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A.S.P.E.N. Position Paper: Clinical Role for Alternative Intravenous Fat Emulsions

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Abstract

The currently available, standard soybean oil (SO)–based intravenous fat emulsions (IVFEs) meet the needs of most parenteral nutrition (PN) patients. There are alternative oil-based fat emulsions, such as medium-chain triglycerides (MCTs), olive oils (OOs), and fish oils (FOs), that, based on extensive usage in Europe, have an equivalent safety profile to SO. These alternative IVFEs are metabolized via different pathways, which may lead to less proinflammatory effects and less immune suppression. These alternative oil-based IVFEs are not currently available in the United States. Many patients who require IVFEs are already in a compromised state. Such patients could potentially have better clinical outcomes when receiving one of the alternative IVFEs to diminish the intake of the potentially proinflammatory ω-6 fatty acid—linoleic acid—which comprises more than 50% of the fatty acid profile in SO. Further research is needed on these alternative oil-based IVFEs to identify which IVFE oils or which combination of oils may be most clinically useful for specific patient populations. (*Nutr Clin Pract*. 2012;27:150-192)

Keywords

fat emulsions; fatty acids, omega-6; fatty acids, omega-3; lipids; parenteral nutrition; parenteral nutrition solutions

Introduction/Background

Fatty acids (FAs) are categorized based on several different characteristics. First is the number of carbons in the FA chain: 2–4 carbons, short-chain FA; 6–12 carbons, medium-chain FA; and ≥14 carbons, long-chain FA. Second is the number of double bonds in the FA molecule. Saturated FAs have no double bonds, monounsaturated FAs (MUFA) have 1 double bond, and polyunsaturated FAs (PUFAs) have 2 or more double bonds. Also, unsaturated FAs are categorized according to which carbon atom in the chain the first double bond occurs, counting from the methyl end of the molecule, which is referred to as the ω carbon. There are 3 principal families of unsaturated FAs in humans—ω-3, ω-6, and ω-9—in which the first double bond occurs at the third carbon, sixth carbon, or ninth carbon, respectively.[1] The nomenclature for FA is X:Y ω-Z, where X is the number of carbons in the FA chain, Y is the number of double bonds, and, for unsaturated FAs, Z is the number of carbons from the ω carbon where the first double bond occurs. Numerous abbreviations are used throughout this position paper. Table 1 summarizes these frequently used abbreviations.

The ω-6 and ω-3 FAs are metabolized through 2 different pathways but use the same enzymes with a preference of ω-3 > ω-6 > ω-9 (Figure 1). Although individual immune function tests may show variable results, clinically, ω-3 FAs are relatively less proinflammatory than ω-6 FAs. In addition, some ω-3 FAs may actually have anti-inflammatory effects (Figure 2).[3-6] These 2 metabolic pathways use and compete for the same enzymes. However, more of 1 FA than another in the diet, and thus in tissue membranes, can drive the process more to the proinflammatory metabolites or to the anti-inflammatory metabolites. Some evidence suggests that certain long-chain FAs may impair immune function by interfering with phagocytosis and chemotaxis and may result in an increased risk of infection.[1]

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Table 1. Frequently Used Abbreviations

AA: arachidonic acid
ALA: α-linolenic acid
ALT: alanine aminotransferase
ARDS: acute respiratory distress syndrome
A.S.P.E.N: American Society for Parenteral and Enteral Nutrition
AST: aspartate aminotransferase
BEE: basal energy expenditure
BOD: board of directors
BSA: body surface area
BW: body weight
CCCN: Canadian Critical Care Nutrition
CHO: carbohydrate
CO_2: carbon dioxide
COPD: chronic obstructive pulmonary disease
COX: cyclooxygenase
CRP: C-reactive protein
DGLA: dihomo-γ-linolenic acid
DHA: docosahexaenoic acid
DPA: docosapentaenoic acid
EFA: essential fatty acid
EFAD: essential fatty acid deficiency
EN: enteral nutrition
EPA: eicosapentaenoic acid
ESPEN: European Society for Clinical Nutrition and Metabolism
ESR: erythrocyte sedimentation rate
ETA: eicosatetraenoic acid
FA: fatty acid
FDA: Food and Drug Administration
FEF: forced expiratory flow
FEV1: forced expiratory volume in 1 second
FFA: free fatty acid
FIO_2: fraction of inspired oxygen
FVC: forced vital capacity
FO: fish oil
GGT: γ-glutamyl transpeptidase
GI: gastrointestinal
GLA: γ-linolenic acid
GVHD: graft vs host disease
HBE: Harris-Benedict equation
HDL: high-density lipoprotein
HPN: home parenteral nutrition
IBW: ideal body weight
ICU: intensive care unit
IFALD: intestinal failure–associated liver disease
IFN: interferon
IL: interleukin
IND: investigational new drug
IV: intravenous
IVFE: intravenous fat emulsion
LA: linoleic acid
LCT: long-chain triglyceride
LDL: low-density lipoprotein
LT: leukotriene
LOS: length of stay
MCT: medium-chain triglyceride
MDD: mean droplet diameter
MUFA: mono-unsaturated fatty acid
NASH: nonalcoholic steatohepatitis
NB: nitrogen balance
ND: not done
ND/NR: not detected or not reported
NDA: new drug application
NEC: necrotizing enterocolitis
NPC: nonprotein calories
NS: not significant
OA: oleic acid
OO: olive oil
PA: pulmonary artery
PaO_2: partial pressure of oxygen in arterial blood
PASI: Psoriasis Area and Severity Index
PEFR: peak expiratory flow rate
$PFAT_5$: percentage of fat residing in globules larger than 5 μm
PL: phospholipid
PN: parenteral nutrition
PO_2: partial pressure of oxygen
POD: postoperative day
pts: patients
PUFA: poly-unsaturated fatty acid
RCT: randomized controlled trial
REE: resting energy expenditure
RES: reticuloendothelial system
Retro: retrospective study
RQ: respiratory quotient
SBS: short bowel syndrome
SCT: stem cell transplant
SI: systemic inflammation
SIRS: systemic inflammatory response syndrome
SFO: safflower oil
SL: structured lipid
SO: soybean oil
SS: statistically significant
TBARS: thiobarbituric acid reactive substance
TG: triglyceride
TNA: total nutrient admixture
TNF: tumor necrosis factor
TNM: tumor, node, metastases
USP: United States Pharmacopeia
VLDL: very low-density lipoprotein
WMD: weighted mean difference
w/v: percent weight/volume

Unsaturated FAs, such as linoleic acid (LA), can undergo lipid peroxidation that involves incorporation of an oxygen molecule into the FA when breaking down the double bonds. This produces lipid peroxides, which are unstable molecules and are converted to volatile metabolites that can trigger chain reactions, resulting in inactivation of enzymes, proteins, and other elements necessary for the viability of cells.[1]

The introduction of the first successful intravenous fat emulsion (IVFE) in 1961[8] was heralded as a major breakthrough in parenteral nutrition (PN) support. The first commercially available product consisted of the long-chain, neutral triglyceride soybean oil (SO). It contained high amounts of the ω-6 essential fatty acid (EFA), LA, comprising about 50% of the total FA profile. Hence, it was intended to prevent the development of EFA deficiency (EFAD) in patients requiring PN. In addition to this FA, the SO-based IVFE contained substantial amounts of the nonessential, ω-9 FA oleic acid, which accounted for about 25% of the FA content, as well as the ω-3 FA, α-linolenic acid (ALA), which accounted for about 10% of the FA content. ALA was later deemed to also be an EFA in humans.[9] Hence, approximately 85% of the FA profile in SO consists of these three 18-carbon, long-chain unsaturated FAs, whereas the remaining FA profile (about 15%) mostly includes saturated FAs such as palmitic and stearic, in descending concentrations.

After approximately a decade of clinical use as a nutrition supplement, the use of this SO-based IVFE as a daily energy source began and rapidly gained acceptance, as the dangers of excessive intakes of parenteral dextrose as the sole energy source were increasingly recognized (eg, hepatic steatosis, increased respiratory quotient causing respiratory insufficiency, hyperglycemia-induced compromised immune function).[10] With the ongoing experience of using daily dextrose and substantially greater amounts of IVFE as a mixed-fuel PN regimen, additional nutrition-related complications emerged (ie, reticuloendothelial system dysfunction, exaggerated systemic

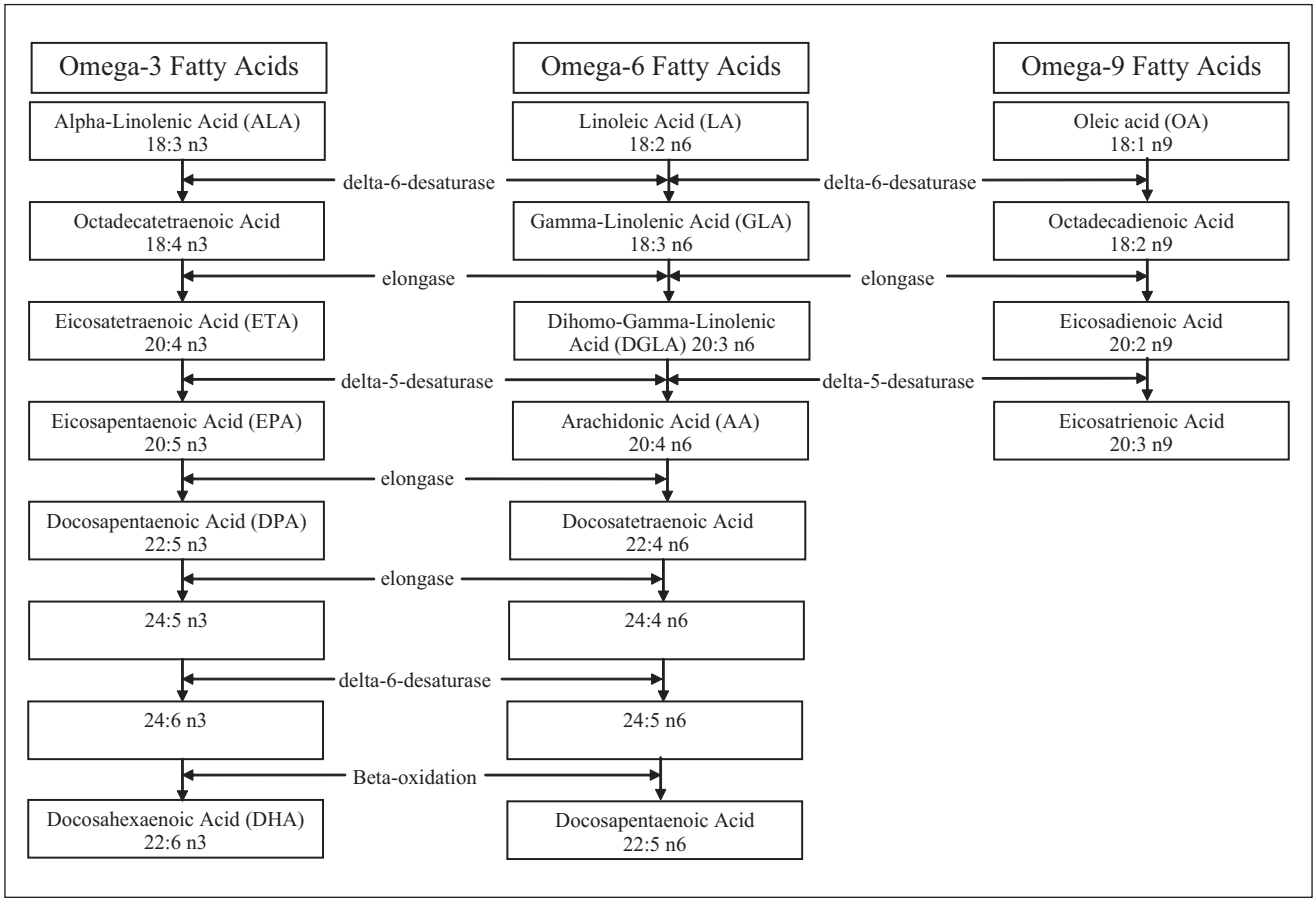

Figure 1. Metabolic pathways of ω-6 and ω-3 fatty acids.
Adapted from Le HD, Meisel JA, de Meijer VE, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81:165-170,[2] with permission from Elsevier.

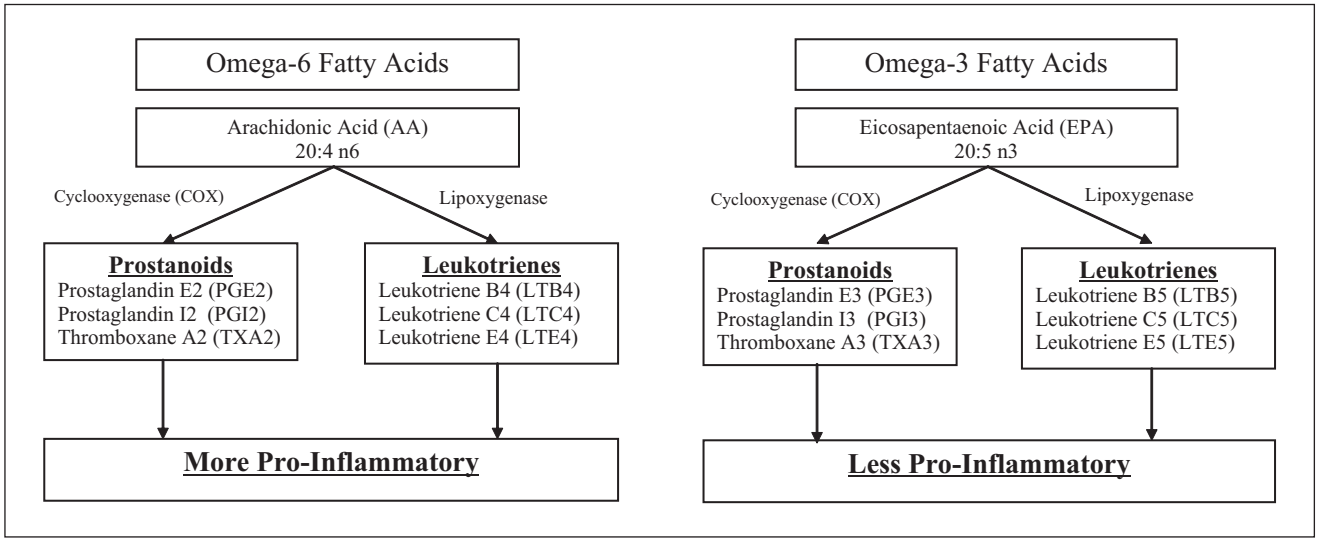

Figure 2. Relative proinflammatory eicosanoids from metabolites of ω-6 and ω-3 fatty acids.
Adapted from Lee S, Gura KM, Kim S, Arsenault DA, Bistrian BR, Puder M. Current clinical applications of omega-6 and omega-3 fatty acids. *Nutr Clin Pract*. 2006;21:323-341.[7]

inflammatory response in the critically ill, and liver dysfunction in acutely ill infants and in patients of any age requiring long-term PN).[11-15] The provision of higher doses of this ω-6-rich fat source (eg, 30–60 g/d) compared with the doses recommended for its original indications to prevent EFAD (50 g/wk) was thought to be the cause of these new complications.[10]

In 1984, a second-generation IVFE was introduced in Europe consisting of a 50:50 (by weight) physical mixture of SO and medium-chain triglycerides (MCTs). This formulation reduced the ω-6 FAs by 50% and now included the clinical use of saturated medium-chain FAs, which mainly consisted of caprylic and capric acids containing 8 carbons and 10 carbons, respectively. MCTs were a readily oxidizable and safe source of lipids that was equally nitrogen sparing as SO and essentially devoid of proinflammatory properties.[16]

In the 1990s, a third-generation IVFE was introduced in Europe that consisted of 80% olive oil (OO) and 20% SO by weight. This further decreased the "load" of ω-6 FAs by approximately 75% of the original SO-based IVFE because only about 5% of the FA acid profile of OO is LA. Like the second-generation IVFE, it too provided an alternative lipid fuel that was essentially "neutral" with respect to the proinflammatory properties of SO, and it was of equivalent caloric value. As the nutrition support field has evolved over time, a concerted effort to modify the composition of the original IVFE by deliberate reductions in the ω-6 FA intake has resulted in making this important source of calories safer, particularly in critically ill patients.

