

Immune modulation by parenteral lipid emulsions^{1,2}

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ABSTRACT

Total parenteral nutrition is the final option for nutritional support of patients with severe intestinal failure. Lipid emulsions constitute the main source of fuel calories and fatty acids (FAs) in parenteral nutrition formulations. However, adverse effects on patient outcomes have been attributed to the use of lipids, mostly in relation to impaired immune defenses and altered inflammatory responses. Over the years, this issue has remained in the limelight, also because technical advances have provided no safeguard against the most daunting problems, ie, infectious complications. Nevertheless, numerous investigations have failed to produce a clear picture of the immunologic characteristics of the most commonly used soybean oil-derived lipid emulsions, although their high content of n-6 polyunsaturated FAs (PUFAs) has been considered a drawback because of their proinflammatory potential. This concern initiated the development of emulsions in which part of the n-6 FA component is replaced by less bioactive FAs, such as coconut oil (rich in medium-chain saturated FAs) or olive oil (rich in the n-9 monounsaturated FA oleic acid). Another approach has been to use fish oil (rich in n-3 PUFA), the FAs of which have biological activities different from those of n-6 PUFAs. Recent studies on the modulation of host defenses and inflammation by fish-oil emulsions have yielded consistent data, which indicate that these emulsions may provide a tool to beneficially alter the course of immune-mediated conditions. Although most of these lipids have not yet become available on the US market, this review synthesizes available information on immunologic characteristics of the different lipids that currently can be applied via parenteral nutrition support. *Am J Clin Nutr* 2007;85:1171-84.

KEY WORDS Total parenteral nutrition, lipid emulsion, immunology, inflammation, fatty acids, eicosanoids

INTRODUCTION

Over the past 4 decades, parenteral nutrition has proven itself to be the therapeutic strategy of choice for nutritional support of patients with severe chronic intestinal failure (1). Total parenteral nutrition (TPN) implies that all macronutrient (carbohydrates, amino acids, and lipids) and micronutrient (electrolytes, vitamins, and trace elements) requirements are met by means of an "all-in-one" sterile, aqueous solution that is administered into a large-bore central vein (2). Although nontunneled catheters positioned in the subclavian or jugular veins can be used for short-term TPN delivery in hospitalized patients, long-term TPN administration in the home setting requires the presence of a tunneled catheter, a subcutaneous port, or an arteriovenous shunt to provide a site for venous access (3). Although the relevance of

TPN support for clinical practice is beyond doubt, its high rate of complications remains a drawback (4). The nature, magnitude, and suggested management of these complications have been addressed (1, 5). Although mechanical (catheter occlusion) and metabolic (disturbances of fluids and electrolytes, liver dysfunction, and bone disease) problems frequently occur, complications related to venous access and infection remain the major problems (4, 6). With respect to the latter, lipids in TPN formulations have long been under scrutiny because of their alleged detrimental effects on immune function. For instance, a meta-analysis in surgical and critically ill patients reported higher complication rates in patients receiving lipid-based TPN than in those receiving lipid-free formulations (7). However, the overall clinical proof for such negative effects is rather weak (8). Also, novel lipids have recently been introduced in the clinical arena, which promise to modulate inflammatory responses in a favorable manner and to improve the outcomes of patients with immune-mediated conditions. These notions provided the background for the present review, which provides an overview of and insights regarding the currently available data on immune modulation by parenteral lipids.

HISTORICAL PERSPECTIVE

Lipids, in the form of olive oil (OO) and milk, for example, have been administered intravenously to humans for therapeutic purposes since the 17th century (9). Numerous adverse events resulting from lipid use led to the notion that the administration of fat by this route invariably causes severe complications, including fat embolism. The demonstration of a strong link between the presence of malnutrition and the development of post-operative mortality in the 1930s by Studley (10) was a strong impetus for the exploration of better ways to deliver adequate fuel calories to these patients. After much trial and error, Schubert and Wretling (11) eventually succeeded in developing a nontoxic lipid emulsion prepared from soybean oil (SO) (Intralipid; Fresenius-Kabi, Bad Homburg, Germany) that was introduced in 1961. Wretling's system of lipid-based TPN found its way into Europe during the 1960s and 1970s (12-14). By

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Received September 7, 2006.

