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Lipid Use in Hospitalized Adults Requiring Parenteral Nutrition

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Abstract

In hospitalized patients, lipid emulsions are an integral part of balanced parenteral nutrition. Traditionally, a single lipid source, soybean oil, has been given to patients and was usually regarded as just a source of energy and to prevent essential fatty-acid deficiency. However, mixtures of different lipid emulsions have now become widely available, including mixtures of soybean oil, medium-chain triglycerides, olive oil, and fish oil. Fish oil is high in the ω-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). There is a growing body of evidence that these ω-3 fatty acids can exert beneficial immunomodulatory, anti-inflammatory, and inflammation-resolution effects across a wide range of patient groups including surgical, cancer, and critically ill patients. At least in part, these effects are realized via potent specialized pro-resolution mediators (SPMs). Moreover, parenteral nutrition including ω-3 fatty acids can result in additional clinical benefits over the use of standard lipid emulsions, such as reductions in infection rates and length of hospital and intensive care unit stay. Clinical and experimental evidence is reviewed regarding lipid emulsion use in a variety of hospitalized patient groups, including surgical, critically ill, sepsis, trauma, and acute pancreatitis patients. Practical aspects of lipid emulsion use in critically ill patients are also considered, such as how to determine and fulfill energy expenditure, how and when to consider parenteral nutrition, duration of infusion, and safety monitoring. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S28–S38)

Keywords

fish oil; infections; inflammation; intensive care unit; lipids; meta-analyses; omega-3; parenteral nutrition; specialized pro-resolving mediator; surgery

Introduction

This manuscript is based upon presentations given at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al[1] that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the use of lipid emulsions in parenteral nutrition and, as such, complement formal nutrition society guidelines on this subject.

Lipid emulsions are a principle part of parenteral nutrition,[2,3] minimizing dependence on glucose as a major source of non-protein energy and preventing essential fatty acid deficiency (EFAD).[3] Lipid oil sources can also be characterized by their relative range of inflammatory effects: soybean oil, which contains a high concentration of linoleic acid, is more inflammatory than either medium-chain triglycerides (MCTs) or olive oil, while fish oil is even less inflammatory and possibly even anti-inflammatory.[4,5] Access to lipid emulsions is variable: ranging from a full spectrum of lipid emulsions available in parts of Europe, to the situation in the United States where pure soybean oil lipid emulsions were the only lipid emulsions available until August 2016.[4,6] The wide range of lipid emulsions obtainable is reviewed elsewhere.[4,6,7] Now that alternatives are available, the transition away from pure soybean oil emulsions is occurring rapidly.[7] However, in some locations a relatively slow transition away from pure soybean oil lipid emulsions is occurring for complex reasons that may reflect differences in healthcare systems. This was discussed by 1 of the authors in his presentation at this meeting, when he detailed the complex process of trying to add SMOFlipid (Fresenius Kabi, Bad Homberg, Germany), a multi-component intravenous lipid emulsion containing 30% soybean oil, 30% MCTs, 25% olive oil, and 15% fish oil (henceforth referred to as SMOF) to the hospital formulary at the Ohio State University in the United States.[8] However, this situation may not be uniform across US healthcare, as other universities' medical centers have accepted SMOF rapidly.

In this article, we discuss the use of lipid emulsions as part of parenteral nutrition in adult hospitalized patients, with a particular emphasis on comparisons between lipid emulsions containing ω-3 fatty acids and other standard lipid emulsions without fish oil, to reflect recent clinical research in this field. While all commercially available lipid emulsions suffice as an energy supply and contain enough essential fatty acids to prevent EFAD, those containing only soybean oil as a lipid source have a high ω-6:ω-3 fatty-acid ratio and abundance of phytosterols, raising concerns about their inflammatory and hepatotoxic potential in some patients.[6] Conversely, there is a growing body of evidence that ω-3 fatty acids can exert beneficial immunomodulatory, anti-inflammatory, and resolution of inflammation effects across a wide range of patient groups including surgical, cancer, and critically ill patients.[9-11] In addition, lipid emulsions based on fish oil contain high levels of the antioxidant vitamin E,[7] which may help to reduce oxidative stress during inflammatory conditions. These potential advantages can translate into clinical benefits such as reductions in infection rates and length of hospital and intensive care unit (ICU) stay, as will be discussed in the following sections.

Surgical Patients

Several changes within the field of parenteral nutrition have emerged that can potentially stimulate changes in clinical practice for surgical patients. These include a closer attention to glycemic control and a broader availability of lipid emulsions in recent years, particularly mixes of lipids containing soybean oil, olive oil, MCT, and fish oil. In addition, we realize that fish oil has anti-inflammatory and immunomodulatory effects, and it contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), now known to be direct precursors of endogenously produced specialized pro-resolution mediators (ie, resolvins, protectins, and maresins) that improve outcomes in many animal disease models.[11,12] Moreover, the resolvins and protectins can promote better macrophage and neutrophil killing without increasing the inflammatory response,[13] which may be of particular benefit in some groups such as those with hyperdynamic septic shock. This has been illustrated by the use of intravenous fish oil to blunt the physiological stress response in healthy volunteers to intravenous endotoxin, which induces a transient inflammatory condition mimicking aspects of sepsis.[14] Fish oil significantly reduced fever, adrenocorticotropic hormone (ACTH), and cortisol plasma levels, but without affecting the inflammatory response (eg, tumor necrosis factor-$\boldsymbol{\alpha}$ [TNF-$\boldsymbol{\alpha}$], interleukin-6 [IL-6], and C-reactive protein [CRP] levels).[14]