The fourth-generation IVFE included fish oil (FO), either alone or in combination with 1 or more of the oils used in previous generations of IVFEs. FO is rich in ω-3 FA, which is highly bioactive compared with MCT and OO. This FO-based IVFE not only is a nutrient and an alternate source of energy but also has anti-inflammatory properties and possesses potentially important pharmacological benefits.[4,5]

In May 2009, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Novel Nutrient Task Force was formed and charged to assess the level of scientific evidence for the clinical use of several different parenteral nutrients and develop position statements for the Society with regard to the use of that nutrient in clinical practice and the need for any modifications in the availability of that nutrient in the United States. Working groups were formed for each of these nutrients. One of these groups, the alternative IVFE Working Group, was directed to review the literature on alternative IVFEs and develop a position statement that would then be reviewed and approved by the A.S.P.E.N. Board of Directors.

Issue/Problem Definition

The procedure for the development, review, revision, and approval process for the A.S.P.E.N. IVFE position paper is outlined in Figure 3. PubMed searches were conducted with keywords as follows: *parenteral*, *fish oil*, *human; fat emulsion*, *fish oil; parenteral*, *olive oil fat emulsion*, *human;* and *parenteral*, *MCT fat emulsions*, *human*. An EMBASE search was conducted with the following keywords: *parenteral and fish oil and fat emulsion and human and English*. The literature searches were cross-referenced, removing duplicate studies. Eighty-nine clinical studies were identified for review, consisting of 68 randomized controlled trials (RCTs), 10 prospective crossover studies, 4 prospective studies without contemporary controls, 6 retrospective studies, and 1 case series.

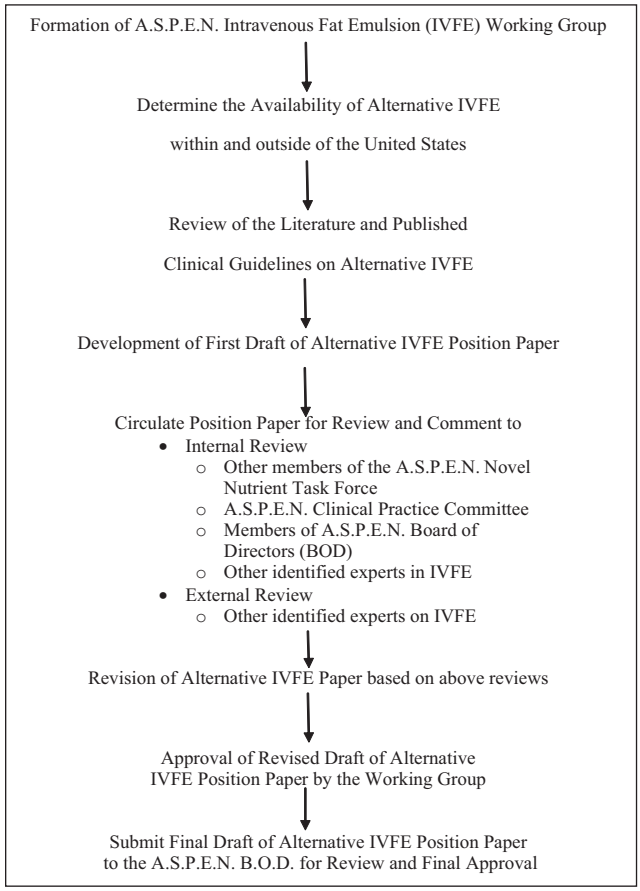

Figure 3. Procedure for the development of American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) position paper on the clinical use of alternative intravenous fat emulsions.

Each clinical study was assigned to a working group member for review, and the study findings were summarized on a standardized data abstraction spreadsheet. Also, 4 meta-analyses[17-20] involving IVFEs were identified and reviewed by all working group members. The recommendations of various published clinical guidelines regarding alternative IVFEs were also reviewed by the entire group.

The concentrations of selected FAs in vegetable and marine oil sources for commercially available IVFEs are shown in Table 2. The working group categorized these different oils in relationship to the degree of systemic inflammatory response generated by the oil (Figure 4). The major differences between

Table 2. Concentrations of Selected Fatty Acids in Vegetable and Marine Oil Sources Used in Commercially Available Fat Emulsions[a]

	Concentrations of Selected FA (% by Weight)[b]									
Oils	Caprylic (8:0)	Capric (10:0)	Palmitic (16:0)	α-Linolenic (18:3 ω-3)	Linoleic (18:2 ω-6)	Oleic (18:1 ω-9)	EPA (20:5 ω-3)	AA (20:4 ω-6)	DPA (22:5 ω-3)	DHA (22:6 ω-3)
Soybean	ND/NR	ND/NR	10	11	49	26	ND/NR	ND/NR	ND/NR	ND/NR
Safflower	ND/NR	ND/NR	6.4	0.1	77	13	ND/NR	ND/NR	ND/NR	ND/NR
Olive	ND/NR	ND/NR	9.4	ND/NR	4	83	ND/NR	ND/NR	ND/NR	ND/NR
MCT[c]	71	22	ND/NR	ND/NR	ND/NR	ND/NR	ND/NR	ND/NR	ND/NR	ND/NR
Fish species[d]										
1. Atlantic mackerel	ND/NR	ND/NR	17.6	1.3	1.8	18.9	7.4	0.183	1.7	11.6
2. Atlantic herring	ND/NR	ND/NR	17.1	1.3	1.6	19.2	8.9	0.060	0.6	10.8
3. European anchovies	ND/NR	ND/NR	17.4	0	2.4	15.2	13.1	0.007	0.7	22.2
4. Rainbow smelt	ND/NR	ND/NR	16.6	2.5	2.3	20.6	13.9	0.055	0.9	21.1
5. Atlantic salmon	ND/NR	ND/NR	11.2	5.2	3.1	24.0	5.7	0.267	5.1	19.8
6. Yellowfin tuna	ND/NR	ND/NR	23.2	1.8	1.2	16.1	5.4	0.020	1.9	26.8
7. Menhaden oil	ND/NR	ND/NR	22.9	1.4	3.8	14.7	13	Trace	ND/NR	5.4

AA, arachidonic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; MCT, medium-chain triglyceride; ND/NR, not detected or not reported (in either situation, there is little or none present).
[a]References 21–24.
[b]Not all FAs are listed, so the percentages do not add up to 100%.
[c]Extracted from coconut and other tropical nut oils.
[d]Fish species selected from the 6 marine families identified (*Carangidae*, *Clupeidae*, *Engraulidae*, *Osmeridae*, *Salmonidae*, and *Scombridae*, 1–6, respectively).[25] Pharmacopeial requirements: ω-3 fatty acid contents: EPA + DHA ≥45%; total ω-3 acids ≥60%.

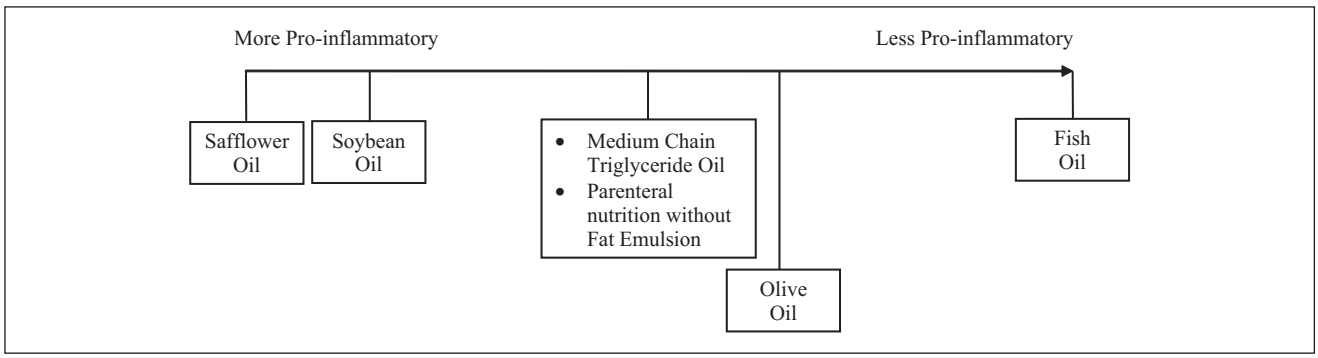

Figure 4. Categorization of oil sources used for commercially available intravenous fat emulsions based on relative systemic inflammatory activity.
Note: this is a relative (not absolute) figurative scale to demonstrate relative inflammatory activity.

the commercially available IVFEs throughout the world are shown in Table 3. Currently, all of the IVFEs available in the United States are SO based. Previously, some IVFEs in the United States used safflower oil (SFO). One product was composed solely of SFO but was removed from the market because of concerns that its low ALA content predisposed patients to neurologically adverse effects as a consequence of EFAD.[9] A subsequent product was a 50:50 blend of SFO and SO and seemed to meet patients' needs. However, it was removed from the market because of a lack of supply of SFO.

Depending on the country where a product is licensed, the package size, final concentration, and dosing recommendations vary. In some cases, products approved for use in neonates and pediatric patients in one country may not be approved in another. Practitioners should refer to population-specific guidelines and the manufacturer's package insert for information regarding a particular product.

Dosing may also vary between clinical practice and the product's package insert. Preterm infants require at least 0.25 g/kg/d IVFE to meet EFA requirements, although doses as high

Table 3. Commercially Available Intravenous Fat Emulsion Products in the United States and Outside the United States[a]

Product Name	Manufacturer/ Distributor	Lipid Source	Concentrations of Selected FA, % by Weight				n-6:n-3 Ratio	α-Tocopherol, mg/L	Phytosterols, mg/L
			Linoleic	α-Linolenic	EPA	DHA			
IVFE available in United States									
Intralipid®	Fresenius Kabi/ Baxter	100% soybean oil	44–62	4–11	0	0	7:1	38	348 ± 33
Liposyn® III	Hospira	100% soybean oil	54.5	8.3	0	0	7:1	NA	NA
IVFE available only outside of the United States									
Intralipid®	Fresenius Kabi	100% soybean oil	44–62	4–11	0	0	7:1	38	348 ± 33
Ivelip®	Baxter Teva	100% soybean oil	52	8.5	0	0	7:1	NA	NA
Lipovenoes®	Fresenius Kabi	100% soybean oil	54	8	0	0	7:1	NA	NA
Lipovenoes® 10% PLR	Fresenius Kabi	100% soybean oil	54	8	0	0	7:1	NA	NA
Intralipos® 10%	Mitsubishi Pharma Guangzhou/Tempo Green Cross Otsuka Pharmaceutical Group	100% soybean oil	53	5	0	0	7:1	NA	NA
Lipofundin-N®	B. Braun	100% soybean oil	50	7	0	0	7:1	180 ± 40	NA
Soyacal	Grifols Alpha Therapeuticas	100% soybean oil	46.4	8.8	0	0	7:1	NA	NA
Intrafat	Nihon	100% soybean oil	NA	NA	0	0	7:1	NA	NA
Structolipid® 20%[b]	Fresenius Kabi	64% soybean oil 36% MCT	35	5	0	0	7:1	6.9	NA
Lipofundin® MCT/LCT	B. Braun	50% soybean oil 50% MCT oil	27	4	0	0	7:1	85 ± 20	NA
Lipovenoes® MCT	Fresenius Kabi	50% soybean oil 50% MCT oil	25.9	3.9	0	0	7:1	NA	NA
ClinOleic® 20%	Baxter	20% soybean oil 80% olive oil	18.5	2	0	0	9:1	32	327 ± 8
Lipoplus®	B. Braun	40% soybean oil, 50% MCT, 10% fish oil	25.7	3.4	3.7	2.5	2.7:1	190 ± 30	NA
SMOFlipid®	Fresenius Kabi	30% soybean oil, 30% MCT, 25% olive oil, 15% fish oil	21.4	2.5	3.0	2.0	2.5:1	200	47.6
Omegaven®	Fresenius Kabi	100% fish oil	4.4	1.8	19.2	12.1	1:8	150–296	0

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; IVFE, intravenous fat emulsion; MCT, medium-chain triglyceride; n-6:n-3 ratio, ratio of ω-6 fatty acids to ω-3 fatty acids; NA, not available.
[a]References 1, 10, 26, 37.
[b]Fat source uses structured lipids.

as 4 g/kg/d have been used to provide additional nonprotein calories.[27] Some centers have opted to limit the amount of IVFE energy their neonates receive to 3 g/kg/d or less.[28,29] Neonates less than 32 weeks' gestation may not be able to tolerate IVFE doses in excess of 2 g/kg/d.[29] In considering IVFE provision guidelines, the desire to prevent intestinal failure–associated liver disease (IFALD) by limiting the IVFE dose to 1 g/kg/d or less must be balanced against the need to provide adequate energy for growth, particularly among preterm infants who may not tolerate high glucose infusion rates to meet energy needs[30] and in whom poor postnatal weight gain is strongly associated with poor neurological developmental outcomes.[31] Practitioners need to base dosing on the clinical situation and in accordance with established national guidelines.

Given that these oils are derived from natural sources, there are variations in the actual FA content for each product, even among different lots of the same product. Rather than report the specific FA content for each product, Table 2 compares the FA content of the oils used in formulating these IVFEs. The IVFEs that are available in the United States and outside of the United States are listed in Table 3, and only the percentage of each oil source is listed, along with the approximate content of selected FAs.

In addition to oils and emulsifying agents, other components may be considered significant when evaluating different IVFEs. In some cases, this is not noted on the product label. For example, phytosterols found in SO are thought to have a deleterious effect on hepatic function.[32] Phytosterol is a main class of plant sterols that includes sitosterol, campesterol, and stigmasterol.[33] Plant sterols are absorbed in small amounts by the body via the gastrointestinal tract. Once absorbed, they are metabolized slowly by the liver.[34] In a neonatal piglet model, it was shown that intravenous (IV) phytosterol injections without the other components of IVFE markedly reduced bile acid excretion.[35] Moreover, long-term use of a SO-based IVFE may lead to a progressive increase and accumulation of phytosterol content in cell membranes and plasma lipoproteins, which has been associated with cholestasis in children on long-term PN.[36]

When considering products containing FO, it is important to recognize that there are 2 monographs from the European Pharmacopeia in use.[37] One monograph[38] is entitled "Fish Oil, Rich in Omega-3 Fatty Acid," whereas another monograph[39] is entitled "Omega-3 Acid Triglycerides." Consequently, the commercially available IVFE products containing FO have different concentrations of ω-3 FA, yet all are in compliance with their respective monographs. This explains how one product, despite having a lower concentration of FO in the oil phase of the emulsion, could have a higher concentration of eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA).[37]

Likewise, the amount of vitamin E present in an IVFE has been considered by some authors an important factor when comparing products.[40] Oxidative stress has been proposed as the second "hit" leading to the cell injury and apoptosis (death) pathway of hepatocytes with an abnormal accumulation of fat.[41] Therefore, antioxidants have been suggested as a therapeutic option in treating IFALD. Despite some benefit of vitamin E in the prevention of hepatic injury in animal models, human data are still lacking, although proponents attribute the addition of α-tocopherol to IVFEs, either at the time of manufacture or exogenously, as being a major factor in minimizing IFALD.[40,42] In addition to the presence of phytosterols, most SO-based IVFEs have a limited amount of α-tocopherol. Prolonged use of these products is thought to lead to a depletion of antioxidant defenses due to reduced α-tocopherol concentrations in plasma lipoproteins.[43] Depending on the product, α-tocopherol content may or may not appear on the product label.

