyses designed to investigate the benefits of FO.^{8-10,14-17} It is also important to note that analysis of all adult RCTs according to the type of FOC-IVLE used did not demonstrate any further benefits of FO. All FOC-IVLEs appear to be safe and efficacious energy providers, but evidence for a beneficial effect of FO on infection and other clinical outcomes remains limited and inconclusive. Thus, based on the current published evidence, it is not possible to recommend ≥ 1 of the available FOC-IVLEs for any specific group of patients.

Recently published joint guidelines from the Society for Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition provide no recommendations regarding the use of 1 IVLE over another.⁵⁴ Although the guidelines suggest that FOC-IVLE may be a suitable choice, they concede that the data are derived primarily from observational studies.⁵⁴ Notably, a systematic review and meta-analysis conducted by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition⁵⁵ concluded that in the neonate and pediatric populations, no recommendation regarding the choice of IVLE could be made, owing to the inadequate evidence. Thus, it appears that the key medical societies are challenged to provide recommendations on the use of FOC-IVLE based on the current levels of evidence.

The strengths of our qualitative review are that we approached the literature search and data collection in a systematic manner and that the evidence gleaned from studies was assessed for its quality per the Cochrane Collaboration

[§]References 20-22, 24, 25, 28-31, 33-35, 38, 39, 42, 44, 45, 49-52.

assessment criteria.¹⁷ Limitations of this review are that most studies did not publish the full study protocol or methodologies in sufficient detail to allow for an appropriate quality assessment and did not use appropriate tests to assess or correct for possible effects of multiplicity on significant outcomes. Additionally, only English-language articles were included.

Based on this review, it is clear that high-quality and adequately powered RCTs are necessary to determine the true effect of PN with FOC-IVLEs and to investigate whether FOC-IVLEs can result in measurable clinical benefits as compared with other IVLEs.

Statement of Authorship

All authors equally contributed to the conception and design of the research; equally contributed to the design of the research; equally contributed to the acquisition and analysis of the data; equally contributed to the analysis of the data; contributed to the acquisition, analysis, and interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