Overall, major guidelines are broadly supportive concerning the use of alternatives to pure soybean oil lipid

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Table 1. Consensus Statements From the International Summit *Lipids in Parenteral Nutrition* on November 2–4, 2018 (Miami, FL, USA), Relevant to This Article.[1]

Statement Number	Consensus Statement	Expert Voting Results
	Critically ill patients	
5	In stable, critically ill, adult patients requiring PN, ILEs are an integral part of PN.	100% agreement (17 agree, 0 do not agree, 0 do not wish to answer)
6	In our view, there is sufficient scientific evidence to justify the indication of fish-oil containing ILEs as part of PN in critically ill, adult surgical patients requiring PN.	100% agreement (17 agree, 0 do not agree, 0 do not wish to answer)
7	In our view, there is sufficient scientific evidence to justify the indication of fish-oil containing ILEs as part of PN in non-surgical, critically ill (sepsis), adult patients requiring PN.	94% agreement (17 agree, 1 does not agree, 0 do not wish to answer)
8	In stable, critically ill, adult patients, the total lipid dose should not exceed 1.5 g lipids/kg/d of ILEs (including non-nutritive lipid sources). A minimum dose of ILE should be given to at least prevent EFA deficiency.	89% agreement (16 agree, 1 does not agree, 1 does not wish to answer)
9	Based on currently available clinical data, we recommend 0.1–0.2 g fish oil/kg/d, provided by lipid emulsions containing fish oil, for stable, critically ill, adult patients requiring PN.	100% agreement (18 agree, 0 do not agree, 0 do not wish to answer)
10	The concentrations of triglycerides (TGs) in serum should be within local or regional guidelines, and should, in general, not exceed 400 mg/dL (4.5 mmol/L) during infusion. If the level is high, ensure the blood sample was drawn from an appropriate location. We recommend assessing serum TG at the baseline in all patients.	100% agreement (17 agree, 0 do not agree, 0 do not wish to answer)
11	If you are using all-in-one admixtures, the preferable infusion duration is 24 h.	82% agreement (14 agree, 0 do not agree, 3 do not wish to answer)
12	In high-risk, critically ill, adult patients (eg, sepsis, ARDS, PICS), we recommend using fish-oil containing ILEs as part of the PN.	82% agreement (15 agree, 0 do not agree, 2 do not wish to answer)
13	In high-risk, critically ill, adult patients (eg, sepsis, ARDS, and PICS), we recommend including fish-oil containing ILEs as part of PN in the first week of PN.	94% agreement (16 agree, 0 do not agree, 1 does not wish to answer)
	Adult surgical patients	
14	In adult surgical patients requiring PN, ILEs are an integral part of PN.	100% agreement (13 agree, 0 do not agree, 0 do not wish to answer)
15	There is sufficient scientific evidence from clinical trials, systematic reviews, and meta-analyses to demonstrate that fish-oil containing ILEs have advantages over standard ILEs (without fish oil) when used in adult surgical patients requiring PN.	100% agreement (13 agree, 0 do not agree, 0 do not wish to answer)
16	When PN in adult surgical patients is required, consider including fish-oil containing ILEs, where possible.	94% agreement (15 agree, 0 do not agree, 1 does not wish to answer)
17	In adult surgical patients, the intravenous lipid dose should not exceed 1.5 g/kg/d (including non-nutritional lipid sources). A minimum dose of ILEs should be given to at least prevent EFA deficiency.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer)
18	Based on currently available clinical data, we recommend 0.1–0.2 g fish oil/kg/d, provided by lipid emulsions containing fish oil, for adult surgical patients requiring PN.	93% agreement (14 agree, 0 do not agree, 1 does not wish to answer)
19	Based on currently available clinical data, there is no need to withhold or limit (for safety concerns) the use of fish-oil containing ILEs for PN during the first week of PN.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer)
20	Based on clinical studies, systematic reviews, and meta-analyses, there is no evidence that fish-oil containing lipids increase the risk of coagulopathy or bleeding abnormalities.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer)

(*continued*)

Table 1. (continued)

Statement Number	Consensus Statement	Expert Voting Results
21	Serum TG levels should be within the ranges recommended by local or regional guidelines; in general, they should not exceed 400 mg/dL (4.5 mmol/L) during infusion. If the level is high on initial testing, ensure that the blood sample was drawn from an appropriate location. We recommend serum TG levels be measured at the baseline in all patients being considered for PN.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer)
22	We recommend considering early initiation of PN in low-risk surgical patients if it is anticipated that the patient will be unable to attain 50–60% of goal energy and proteins within the first 5 days.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer)
23	We recommend considering early initiation of PN in malnourished/high nutrition risk surgical patients if enteral or oral nutrition is contraindicated or insufficient.	100% agreement (15 agree, 0 do not agree, 0 do not wish to answer)
24	In surgical patients, the main indication for PN is intestinal failure. *Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.*	100% agreement (15 agree, 0 do not agree, 0 do not wish to answer)
25	Although enteral nutrition is considered as the first line of treatment in severe pancreatitis, if the patient requires PN, ILEs are an integral part of this PN.	100% agreement (15 agree, 0 do not agree, 0 do not wish to answer)