Accepted for publication October 23, 2006.

contrast, high-osmolar glucose solutions, based on Dudrick's concept of hyperalimentation, remained the sole intravenous nonprotein energy supply for patients in the United States, where lipid emulsions had as yet not been accepted (15, 16). This changed when the glucose system was found to cause serious side effects, including hyperglycemia, liver steatosis, and deficiencies of fatty acids (FAs) and fat-soluble vitamins, whereas lipid infusion was shown to prevent fatty infiltration of the liver and to minimize metabolic stress (9, 17).

PARENTERAL LIPID EMULSIONS: COMPOSITION AND METABOLISM

Lipids are an energy-dense source of fuel calories (≈ 9 kcal/g) compared with proteins and carbohydrates (both ≈ 4 kcal/g). It is generally recommended in clinical practice that the lipid supply should provide 15–30% of the total calorie intake, or 30–50% of nonprotein calories (18). Infusion of parenteral lipid emulsions at rates of 0.8–1.5 g/kg body wt per day is safe but should not exceed 2.6 g/kg per day (0.11 g/kg per hour), because side effects have been reported above this threshold (19). Especially in metabolically stressed patients, the safest way to administer parenteral lipids is by continuous infusion at the lowest possible rate, because the discontinuous administration with condensing of daily dosages promotes the development of problems related to fat overload, such as hypertriglyceridemia, liver- and respiratory dysfunction, and coagulopathy (18, 20–22).

Lipid emulsions for parenteral use are provided at triacylglycerol concentrations of 10%, 20%, or 30% (wt:vol). These emulsions are isoosmotic (mean pH: 7.5), whereas TPN formulations as a whole are hypertonic (pH: ≈ 6.0) (22). Lipid emulsions consist of 100–500-nm droplets to simulate chylomicrons, the lipoproteins that transport dietary FAs in circulating blood, with a monolayer of phospholipids enveloping a triacylglycerol core (23). The phospholipids act as an emulsifier and are usually derived from egg yolk. The emulsions also contain other lipid-soluble substances, such as vitamins E and K, lipid peroxidation products, and phytosterols (24). Emulsion metabolism, similar to that of chylomicrons, is enhanced by the acquisition of apoproteins, mainly types C and E, which are transferred from HDLs and cover the lipid droplets very rapidly on infusion. The degradation of emulsion droplets takes place at endothelial sites of extrahepatic tissues by lipoprotein lipase-mediated hydrolysis, which results in FA release and a reduction in size of the emulsion remnant particles (23, 25). Hormonal (eg, insulin) and cytokine [eg, tumor necrosis factor α (TNF- α)] balance and lipid composition regulate this process. The final step in the intravascular emulsion degradation process involves tissue uptake of remnant particles in the liver, which results in the intracellular delivery of fat-soluble vitamins and FAs that have not been released by lipoprotein-lipase-mediated hydrolysis. A nonspecific hepatic lipase that hydrolyzes triacylglycerols, mono- and diglycerides, cholesteryl esters, and phospholipids controls this process (26). Lipid emulsions contain more phospholipids than necessary to solubilize their triacylglycerol content. Emulsions containing 10% lipids have an especially high ratio of phospholipids to triacylglycerols, greater than that of 20% emulsions and even more than 30% emulsions. Part of this is present as 80–100 nm liposome-resembling particles that impede lipid metabolism and

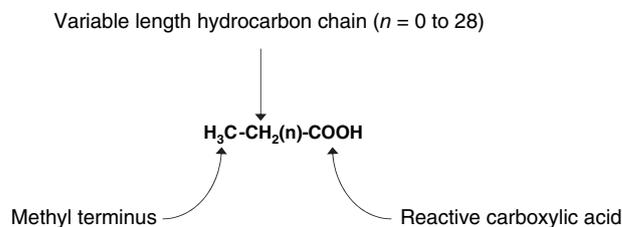


FIGURE 1. Generic structure of a fatty acid.

accumulate as an abnormal lipoprotein X, which leads to hypercholesterolemia. It is therefore recommended that lipid emulsions be administered at higher concentrations and at a low speed to prevent liposome accumulation (23, 24, 27).