References

- Carpentier YA, Dupont IE. Advances in intravenous lipid emulsions. *World J Surg.* 2000;24(12):1493-1497.
- Calder PC. Rationale and use of n-3 fatty acids in artificial nutrition. *Proc Nutr Soc.* 2010;69(4):565-573.
- Adolph M. Lipid emulsions in parenteral nutrition. *Ann Nutr Metab.* 1999;43(1):1-13.
- Calder PC. Use of fish oil in parenteral nutrition: rationale and reality. *Proc Nutr Soc.* 2006;65(3):264-277.
- Vanek VW, Seidner DL, Allen P, et al. Novel Nutrient Task Force; Intravenous Fat Emulsions Workgroup; American Society for Parenteral and Enteral Nutrition Board of Directors. ASPEN position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2012;27(2):150-192.
- Calder PC. Mechanisms of action of (n-3) fatty acids. *J Nutr.* 2012;142(3):592S-599S.
- Calder PC. Immunonutrition in surgical and critically ill patients. *Br J Nutr.* 2007;98(suppl 1):S133-S139.
- Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis [erratum appears in *Crit Care.* 2012;17(1):405]. *Crit Care.* 2012;16(5):R184.
- Manzanares W, Langlois PL, Dhaliwal R, Lemieux M, Heyland DK. Intravenous fish oil lipid emulsions in critically ill patients: an updated systematic review and meta-analysis. *Crit Care.* 2015;19:167.
- Wei C, Hua J, Bin C, Klassen K. Impact of lipid emulsion containing fish oil on outcomes of surgical patients: systematic review of randomized controlled trials from Europe and Asia. *Nutrition.* 2010;26(5):474-481.
- Li NN, Zhou Y, Qin XP, et al. Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomized controlled trials. *Clin Nutr.* 2014;33(2):226-239.
- Higgins JPT, Green S. Chapter 16: special topics in statistics. In: Higgins JPT, Deeks JJ, Altman DG eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 510* [updated March 2011]. Oxford, UK: Cochrane Collaboration; 2011.
- Mascha EJ. Alpha, beta, meta: guidelines for assessing power and type I error in meta-analyses. *Anesth Analg.* 2015;121(6):1430-1433.
- Palmer AJ, Ho CK, Ajibola O, Avenell A. The role of omega-3 fatty acid supplemented parenteral nutrition in critical illness in adults: a systematic review and meta-analysis. *Crit Care Med.* 2013;41(1):307-316.
- Chen W, Jiang H, Zhou ZY, et al. Is omega-3 fatty acids enriched nutrition support safe for critical ill patients? A systematic review and meta-analysis. *Nutrients.* 2014;6(6):2148-2164.
- Tian H, Yao X, Zeng R, et al. Safety and efficacy of a new parenteral lipid emulsion (SMOF) for surgical patients: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev.* 2013;71(12):815-821.
- Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: an updated systematic review and meta-analysis [published online May 27, 2016]. *Clin Nutr.*
- Higgins JPT, Green S. Chapter 8: assessing the risk of bias in included studies. In: Higgins JPT, Deeks JJ, Altman DG eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 510* [updated March 2011]. Oxford, UK: Cochrane Collaboration; 2011.
- de Miranda Torrinhas RS, Santana R, Garcia T, et al. Parenteral fish oil as a pharmacological agent to modulate post-operative immune response: a randomized, double-blind, and controlled clinical trial in patients with gastrointestinal cancer. *Clin Nutr.* 2013;32(4):503-510.
- Jiang ZM, Wilmore DW, Wang XR, et al. Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. *Br J Surg.* 2010;97(6):804-809.
- Klek S, Chambrier C, Singer P, et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid)—a double-blind, randomized, multicentre study in adults. *Clin Nutr.* 2013;32(2):224-231.
- Liang B, Wang S, Ye YJ, et al. Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients. *World J Gastroenterol.* 2008;14(15):2434-2439.
- Long H, Yang H, Lin Y, Situ D, Liu W. Fish oil-supplemented parenteral nutrition in patients following esophageal cancer surgery: effect on inflammation and immune function. *Nutr Cancer.* 2013;65(1):71-75.
- Ma CJ, Sun LC, Chen FM, et al. A double-blind randomized study comparing the efficacy and safety of a composite vs a conventional intravenous fat emulsion in postsurgical gastrointestinal tumor patients. *Nutr Clin Pract.* 2012;27(3):410-415.
- Metry AA, Abdelaal W, Ragaai M, Revaat M, Nakhala G. SMOFlipid versus intralipid in postoperative ISU patients. *J Anesth Crit Care Med.* 2014;1(6):1-8.
- 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(3):236-241.
- Wei Z, Wang W, Chen J, Yang D, Yan R, Cai Q. A prospective, randomized, controlled study of omega-3 fish oil fat emulsion-based parenteral nutrition for patients following surgical resection of gastric tumors. *Nutr J.* 2014;13:25.
- Wu MH, Wang MY, Yang CY, Kuo ML, Lin MT. Randomized clinical trial of new intravenous lipid (SMOFlipid 20%) versus medium-chain triglycerides/long-chain triglycerides in adult patients undergoing gastrointestinal surgery. *JPEN J Parenter Enteral Nutr.* 2014;38(7):800-808.
- Zhu MW, Tang DN, Hou J, et al. Impact of fish oil enriched total parenteral nutrition on elderly patients after colorectal cancer surgery. *Chin Med J (Engl).* 2012;125(2):178-181.
- 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(5):304-309.