The articles from the literature review were divided into 5 groups based on the source of oil used in the IVFE in the study group (ie, MCT, OO, FO alone, FO with SO and/or MCT, and commercially compounded IVFEs with combinations of FO, OO, MCT, and/or SO). The results of these reviews are shown in Tables 4 through 8. The patient populations included in these studies were categorized according to their estimated amount of systemic inflammation (ie, none, mild to moderate, or severe) (Figure 5). In the tables, the category of systemic inflammation in the patient population for each study is noted. The tables also provide a brief summary of the findings of each study and categorize the results of the biochemical and clinical outcome variable reported (ie, ND, not done; NS, no statistically significant differences between groups; SS, statistically significant improvement in the study group compared with the control group).

There is marked heterogeneity between the studies with regard to patient population, types of controls and study IVFE used, and biochemical and clinical end points, which resulted in marked variability in findings and conclusions. Several other confounding factors should be noted. In several of the studies in Tables 4 through 8, the recommended maximum IVFE infusion rate of 0.11 g/kg/h was exceeded, which can result in fat overload syndrome, causing impaired immune, pulmonary, hepatic, and platelet function and adversely affecting the outcome of the study.[133,134] Although these IVFE side effects have been seen when using SO IVFE in adults and infants, in a limited number of studies involving infants with FO IVFE, fat overload syndrome has not been seen even with infusion rates up to 5 g/kg/h.[135] Also, it should be noted that the study IVFEs used in the studies listed in Table 7 are either physical combinations of SO and FO IVFE that are not commercially available or are situations in which the SO and FO IVFE were infused separately. It is unclear how the results of these studies may differ from the studies in Table 8, which are commercially available combined oil IVFEs. Last, in Table 7, the study by Heller et al (2004)[107] is a post hoc analysis of the same patients used in the study by Heller et al (2002).[109]

Because of the heterogeneity among the studies reviewed, their results cannot be combined and analyzed with any scientific validity. Despite this, assessing the percentage of studies that showed a statistically significant difference between study groups with regard to biochemical or clinical outcomes showed some interesting trends. Combining all 5 groups of IVFEs, 82 of the 89 studies assessed at least one type of biochemical or physiological outcome variable, and 84% of these studies demonstrated a statistically significant improvement. There was little variation in this percentage between the 5 IVFE groups (78%–100%), with the MCT group having the lowest percentage and the FO-alone group having the highest percentage. Fifty-one studies assessed at least one type of clinical outcome variable, and 37% of these studies found a statistically significant improvement. There was much more variability in

Table 4. Review of the Literature Comparing Soybean Oil Intravenous Fat Emulsions to Soybean Oil Plus Medium-Chain Triglyceride Intravenous Fat Emulsions

Lead Author (Reference No.)/Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Adult studies								
Piper (44) 2008	RCT	45 post–abdominal surgery pts	SO SO/MCT as SL (50:50) SO/MCT (50/50)	PN at 25 kcal/kg/d, CHO:IVFE (60:40), IVFE dose of 0.8 g/kg/d × 5 days	Lower serum TG and reduced α-glutathione S-transferase with SL suggesting improved hepatic function	1	SS	ND
Versleijen (45) 2008	Prospective crossover	12 healthy volunteers	Saline (control) SO SO/MCT (50:50)	Infused over 4.5 hours after overnight fast, then after 2-week washout crossover to next treatment group	SO/MCT significantly decreased lymphocyte counts No evidence of neutrophil activation found with either IVFE Clearance of radiolabeled leukocytes from liver, spleen, and lungs was not altered by either IVFE, suggesting it does induce leukocyte sequestration	0	NS	ND
Iovinelli (46) 2007	RCT	24 pts with ICU/COPD on mechanical ventilation	SO SO/MCT (50:50)	PN at 1.3 × HBE, CHO:IVFE (50:50), IVFE dose of 1.3 g/kg/d, 10–13 days	One measure of immune function (T4/T8 ratio) was significantly decreased with SO. Other measures of immune function were no different between groups. TGs increased in both groups with greater increase in the SO group No significant difference in time on mechanical ventilation, but SO/MCT group had a significantly shorter weaning time No significant difference in mortality	1	SS	SS
Chen (47) 2005	RCT	30 GI cancer surgery pts	SO SO/MCT (50:50)	PN at 31 kcal/kg/d, CHO:IVFE (65:35), IVFE dose 0.88 g/kg/d × 7 days	Prealbumin concentration significantly improved in SO/MCT group; serum insulin levels were higher in this group as well Measures of immune function were similar in each group Serum TG and cholesterol levels were constant in both groups Anthropometrics, postoperative complications, and LOS were similar in both groups	1	SS	NS
Chambrier (48) 2004	Prospective crossover	11 PN-dependent pts	SO SO/MCT (50/50)	PN (TNA) at 1.3 × REE 2–5 times weekly to maintain weight, SO at baseline switched to SO/MCT for 4 months	No clinical EFAD No difference in TG levels Significant decrease in plasma vitamin K	1	SS	ND
Grau (49) 2003	RCT	72 severely malnourished pts requiring laparotomy, stratified by presence or absence of cancer	SO SO/MCT (50/50)	PN (TNA) at 150% HBE, NPC: N 150:1, IVFE at a fixed dose of 500 mL daily so CHO:IVFE ratio varied between patients, × 8 days (range, 5–15 days)	15 pts did not complete the study The SO/MCT group experienced a lower number of intra-abdominal abscesses in all pts and the cancer subgroup Mortality was improved by SO/MCT in the cancer subgroup but not for the entire group	1	ND	SS

(continued)

Table 4. (continued)

Lead Author (Reference No.)/Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Kuse (50) 2002	RCT	22 post–hepatic transplant pts	SO SO/MCT (50:50)	PN at REE, initially IVFE at 0.5–1 g/kg/d increasing to 1–2 g/kg/d on days 3–10; dextrose at 3–5 g/kg/d	Both groups showed a significant increase in RES function posttransplant with the most improved RES function at day 7 with SO/MCT	1	SS	ND
Garnacho-Montero (51) 2002	RCT	72 ICU pts with abdominal sepsis	SO 10% SO/MCT 10% (50:50)	PN at 35 kcal/kg/d, CHO:IVFE (60:40), IVFE dose 1.2 g/kg/d × 10 days	20 pts did not complete study SO/MCT group had improved nutrition status (retinol binding protein and NB) No difference in liver cholestasis No difference in mortality or LOS	2	SS	NS
Martín-Peña (52) 2002	RCT block randomized by degree of stress	83 mixed medical-surgical pts in hospital	SO SO/MCT (50:50)	PN (TNA) at 1.2, 1.4, or 1.6 × HBE (none, moderate, severe stress) with 40% of total energy as IVFE, plasma PL measured weekly, up to 28 days	LA increased and AA decreased significantly in the SO group LA decreased significantly and AA remained level in the SO/MCT group PL concentrations in the SO/MCT group were more similar to healthy controls No significant difference in duration of PN	1	SS	NS
Smyrniotis (53) 2001	Prospective crossover	9 acute pancreatitis pts with ARDS	SO SO/MCT (50:50)	PN at 40 kcal/kg/d, CHO:IVFE (50:50), IVFE infused over 8 hours on consecutive days in random order	Measures of pulmonary gas exchange were done before, during, and 4 hours after IVFE infusion In the SO group, mean PA pressure and pulmonary venous admixture were significantly increased and PaO_2/FIO_2 was decreased SO/MCT significantly increased oxygen consumption, cardiac output, and CO_2 production	2	ND	SS
Lindgren (54) 2001	RCT	30 trauma or postsurgical pts with sepsis	SO SO/MCT as SL (50:50)	PN at REE infused over 24 hours, IVFE infused at 1.5 g/kg/d over 12 hours × 5 days	10 dropped out (4 SO and 6 SO/MCT) Daily and cumulative NB was significant better in SL group in pts who completed the study There were no differences in TG level or energy expenditure in either group There was no difference in complications rates	2	SS	NS
Kruimel (55) 2001	RCT	25 post–vascular surgery pts	SO/MCT (50:50) SO/MCT as SL (64%/36%)	PN at HBE plus 300 kcal/d, CHO:IVFE (67:33), IVFE infused over 6 hours × 5 days	Improved cumulative NB with SL Less increase in TGs and medium-chain FA on first postoperative day with SL consistent with more rapid clearance when compared with physical mixture	1	SS	ND
Demirer (56) 2000	RCT	36 pts with hematologic malignancy after SCT	SO SO/MCT (50:50)	PN at median dose of 36 and 38 kcal/kg/d, CHO:IVFE (70:30), IVFE infused at 0.87 and 0.95 g/kg/d (respectively) for an average of 8 days	No difference in duration of engraftment, coagulopathy, hospitalization, GVHD, or 100-day mortality Duration of febrile neutropenia and antibiotic administration was significantly less with SO/MCT	1	ND	NS

(continued)

Table 4. (continued)

Lead Author (Reference No.)/Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Planas (57) 1999	RCT	12 ICU pts	SO SO/MCT (50:50)	PN at 35 kcal/kg/d, CHO:IVFE ratio not reported, IVFE infused over 12 hours × 7 days	Oleic acid increased and caprylic and DHA levels decreased in the SO group, whereas palmitoleic and arachidonic acid levels decreased in the SO/MCT group	1	SS	ND
Bellantone (58) 1999	RCT	19 postcolectomy pts	SO SO/MCT as SL (50:50)	PN at 27 kcal/kg/d, CHO:IVFE (55:45), IVFE at 1.24 g/kg/d infused over 12 hours × 6 days	SO/MCT as a SL was found to be safe when compared with SO Both groups were in positive NB: cumulative NB favored the SL group Maximum TG concentration was at 135 mg/dL	1	NS	ND
Chambrier (59) 1999	RCT	40 post–abdominal surgery pts	SO/MCT (50:50) SO/MCT as SL (50:50)	PN at REE infused over 24 hours, CHO:IVFE (50:50), IVFE infused at 0.86 and 0.85 g/kg/d (respectively) over 8 hours × 7 days	There was nearly a 2-fold increase in TG and serum transaminase levels over baseline in the physical mixture group These measures were unchanged in the SL group NB was similar in both groups	1	SS	ND
Hailer (60) 1998	RCT	25 abdominal surgery pts on PN for 7 days	No IVFE SO 10% SO 20% SO/MCT 10% (50:50) SO/MCT 20% (50:50) (5 pts in each group)	PN at 1.5 × HBE, CHO:IVFE (50:50), IVFE infused over 16 hours × 7 days	Abnormal lipoprotein X occurred least with the MCT/SO 20% MCT/SO 20% seemed to have the most effect on normalizing plasma lipoproteins, and best tolerance was in pts after surgery	1	SS	ND
Gelas (61) 1998	RCT	33 stage 3 AIDS pts	SO SO/MCT (50:50)	PN at 36 kcal/kg/d, CHO:IVFE (40:60) infused over 12 hours, IVFE infused at 1.8 g/kg/d or 0.15 g/kg/h × 7 days	In the SO group, there was a significant decrease in lymphocyte function (phytohemagglutinin) In the SO/MCT group, there was a significant decrease in IgM levels and an increase in complement 3 levels Serum TG levels decreased and weight increased in both groups	1	SS	NS
Smirniotis (62) 1998	RCT	21 surgical ICU pts with sepsis and ARDS	SO SO/MCT (50:50)	PN at 36 ± 3 and 35 ± 3 kcal/kg/d, CHO:IVFE (50:50); IVFE was infused at 12 g/h × 8 hours	Measures of pulmonary gas exchange were done before, during, and 4 hours after IVFE infusion SO led to a significant increase in pulmonary venous admixture and mean PA pressure and a decrease in PaO_2/FIO_2 SO/MCT only led to a significant increase in oxygen consumption	2	ND	SS

(continued)

Table 4. (continued)

Lead Author (Reference No.)/Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Waitzberg (63) 1997	Prospective crossover	10 preoperative gastric cancer pts	SO 10% SO/MCT 10% (50:50)	PN at 40 kcal/kg/d, CHO:IVFE (70:30), IVFE infusion rate 0.08 g/kg/h for 48 hours, PN without IVFE during 48-hour baseline and washout period	Significant decrease in bacterial killing activity with SO No significant change in phagocytosis index, chemotaxis, spontaneous migration, or nitroblue tetrazolium reduction for neutrophils or monocytes with infusion of either IVFE	1	SS	ND
Sandström (64) 1995	Prospective crossover	19 post–abdominal surgery pts	SO SO/MCT as SL (50:50)	PN infused over 6 days randomly giving one IVFE on days 1, 3, and 5 and the other on days 2, 4, and 6; IVFE infused over 8 hours. PN dosed at 2 levels: PN (80% BEE) and IVFE 1 g/kg/d or PN (120% BEE) and IVFE 1.5 g/kg/d	No signs of intolerance; SL was rapidly cleared from the plasma compartment and was rapidly oxidized without any significant hypertriglyceridemia or ketosis Significantly higher whole-body fat oxidation with SL occurred during part 2 of the study when excess NPC was provided	1	SS	ND
Jeevanandam (65) 1995	RCT	10 ICU pts	SO SO/MCT (25:75)	PN at 30 kcal/kg/d, CHO:IVFE (68:37), IVFE infused over 8 hours × 7 days	Net fat oxidation was greater and FFA re-esterification less with SO/MCT	1	SS	ND
Ball (66) 1993	RCT	20 ICU pts	SO SO/MCT (50:50)	PN at 2200 kcal vs 2600 kcal for trauma, CHO:IVFE (40:60 vs 50:50 for trauma), 100 g of IVFE infused over 8 hours × 8 days	No significant differences in plasma ketones, TGs, nonesterified FA, or urinary carnitine excretion	2	NS	ND
Jiang (67) 1993	RCT	12 postoperative surgical pts vs 6 healthy participants (tested twice)	SO 10% SO/MCT 10% (50:50)	PN at 35 kcal/kg/d. CHO:IVFE (50:50), × 10 days, IVFE clearance test done twice on pts and healthy participants infusing IVFE at 0.140 g/kg/h × 6 hours (2.2 × the rate given with PN), test done pre- and postoperatively in pts	SO/MCT was cleared more readily by peripheral tissue than SO Higher ketone body levels with SO/MCT but remained in normal range Postoperative weight loss was significantly less with SO/MCT Trend toward more positive NB with SO/MCT	1	SS	ND
Pediatric studies								
Socha (68) 2007	Prospective crossover	9 infants with severe cholestatic liver disease	SO SO/MCT (50:50)	PN at 72 kcal/kg/d, CHO:IVFE (63:27), two 3-day courses of IVFE; 3-day washout; 1 g/kg/d on day 1, then 2 g/kg/d on days 2 and 3, EN at 28 kcal/kg/d	Small but significant improvement in bilirubin occurred after each IVFE Cholesterol, TGs, and PL concentrations in plasma and lipoproteins did not change after either IVFE PUFA was low at baseline and EFAD was present N-6 PUFA improved with both emulsions but only SO increased DHA	1	NS	ND

(continued)

Table 4. (continued)

Lead Author (Reference No.)/Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Lehner (69) 2006	RCT	12 premature neonates	SO SO/MCT (50:50)	PN at 60 kcal/kg/d, CHO:IVFE (60:40), IVFE dose of 2.3 ± 1.2 g/kg/d, EN 14% of total intake (breast milk); ^{13}C-labeled LA and ALA given orally after 1 week of IVFE	A trend toward higher concentrations of long-chain PUFA (AA and DHA) occurred in the SO/MCT group, suggesting reduced β-oxidation of the long-chain PUFAs Similar changes in TG occurred in both groups Plasma PL concentrations were similar between groups; LA and ALA levels were slightly higher in the SO/MCT group Conversion of EFA to long-chain PUFA was similar between groups	1	NS	ND
Lai (70) 2000	RCT	38 children after abdominal or esophageal surgery	SO 10% SO/MCT 10% (50:50)	PN at 71 kcal/kg/d with 12 g/kg/d dextrose, IVFE infused at 1.5 g/kg/d × 14 days	Fat oxidation increased and NB and serum albumin levels improved in the SO/MCT group Increased number and percentage of lymphocytes Reduced AST and bilirubin	1	SS	ND

AA, arachidonic acid; ALA, α-linolenic acid; ARDS, adult respiratory distress syndrome; AST, aspartate aminotransferase; BEE, basal energy expenditure; CHO, carbohydrate; COPD, chronic obstructive pulmonary disease; DHA, docosahexaenoic acid; EFA, essential fatty acids; EFAD, essential fatty acid deficiency; EN, enteral nutrition; FFA, free fatty acid; FIO_2, fraction of inspired oxygen; GI, gastrointestinal; GVHD, graft vs host disease; HBE, Harris-Benedict equation; ICU, intensive care unit; IVFE, intravenous fat emulsion; LA, linoleic acid; LOS, length of stay; MCT, medium-chain triglyceride; NB, nitrogen balance; NPC, nonprotein calories; NPC:N, nonprotein calories: g nitrogen; PA, pulmonary artery; PaO_2, partial pressure of oxygen in arterial blood; PL, phospholipid; PN, parenteral nutrition; pts, patients; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; REE, resting energy expenditure; RES, reticuloendothelial system; SCT, stem cell transplant; SL, structured lipid; SO, soybean oil; TG, triglyceride; TNA, total nutrient admixture.