Bioactive emulsion components other than lipids

Lipid emulsions are prepared from biological materials that may differ between batches in their content of bioactive substances, such as antioxidants (eg, various tocopherol isoforms) (28). Polyunsaturated FAs (PUFAs) in lipid emulsions, depending on the degree of protection by antioxidants and under the influence of various storage conditions (eg, light exposure and temperature), can peroxidize to potentially harmful lipid hydroperoxides (29, 30). The discussion on the immunologic effects of these substances is beyond the scope of this article and will not be considered further.

STRUCTURALLY DIFFERENT FATTY ACIDS AND LIPIDS IN TPN

Structure of lipids and fatty acids

Lipids supply most of the nonglucose fuel calories and they are building blocks for cellular components and essential FAs. Lipids in TPN formulations are triacylglycerols consisting of 3 FAs attached to a glycerol backbone. FAs are hydrocarbon chains with a methyl group at one end of the chain and a reactive carboxyl group at the other end (Figure 1). In most biological systems, the chain length of the component FAs varies from 2 to 30 carbons. FA and their corresponding triacylglycerols can be classified as short chain (up to 4 carbons), medium chain (MCFA or MCT; 6–12 carbons), or long chain (LCFA or LCT; ≥ 14 carbons) (31). Double bonds can be inserted into the hydrocarbon chain, and FAs can also be classified based on the number of double bonds present. A saturated FA has no double bonds in the hydrocarbon chain, whereas monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs) have 1 or 2 or more double bonds, respectively (Figure 2). The final means of classification of FAs is the position of the double bonds within the hydrocarbon chain. This is what gives rise to the n - or ω nomenclature for FAs. The 3 principal families of unsaturated FAs are the n -9, n -6, and n -3 families. This means of classification indicates the carbon on which the first double bond occurs when counting from the methyl carbon of the hydrocarbon chain. The simplest n -6 and n -3 PUFAs are linoleic acid (18:2 n -6) and α -linolenic acid (18:3 n -3), respectively (Figure 2).

In humans, linoleic and α -linolenic acids are termed essential FAs because their *de novo* synthesis is not possible and availability, therefore, completely depends on the diet (32). These FAs are synthesized in plants; therefore, plant tissues, seeds, and seed oils tend to be good sources of essential FAs. Although

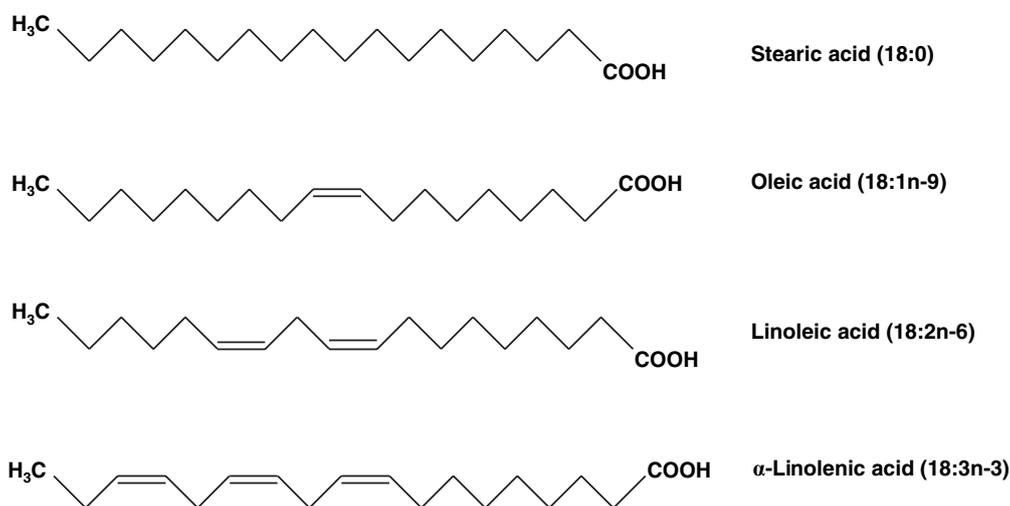


FIGURE 2. Structure and naming of selected 18-carbon fatty acids.