ARDS, acute respiratory distress syndrome; EFA, essential fatty acid; FA, fatty acid; ILE, intravenous lipid emulsion; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; PN, parenteral nutrition; TG, triglyceride.

emulsions in surgical patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for clinical nutrition in surgery stated that postoperative parenteral nutrition including ω-3 fatty acids should be considered in patients that require parenteral nutrition if they cannot be fed adequately via the enteral route.[15] Furthermore, an ESPEN expert group stated that parenteral nutrition including fish oil appears to be well tolerated and confers additional clinical benefits, particularly in surgical ICU patients, owing to its anti-inflammatory and immune-modulating effects.[9] Guidelines for nutrition support therapy from Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) for adult critically ill patients also extend to a target patient population including surgical patients (eg, trauma, traumatic brain injury, open abdomen, burns, sepsis, and postoperative major surgery), and thus are relevant to this discussion.[16] This guideline was produced before SMOF was approved in the United States, so although it states that alternatives to soybean-oil intravenous lipid emulsions may provide outcome benefits, the authors could not make a recommendation owing to a lack of availability of alternative lipid emulsions. However, the guideline specified that when alternatives (SMOF, MCTs, olive oil, and fish oil) become available in the United States, based on expert opinion, their use should be considered in the critically ill patient who is an appropriate candidate for parenteral nutrition.[16]

In this section the clinical data from systematic reviews and meta-analyses will be considered regarding the use of parenteral nutrition enriched with ω-3 fatty acids in a range of hospitalized patients, including surgical patients. Since 2010, at least 11 meta-analyses have been published concerning parenteral nutrition with and without ω-3 fatty acids (Table 2).[17-27] These meta-analyses have covered surgical patients,[18,19,21,23,25] a mixture of ICU and non-ICU (surgical) patients,[20,26,27] and ICU and/or critically ill patients.[17,22,24] Overall, 9 out of 11 meta-analyses found at least 1 significant clinical benefit in those given ω-3 fatty acids,[18-20,22-27] but none favored standard parenteral nutrition for any clinical outcome.

The meta-analyses show the following clinical benefits for parenteral nutrition with ω-3 fatty acids rather than standard lipid emulsions:

- infectious complications were significantly reduced in non-ICU/surgical patients,[18-20,23,25,26] ICU patients,[24,26] and a mixed population of ICU and non-ICU (surgical) patients[20,27]
- significantly shorter hospital length of stay[19,20,22-27]
- significantly shorter ICU length of stay.[18-20,27]

It is notable that the 2 meta-analyses showing no significant differences included the fewest trials (6 in each case) and very few (<400) patients.[17,21]

Results from the largest and most comprehensive meta-analysis published to date, including 49 randomized controlled trials (RCTs) and 3641 patients,[27] showed that the use of ω-3 fatty acids was associated with 40% fewer

Table 2. Meta-Analyses Comparing Clinical Outcomes for PN Enriched With Ω-3 Fatty Acids vs Standard PN (ie, Containing Only MCT/LCT Emulsions, Olive/Soybean Oil Emulsion or Soybean Oil Emulsions).