[a]Coding key: SI, categorized by amount of systemic inflammation: 0 = none, 1 = mild to moderate, or 2 = severe. Bio and Clin, result of biochemical marker and clinical end points: ND, not done; NS, no significant difference between groups; SS, statistically significant difference between groups.

Table 5. Review of the Literature Comparing Olive Oil and Soybean Oil Intravenous Fat Emulsions to Soybean Oil Alone or Soybean Oil Plus Medium-Chain Triglyceride Intravenous Fat Emulsions

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Adult studies								
Puiggròs (71) 2009	RCT	28 post–abdominal surgery pts	SO SO/MCT (50:50) SO/MCT as SL (50:50) OO/SO (80:20)	PN at 31 kcal/kg/d, CHO:IVFE (60:40), IVFE infused at 1.2 g/kg/d × 5 days	No significant differences in liver function tests or lipid profiles OO/SO group achieved FA composition of serum lipids that could offer major therapeutic or biological advantages	1	SS	ND
Mateu-de Antonio (72) 2008	Retrospective	39 ICU pts	SO (first cohort) OO/SO (80:20) (second cohort)	PN at 1–1.5 HBE, CHO:IVFE (65:35), IVFE infused at 0.5–1.5 g/kg/d × ≤5 days, macronutrients adjusted for elevated glucose and TG	OO/SO had higher leukocyte counts at end of PN and trend to higher peak leukocyte counts No difference in infections, acute phase proteins, ICU or hospital LOS, or mortality	1	SS	NS
Pálová (73) 2008	Retrospective	21 pts with digestive disease with >10% weight loss	SO OO/SO (80:20)	PN at 140% HBE, CHO:IVFE (45:55) × 14 days	Significantly better weight gain and increase of prealbumin enzymes and/or bilirubin was seen in the OO/SO group Significantly less hypertriglyceridemia serum occurred in the OO/SO group Measures of cholestatic liver dysfunction were less severe in the OO/SO group, but this did not reach significance	1	SS	SS
Cano (74) 2006	RCT	41 malnourished pts on outpatient hemodialysis	SO OO/SO (80:20)	PN at 1125 kcal/d, CHO:IVFE (46:54), infused over 4 hours during hemodialysis for 35 treatments	Serum albumin, total cholesterol, and LDL increased similarly in both groups Increased transthyretin and creatinine in SO group Increased α-tocopherol and α-tocopherol/cholesterol ratio in OO/SO group Significant increase in TNF-α in OO/SO group IL-2 increased similarly in both groups	1	SS	ND
García-de-Lorenzo (75) 2005	RCT	22 severely burned pts	SO:MCT (50:50) OO/SO (80:20)	PN at 35 kcal/kg/d, CHO:IVFE (40:60), IVFE infused at 1.3 g/kg/d × 6 days	Mortality 32% with no difference between groups, and all died after completing study TGs increased in both groups to about 190 mg/dL Fewer abnormalities in the indicators of cholestasis (liver function tests) in OO/SO group at day 6, but that group had fewer abnormalities in these tests at baseline	2	NS	NS

(continued)

Table 5. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Reimund (76) 2005	Prospective nonrandomized	14 PN-dependent pts who were on a stable formula with a single IVFE for 3 months	SO or SO/MCT (50:50) OO/SO (80:20)	PN given as TNA, median NPC dose 5160 kcal/wk, IVFE provided a median of 31% of NPC, × 3 months. Amino acid dose and frequency of infusion not stated 13 pts ate food, median 2075 kcal/d intake	The pts on SO/MCT (n = 6) were placed on this IVFE to allow "stabilization" of elevated liver enzymes No change in usual nutrition, hepatic, or clinical parameters No change in ESR, CRP, TNF, IL-6, and IL-8 Significantly decreased ALA after OO	1	NS	NS
Huschak (77) 2005	RCT	33 trauma pts	SO OO/SO (80:20)	PN at REE up to 14 days, CHO:IVFE (25:57) for OO/SO vs (63:37) for SO, EN at 5 kcal/kg/d × 6 days, a high-fat EN (40/60) for the OO/SO, a standard fat EN (56/44) for the OO. The OO/SO received less energy than the SO group: 18 vs 22 kcal/kg/d	OO/SO group had significantly lower blood sugars, CO_2 production, and respiratory quotient and shorter ventilator days and ICU LOS Expression of HLA-DR on CD14+ monocytes was equally depressed by trauma and returned to normal in both groups No difference in hospital LOS It is unclear if these results are due to the different IVFE used vs the relative amount of total fat given to each group	2	SS	SS
Vahedi (78) 2005	RCT	13 PN-dependent pts on PN for >6 months	SO OO/SO (80:20)	PN 25 kcal/kg/d × 3 months, CHO:IVFE (72:28), infused over 12-to 14-hour cycle 4–7 times per week, IVFE dose 50 g 4–6×/wk. SO/MCT (50:50) given to all pts during run-in phase days –30 to 0 to standardized lipid profile	There was a significant increase in GLA in plasma and lymphocyte and OA in the plasma with OO/SO EFAD did not occur in either group as measured by the triene:tetraene ratio	1	SS	ND
Thomas-Gibson (79) 2004	Prospective crossover with retrospective component	13 PN-dependent pts requiring >50% of their energy from PN	SO 10% and 20% OO/SO 20% (80:20)	PN at 26 NPC/kg/d, CHO:IVFE (72:18), IVFE given 2–3 d/wk, giving a median dose of 0.48 g/kg/d; baseline SO was switched to OO/SO for 6 months, then switched back to original SO for another 6 months	There were no intergroup differences in infections or readmissions to hospital There was a trend toward fewer thromboses in the OO/SO group Liver enzymes were not significantly changed while patients received OO/SO OO/SO appears to be a safe alternative to SO	1	NS	NS

(continued)

Table 5. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Pediatric studies								
Hartman (80) 2009	RCT	28 pediatric BMT pts	SO/MCT (50:50) OO/SO (80:20)	PN (TNA) at 38 kcal/kg/d, CHO:IVFE (70:30), IVFE infused at 1.1 g/kg/d × 14 days	Plasma OA, LA, and AA increased and cholesterol significantly decreased in the OO/SO group EPA and DHA levels were comparable between groups There was no significant difference in hematological parameters, liver enzymes, plasma peroxidation status, percentage, and time to engraftment	1	SS	NS
Deshpande (81) 2009	RCT	44 premature infants 23–<28 wk	SO OO/SO (80:20)	PN at 70–80 kcal/kg/d, CHO:IVFE (60:40), IVFE increased over 4 days to target 3 g/kg/d infused over 20 hours each day × 5 days	OA and LA levels significantly increased OO/SO and SO groups, respectively Long-chain PUFA levels were similar between groups F2-isoprostane levels, a measure of lipid peroxidation, decreased in both groups to the same extent There was a significantly higher level of C18:4n-3 in the OO/SO group, suggesting Δ6-desaturase enzyme inhibition in the SO group	1	SS	NS
Gawecka (82) 2008	RCT	44 premature infants in NICU	SO OO/SO (80:20)	PN at 100 kcal/kg/d, CHO:IVFE (65:35), IVFE infused at 3–3.5 g/kg/d infused over 24 hours × 14 days	No difference in TNF-α and IL-10 production Trend toward increased IL-6 synthesis in SO group After anti-CD-3 stimulation, IL-6 production significantly higher in peripheral blood mononuclear cells in SO group No difference in ventilator days or incidence of bronchopulmonary dysplasia, retinopathy of prematurity, or necrotizing enterocolitis No difference in incidence of nosocomial infection	1	SS	NS
Webb (83) 2008	RCT	78 critically ill neonates	SO OO/SO (80:20)	PN at 77 kcal/kg/d, unable to calculate CHO:IVFE ratio, IVFE increased over 4 days to target 3 g/kg/d; on day of repeat measures, IVFE infused at 2.3 g/kg/d × 5 days	Increased OA in OO/SO group and increased LA in SO group AA decreased in both groups with a greater decrease in the OO/SO group DHA was best maintained by SO group No difference in clinical outcomes	1	SS	NS

(continued)

Table 5. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Göbel (84) 2003	RCT	33 premature infants 28–37 weeks of age	SO OO/SO (80:20)	PN at 55 kcal/kg/d, IVFE infused at 2 g/kg /d, for 2–7 days	No significant changes in AA, total n-6 or n-3 metabolites with some increase in PUFA intermediates in the OO/SO group Higher levels of LA in SO and OA with OO/SO Higher vitamin E/total IVFE with OO/SO suggests better antioxidant status No clinical differences	1	SS	NS
Goulet (85) 1999	RCT	18 pediatric PN-dependent pts on PN for >3 months	SO OO/SO (80:20)	PN at 75 kcal/kg/d, CHO:IVFE (60–80:20–40), IVFE 1.80 g/kg/d infused over 8 hours 3–5 days per week, × 2 months. SO/MCT (50:50) given to all pts during run-in phase days –30 to 0 to standardized lipid profile	There was no difference in TG, apolipoproteins A-I and B, or HDL cholesterol between the groups Total and LDL cholesterol were higher in the SO group EFA status was maintained in OO/SO group Measures of lipid peroxidation were lower in the OO/SO group	1	SS	ND

AA, arachidonic acid; BMT, bone marrow transplantation; CHO, carbohydrate; CRP, C-reactive protein; DHA, docosahexaenoic acid; EFA, essential fatty acids; EFAD, essential fatty acid deficiency; EN, enteral nutrition; EPA, eicosapentaenoic acid; ESR, erythrocyte sedimentation rate; FA, fatty acid; GLA, *γ-linolenic acid;* HBE, Harris-Benedict equation; HDL, high-density lipoproteins; ICU, intensive care unit; IL, interleukin; IVFE, intravenous fat emulsion; LA, linoleic acid; LDL, low-density lipoproteins; LOS, length of stay; MCT, medium-chain triglycerides; NICU, neonatal intensive care unit; NPC, nonprotein calories; OA, oleic acid; OO, olive oil; PN, parenteral nutrition; pts, patients; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trial; REE, resting energy expenditure; SL, structured lipid; SO, soybean oil; TG, triglyceride; TNA, total nutrient admixture; TNF, tumor necrosis factor.

[a]Coding key: SI, categorized by amount of systemic inflammation: 0 = none, 1 = mild to moderate, or 2 = severe. Bio and Clin, result of biochemical marker and clinical end points: ND, not done; NS, no significant difference between groups; SS, statistically significant difference between groups.

Table 6. Review of the Literature Describing the Effect of Fish Oil–Alone Intravenous Fat Emulsion Compared With Soybean Oil–Alone or Soybean Oil and Safflower Oil Intravenous Fat Emulsions

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Adult studies								
Pluess (86) 2007	RCT	16 healthy male volunteers	No IVFE FO 10%	FO group received 0.5 g/kg infused over 6 hours, 48 hours and 24 hours before lipopolysaccharide challenge	EPA and DHA content in platelet phospholipids was low and increased significantly after FO Temperature increased in both groups, but the increase was significantly less in the FO group Increases in norepinephrine, adrenocorticotropin hormone, and TNF-α were significantly blunted by FO	0	SS	ND
Tappy (87) 2006	RCT	24 surgical ICU pts	SO 10% FO 10%	PN at 30 kcal/kg/d, CHO:IVFE (90:10), IVFE infused at 0.25 g/kg/d × 4–5 days	Significantly lower energy expenditure in SO/FO group Glucose and lipid oxidation, glucose production, gluconeogenesis, hepatic de novo lipogenesis, plasma glucose, insulin and glucagon concentrations did not differ between the 2 groups PN was hypercaloric and extremely low (about 10% of calories) in fat producing insulin levels of about 100 μU/mL	1	ND	SS
Mayer (88) 2003	Prospective crossover	12 healthy volunteers	SO 10% FO 10%	IVFE dose 35 g/d infused over 12 hours on 2 consecutive days. This was repeated in 12 weeks using the alternative IVFE	No difference in expression of adhesion molecules CD11b, CD18, CD49, CCR2, and CCR5 Significant inhibition of monocytes' endothelium adhesion and transendothelial monocytes' migration in the FO group Decreased monocyte proinflammatory cytokine (TNF-α, IL-1, IL-6, and IL-8) in FO group with no change in IL-10 generation in response to endotoxin FO increased n-3/n-6 ratio in the plasma free fatty acids fraction and in monocyte membrane lipid pool	0	SS	ND
Mayer (89) 2003	RCT	10 patients with septic shock for 10 days, 8 healthy controls	SO 10% FO 10%	PN dose not stated. CHO:IVFE ratio could not be determined. Infused IVFE 400 mL/d in 3 divided doses (total time 12 h/d) 10 days	Elevated FFA in pts with sepsis vs healthy controls with AA up to 10 times higher In the FO group, there was a decrease in AA levels and an increase in DHA and EPA levels Ex vivo measures of leukocyte function were impaired at baseline in pts with sepsis and did not change or deteriorate in the SO group, whereas these measures improved in the FO group No clinical differences	2	SS	NS

(continued)

Table 6. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Mayer (90) 2003	RCT	21 critically ill pts with sepsis vs 6 healthy participants	SO 10% FO 10%	PN dose not stated. CHO:IVFE ratio could not be determined. Infused IVFE 350 mL/d in 3 divided doses (total time 18 h/d) × 5 days	Plasma FFA concentrations increased in all pts before IVFE infusion vs controls with the greatest increase seen for AA followed by EPA and DHA EPA and DHA increased reversing the ratio of n-6 to n-3 in the FO group Lower mononuclear leukocyte membrane FA levels in pts with sepsis vs controls Compared with baseline, cytokine release was increased 2-fold in the SO group and reduced by one-third in the FO group Serum cytokine levels were increased in pts with sepsis but were similar in both groups	2	SS	ND
Mayser (91) 1998	RCT multicenter	83 chronic plaque-type psoriasis pts with a PASI ×15	SO 10% FO 10%	100 mL IVFE infused over 90 minutes twice daily × 14 days	Both groups had improvement in PASI, but there was a greater decrease in PASI scores in the FO group Significant increase in plasma-free EPA concentration, neutrophil LTB_5, and platelet thromboxane B_3 generation in the FO group	1	SS	SS
Katz (92) 1996	RCT	18 cystic fibrosis pts, underweight with poor oral intake	SO 10% FO 10%	Base formula: PN at 1.15 REE, CHO:IVFE (80:20), SO 20% used, rate infused not stated × 1 month. Study IVFE at dose of 150 mg/kg over 4 hours daily. Oral intake allowed	Pts were >10 years with mean age of 18 years and FEV1 <60% Plasma levels of the n-6 FA series did not change in either group Levels of EPA and DHA significantly increased in the FO group No significant changes occurred in FVC, FEV1, PEFR, FEV1/FVC, or FEF 25–75 (abs value or %) over the 4 weeks in either group	1	SS	NS
Elmadfa (93) 1993	Prospective	13 healthy, young males	FO 10%	50 mL of 10% FO IV over 1 hour	Plasma n-3 FA increased at 1 hour and platelet aggregation and thromboxane synthesis decreased with return to baseline of FA and aggregation at 24 hours	0	SS	ND
Grimminger (94) 1993	RCT	20 acute guttate psoriasis pts	SO 10% FO 10%	50 mL IVFE infused over 60 minutes twice daily × 10 days	Both groups improved, but improvement was marked and significantly better in the FO group EPA-derived 5-lipoxygenase product formation was noted in the FO group but not in the SO group Neutrophil platelet-activating factor generation increased in the SO group but decreased in the FO group	1	SS	SS