linoleic and α -linolenic acids cannot be synthesized in humans, both FAs can be elongated and desaturated by mammalian enzymes, principally in the liver. This pathway of metabolism is shown in **Figure 3**, which indicates the direct competition for metabolism between the 2 families of PUFAs. Metabolism of linoleic acid yields arachidonic acid (AA, 20:4n-6) as the major end product, while eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) are end products of the metabolism of α -linolenic acid. Although α -linolenic acid is the preferred substrate for the Δ^6 -desaturase enzyme, on most typical Western diets the metabolism of linoleic acid is quantitatively

more important because the diet contains 5 to 20 times more linoleic than α -linolenic acid. Thus, blood and cell lipids typically contain much more AA than do very-long-chain n-3 PUFAs. The only rich dietary source of very-long-chain n-3 PUFAs is seafood, especially fatty fish such as salmon, herring, and mackerel. These FAs are also found in commercial products termed fish oils (FOs). Just as there is competition for metabolism between linoleic and α -linolenic acids, there is competition between AA and EPA for incorporation into cell membranes and for metabolism to bioactive eicosanoid mediators.

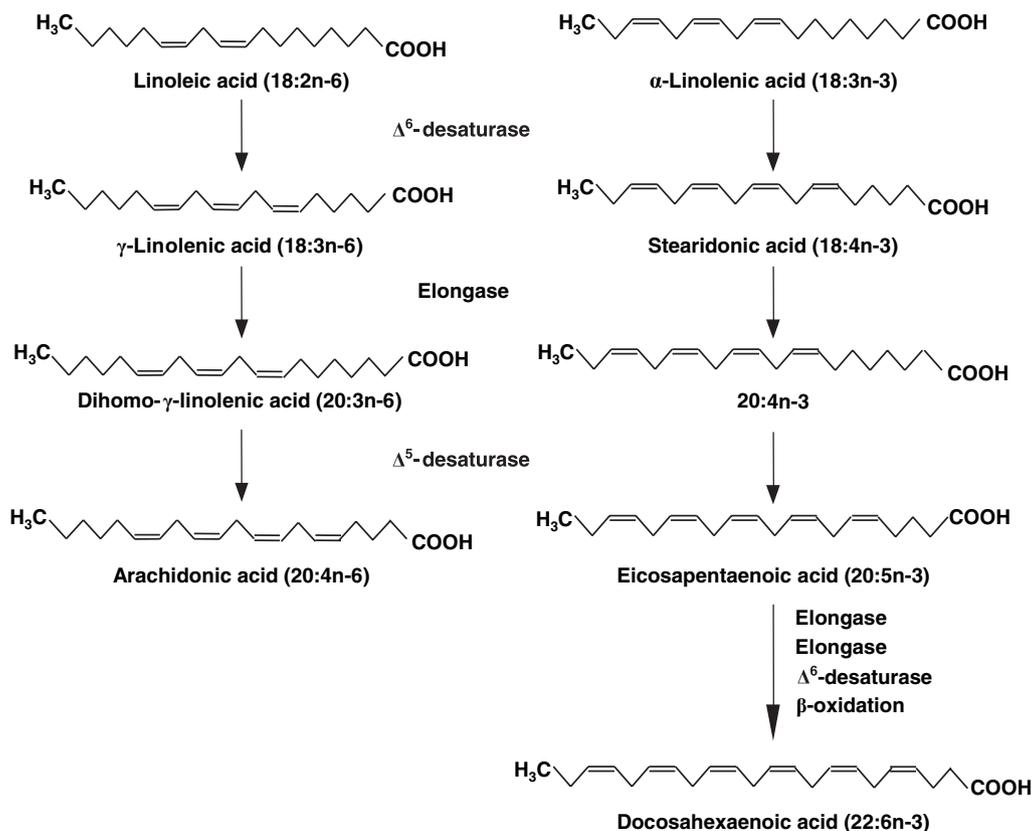


FIGURE 3. Synthesis of long-chain n-6 and n-3 polyunsaturated fatty acids from their precursors.