Authors	Patient Types(s), Number Of Trials (N) and Patients (n)	Significant Differences Detected in Favor of Parenteral Nutrition Enriched With ω-3 Fatty Acids[a]
Wei et al, 2010	Surgery (postoperative) N = 6 n = 611	Significantly fewer infections: RR 0.49; 95% CI, 0.26–0.93; *P* = .03. Significant reduction in ICU LOS: −2.07 mean days' difference; 95% CI −3.47 to −0.67; *P* = .004.
Chen et al, 2010	Major abdominal surgery N = 13 RCTs n = 892	Significantly fewer infections: OR 0.56; 95% CI, 0.32–0.98; *P* = .04. Significant reduction in hospital LOS: WMD −2.98 days; 95% CI, −4.65 to −1.31 days; *P* < .001. Significant reduction in ICU LOS: WMD −1.80 days; 95% CI, −3.04 to −0.56 days; *P* = .004.
Pradelli et al, 2012	ICU and non-ICU (surgical) patients N = 23 RCTs n = 1502	Significantly fewer infections: RR 0.61; 95% CI, 0.45–0.84; *P* = .002. (Note: results were also significant for non-ICU but not ICU subpopulation.) Significant reduction in hospital LOS: −3.29 mean days' difference; 95% CI, −5.13 to −1.45; *P* = .0005. (Note: results were also significant for both ICU and non-ICU subpopulations.) Significant reduction in ICU LOS: −1.92 mean days' difference; 95% CI, −3.27 to −0.58; *P* = .005.
Tian et al, 2013	Surgery (postoperative) N = 6 RCTs n = 306	No significant differences detected in hospital LOS in the 2 studies reporting this parameter.
Palmer et al, 2013	ICU N = 9 studies n = 431	Significant reduction in hospital LOS: −9.49 days' difference; 95% CI, −16.51 to −2.47; *P* = .008.
Manzanares et al, 2014	ICU N = 6 RCTs n = 390	No significant differences found in mortality rates, infections, ICU LOS, or duration of mechanical ventilation.
Li et al, 2014	Surgery (postoperative) N = 21 RCTs n = 1487	Significantly fewer infections: OR 0.53; 95% CI, 0.35–0.81; *P* = .003. Significant reduction in hospital LOS: −2.14 mean days' difference; 95% CI, −3.02 to −1.27; *P* < .00001.
Manzanares et al, 2015	ICU N = 10 RCTs n = 733	Significantly fewer infections: RR 0.64; 95% CI, 0.44–0.92; *P* = .02. Significant reduction in hospital LOS for in 4 higher-quality trials: WMD −7.42 days; 95% CI, −11.89 to −2.94; *P* = .001.
Bae et al, 2017	Surgery N = 19 RCTs n = 1167	Significantly fewer infections: OR 0.44; 95% CI 0.30–0.65; *P* < .0001 Significant reduction in hospital LOS: WMD −1.81 days; 95% CI −2.89 to −0.74 days; *P* = .0009
Kreymann et al, 2018	RCTs in critically ill (N = 3 for infection rates; N = 3 for ICU LOS), surgical patients (N = 1 for infection rates), surgical patients with cancer (N = 14 for infection rates; N = 13 for hospital LOS) Patient numbers not reported.	Even though very few trials were included in each category, there were significant benefits for PN enriched with ω-3 fatty acids vs standard PN for: - critically ill patients (fewer infections) - surgical patients (fewer infections) - surgical patients with cancer (fewer infections and reduced hospital LOS)
Pradelli et al, 2019	ICU and non-ICU (surgical) patients N = 49 RCTs n = 3641	Significantly fewer infections: RR 0.60; 95% CI, 0.49–0.72; *P* < .00001. Significant reduction in hospital LOS: −2.14 mean days' difference; 95% CI, −1.36 to −2.93; *P* < .00001. Significant reduction in ICU LOS: −1.95 mean days' difference; 95% CI −0.42 to −3.49; *P* = .01. Significant reduction in sepsis: RR 0.44; 95% CI, 0.28–0.70; *P* = .0004.

CI, confidence interval; ICU, intensive care unit; LOS, length of stay; MCT/LCT, medium-chain triglycerides/long-chain triglycerides; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; RR, relative risk; WMD, weighted mean difference.
[a]Results showed significant differences in favor of ω-3 fatty acids in 8 out of 11 studies. No significant differences were detected in favor of standard PN in any meta-analyses.

infections (relative risk [RR] 0.60; 95% confidence interval [CI], 0.49–0.72; $P < .00001$), ≈2 days shorter hospital stay (2.14 days; 95% CI, 1.36–2.93; $P < .00001$), and ≈2 days shorter ICU stay (1.95 days; 95% CI, 0.42–3.49; $P = .01$), and sepsis was reduced by 56% (RR 0.44; 95% CI, 0.28–0.70; $P = .0004$). In addition, this meta-analysis also showed a potential hepatoprotective effect by ω-3 fatty acids, with significant benefits in marker liver enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transferase [GGT] levels), as well as higher levels of the antioxidant α-tocopherol, and lower levels for markers of inflammation such as TNF-α.[27]

Previous to the 2019 meta-analysis, a 2012 meta-analysis by the same group had similar clinical outcome results,[20] and these have been used in pharmacoeconomic analyses showing that the use of ω-3 fatty acids can also be cost-effective (ie, they improve patient outcomes while saving money, with the acquisition cost of ω-3 fatty acids being completely offset by reductions in hospital-stay costs and antibiotic costs).[28-30] Thus, parenteral nutrition regimens including ω-3 fatty acids were cost-effective vs standard parenteral nutrition for Italian, French, German, and UK hospitals for ICU and non-ICU patients,[28] and for Chinese ICU patients.[29,30]

Taken together, there appears to be sufficient clinical and laboratory data available to conclude that lipid emulsions containing ω-3 fatty acids are a valuable parenteral nutrition component for surgical patients, including surgical ICU patients. Some of these advantages are covered in the ESPEN expert group publication.[9] Additional points made in this publication are that doses of fish oil between 0.1 and 0.2 g/kg/d are needed to show clinical benefits such as decreased length of hospital/ICU stay and lower antibiotic requirements. Moreover, concerns that ω-3 fatty acids might cause an increased incidence of bleeding events have not been substantiated when evaluating the incidence of coagulation abnormalities.[20,27]

In summary, lipid emulsions containing ω-3 fatty acids offer a number of advantages in surgical patients. These include increased safety and tolerability, less inflammation, and a more hepatoprotective effect vs soybean oil emulsions.[4,10,31] Moreover, lipid emulsions containing ω-3 fatty acids can decrease the risk of cholestasis, as well as improve a number of clinical outcomes discussed previously (eg, decreased infections and decreased length of hospital/ICU stay).[4] In practice, the use of lipid emulsions containing ω-3 fatty acids could eliminate the practice of withholding intravenous (soybean oil) lipid emulsions for some groups such as hyperdynamic patients (surgical and mixed ICU patients) and in stable patients with sepsis, and could decrease the incidence of hypertriglyceridemia and the resultant need to discontinue or decrease the supply of intravenous lipid emulsions.