(continued)

Table 6. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Pediatric studies								
de Meijer (95) 2010	Open labeled study; prospectively collected data	10 PN-dependent infants and children with IFALD and direct bilirubin × 2 mg/dL	FO 10%	PN at 100 kcal/kg/d, CHO:FO (86:12), FO at 1 g/kg/d as the sole source of fat energy for at least 1 month. PN was the sole source of nutrition for these pts	Median gestational age at the time of birth was 35 weeks, and median age at the start of treatment was 3.5 months After a median time of 3.8 months on exclusive PN and FO, none of the patients developed biochemical or clinical evidence of EFAD *z* scores were not statistically different, indicating no growth impairment Median direct bilirubin levels improved in 9 pts from 6.8–0.9 mg/dL	1	SS	SS
Soden (96) 2010	Case series	2 children with irreversible IFALD	FO 10%	PN at 100–110 kcal/kg/d; CHO:IVFE (70–90:10–30) FO infused at 1 g/kg/d; both had previously received SO 1–3 g/kg/d	Cholestasis (bilirubin, GGT) improved in both patients, although hepatocellular enzymes (AST, ALT) remained increased while on FO Liver biopsies before FO revealed moderately severe portal fibrosis and hepatitis. After FO, hepatitis improved, but portal fibrosis advanced despite improved biochemical parameters Biopsies were not done exactly when FO was begun, so it is possible that liver disease progressed while the pt was still on SO	1	SS	NS
Puder (97) 2009	Retrospective with historical controls	91 PN-dependent children <2 years of age with IFALD and direct bilirubin × 2 mg/dL	SO (49 pts) FO 10% (42 pts)	PN with SO 1–4 g/kg/d compared with PN with FO 1 g/kg/d infused over 12–24 hours	Three deaths and 1 liver transplantation occurred in the FO group, compared with 12 deaths and 6 transplants in the SO group, which was significant Among survivors not transplanted during PN, cholestasis reversed while receiving PN in 19 of 38 pts in the FO group vs 2 of 36 pts in the SO group The reversal of cholestasis was 6 times faster in the FO group (95% CI, 2.0–37.3) FO was not associated with hypertriglyceridemia, coagulopathy, or EFAD	1	SS	SS
Lee (98) 2009	Prospective with historical control	77 PN-dependent children <2 years of age with IFALD and direct bilirubin × 2 mg/dL	SO (59 pts) FO 10% (18 pts)	PN with SO 1–4 g/kg/d compared with PN with FO 1 g/kg/d infused over 12 hours; both groups on PN for about 2 months	TG levels decreased significantly in the FO group but not in the SO group Triglyceride correlated positively with direct bilirubin in both groups Inverse association between TGs and serum albumin	1	SS	ND

(continued)

Table 6. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Gura (99) 2008	Retrospective with historical controls	39 PN-dependent children <2 years of age with IFALD and direct bilirubin 2 mg/dL	SO or SO/SFO (50:50) in controls FO 10%	PN (median dose) at 84 kcal/kg/d for SO or SO/SFO and 69 with FO, CHO:IVFE (81:19), SO and SO/SFO at 1–4 g/kg/d vs FO at 1 g/kg/d, FO infused over 12–20 hours	Cholestasis reversed 4.8 times faster in the FO group than conventional IVFE (6.8 times faster in analysis adjusted for baseline bilirubin concentration, gestational age, and NEC diagnosis) 2 deaths and 0 liver transplantations in the FO group 7 deaths and 2 transplantations in the conventional IVFE group FO not associated with EFAD, hypertriglyceridemia, coagulopathy, infections, or growth delay	1	ND	SS

AA, arachidonic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHO, carbohydrate; CI, confidence interval; DHA, docosahexaenoic acid; EFAD, essential fatty acid deficiency; FEF, forced expiratory flow; *FEV1, f*orced expiratory volume in 1 second; FA, fatty acid; FFA, free fatty acid; FO, fish oil; *FVC, f*orced vital capacity; EPA, eicosapentaenoic acid; GGT, γ-glutamyl transpeptidase; GI, gastrointestinal; ICU, intensive care unit; IFALD, intestinal failure–associated liver disease; IL, interleukin; IV, intravenous; IVFE, intravenous fat emulsion; NEC, necrotizing enterocolitis; PASI, Psoriasis Area and Severity Index; *PEFR, peak expiratory flow rate*; PN, parenteral nutrition; pts, patients; RCT, randomized controlled trial; REE, resting energy expenditure; SFO, safflower oil; SO, soybean oil; TG, triglyceride; TNF, tumor necrosis factor.

[a]Coding key: SI, categorized by amount of systemic inflammation: 0 = none, 1 = mild to moderate, or 2 = severe. Bio and Clin, result of biochemical marker and clinical end points: ND, not done; NS, no significant difference between groups; SS, statistically significant difference between groups.

Table 7. Review of the Literature Comparing Fish Oil Intravenous Fat Emulsion Combined or Infused With Soybean Oil or Soybean Oil and Medium-Chain Triglyceride Intravenous Fat Emulsion to Either Soybean Oil or Soybean Oil and Medium-Chain Triglyceride Intravenous Fat Emulsions

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Adult studies								
Jiang (100) 2010	RCT multicenter	206 GI cancer surgery pts	SO SO/FO 10% (5:1)	PN at 27 kcal/kg/d, CHO:IVFE (45:55), IVFE infused at 1.2 g/kg/d × 7 days	Median difference between CD4/CD8 between postoperative days 1 and 8 was significantly greater for the SO/FO group Trend toward reduced infection rate in SO/FO group Lower incidence of SIRS in SO/FO group LOS less for SO/FO group Medical costs were similar for both groups	1	SS	SS
Wang (101) 2009	RCT	56 pts with severe acute pancreatitis	SO SO/FO 10% (75–80:15–20)[b]	PN at 25 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1g/kg/d × 5 days, FO dose ranged from 0.15–0.2 g/kg/d	Increased IL-10 ($P = .04$) and HLA-DR ($P = .01$) expression in SO/FO group No significant differences in CD4/CD8 No significant difference in infection or surgery rates	2	SS	NS
Liang (102) 2008	RCT	42 postoperative pts for colorectal cancer TNM stage I–III	SO SO/FO 10% (5:1)	PN at 27 kcal/kg/d, CHO:IVFE (45:55), IVFE as 1.2 g/kg/d × 7 days	Serum IL-6 levels were significantly less in the SO/FO group $CD4^+/CD8^+$ lymphocyte ratio was significantly higher in the SO/FO group Serum TNF levels decreased and $CD3^+$ and $CD4^+$ lymphocytes were increased in the SO/FO group, but not significantly Hospital LOS was shorter for the SO/FO group, but not significantly There was no difference in overall mortality	1	SS	NS
Friesecke (103) 2008	RCT	166 critical care pts stratified SIRS vs non-SIRS (115 vs 51)	SO/MCT (50:50) SO/MCT/FO (42:42:16)[b]	PN 22 kcal/kg /d (IBW), CHO:IVFE (45:55), IVFE infused at 0.92 g/kg/d × 7 days EN given as tolerated, providing up to 25% of IVFE	No difference in IL-6 and monocyte HLA-DR expression No difference in clinical outcomes, which included nosocomial infections, duration of mechanical ventilation, length of ICU stay, and 28-day mortality	1–2	NS	NS
Wang (104) 2008	RCT	40 pts with severe acute pancreatitis	SO SO/FO 10% (75–80:15–20)[b]	PN at 25 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1 g/kg/d × 5 days, FO dose ranged from 0.15–0.2 g/kg/d	The SO/FO group had a significant increase in serum EPA levels, decreased CRP, and better oxygenation Decreased days on continuous renal replacement therapy	2	SS	SS

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Table 7. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Wendel (105) 2007	RCT	44 postoperative GI and pancreas cancer pts	SO 10% SO/FO 10% (4:1)	PN at 25 kcal/kg/d, CHO:IVFE (57:43), IVFE infused at 1 g/kg/d × 5 days	Higher TG levels for the SO/FO group Total cholesterol, LDL-cholesterol, and TGs increased in both groups LDL-cholesterol was significantly higher in the SO group compared with the SO/FO group on postoperative days 3 and 4 but not on day 5 VLDL-cholesterol rose earlier and reached significantly higher in the SO/FO group compared with the SO group	1	SS	ND
Klek (106) 2005	RCT	90 pts postgastrectomy for gastric carcinoma, nutrition normal to mildly abnormal	SO/MCT SO/MCT/ glutamine SO/MCT/FO	PN provided 0.15–0.2 g/kg/d of N, NPC:N 130–170:1, for 7–11 days. Total CHO and IVFE dose not given. SO/MCT (1:1) 10% and 20%; FO 10% at 1 g/kg/d	Faster and greater rise in prealbumin in both immunomodulating groups Total lymphocyte count also better in these groups, but NS Short LOS for both study groups compared with SO/MCT Significant increased cost for FO group No difference in surgical complications or liver or kidney function	1	SS	NS
Heller (107) 2004[c]	RCT	44 ICU pts after GI and pancreas cancer surgery	SO 10% SO/FO 10% (4:1)	PN at 25 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1 g/kg/d × 5 days	Decrease in liver function tests with SO/FO group No difference with GI function or acute phase parameters No difference in ICU or hospital LOS and complication rates	1	SS	NS
Tsekos (108) 2004	Retrospective	249 ICU pts post–abdominal and urogenital surgery	SO/MCT (50:50) (n = 110) SO/MCT/FO (42:42:16)[b] (n = 86) SO/MCT/FO (42:42:16)[b] given preoperatively (n = 53)	PN at 26 kcal/kg/d, CHO:IVFE (67:33), IVFE infused at 0.68 g/kg/d (rate of IVFE infusion not stated) × 5.3–6.2 days Groups 1 and 2 received postoperative PN. Group 3 also received preoperative PN for 2–3 days	Mortality rates were significantly lower in the group that received preoperative SO/MCT/FO compared with SO/MCT The need for mechanical ventilation and the hospital LOS were similarly affected There was no difference in ICU LOS, although readmission to the ICU was lower in both SO/MCT/FO groups	1	ND	SS
Heller (109) 2002[c]	RCT	44 ICU pts after GI and pancreas cancer surgery	SO 10% SO/FO 10% (4:1)	PN at 25 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1 g/kg/d × 5 days	No difference in coagulation factors (thromboplastin, partial thromboplastin, fibrinogen, antithrombin III, factor VIIa, and factor XIIa) or platelet number and function was seen between groups FO at a maximal dose of 0.2 g/kg/d does not result in abnormalities in hemostasis	1	NS	ND

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Table 7. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Weiss (110) 2002	RCT	24 pts undergoing elective major abdominal surgery without malnutrition	SO SO/FO 10% (5:1)[b]	PN on postoperative days 4 and 5 to all pts; 90 g amino acids, 180 g dextrose, and 50 g SO/d FO was given on days –1 (preoperatively) –5 (postoperatively)	Significantly lower IL-6 and higher HLA-DR levels were seen in the FO group, suggesting a lower inflammatory response and improved immunoregulation to surgery Reduced postoperative stay in medical wards, but not significant No significant difference in ICU or total LOS	1	SS	NS
Schauder (111) 2002	RCT	60 pts after colorectal surgery, mostly for malignancy	No IVFE SO 10% SO/FO 10% (83:17)	PN at 30 kcal/kg/d, CHO:IVFE (45:55), IVFE infused at 1.2 g/kg/d, 1 day preoperatively and 5 days postoperatively	Production of IL-2 and TNF-α was significantly enhanced in the SO/FO group IFN-γ declined significantly in the no IVFE group and was best maintained in the SO/FO group There was a significant decrease in total number of lymphocytes in all groups, but the ratio of CD4/CD8 lymphocytes improved only in the IVFE groups	1	SS	ND
Roulet (112) 1997	RCT	19 after total esophagectomy for squamous cell cancer	SO SO/FO 10% (90:10)[b]	PN at 33 kcal/kg/d, CHO:IVFE (47:53), IVFE infused at 1.45 g/kg/d × 7 days	Compared with SO, the SO/FO group had a significant increase in the weight percent of EPA in platelet phosphatidylcholine and phosphotidylethanolamine The SO/FO group experience a decrease of maximal reaction speed and an increase of latency with collagen as an aggregating factor	1	SS	ND
Morlion (113) 1996	RCT	20 pts after abdominal surgery for benign and malignant disease	SO SO/FO 10% (85:15)[b]	PN at 26 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1 g/kg/d × 5 days	Plasma PL content of EPA, DHA, and ALA increased with SO/FO LT generation of activated leukocytes found LTB_5 increased 1.5-fold and LTC_5 increased 7-fold in the SO/FO group LTC_5 generation doubled in the SO group	1	SS	ND

(continued)

Table 7. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Ikehata (114) 1992	RCT	10 Crohn's patients	SO 10% SO/FO 10% (85:15)	PN at 35 kcal/kg/d, CHO:IVFE (85:15), IVFE dose 25 g daily × 2 weeks	Polymorphonuclear leukocyte generation of leukotrienes was measured at 0, 1, and 2 weeks Both groups had improvement in markers of clinical activity of disease that were not significantly different Compared with healthy controls, LTB_5 generation in the pts was significantly diminished LTB_4 generation was similar in pts and controls and did not change in either group LTB_5 generation and LTB_5:LTB_4 ratio decreased with SO/FO	1	SS	NS
Pediatric studies								
Diamond (115) 2009	Retrospective	12 PN-dependent children with advanced IFALD	SO/FO 10% (1:1)	Chronic PN pts had been on SO 0.9–2.9 g/kg/d. For first week, received 1.5 g/kg/d SO with 0.05 g/kg/d FO, then continued 2 g/kg/d SO/FO 1:1, × 24 weeks	The median age was 7.5 (range, 3.6–46) months, and median PN duration before starting FO was 28.4 (range, 15.3–55.3) weeks Median initial serum conjugated bilirubin was 137 (range, 54–203) µmol/L (8.06 [3.18–11.94] mg/dL) Markers of hepatic inflammation and nutrition status improved while on treatment 9 of 12 (75%) pts had resolution of hyperbilirubinemia within a median of 24 weeks: 4 pts while on SO/FO and 5 after stopping SO and taking FO monotherapy 3 other pts had a liver-intestine transplant Improved outcomes compared with historical controls	1	SS	SS

ALA, α-linolenic acid; CHO, carbohydrate; CRP, C-reactive protein; DHA, docosahexaenoic acid; GI, gastrointestinal; EN, enteral nutrition; EPA, eicosapentaenoic acid; FO, fish oil; IBW, ideal body weight; ICU, intensive care unit; IFALD, intestinal failure–associated liver disease; IFN, interferon; IL, interleukin; IVFE, intravenous fat emulsion; LDL, low-density lipoproteins; LOS, length of stay; LT, leukotriene; MCT, medium-chain triglycerides; N, nitrogen; NPC, nonprotein calories; NS, not significant; PN, parenteral nutrition; PL, phospholipid; pts, patients; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome; SO, soybean oil; TG, triglyceride; TNF, tumor necrosis factor; TNM, tumor, node, metastases; VLDL, very low-density lipoprotein.