31. Gultekin G, Sahin H, Inanc N, Uyanik F, Ok E. Impact of omega-3 and omega-9 fatty acids enriched total parenteral nutrition on blood chemistry and inflammatory markers in septic patients. *Pak J Med Sci.* 2014;30(2):299-304.
32. Friesecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P. Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomized controlled trial. *Intensive Care Med.* 2008;34(8):1411-1420.
33. 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(1):91-98.
34. Sungurtekin H, Degirmenci 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(6):665-671.
35. 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):1-10.
36. Berger MM, Delodder F, Liaudet L, et al. Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. *Am J Clin Nutr.* 2013;97(2):246-254.
37. Burkhart CS, Dell-Kuster S, Siegemund M, et al. Effect of n-3 fatty acids on markers of brain injury and incidence of sepsis-associated delirium in septic patients. *Acta Anaesthesiol Scand.* 2014;58(6):689-700.
38. Badia-Tahull MB, Llop-Talaveron JM, Leiva-Badosa E. A randomized 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(5):737-741.
39. Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC. Effects of a 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(1):R5.
40. Grau-Carmona T, Bonet-Saris A, Garcia-de-Lorenzo A, et al. Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU lipids study. *Crit Care Med.* 2015;43(1):31-39.
41. Wohlmuth C, Dunser MW, Wurzinger B, et al. Early fish oil supplementation and organ failure in patients with septic shock from abdominal infections: a propensity-matched cohort study. *JPEN J Parenter Enteral Nutr.* 2010;34(4):431-437.
42. Grimm H, Mertes N, Goeters C, et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr.* 2006;45(1):55-60.
43. Heidt MC, Vician M, Stracke SK, et al. 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(5):276-280.
44. Mertes N, Grimm H, Furst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFLipid) in surgical patients: a randomized, double-blind, multicenter study. *Ann Nutr Metab.* 2006;50(3):253-259.
45. Berger MM, Tappy L, Revely JP, et al. Fish oil after abdominal aorta aneurysm surgery. *Eur J Clin Nutr.* 2008;62(9):1116-1122.
46. Tsekos E, Reuter C, Stehle P, Boeden G. Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. *Clin Nutr.* 2004;23(3):325-330.
47. Lomivorotov VV, Efremov SM, Pokushalov EA, et al. Randomized trial of fish oil infusion to prevent atrial fibrillation after cardiac surgery: data from an implantable continuous cardiac monitor. *J Cardiothorac Vasc Anesth.* 2014;28(5):1278-1284.
48. Edmunds CE, Brody RA, Parrott JS, Stankorb SM, Heyland DK. The effects of different IV fat emulsions on clinical outcomes in critically ill patients. *Crit Care Med.* 2014;42(5):1168-1177.
49. Kolesnikov V, Boeva O, Yagoda A, Ivaneko A, Danilova E, Danilov S. Prevention of new-onset atrial fibrillation after direct myocardial revascularization surgery: randomized comparative study. *Med News North Caucasus.* 2015;10(2):120-127.
50. Gupta A, Govil D, Bhatnagar S, et al. Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. *Indian J Crit Care Med.* 2011;15(2):108-113.
51. Hall TC, Bilku DK, Al-Leswas D, et al. A randomized controlled trial investigating the effects of parenteral fish oil on survival outcomes in critically ill patients with sepsis: a pilot study. *JPEN J Parenter Enteral Nutr.* 2015;39(3):301-312.
52. Heller AR, Rossler S, Litz RJ, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med.* 2006;34(4):972-979.
53. Liddle J, Williamson M, Irwig L. *Method for Evaluating Research and Guideline Evidence.* North Sydney, Australia: New South Wales Department of Health; 1996.
54. Taylor B, McClave SA, Martingdale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *Crit Care Med.* 2016;44(2):390-438.
55. Hojsak I, Colomb V, Braegger C, et al. ESPGHAN Committee on Nutrition position paper. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: a systematic review and meta-analysis. *J Ped Gastroenterol Nutr.* 2016;62(5):776-792.