Critically Ill Patients

As mentioned briefly in the previous section, SCCM/ASPEN guidelines acknowledge the potential risk of using pure soybean oil emulsions in critically ill patients by recommending withholding or limiting their use during the first week after starting parenteral nutrition.[16] Furthermore, a consensus statement regarding critically ill patients at the current summit, with experts from around the globe, stated that based on currently available clinical data, there is no need to withhold or limit (for safety concerns) the use of fish-oil containing lipid emulsions during the first week of parenteral nutrition (Table 1). Moreover, other consensus statements agreed that in high-risk, critically ill, adult patients (eg, sepsis; acute respiratory distress syndrome [ARDS]; persistent inflammation, immunosuppression, and catabolism syndrome [PICS]), fish-oil containing lipid emulsions should be used as part of parenteral nutrition, particularly during the first week of parenteral nutrition (Table 1).

ESPEN guidelines for parenteral nutrition in ICU patients recommend that the administration of intravenous lipid emulsions should be generally a part of parenteral nutrition and that lipid emulsions enriched with EPA and DHA (fish oil dose 0.1–0.2 g/kg/d) can be provided in patients receiving parenteral nutrition.[2] The authors at the current lipid meeting were also in agreement with this dose range, for stable, critically ill, adult patients requiring parenteral nutrition (Table 1). The ESPEN guidelines[2] report that evidence of ω-3 enriched emulsions in non-surgical ICU patients is not sufficient to mention this as a stand-alone recommendation, referencing the 2018 review by the ESPEN expert group.[9] This review stated that fish-oil enriched parenteral nutrition was well tolerated and confers additional clinical benefits, particularly in surgical patients, but that the evidence in non-surgical ICU patients is less clear.[9] Although this is an excellent review, it may require updating because the meeting was held before the more recent data noted below.

When considering evidence to inform healthcare decisions, some consider meta-analyses to be the most powerful methods, forming the highest level of the evidence-based medicine hierarchy,[32] whereas others believe that large RCTs represent the highest level of evidence. Currently, the evidence is limited because few large RCTs are available for studying the mixed-oil lipid emulsions, so we must rely on meta-analyses to make evidence-based clinical decisions. The previous section summarized meta-analyses assessing the effectiveness of ω-3 fatty acids for parenteral nutrition in a variety of hospitalized patients, including critically ill patients (Table 2). Of these meta-analyses, the largest published up to 2019 included 13 trials (n = 762 patients) covering the ICU population.[20] While there was not a significant decrease in mortality with ω-3 fatty-acid enriched emulsions, they were associated with significant reductions in the infection rate (RR 0.61; 95% CI, 0.45–0.84; P = .002) and the length of stay, both in the ICU (−1.92 days; 95% CI, −0.58 to −3.27; P = .005) and in hospital overall (−3.29 days; 95% CI, −1.45 to −5.13; P = .0005). Moreover, there were beneficial improvements in many laboratory parameters including AST and ALT, suggesting a potential hepatoprotective effect, as well increases in DHA and EPA, and a positive effect on inflammation such as reductions in CRP and IL-6 levels, increases in leukotriene (LTB)5, and better LTB5:LTB4 ratio.[20] Furthermore, based on the aforesaid results,[20] ω-3 fatty-acid enriched parenteral nutrition was shown to be cost-effective vs standard parenteral nutrition as increases in (direct) acquisition cost are offset by savings through reduced length of stay and antibiotic requirements.[28] These savings were €3972–€4897 per ICU patient and €561–€1762 per non-ICU patient.[28]

Some meta-analyses have considered the use of ω-3 fatty acids in the subgroup of critically ill patients with sepsis, 1 including 11 studies (7 parenteral nutrition, 5 enteral nutrition; 808 patients)[33] and the other 17 clinical trials (10 parenteral nutrition, 7 enteral nutrition studies; 1239 patients).[34] They found that ω-3 nutrition supplementation reduced ICU length of stay by ≈4 days[34] and duration of mechanical ventilation by ≈2–4 days,[33,34] but were cautious about generalizing from these results because of small sample size, a relatively high degree of heterogeneity, and low quality of evidence.[33,34]

When considering those RCTs that are available in critically ill patients, Grau-Carmona et al performed a randomized controlled double-blind study involving 159 critically ill medical and surgical patients in 17 Spanish ICUs over a period of 4 years.[35] Patients were randomized to receive either a lipid emulsion containing 50% MCT, 40% soybean oil, and 10% fish oil or 50% MCT/50% soybean oil. Forty percent of energy intake was covered by lipids up to a total of 1.5 g/kg/d, with parenteral nutrition given for at least 5 days, but as long as required. The number of patients with nosocomial infections (primary outcome) was significantly reduced in the fish-oil group compared with the control (no fish oil) group (21% vs 37.2%, respectively; P = .03), and the predicted time free of infection was greater in the fish-oil group (21 ± 2 vs 16 ± 2 days, respectively; P = .03) (Figure 1). While the length of hospital stay was not significantly different between groups, it did approach the point of significance (medians of 25 vs 37 days, respectively, for fish-oil and control groups; P = .059).