[a]Coding key: SI, categorized by amount of systemic inflammation: 0 = none, 1 = mild to moderate, or 2 = severe. Bio and Clin, result of biochemical marker and clinical end points: ND, not done; NS, no significant difference between groups; SS, statistically significant difference between groups.
[b]Indicates that 10% FO was added to the 20% control emulsion in the g% concentrations shown.
[c]The study by Heller et al (2004)[107] is a post hoc analysis of the same patients used in the study by Heller et al (2002).[109]

Table 8. Review of the Literature Comparing Commercially Compounded Combinations of Fish Oil, Olive Oil, Medium-Chain Triglycerides, and/or Soybean Oil Intravenous Fat Emulsions to Soybean Oil–Alone or Soybean Oil and Medium-Chain Triglyceride Intravenous Fat Emulsions

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Adult studies								
Barbosa (116) 2010	RCT	23 pts with sepsis and SIRS with or without organ failure and hypotension	SO/MCT (50:50) SO/MCT/FO (40:50:10)	SO/MCT group received 25 kcal/kg/d, CHO:IVFE (60:40), IVFE infused at 0.9 g/kg/d. SO/MCT/FO group received 29 kcal/kg/d, CHO:IVFE (66:34), IVFE infused at 0.9 g/kg/d × 5 days for both	IL-6 and IL-10 decreased significantly in the SO/MCT/FO group compared with the SO/MCT group PO_2/FiO_2 ratio was significantly higher for the SO/MCT/FO group No significant difference in ventilator days, hospital or ICU LOS, or mortality	2	SS	ND
Badía-Tahull (117) 2010[b]	RCT	27 pts after surgery for gastric, pancreatic, esophageal cancer and 1 pt each with colon polyps and a locally advanced gynecologic cancer	OO/SO (80:20) OO/SO/FO (66.7:16.7:16.6)	PN as TNA at 26 kcal/kg/d, CHO:FO (56:44), IVFE infused at 0.88 g/kg/d × 5 days	There was a significantly lower incidence of infections in the OO/SO/FO group CRP, prealbumin, WBC, and other safety parameters were similar for both groups	1	NS	SS
Piper (118) 2009	RCT	44 pts with cancer after abdominal surgery (GI and GU) or large craniomaxillofacial resections	SO/MCT/OO/FO (30:30:25:15) OO/SO (80:20)	PN at NPC dose of 25 kcal/kg/d, CHO:IVFE (60:40), IVFE infused at 1 g/kg/d × 5 days	AST, ALT, and α-glutathione S-transferase were normal at baseline and remained in this range in the SO/MCT/OO/FO group and significantly increased in the OO/FO group TG increased significantly in the OO/FO group	1	SS	ND
Simoens (119) 2008	Prospective crossover	8 normolipemic pts	SO/MCT (1:1) SO/MCT/FO (40:50:10)	Hypertriglyceridemic clamp technique with TG of 3 mmol/L using 0.164–0.204 g/kg/h × 5 hours on 4 consecutive days, then crossed over 6 weeks later to repeat the protocol with the other IVFE. Patients also received amino acids 0.05 g/kg from −2.5 hours to +5 hours and CHO 0.25 g/kg from −2.5 hours to 0 hours, then 0.16 g/kg to +5 hours	There was rapid enrichment of LDL and HDL for both emulsions: LDL enrichment was significantly higher at 5 hours on day 4 and HDL enrichment was significantly higher at 5 hours on days 1 and 4 for the SO/MCT/FO group Triacylglycerol clearance significantly improved in the SO/MCT/FO group EPA, but not DHA, enrichment occurred in the PL content of platelets and WBC with SO/MCT/FO AA enrichment occurred in the PL content of platelets in the SO/MCT group, whereas other PUFAs did not	0	SS	ND

(continued)

Table 8. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Berger (120) 2008	RCT	24 pts after abdominal aortic aneurysm repair	SO/MCT (50:50) SO/MCT/FO (40:50:10)	PN at 130% preoperative REE; approximately 22 kcal/kg/d, CHO:IVFE (53:47), IVFE infused 1 g/kg/d, metabolic studies done on days 3–4	Trends toward lower temperature, EPA and DHA enrichment, and shorter ICU and hospital LOS in the SO/MCT/FO group There were no differences in laboratory, inflammatory, or metabolic data or organ failure Endogenous glucose production and gluconeogenesis were not suppressed and were not different between groups	1	NS	NS
Wichmann (121) 2007	RCT multicenter	256 pts after abdominal surgery for benign and malignant disease	SO SO/MCT/ FO (40:50:10)	PN dose and CHO:IVFE not stated. IVFE infused at 1.4 g/kg/d × 5 days	Plasma levels of EPA, leukotriene B_5, and antioxidant content were significantly increased in the SO/MCT/FO group There was a statistically faster decrease in WBC, increase in platelet count, and lower TG level after surgery in the SO/MCT/FO group, although the values were mildly abnormal Significantly shorter LOS	1	SS	SS
Senkal (122) 2007	RCT	40 pts after elective colorectal surgery	SO/MCT (50:50) SO/MCT/FO (40:50:10)	PN provided 2297 kcal/d, with IVFE dose of 100 g/d × 5 days. Dosing was not weight based	Both IVFEs were well tolerated and clinical outcome measures were similar between groups EPA levels were increased significantly in serum PLs and erythrocyte membranes, whereas DHA levels were increased significantly in the serum PLs in the SO/MCT/FO group AA levels did not change and were similar in both groups	1	SS	NS
Grimm (123) 2006	RCT 2 centers	31 well-nourished pts after major abdominal surgery	SO SO/MCT/OO/FO (30:30:25:15)	PN at 33 kcal/kg/d, CHO:IVFE (44:56), IVFE infused at 1.5 g/kg/d × 5 days	Significantly lower LOS in the SO/MCT/OO/FO group SO/MCT/OO/FO group resulted in a significant increase in total n-3 FA, EPA, and DHA and significant decrease in total n-6 FA, LA, and AA There was a significant increase in the ratio of n-3/n-6 in the SO/MCT/OO/FO group Leukocyte generation of LTB_5 was significantly increased in the SO/MCT/OO/FO group	1	SS	SS

(continued)

Table 8. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Mertes (124) 2006	RCT multicenter	249 pts after thoracoabdominal surgery	SO SO/MCT/OO/FO (30%/30%/25%/15%)	PN at 33 kcal/kg/d, CHO:IVFE (44:56), IVFE infused at 1.2 g/kg/d × 5 days	Study powered to show that control and study emulsion were equivalent for the effect on serum TG 50 pts excluded from the analysis for protocol violation, most often incorrect dextrose or amino acid dose Trend toward lower liver function tests and LOS in the SO/MCT/OO/FO group Adverse events were reported in 6.8% of the intention-to-treat population; nausea and vomiting were the most common symptoms	1	NS	NS
Schlotzer (125) 2004	Prospective crossover	12 healthy adult male volunteers	SO SO/MCT/OO/FO (30%/30%/25%/15%)	IVFE infused at 0.125 g/kg/h over 6 hours; other IVFE infused at same rate after 6-day washout period; study parameters measured before, during, and within 24 hours postinfusion of IVFE	5 pts in the SO/MCT/OO/FO group and 1 pt in the SO group had an adverse event. All were mild and reversible; headache was the most common. There was no clinically relevant change in vital signs and lab parameters in either group. Lipid metabolism/routine biochemistry parameters comparable in both groups The SO/MCT/OO/FO group had a significantly lower serum TG, had a reduced $t_{1/2}$ of serum TGs, and had a faster steady state (after the start of infusion) and faster baseline values (after the end of the infusion) of serum TG levels	0	SS	ND
Antébi (126) 2004	RCT	20 pts after thoracoabdominal surgery	SO SO/MCT/OO/FO (30:30:25:15)	PN at 33 kcal/kg/d, CHO:FO (44:56), IVFE at 1.5 g/kg/d × 5 days	Liver function tests and CRP were similarly increased in both groups, but ALT and CRP were statistically increased in the SO group Increased plasma lipophilic antioxidant vitamins and LDL–α-tocopherol levels in the SO/MCT/OO/FO group	1	SS	ND
Köller (127) 2003	RCT	30 pts after colorectal surgery for benign and malignant disease	SO SO/MCT/FO (40:50:10)	PN at 35 kcal/kg/d, CHO:IVFE (50:50), IVFE infused at 1.4 g/kg/d ×5 days	Leukocyte-stimulated leukotriene generation found a significant increase in LTB_5 series, but not LTB_4 or LTC_5, in the SO/MCT/FO group There was also a significant increase in the LTB_5/LTB_4 ratio in the SO/MCT/FO group	1	SS	ND

(continued)

Table 8. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Linseisen (128) 2000	RCT	33 pts undergoing major abdominal surgery	SO SO/MCT/FO (40:50:10)	PN at 35 kcal/kg/d, CHO:IVFE (48:52), IVFE infused at 1.4 g/kg/d × 5 days	There was a significant increase in EPA in the SO/MCT/FO group and an increase in LA in the SO group Tocopherol concentrations reflected the relative amounts in the IVFE with α-tocopherol increasing in the SO/MCT/FO group and γ-tocopherol increasing in the SO group Plasma concentrations of carotenoids, vitamin C, or selenium decreased on PN to a similar degree in both groups Cholesterol oxidation products as a measure of in vivo lipid peroxidation revealed no changes in either group	1	SS	ND
Wachtler (129) 1997	RCT	40 pts after surgery for colorectal cancer	SO/MCT (50:50) SO/MCT/FO (40:50:10)	PN, based on stated amounts of substrate, 2600 kcal/d, CHO:IVFE (50:50), IVFE infused at 1.32 kcal/kg/d × 5 days	Stimulated leukocytes generated significantly higher LTB_5 and lower LTB_4 levels, resulting in a lower (less inflammatory) ratio of LTB_4/LTB_5 in the SO/MCT/FO group There was a significantly lower concentration of IL-6, IL-10, and TNF-α in the SO/MCT/FO group No difference in postoperative infections, Acute Physiology and Chronic Health Evaluation II scores, or ICU or hospital LOS	1	SS	NS
Pediatric studies								
Tomsits (130) 2010	RCT	60 premature infants (gestational age <34 weeks), BW 1–2.5kg,	SO SO/MCT/OO/FO (30:30:25:15)	PN started 3–7 days after birth, given 7–14 days, block randomized by weight, IVFE started at 0.5 g/kg/d on day 1 and increased by 0.5-g increments to a goal dose of 2 g/kg/d by day 4. Dose of amino acids 2.5 g/kg, CHO 10.3 g/kg, CHO:IVFE (64:34)	Primary study end points were TG level and growth Adverse events, serum TG, vital signs, local tolerance, and clinical laboratory did not show noticeable group differences At study end, γ-glutamyl transferase was significantly lower in the SO/MCT/OO/FO group vs the SO group The relative increase in body weight was not different between groups There was a significant increase in n-3 FA in red blood cell phospholipids and n-3:n-6 FA ratio in the SO/MCT/OO/FO group vs the SO group Plasma α-tocopherol was increased significantly as a result of the supplement added to SO/MCT/OO/FO	1	SS	NS

(continued)

Table 8. (continued)

Lead Author (Reference No.)/ Year	Study Design	Patient Population	Groups	Treatments	Outcome Results/Conclusions/Comments	SI[a]	Bio[a]	Clin[a]
Goulet (131) 2010	RCT	28 PN-dependent children on PN for 5 months to 11 years	SO SO/MCT/OO/FO (30:30:25:15)	All pts were given a 1-week run-in period to stabilize their PN formula using the SO. Throughout the study, PN was given 4–7 nights/wk × 28 days. IVFE infused 4–5 times/wk with goal dose of 2 g/kg/d. Average PN dose received was 61.5 kcal/kg/d, CHO:IVFE (74:26; range, 60–80:40–20), IVFE infused 1.42 g/kg/d	There were no significant differences in laboratory safety parameters, including liver enzymes, between the groups following treatment The mean changes in the total bilirubin concentration between the initial and final values were significantly lower in the SO/MCT/OO/FO group vs SO group, but all values were within the normal range In plasma and red blood cell phospholipids, EPA and DHA increased significantly in the SO/MCT/OO/FO group following treatment The n-3:n-6 FA ratio was significantly elevated with SO/MCT/OO/FO compared with SO following treatment Plasma α-tocopherol was increased significantly as a result of the supplement added to SO/MCT/OO/FO The low-density lipoprotein thiobarbituric acid reactive substances (TBARS) concentrations (a measure of lipid peroxidation) were not significantly different between the groups	1	SS	NS
Skouroliakou (132) 2010	RCT	38 premature infants (gestational age <32 weeks), BW <1.5 kg	SO SO/MCT/OO/FO (30:30:25:15)	PN at 72 kcal/kg/d, CHO:IVFE (65:35), IVFE infused at 2.3 g/kg/d × 14 days. EN provided <20% of energy intake	Study powered to see difference in antioxidant markers; 5 pts excluded after randomization Serum vitamin A concentrations were improved in both groups, and vitamin E was improved only in the SO/MCT/OO/FO group Total antioxidant potential, measured using a commercially obtained kit, significantly increased in the SO/MCT/OO/FO group, whereas the increase in the SO group was minimal Growth, infections, ventilator days, and LOS were similar for both groups	1	SS	NS

AA, arachidonic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; CHO, carbohydrate; CRP, C-reactive protein; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; FA, fatty acid; FIO_2, fraction of inspired oxygen; FO, fish oil; GI, gastrointestinal; GU, genito-urinary; HDL, high-density lipoproteins; ICU, intensive care unit; IL, interleukin; IVFE, intravenous fat emulsion; LA, linoleic acid; LDL, low-density lipoproteins; LOS, length of stay; MCT, medium-chain triglycerides; NPC, nonprotein calories; OO, olive oil; PL, phospholipid; PN, parenteral nutrition; PO_2, partial pressure of oxygen; pts, patients; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; REE, resting energy expenditures; SIRS, systemic inflammatory response syndrome; SO, soybean oil; TG, triglyceride; TNA, total nutrient admixture; TNF, tumor necrosis factor; WBC, white blood count.

[a]Coding key: SI, categorized by amount of systemic inflammation: 0 = none, 1 = mild to moderate, or 2 = severe. Bio and Clin, result of biochemical marker and clinical end points: ND, not done; NS, no significant difference between groups; SS, statistically significant difference between groups.
[b]The study IVFE used in this study was extemporaneously prepared, so although it complies with the criteria for this table, it does not use a commercially available product.