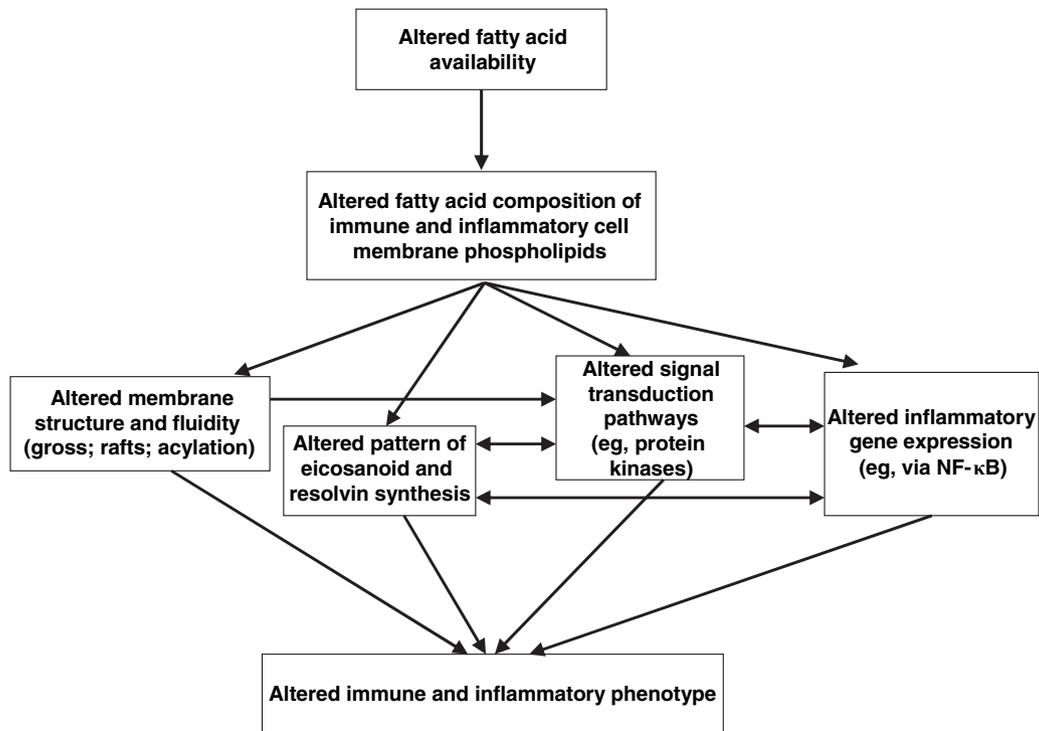


FIGURE 4. Mechanisms by which fatty acids can affect immune cell function. NF- κ B, nuclear factor κ B.

MECHANISMS INVOLVED IN IMMUNE MODULATION BY PARENTERAL LIPIDS

FAs are key determinants of the structural integrity of cell membranes. FA structure, especially chain length and degree of unsaturation, is critical to the interaction of lipids with immune cells (33). Exposure to lipids with different FA compositions may influence immune cells through several features relating to cell membrane structure and function that are highly interactive (Figure 4) (34–36).

Membrane fluidity

This refers to a complex property involving the mobility of membrane components and permeability characteristics, with a key role in enzyme and surface receptor functions. FAs have been shown to affect lymphocyte membrane fluidity in a structure-dependent manner (37). Effects of parenteral lipids on membrane fluidity have been shown in vitro and were found to depend on FA structure (38). MCT, and, to a lesser extent, MCFA-containing structured lipids (SLs), increase the membrane fluidity of isolated neutrophils, whereas an SO-based LCT emulsion, rich in the n-6 PUFA linoleic acid, exert no effect. Within the cell membrane, phospholipid bilayer microdomains exist, so-called lipid rafts, with a unique lipid environment that facilitates intercellular signaling and cross talk. Many receptors and signaling proteins are localized in such rafts (39). Although one study has reported that infusion of an SO-based emulsion rich in n-6 PUFAs alters lipid raft organization and decreases the membrane fluidity of human T cells, others found that pure n-3 PUFAs displace acylated proteins from rafts in these cells and thus alter cell function (40, 41). Other than these sparse data, data concerning the effects of parenteral lipids on the distribution and composition of lipid rafts in immune cells are unavailable.