Finally, a review of the evidence surrounding the use of ω-3 fatty acids in parenteral nutrition, including critical care, stated that there is a strong scientific rationale for using ω-3 polyunsaturated fatty acids in parenteral nutrition: they improve outcomes in critically ill patients as well as a wide variety of other groups.[10] Moreover, lipid emulsions containing fish oil have a proven safety and tolerability profile and represent a cost-effective component of parenteral nutrition regimens.[10] Importantly, a consensus statement at the current meeting stated that based on clinical studies, systematic reviews, and meta-analyses, there is no evidence that fish-oil containing lipids increase the risk of coagulopathy or bleeding abnormalities (Table 1).[1] Nevertheless, controversy remains regarding the use of ω-3 fatty-acid enriched parenteral nutrition. This is not only because of the quality of some RCTs, but also as there are some conflicting results from previous reviews and meta-analysis.[36] Some controversy continues, but it seems likely that this may be because of a low concordance in source data (ie, references selected). Factors contributing to this might be differences in selection of keywords and search methods, and perhaps intellectual conflicts of interest for some authors. In conclusion, and on balance, this consensus of the expert group was that there is sufficient scientific evidence to justify the use of ω-3 fatty acids in the parenteral nutrition of surgical and non-surgical (septic) critically ill patients.

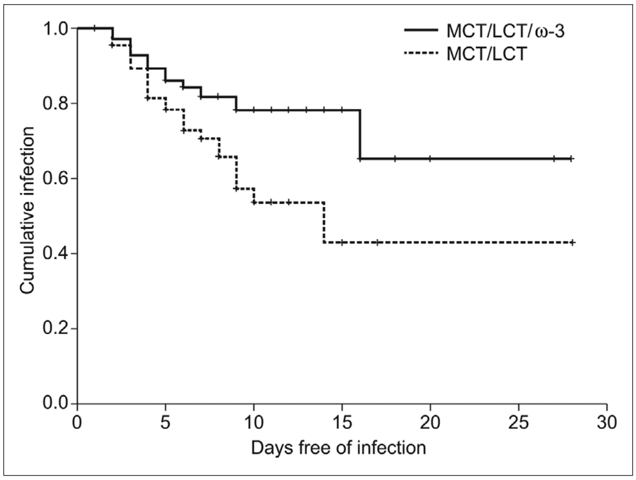

Figure 1. Time free of infection (TFI) for patients given parenteral nutrition containing 50% medium-chain triglycerides (MCTs), 40% soybean oil (LCT),10% fish oil (ω-3) (n = 68) vs those given 50% MCT/50% LCT (n = 71). TFI was significantly longer in the MCT/LCT/ω-3 group (21 vs 16 days, respectively; P = .03). LCT, long-chain triglyceride. Reproduced with permission from Grau-Carmona et al, 2015. 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.[35]

Specific Groups: Trauma and Acute Pancreatitis

Several additional groups of patients may benefit from ω-3 enriched lipid emulsions. These include patients with sepsis

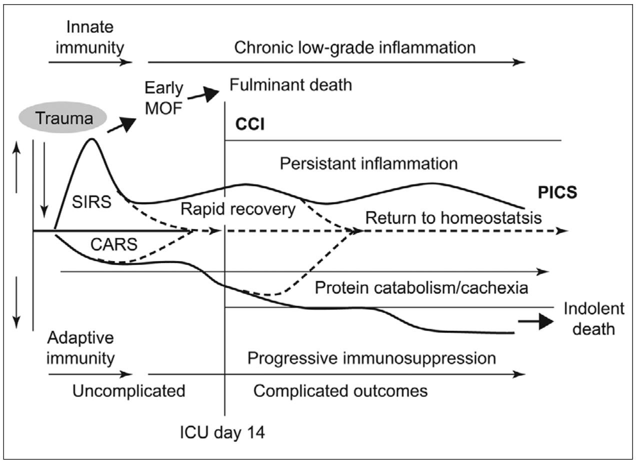

Figure 2. Response after traumatic injury. CARS, compensatory anti-inflammatory response syndrome; CCI, chronic critical illness; ICU, intensive care unit; MOF, multiple organ failure; PICS, persistent inflammation, immunosuppression and catabolism syndrome; SIRS, systemic inflammatory response syndrome. Reproduced with permission from Vanzant et al, 2014. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg*. 2014;76(1):21-29.[37]

(as discussed in the previous section), trauma or emergency surgery patients. Under these conditions of acute stress, a myriad of metabolic responses can occur that can result in conditions such as systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), or PICS (Figure 2).[37] RCTs are nearly impossible to do in these populations, but one can make inferences from research in other fields in which parenteral nutrition including ω-3 fatty acids has proven beneficial, such as major elective surgery or sepsis, which involves similar stress responses to injury. As ω-3 fatty acids are known to be effective in modulating immune response, they may have a key role in treating these inflammatory conditions arising from trauma. Thus, when patients sustain major injuries, and are critically ill they can enter a constant dynamic state of SIRS, and compelling evidence supports both immune- and metabolic-response modulation by specific nutrients, including ω-3 fatty acids.[38] Early diagnosis of these immune disorders and systemic hypermetabolic states, and the use of appropriate nutrition therapy including immune- and metabolic-modulating nutrients, can potentially reduce the incidence of complications, length of hospital stay, and mortality rates.[39]