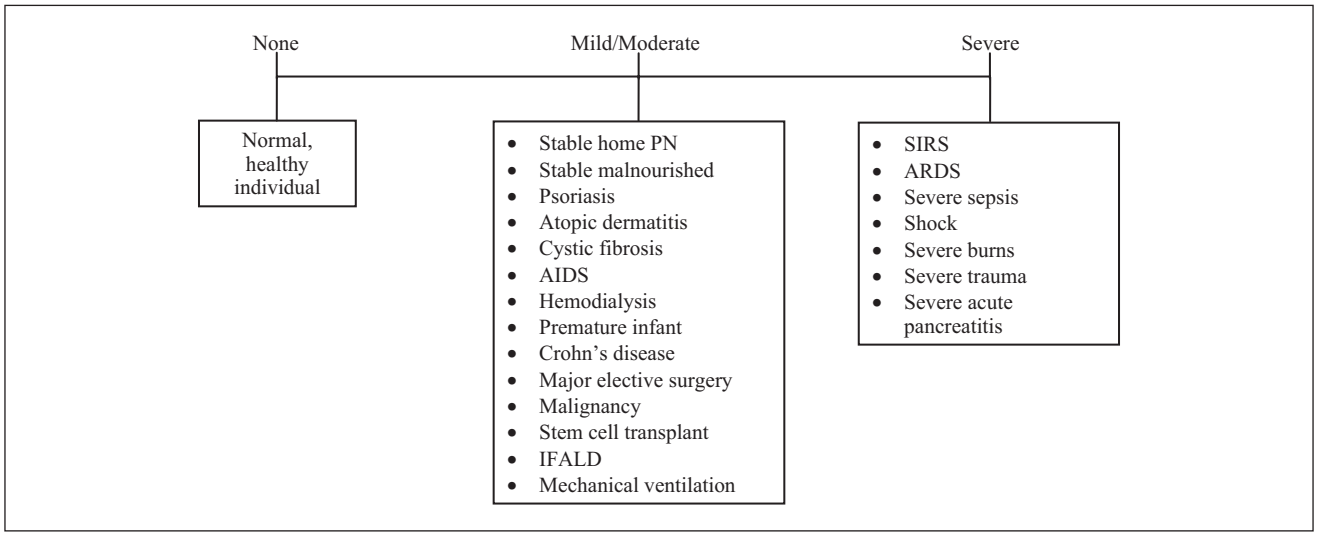

Figure 5. Categorization of patient populations studied regarding their degree of systemic inflammation.
AIDS, acquired immune deficiency syndrome; ARDS, adult respiratory distress syndrome; IFALD, intestinal failure–associated liver disease; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome.

this percentage across the 5 groups of IVFEs, but again, the FO-alone group had the highest percentage (FO alone, 67%; MCT, 40%; FO with SO and/or MCT, 36%; combination IVFE, 30%, and OO, 18%).

When dividing the studies according to the degree of systemic inflammation in the patient population, there was a slight trend toward increasing the percentage of studies that revealed a significant improvement in biochemical markers with increasing systemic inflammation (none, 83%; mild to moderate, 86%; and severe, 87%). Because clinical outcomes are not an appropriate outcome variable in normal healthy individuals, there were no clinical outcome data on individuals with no systemic inflammation. However, the percentage of studies with positive clinical outcomes was similar for patients with mild to moderate and severe systemic inflammation (mild to moderate, 37%; severe, 40%). But the studies are too heterogeneous to make a definitive conclusion on this point.

Use of FO IVFE seems to be especially advantageous in treating infants and children with IFALD. Several different approaches to IVFE therapy have been tried in this clinical setting. The original approach was to use monotherapy with FO IVFE alone.[97,99,136-139] All forms of SO IVFE were discontinued, and treatment with FO IVFE alone was initiated with a minimum goal dose of 1 g/kg/d, a much higher dose than the manufacturer's labeled dose of 0.2 g/kg/d, which was based on the FO IVFE being administered in conjunction with a conventional SO IVFE. In 1 case report, FO IVFE dosed at 1.5 g/kg/d was used and was well tolerated.[136] In most instances, clinical improvement was seen approximately 30 days later, with resolution of biochemical evidence of cholestasis within 60–90 days. Confounding factors such as sepsis or surgical procedures may have delayed treatment response. Early treatment has been shown to be more effective, as critically ill patients or those with severe cholestasis and/or cirrhosis failed to show improvement.[137] To date, no RCT has been performed comparing equal doses of SO IVFE with FO IVFE in the treatment of preexisting IFALD. Concerns with the use of FO monotherapy include the development of EFAD or bleeding. Neither complication has been reported to date, although EFAD can occur if doses <1 g/kg/d are used.[95,97,99,140,141] One case report described Burr cell anemia in an infant receiving FO monotherapy that resolved with discontinuation of the FO IVFE, but other factors may have contributed to the development of the anemia.[142] Another case report evaluating liver biopsy findings in 2 children treated with FO monotherapy failed to draw any meaningful conclusions due to the timing of the biopsies in relation to the start of therapy with FO.[96] Currently, IVFEs composed solely of FO are only available on a compassionate use basis and require prior approval via an investigational new drug (IND) application from the U.S. Food and Drug Administration (FDA).

A second approach has emerged in which patients receive 50:50 doses by weight of both SO and FO IVFE for the treatment of IFALD.[143] The rationale for this treatment regimen was to prevent the development of EFAD and to theoretically provide a more balanced IVFE source. In 12 patients treated with this combination therapy of 1 g/kg/d of each fat source (total 2 g/kg/d), no patients succumbed due to liver failure, but several patients did require a liver transplant. Five other patients had to have the SO IVFE discontinued in order for serum bilirubin levels to normalize.[143] These findings suggest that in patients with preexisting IFALD, FO monotherapy may

be more effective and that combination therapy may delay clinical response. Because of its low arachidonic acid content and low LA content, concerns with FO as monotherapy continue to be raised as growth retardation and delayed psychomotor neurodevelopment have been seen in various animal models fed FO in the perinatal period, suggesting that the need for mixed fat emulsions containing FO would be preferable over FO alone.[144]

The third approach uses a combination IVFE that contains SO, MCT, OO, and FO. The total amount of FO provided in this blended IVFE was less than the FO IVFE-alone regimens described previously. In 1 study, the combination IVFE was well tolerated, but the only significant difference in outcomes was that the combination IVFE group had a significantly lower serum γ-glutamyl transferase concentration. One double-blind RCT to assess the efficacy and safety of this new IVFE in children receiving home parenteral nutrition (HPN) has been conducted. Patients were randomized to either the same combination IVFE as described previously or a standard SO IVFE.[131] The IVFE was administered 4–5 times per week at a goal dose of 2 g/kg/d. The changes in the total bilirubin concentration between the initial and final values were significantly different between groups, with the children receiving the combination IVFE having lower levels in comparison with the SO IVFE.

Goulet et al[145] suggested that using a combination of 80:20 by weight of OO and SO IVFE may be beneficial in preventing IFALD, but no studies have been conducted using this IVFE. Presumably, if this IVFE demonstrates effectiveness in future trials, it would most likely be due to the reduction in the amount of SO provided to the patient.

Although different, each of these approaches with respect to types of oils provided has demonstrated improvement in patients with IFALD. In each instance, patients had the overall dose of the SO component reduced, which may have also been a contributing factor for why these children experienced improvement in hepatic function. It has been suggested that simply reducing the dose of SO IVFE to 1 g/kg/d[146] may be effective in preventing IFALD, although head-to-head trials comparing equal doses of these products have not occurred. Until such studies are conducted or these alternative IVFEs become available, it may be prudent to limit IVFE intake in infants and children on prolonged (ie, >3 weeks) PN therapy to a maximum of 1 g/kg/d of SO IVFE as an effort to prevent IFALD.

Several meta-analyses have been performed[17-20] to systematically review the available evidence of the various IVFE studies in hopes of deriving some meaningful conclusions regarding the safety and efficacy of these products (Table 9). Two such meta-analyses[17,18] were unable to demonstrate any significant harmful or beneficial effects when comparing the various IVFEs because of the heterogeneity of the selected studies coupled with an underpowering of the sample size such that investigators were unable to detect even a small effect of the different regimens on outcomes. These earlier meta-analyses included a wide variety of studies that used an assortment of dosing schemes, different durations of therapy, and patient characteristics, which made it impossible to draw any meaningful conclusions. Chen et al[19] attempted to address the limitations of these earlier meta-analyses by limiting the patient population in their meta-analysis to patients undergoing major abdominal surgery. They found that doses of 0.07–0.225 g/kg/d of FO IVFE were safe, well tolerated, and resulted in altering fatty acid profiles as well as leukotriene synthesis. Use of FO IVFE in patients undergoing major abdominal surgery was also associated with a decreased incidence of postoperative infections and shorter hospital and intensive care unit (ICU) length of stay (LOS). However, they were unable to demonstrate that using FO IVFE improved the postoperative mortality rate and, like the authors of previously published IVFE meta-analyses, concluded that larger trials with more rigorous design are still needed. The most recently published meta-analysis[20] also limited the analysis to studies involving surgical patients receiving FO IVFE and had similar findings to Chen et al[19] with a significant decrease in postoperative infectious complications and ICU LOS as well as a trend in a decrease toward a hospital LOS. Again, there was no significant difference in postoperative mortality.

Published guidelines on the clinical use of IVFEs are provided in Table 10. The combined A.S.P.E.N. and Society for Critical Care Medicine (SCCM) guidelines for critically ill patients recommend withholding IVFE during the first week in the ICU because of concerns about the proinflammatory effects of SO IVFE, the only IVFE available in the United States. The Canadian Critical Care Nutrition (CCCN) group suggests that withholding IVFE high in SO should be considered when PN is given for <10 days. The European Society for Clinical Nutrition and Metabolism (ESPEN), on the other hand, takes a more aggressive stance that IVFEs are well tolerated at doses up to 1.5 g/kg/d administered over as little as 12 hours. ESPEN further points out the safety of SO/MCT IVFEs in the ICU patient population, although additional studies are needed to confirm the advantages of these mixtures over IVFEs containing SO alone.

ESPEN states that OO IVFEs are also well tolerated and that the use of FO IVFE may decrease LOS in the critically ill, and it cites grade C evidence that favors the use of SO and MCT IVFEs and FO IVFEs in patients requiring HPN. However, there is insufficient evidence to support the use of FO IVFEs in patients with inflammatory bowel disease. For patients with cirrhosis or nonalcoholic steatohepatitis (NASH), IVFEs with lower ω-6 FA content than SO IVFEs are recommended.

Thus, there is considerable divergence of opinion regarding the use of SO IVFEs in the critically ill. An IVFE dose of 1.5 g/kg/d, especially when administered over 12 hours, provides lipid energy in excess of fat oxidation capacity in many if not most patients. Moreover, when IVFEs are withheld for short

Table 9. Summary of Published Meta-Analyses of Various Intravenous Fat Emulsions[a]

Lead Author (Reference No.)/Year	No. Studies (No. Patients)	Patient Population	Study Groups	Findings/Conclusions
Wei (20) 2010	6 studies (611 patients)	Surgical patients	PN with vs without FO	No significant difference in mortality (OR, 1.42; CI, 0.57 to 3.53)—4 studies (543 pts) Significant decrease in postoperative infectious complications in FO group (OR, 0.49; CI, 0.26 to 0.93)—4 studies (533 pts) Trend toward decreased hospital LOS in FO group (mean difference –3.06; CI, –7.09 to 0.98)—4 studies (325 pts) Significant decreased ICU LOS in FO group (mean difference –2.07; CI, –3.47 to –0.67)—3 studies (122 pts)
Chen (19) 2010	13 studies (892 patients)	Major abdominal surgery pts	Standard PN vs PN with FO	No significant difference in mortality (OR, 1.43; CI, 0.53 to 3.80)—3 studies (478 pts) Significant decrease in postoperative infection rate in FO group (OR, 0.56; CI, 0.32 to 0.98)—7 studies (539 pts) Significant decrease in hospital LOS in FO group (WMD –2.98; CI, –4.65 to –1.31)—7 studies (627 pts) Significant decrease in ICU LOS in FO group (WMD –1.80; CI, –3.04 to –0.56)—5 studies (387 pts) No significant difference in postoperative cardiac complications (OR, 0.62; CI, 0.20 to 1.94)—3 studies (338 pts) Comparison of lab tests on sixth postoperative day: o significant difference in serum bilirubin, triglyceride, arachidonic acid, or LTB_4 FO group had significantly lower serum AST and ALT concentrations FO group had significantly higher plasma α-tocopherol levels, EPA, DHA, LTB_5, LTB_5:LTB_4
Wirtitsch (18) 2007	14 studies (433 patients)	Cancer surgery (63 pts), sepsis (73 pts), surgery (41 pts), psoriasis (83 pts), malnourished and critically ill (43 pts), cancer (40 pts), critically ill (17 pts), AIDS (33 pts), atopic dermatitis (20 pts), septic shock (10 pts), Crohn's disease (10 pts)	SO vs dextrose (no IVFE)	No significant difference in T c ells (CD3+), T helper cells (CD4+), T suppressor cells (CD8+), or natural killer cells (NKC) (pooled effect size: –0.02; CI, –0.24 to 0.19)—3 studies (87 pts) No significant difference in mortality (data not reported)—1 study (15 pts)
			MCT/SO vs SO	No significant difference in ConA-stimulated lymphoproliferation or lymphocyte count (pooled effect size: –0.12; CI, –0.41 to 0.16)—4 studies (106 pts) No significant difference in mortality (OR, 1.37; CI, 0.51 to 3.69)—2 studies (81 pts) No significant difference in hospital LOS (data not reported)—1 study (49 pts) No significant difference in ICU LOS (data not reported)—1 study (52 pts)
			FO vs SO	No significant difference in C-reactive protein, interleukin-6, or LTB_4 (pooled effect size: 0.16; CI, –0.13 to 0.45)—6 studies (250 pts) No significant difference in mortality (OR, 0.51; CI, 0.11 to 2.33)—2 studies (44 pts) No significant difference in hospital LOS (data not reported)—1 study (21 pts) No significant difference in ICU LOS (data not reported)—1 study (21 pts)

(continued)

Table 9. (continued)

Lead Author (Reference No.)/Year	No. Studies (No. Patients)	Patient Population	Study Groups	Findings/Conclusions
			SMOF vs SO	No significant difference in mortality (data not reported)—1 study (199 pts) No significant difference in hospital LOS (data not reported)—2 studies (232 pts)
Zhou (17) 2006	10 studies (1124 patients)	PN pts (no further description)	SL vs SO 8 studies (1057)	Significant increase in REE in SL group (WMD 1.54; CI, 1.26 to 1.82, $P < .00001$) Significant decrease in plasma glycerol (WMD 0.14; CI, 0.06 to 0.22, $P < .001$), free FA (WMD 0.24; CI, 0.10 to 0.37, $P < .001$), and β-hydroxybutyric acid (WMD 0.14; CI, 0.06 to 0.22, $P < .001$) in SL group No significant difference in nitrogen balance (WMD 0.64; CI, –0.30 to 1.59, $P = .18$), RQ (WMD –0.02; CI, –0.04 to 0.01, $P = .18$), or plasma triglycerides (WMD –0.10; CI, –0.30 to 0.10, $P = .32$)
			SL vs SO/MCT 2 studies (67)	Could not combine the 2 studies due to clinical differences between the studies Due to small number of patients, no conclusions could be drawn SL appeared to be safe and well tolerated

AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, 95% confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FO, fish oil; ICU, intensive care unit; IVFE, intravenous fat emulsion; LOS, length of stay; LT, leukotriene; MCT, medium-chain triglyceride; OR, odds ratio; PN, parenteral nutrition; pts, patients; REE, resting energy expenditure; RQ, respiratory quotient; SMOF, SO, MCT, olive oil, and FO combination; SL, structured lipid; SO, soybean oil; WMD, weighted mean difference.
aOnly meta-analyses published in English were included.

periods (<10 days), EFAD is not usually a major concern. On the other hand, if caution is not exercised, PN without IVFE may lead to carbohydrate overfeeding and increased incidence of hyperglycemia and hyperinsulinemia.

Counterissues/Problems Definition

As previously mentioned, the first successful IVFE was initially used in clinical practice in 1961 and was composed solely of SO. Since then, 3 "generations" of alternative oil-based IVFEs have been made commercially available in Europe and other parts of the world. However, in the United States, the only option is the original SO IVFE. There is a need for alternative oil-based IVFEs in the United States and a mechanism for approval through the FDA, which can be accomplished by filing a new drug application (NDA).

Before a drug product can be marketed in the United States, it must undergo a thorough safety and efficacy evaluation by the FDA. Part of the approval process includes an evaluation of the nonclinical data, chemistry and manufacturing, and efficacy and safety assessment. Clinical studies may be required. If clinical studies are needed, suitable outcome variables to establish safety and efficacy must be determined. A major clinical motivation for developing alternative IVFEs is to reduce the intake of ω-6 FAs and offer alternatives that may have greater clinical benefits.