Production of bioactive mediators

AA, EPA, and DHA all give rise to bioactive lipid mediators. The best characterized of these are the eicosanoids produced from AA: prostaglandins, thromboxanes, and leukotrienes. Before synthesis of these mediators, the parent FA (ie, AA, EPA, or DHA) is released from these cell membrane phospholipids by the action of phospholipase A2. The subsequent metabolism of AA by cyclooxygenase enzymes yields the 2-series prostaglandins and thromboxanes, whereas the metabolism by 5-lipoxygenase yields the 4-series leukotrienes. In general, these mediators have pro-inflammatory actions (42, 43). EPA also acts as a substrate for cyclooxygenase and lipoxygenase, giving rise to 3-series prostaglandins and thromboxanes and 5-series leukotrienes. The functional significance of this is that the products formed from EPA are typically less potent than are those formed from AA. Increased provision of EPA results in partial replacement of AA in cell membrane phospholipids, with a resulting decrease in capacity to produce the AA-derived eicosanoids and an increased capacity to produce those from EPA. In addition to very-long-chain n-3 PUFAs modulating the generation of eicosanoids from AA and to EPA acting as substrate for the generation of alternative eicosanoids, recent studies have identified a novel group of protective mediators, termed E- and D-series resolvins, formed from EPA and DHA, respectively, that dampen acute leukocyte responses and facilitate the resolution of inflammation (44, 45). These substances may well underlie at least some of the beneficial actions of n-3 PUFAs, especially in chronic disorders in which unresolved inflammation is a key mechanism of pathogenesis (46).

Cell signaling

Lipid-induced changes in membrane composition alter properties of phospholipid-derived second messengers involved in

cell signal transduction (47, 48). Indeed, parenteral lipids have been found to influence Ca^{2+} - and protein kinase C-mediated signaling of activated neutrophils, depending on their structure (49, 50). Specifically, MCT-containing emulsions, but not SO-based LCTs, mimic the potent protein kinase C-activating phorbol ester phorbol myristyl acetate (PMA) by markedly increasing the rise in intracellular Ca^{2+} concentrations that are brought about by opsonized particles, as a mimic for invading microorganisms. MCT, similar to PMA, also evoke a leftward shift of the dose-response curve for these Ca^{2+} -concentration rises, suggesting protein kinase C-dependent sensitization of neutrophils for stimulation (49). Of note, this MCT-related phenomenon was not observed with MCFA-containing SLs.

Saturated FAs and PUFAs differentially regulate pathways involved in the coordination of innate and acquired immune responses. The former involves the action of so-called Toll-like receptors (TLRs), which signal the presence of invading microbes by recognizing conserved pathogen-associated molecular patterns (51). For example, TLR-4 is the receptor for microbial lipopolysaccharide. Although saturated FAs activate TLR-4-mediated pro-inflammatory pathways, with stimulation of nuclear transcription factor κB and expression of cyclooxygenase-2, these events are inhibited by very-long-chain $n-3$ PUFAs (52, 53). Thus, differential TLR subtype stimulation may bring specificity to innate immunity (54).

Regulation of gene expression

FAs can affect cell responses through the regulation of gene expression and subsequent downstream events by acting as ligands for nuclear receptors. For instance, very-long-chain $n-3$ PUFAs control transcription factors such as peroxisome proliferator-activated receptors (PPARs) and sterol-regulatory-element binding proteins (55). PPARs can bind to DNA and are involved in the regulation of inflammatory processes, lipid metabolism, and energy utilization by modulating the expression of target genes, for instance by repressing signaling through nuclear transcription factor κB (35, 55). Because FAs influence many genes, their effects on cellular responses vary widely, ranging from changes in surface adhesion molecule expression to altered cytokine production.

Modulation of apoptotic pathways

Infusion of SO-based LCTs in humans has been found to increase the apoptotic rate of cultured lymphocytes, whereas cell necrosis was not influenced (40). Because of its design, this study could not determine whether this is a lipid-specific effect. FAs seem to promote *in vitro* apoptosis and necrosis in lymphocytes, with the parent $n-6$ PUFA linoleic acid acting on mitochondrial depolarization and oxygen radical production, whereas the $n-9$ MUFA oleic acid is less toxic and affects the activation of caspase 3 (56). Invading microorganisms, depending on their nature, trigger specific human immune responses that involve the differentiation of T helper type 0 lymphocytes (Th0) into type 1 (Th1) cells that are involved in phagocyte activation and antibody-dependent cellular cytotoxicity, whereas type 2 (Th2) cells mainly act against parasitic infections. When compared with $n-6$ PUFAs, $n-3$ PUFAs enhance the activation-induced cell death of Th1 cells, but leave Th2 cell apoptosis unaffected (57). This suggests that $n-3$ PUFAs modulate T cell-mediated immunity by selective deletion of Th1-like cells while maintaining Th2-mediated responses.