The epidemiology of chronic illness after severe trauma has been explored in a prospective observational study involving 135 trauma ICU patients with hemorrhagic shock who survived beyond 48 hours after injury.[40] Of those surviving 48 hours, relatively few patients (3 patients, 2%) died within 7 days, 107 (79%) exhibited rapid recovery, but 25 (19%) progressed to chronic critical illness (CCI). Patients who developed CCI rather than recovering tended to be those who had an infection during the first 7 days of hospitalization (64% vs 28%, respectively; $P = .0019$). In addition, 56% of those developing CCI either died prior to discharge or had a poor discharge disposition (discharge to skilled nursing or long-term acute care facility) associated with poor outcomes. At 4 months, CCI patients had higher mortality rates than patients who had a rapid recovery (16% vs 1.9%, respectively; $P < .05$), with survivors also scoring lower for general health measures ($P < .005$). Thus, while early mortality is low after severe trauma, CCI is a common course in survivors and is associated with poor long-term outcomes. To prevent this response to injury, early identification may allow targeted interventions to change the trajectory of this morbid phenotype.[40] As we know that catabolism is driven by a persistent inflammatory response, it seems reasonable to use parenteral nutrition enriched with ω-3 fatty acids that may help to resolve inflammation and thus decrease the likelihood of CCI/PICS.

When associated with pancreatic necrosis, severe acute pancreatitis (SAP) continues to be associated with high mortality rates, and is characterized by marked nutrition depletion so nutrition support is required. SAP is a biphasic disease: the early stage is characterized by an inflammatory response resulting in SIRS, which can progress to early multiple-organ dysfunction syndrome (MODS), while the late phase involves a transition to an anti-inflammatory response and potential development of secondary infections of necrotic tissue, that can result in sepsis and late MODS.[41] Some of these patients may be required to be fed parenterally when attempts at enteral feeding have failed or been insufficient to meet their needs, particularly as gastrointestinal dysmotility is common in SAP, and so the parenteral route becomes the only option for macronutrient delivery.[41]

Lipid emulsions containing ω-3 fatty acids may have a role in the parenteral nutrition of patients with SAP owing to their anti-inflammatory, inflammation-resolving, and immunomodulatory characteristics. As an example, a small RCT involving 40 patients with SAP compared parenteral nutrition including 2 different lipid emulsions: pure soybean oil or soybean oil supplemented with fish oil.[42] The group given fish oil had a significantly higher blood EPA concentration ($P < .01$), lower CRP level ($P < .05$), and better oxygenation index ($P < .05$) after 5 days of parenteral nutrition. Furthermore, patients in the fish-oil group had fewer days of continuous renal replacement therapy than the control group ($P < .05$).[42] Overall, these results suggest that ω-3 fatty-acid enriched parenteral nutrition may attenuate the systemic response to pancreatic and organ injury in this group of patients. However, large-scale RCTs are still needed to prove whether or not this strategy can reduce organ failure and mortality rates associated with SAP.

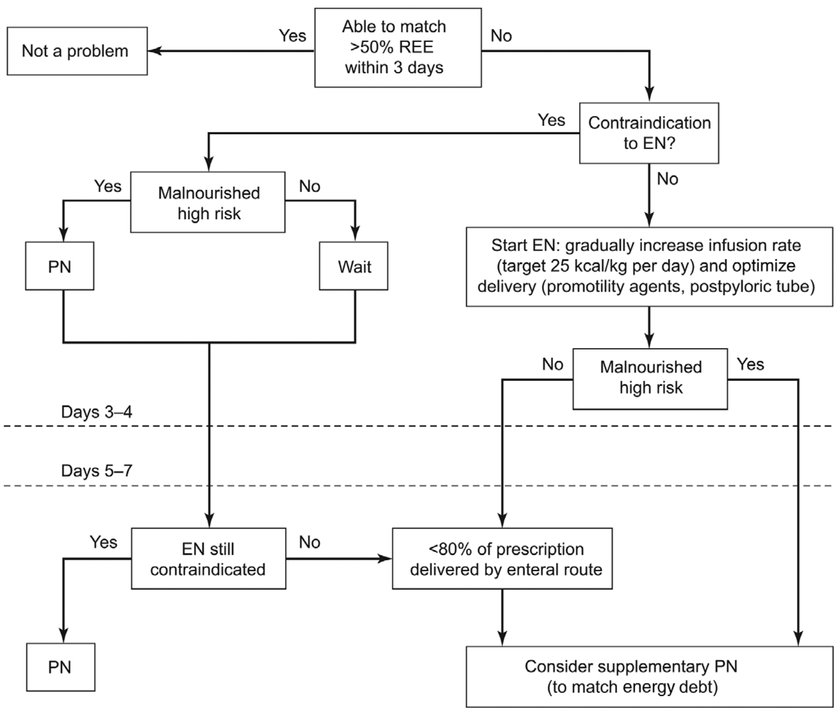

Figure 3. Algorithm for starting PN in severely ill patients. EN, enteral nutrition; PN, parenteral nutrition; REE, resting energy expenditure. Reproduced with permission from Weimann A, Singer P. Avoiding underfeeding in severely ill patients. *Lancet*. 2013;381(9880):1811.[46]