During the NDA process, the principal indications for alternative IVFEs should be identified to determine if there are special uses or advantages over conventional SO IVFEs. Such indications could include the use of ω-3 FAs, EPA and DHA, and/or FO IVFE to prevent IFALD in pediatric patients receiving PN, to modulate the systemic inflammatory response syndrome (SIRS) in critically ill patients, or to delay or avoid the development of end-stage liver disease in patients receiving long-term HPN. In all cases, the dosage and appropriate monitoring parameters may have different measures of safety and efficacy.

Submissions for FDA approval may be for equivalency to existing IVFEs in the United States, or they may be submitted for special indications as noted previously. It is also important to distinguish patient populations for whom a given product is intended. For example, the development of EFAD in acutely ill, hospitalized adult patients is extremely rare in the absence of severe malnutrition or short bowel syndrome.[156] This is especially true for short-term PN therapy (7–10 days) when EFA stores are adequate in most patients. In contrast, for premature infants or critically ill neonates who cannot tolerate enteral nutrition, IVFEs that provide a safe energy source and that provide EFA are very important. This is also true for long-term or HPN therapy in adults. These are important distinctions that must be made during the drug development process for alternative IVFEs and must be clearly articulated from the

Table 10. Summary of Published Clinical Guidelines on Intravenous Fat Emulsions

Organization	Clinical Guidelines (Reference No.)	Guideline Statement	Grade
Critically ill patients			
A.S.P.E.N./SCCM	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 (A.S.P.E.N.) (147)	G3. In the first week of hospitalization in the ICU, when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids. Rationale: Currently in North America, the choice of parenteral lipid emulsion is severely limited to a soy-based 18-carbon ω-6 fatty acid preparation (which has proinflammatory characteristics in the ICU population).	Grade: D[a]
CCCN	Canadian Clinical Practice Guidelines for Nutrition Support in the Mechanically Ventilated, Critically Ill Adult (148)	9.2 Composition of PN: Type of lipids There are **insufficient data** to make a recommendation on the type of lipids to be used in critically ill patients who are receiving parenteral nutrition.	Insufficient data[b]
		10.2 Use of Lipids: Based on 2 level 2 studies, in critically ill patients who are not malnourished, are tolerating some EN, or when parenteral nutrition is indicated for short term use (<10 days), withholding lipids high in soybean oil should be considered.	Should be considered[b]
		10.2 Use of Lipids: There are insufficient data to make a recommendation about withholding lipids high in soybean oil in critically ill patients who are malnourished or those requiring PN for long term (>10 days). Practitioners will have to weigh the safety and benefits of withholding lipids high in soybean oil on an individual case-by-case basis in these latter patient populations.	Insufficient data[b]
		10.3 Strategies to optimize benefits and minimize risks of PN: Mode of lipid delivery: There are **insufficient data** to make a recommendation on mode of lipid delivery in critically ill patients who are receiving parenteral nutrition.	Insufficient data[b]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Intensive Care (149)	Lipids should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients.	Grade: B[c]
		Intravenous lipid emulsions (LCT, MCT, or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h.	Grade: B[c]
		The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies.	Grade: C[c]
		Olive oil–based parenteral nutrition is well tolerated in critically ill patients.	Grade: B[c]
		Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil–enriched lipid emulsions probably decrease length of stay in critically ill patients.	Grade: B[c]
Other patient populations			
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Gastroenterology (150)	Although there are encouraging experimental data, the present clinical studies are insufficient to permit the recommendation of glutamine, n-3 fatty acids or other pharmaconutrients [added to PN] in CD [patients].	Grade: B[c]
		The value of specific substrates (n-3 fatty acids, glutamine) [added to PN] is not proven [in UC patients].	Grade: B[c]

(continued)

Table 9. (continued)

Organization	Clinical Guidelines (Reference No.)	Guideline Statement	Grade
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Hepatology (151)	Liver Cirrhosis: Use lipid emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soybean oil emulsions.	Grade: C[c]
		Alcoholic Steatohepatitis: Use lipid emulsions with a content of n-6 unsaturated fatty acids lower than in traditional pure soybean oil emulsions.	Grade: C[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Home Parenteral Nutrition (HPN) in Adult Patients (152)	For long-term HPN treatment (>6 months) the provision of intravenous lipid should not exceed 1 g/kg per day. Essential fatty acids should be supplied. The daily requirement for essential fatty acids is 7–10 g, which corresponds to 14–20 g LCT fat from soya oil and 30–40 g LCT fat from olive/soya oil. MCT/LCT and fish oil emulsions also appear safe and effective.	Grade: C[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Non-Surgical Oncology (153)	Using a higher than usual percentage of lipid (eg, 50% of non-protein energy) may be beneficial for those with frank cachexia needing prolonged PN.	Grade: C[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: Surgery (154)	The optimal parenteral nutrition regimen for critically ill surgical patients should probably include supplemental n-3 fatty acids. The evidence-base for such recommendations requires further input from prospective randomised trials.	Grade: C[c]
ESPEN	ESPEN Guidelines on Parenteral Nutrition: On Cardiology and Pneumology (155)	In patients with stable COPD, glucose-based PN causes an increase in the respiratory CO_2 load. PN composition should accordingly be orientated towards lipids as the energy source. There is not sufficient evidence to recommend specific lipid substrates.	Grade: B[c]

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition; CCCN, Canadian Critical Care Nutrition; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; ESPEN, European Society for Clinical Nutrition and Metabolism; ICU, intensive care unit; LCT, long-chain triglycerides; MCT, medium-chain triglycerides; PN, parenteral nutrition; SCCM, Society for Critical Care Medicine; UC, ulcerative colitis.
[a]Grade of Recommendation ranges from A (highest level) to E (lowest level).
[b]Grade of Recommendation ranges from "strongly recommend" (highest) to "recommend" to "should consider" to "insufficient data" (lowest).
[c]Grade of Recommendation ranges from A (highest level) to C (lowest level).

outset, especially when designing the clinical studies for FDA approval.

It is important to identify the main differences between the currently available IVFEs. In the United States, 2 companies provide SO IVFEs. The differences in their compositions are subtle and include differences in glycerin concentrations (2.25% vs 2.5%) and ranges in pH (6.0–8.9 vs 6.0–9.0). In addition to these 2 differences, the IVFEs that are available outside the United States also have differences in the source oil (SO, MCT, OO, and/or FO), the addition of sodium oleate as a stabilizing agent (in concentrations of 0.25–0.3 g/L), and the addition of various antioxidants such as dl–α-tocopherol. Despite these differences, the compositions of the different IVFEs are remarkably similar, and all current IVFEs in Europe would conform to the pharmacopeial specifications of U.S. Pharmacopeia (USP) Chapter <729>, titled "Globule Size Distributions in Lipid Injectable Emulsions."[157]

Pharmacopeial issues also are related to the approval of these alternative IVFEs. Recognizing the heightened dangers of intravascular therapy, as compared with orally administered drugs such as tablets or capsules, a higher standard of pharmaceutical quality is necessary. For IVFEs, the main safety concern is the stability of the emulsion over its shelf life and during clinical use. For the manufacturer, compliance with USP Chapter <729>, titled "Globule Size Distribution in Lipid Injectable Emulsions,"[157] and the corresponding USP drug monograph, titled "Lipid Injectable Emulsion,"[158] with respect to oils, mean droplet diameter, concentration of large-diameter (>5 μm) globule content (applying Method II), potentially embolic fat globules, free fatty acid concentration, pH, and excipients is essential throughout the shelf life of the product. USP Chapter <729> states the following pharmacopeial specifications regarding globule size limits:

- Mean droplet diameter (applying Method I): The intensity-weighted mean droplet diameter (MDD) for lipid injectable emulsions must be <500 nm or 0.5 μm, irrespective of the concentration of the dispersed lipid phase.

- Large globule content (applying Method II): The volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat-residing globules >5 µm ($PFAT_5$) for a given lipid injectable emulsion (irrespective of the concentration of the dispersed lipid phase), must not exceed 0.05%.

The corresponding USP "Lipid Injectable Emulsion" monograph[158] states the following pharmacopeial specifications regarding the composition:

Lipid Injectable Emulsion: 10%, 20%, and 30% oil-in-water emulsions

The aqueous phase contains:

0.6 to 1.8 percent weight/volume (w/v) parenteral Egg Phospholipids in Water for injection and contains, if necessary, an osmotic agent, such as glycerin in amounts of 1.7 percent to 2.5 percent w/v, or a suitable stabilizer, such as a fatty acid salt (i.e., sodium oleate).

The most frequently used oil present is Soybean Oil, which provides an ample supply of the essential fatty acids: linoleic and linolenic acid. Other oils, such as Safflower Oil, Medium-Chain Triglycerides, Olive Oil, Fish Oil, or other suitable oils, can be mixed with Soybean Oil. Soybean Oil can be the only oil or be part of a mixture of these other oils. It contains not less than 90.0 percent and not more than 110 percent of the labeled amount of the total oil(s).

When considering products containing FO, it is important to recognize that 2 monographs from the European Pharmacopeia (Pharm Eur) are in use.[39,159] In 1999, Pharm Eur monograph number 1352, titled "Omega-3 Acid Triglycerides," was adopted. The monograph specifies the following with regard to the composition of ω-3 fatty acids:

Omega-3 acidorum triglicerida

Content:
Sum of the contents of the omega-3 acids EPA and DHA, expressed as triglycerides: minimum 45.0 per cent;
Total omega-3 acids, expressed as triglycerides: minimum 60.0 percent.
Tocopherol may be added as an antioxidant.

The ω-3 FA specifications for Pharm Eur 1352 are above the typical total amounts found in natural marine sources, which average about 30%. For example, the label for any standard 1-g soft-gelatin capsule of an ω-3 FA supplement states that each contains 180 mg EPA (20:5n3) and 120 mg DHA (22:6n3). Therefore, to achieve the levels specified in Pharm Eur 1352, the natural FO triglyceride source must be enriched. Typically, the triglyceride is hydrolyzed, releasing the individual free FA. The less desirable saturated fatty acids—myristic (14:0), palmitic (16:0), and stearic (18:0) acids—and the MUFA palmitoleic acid (16:1) are reduced in quantity, and then the FAs are re-esterified, resulting in higher concentrations of ω-3 fatty acids. This FO is specifically indicated for parenteral use.[159,160]

In 2005, Pharm Eur monograph number 1912, titled "Fish Oil, Rich in Omega-3 Acids," was adopted.[38] The monograph specifies the following with regard to ω-3 fatty acids:

Piscis oleum omega-3 acidis abundans

Content:
EPA, expressed as triglycerides: minimum 13.0 per cent,
DHA, expressed as triglycerides: minimum: 9.0 per cent,
Total omega-3 acids, expressed as triglycerides: minimum 28.0 per cent.
Authorized antioxidants in concentrations not exceeding the levels specified by the competent authorities may be added.

The ω-3 FA specifications for Pharm Eur 1912 are approximately equal to the typical total amounts found in natural marine sources, about 30%. Thus, when comparing the FA content of the various products, it is important to establish the ω-3 FA contents of the individual IVFE, especially if it is used for the treatment of inflammation, and accompanying adverse sequelae to vital organs. Consequently, such differences suggest that all IVFEs containing FO are not bioequivalent.[161]

Physicochemical stability issues are also related to IVFE. During the preparation of an IVFE for clinical use, USP Chapter <797>, titled "Pharmaceutical Compounding—Sterile Preparations," deals specifically with sterility risks but not stability issues. At least with respect to embolic risk, some have advocated the use of the globule size standards of USP Chapter <729> (specifically, that the $PFAT_5$ level must not exceed 0.05%), as applied to the manufacturer, and as stability indicators to determine the pharmacist-assigned, beyond-use date that specifies the time frame during which it is stable, compatible, and safe for IV administration.[161] Several admixture stability studies have shown that the $PFAT_5$ standard is indeed achievable when applied to an extemporaneously prepared syringe of undiluted IVFE[162] or when diluted into a total nutrient admixture (TNA) containing crystalline amino acids, dextrose, electrolytes, vitamins, and trace minerals.[163-171] It is the latter dosage form (ie, TNA) that poses the greatest embolic risk because of the ionic stress

imposed on the IVFE from the electrolyte and mineral ingredients. Specifically, studies have shown that the presence of MCTs vs the standard long-chain triglycerides (LCTs) (ie, SO and/or SFO alone) in commercially available IVFEs has a positive influence on the stability of TNA dosage forms.[172] These effects appear to occur in MCT/LCT emulsion products containing physical mixtures of the oils and have been explained to be similar to the role MCTs play in the plasma clearance of MCT/LCT physical mixtures. Hamilton et al[173] showed, employing ^{13}C nuclear magnetic resonance (NMR) spectroscopy, that MCT displaces LCT at the droplet surfaces, and hence the mixed oil droplet has more efficient in vivo hydrolysis via lipoprotein lipase compared with pure LCT emulsions. This same affinity for the droplet surface has been proposed to underlie the greater stability routinely seen in MCT/LCT-based TNA vs pure LCT-based TNA, as the significantly shorter hydrocarbon chain length of MCT (8–10 carbons) vs the typical 18-carbon LCT produces less physical stress on the emulsifier (interfacial tension) that keeps the "lipid" phase miscible with the "aqueous" phase of the emulsion. This appears to be a clear stability advantage over the current SO IVFEs available in the United States and may make TNA therapy safer than current practice.

Summary/Recommendations

IVFE is an essential component of PN, which helps to prevent EFAD and can also be used as an alternate energy source to dextrose, avoiding the complications of excessive dextrose administration. The currently available, standard SO IVFEs meet the requirement to prevent EFAD in patients receiving PN. Based on substantial biochemical and clinical evidence, alternative oil-based IVFEs may have less proinflammatory effects, less immune suppression, and more antioxidant effects than the standard SO IVFEs and may potentially be a better alternative energy source. However, the evidence for the clinical use of these alternative IVFEs is still not clearly defined, particularly with regard to specific indications, because of the heterogeneity in the published studies in the patient populations studied, the differences in IVFEs studied, the wide variations in biochemical markers studied, and the lack of consistent clinical outcome data. Alternative oil-based IVFEs are safe and effective alternatives to SO IVFEs for a source of energy and essential FAs and may have potential biochemical and/or clinical benefits. Alternative IVFEs should be made available in the United States for clinical use based on the clinical judgment of the clinician prescribing the PN, which will facilitate further research on alternative IVFEs in the United States.

Further research is needed on these alternative oil-based IVFEs in the following areas:

1. Determining the clinical conditions in hospitalized patients in which IVFEs with substantial amounts of EPA and DHA can improve clinical outcomes, including hospital mortality and morbidity such as infection rate, duration of mechanical ventilation, and ICU and/or hospital LOS. Such trials should include homogeneous populations and should be adequately powered so as to provide definitive evidence of efficacy.
2. Distinguishing the proper mixture of oils, whether exclusively FO, FO plus MCT, or FO plus ω-6 triglycerides with or without MCT required to achieve clinical benefits, using both currently available commercial products as well as newer mixtures of these source oils.
3. Defining patient conditions that alterative IVFE administration may be beneficial based on other characteristics of the ω-3 FAs, EPA, and DHA, such as antiarrhythmic effects or enhanced protein synthesis (eg, their potential use in patients undergoing cardiac surgery for the prevention of arrhythmias or the amelioration of sarcopenia in elderly patients).
4. Investigating further the role of FO IVFEs alone or in combination with other oils in chronic conditions that develop in patients receiving HPN, such as IFALD and chronic inflammatory disorders.
5. Now that FO IVFEs are being used in higher doses as an alternative energy source to dextrose and for their pharmacological anti-inflammatory effects, dosing studies need to be conducted on the FO IVFEs to further define the optimal dose range to obtain the desired effects and avoid undesirable side effects.

Our hypothesis is that alternative oil-based IVFEs that potentially have the greatest anti-inflammatory and antioxidant effects (ie, ones containing significant amounts of ω-3 FA) will significantly improve clinical outcomes in patients who are experiencing severe local or systemic inflammation when studied against the standard SO IVFEs.

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