Critically Ill Adult Patients: Practical Aspects

A number of practical aspects are worth considering when using lipid emulsions as part of parenteral nutrition, such as the optimum duration of infusion, monitoring safety, how and when to consider parenteral nutrition, whether to consider parenteral nutrition as a supplement to enteral nutrition or alone, and how to determine/fulfill energy expenditure.

A randomized controlled crossover study compared slow (24 hours) and fast (6 hours) soybean oil intravenous lipid emulsion infusions alongside parenteral nutrition in patients with ARDS (n = 8) or severe sepsis (n = 10).[43] For patients with ARDS, the fast but not the slow infusion was associated with a significant deterioration in hemodynamics and the partial pressure arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio, potentially because of increased arachidonic acid derived prostaglandins and thromboxane synthesis.[43,44] Thus, in clinical practice, it seems preferable to give lipid emulsions over 12–24 hours as part of parenteral nutrition. This was also agreed as a consensus statement, which stated that if all-in-one admixtures are used, the preferable infusion duration is 24 hours (Table 1).[1]

Monitoring of clinical nutrition is required as it has become an important part of critical care, evolving from a support tool into a therapy that requires close attention and monitoring.[45] An ESPEN guideline group produced a consensus document that looked into what should be monitored, with particular attention toward triglycerides and energy delivery.[45] Hypertriglyceridemia in the ICU may be caused by sepsis, administration of propofol, lipid emulsions, or overfeeding. Thus, it is important to monitor triglycerides, with the ESPEN guideline group setting an upper limit of 500 mg/dL (5.6 mmol/L) for critically ill patients.[45] To some this limit might seem somewhat high. For example, the consensus at the current meeting was that serum triglyceride levels should be within the ranges recommended by local or regional guidelines, and in general, they should not exceed 400 mg/dL during infusion (Table 1).[1] The ESPEN guideline group also agreed that energy and substrate delivery should preferably be monitored using computerized systems in order to ensure the inclusion of energy from all routes and sources, including non-nutritional supplies such as propofol and citrate.[45]

How and when to consider using parenteral nutrition is also an area of concern. It is important that local institutions develop their own decision-making protocols that can perhaps be summarized as an algorithm. One example is shown in Figure 3.[46] Another topic to consider is the determination of energy expenditure. The use of indirect calorimetry for determining energy expenditure is highly recommended in the ESPEN guidelines for critically ill patients.[2] However, this is not always available, and in these instances the guidelines recommend calculating energy expenditure using oxygen consumption (VO_2) from a pulmonary arterial catheter or carbon dioxide production (VCO_2) derived from the ventilator, and that these methods will give a better estimate of energy expenditure than predictive equations.[2] However, in the absence of indirect calorimetry, VO_2, or VCO_2 measurements, these guidelines recommend the use of simple weight-based equations (such as 20–25 kcal/kg/d), and that "the simplest option may be used."[2] It is clear that under- and overfeeding can both be harmful, and that the optimal energy supply is estimated to be between 70% and 100% of measured energy expenditure.[2,47] The SCCM/ASPEN nutrition guidelines for the ICU recommend using predictive equations when indirect calorimetry is not available.[16]

Conclusions

The use of lipid emulsions in hospitalized adult patients requiring parenteral nutrition continues to evolve: from the use of traditional lipid emulsions containing only soybean oil as a lipid source, to now moving to those containing multiple lipid components in many groups of patients. There is currently considerable interest in ω-3 fatty-acid enriched lipid emulsions and their comparison with other standard lipid emulsions without fish oil, and studies comparing these lipid emulsions are being published. The current globally represented expert consensus group and the ESPEN expert group hold the view that fish-oil enriched parenteral nutrition confers additional clinical benefits over other, particularly single-source, lipid emulsions.[9] The potential benefits include reductions in infection rates and length of hospital and ICU stay.[27] As discussed in this review, it is clear that such clinical benefits can extend over a wide range of patients, such as surgical, critically ill, and severe trauma patients, as well as those with acute pancreatitis. Moreover, some practical aspects of administering lipid emulsions are particularly important to consider. These include optimum duration of infusion, monitoring safety, as well as how and when to consider parenteral nutrition.

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Statement of Authorship

K. Mayer, S. Klek, A. Garcia-de-Lorenzo, M.D. Rosenthal, A. Li, D.C. Evans, M. Muscaritoli, and R.G. Martindale, equally contributed to the conception and design of the research; K. Mayer, S. Klek, A. Garcia-de-Lorenzo, M.D. Rosenthal, A. Li, D.C. Evans, M. Muscaritoli, and R.G. Martindale, contributed to the acquisition, analysis, and interpretation of the data; R. Clark drafted the manuscript. All authors 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.

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