Effects on other immune-modulating substances

FAs may also exert effects through their influence on the metabolism of other compounds that are involved in the regulation of immune responses. For instance, eicosanoids derived from AA increase the expression of the arginase I enzyme and thus may decrease the amount of available arginine, whereas eicosanoids from EPA have the opposite effect (58).

IMMUNOLOGIC EFFECTS OF STRUCTURALLY DIFFERENT PARENTERAL LIPIDS

It is generally accepted that a lipid emulsion in its ideal form should be easily accessible for metabolic breakdown, but should not confer any inflammatory or oxidative stress or impair the function of the immune system (8). On the basis of these notions, several lipid emulsions have been developed over the years. Relevant information regarding some of these emulsions is presented in **Tables 1** and **2**.

SO-based lipid emulsions

Parenteral LCT, derived from SO or safflower oil, such as Intralipid and Ivelip (Baxter, Maurepas, France), have a high ratio of $n-6$ to $n-3$ PUFAs (7:1) because of their high content of linoleic acid and only moderate amounts of α -linolenic acid (Table 1). This has been considered a drawback that might promote the overproduction of pro-inflammatory eicosanoids and increase oxidative stress in clinical situations (eg, sepsis and trauma) that are already dominated by imbalanced immune responses (59, 60).

With reference to clinical outcome, concerns regarding detrimental effects of parenteral SO on immune function were raised by early clinical observations in the 1980s that showed an increased risk of bacteremia in neonatal patients using lipid-based TPN (61–63). Snyderman et al (64) observed that intravenous lipids increased infection rates in surgical patients and were the first to propose the lipid-induced promotion of bacterial growth in intravenous lines as an underlying mechanism. Lipid-induced immune suppression was also suggested in clinical studies that found an increased risk of infectious complications in mildly malnourished surgical patients and lower rates of graft versus host disease after bone marrow transplantation in patients using SO-based TPN (65, 66). On the other hand, a large randomized clinical trial in 482 patients undergoing bone marrow transplantation found no evidence of a role of Liposyn II (Abbott Laboratories, North Chicago, IL), a safflower-based emulsion, on the incidence of bacteremia or fungemia when patients were assigned to receive either 6–8% (the low-dose group) or 25–30% (the standard-dose group) of total daily energy as a 20% lipid emulsion (67).

Understandably, these conflicting clinical reports evoked a flood of experimental work aiming to characterize lipid effects on immune functions and provide pathophysiologic explanations for these lipid effects. Some studies indeed showed SO-induced impairments in phagocyte functions, such as granulocyte migration and phagocytosis, *in vitro* and *ex vivo* (68–71). Importantly however, these investigations used lipids at supraphysiologic concentrations up to 100 mg/mL, or 115 mmol/L (ie, a dose well above the upper threshold of ≈ 10 mmol/L that can be considered clinically relevant) (68–70). Also, the study by Fisher et al (71)



TABLE 1Characteristics of commercial lipid emulsions according to the manufacturers¹

Emulsion	SO	SO-MCT	SL	OO	FO	SMOF
Brand name	Intralipid 20% ²	Lipofundin 20% ³	Structolipid 20% ²	ClinOleic 20% ⁴	Omegaven 10% ²	SMOFlipid 20% ²
Oil source (% by wt)	Soybean	Coconut (50%), soybean (50%)	Coconut (36%), soybean (64%)	Olive (80%), soybean (20%)	Fish	Soybean (30%), coconut (30%), olive (25%), fish (15%)
Ratio of n-6 to n-3 PUFAs	7:1	7:1	7:1	9:1	1:8	2.5:1
Fat content (g/L)	200	200	200	200	100	200
Molecular weight	865	634	683	873	882	732
Phospholipids (g/L)	12	12	12	12	12	12
Glycerol (g/L)	22	25	22.5	22.5	25	25
pH	8.0	6.5–8.5	8.0	7.0–8.0	7.5–8.7	8.0
Osmolarity (mOsmol/L)	350	380	350	270	273	380
Energy (kcal/L)	2000	1908	1960	2000	1120	2000
α -Tocopherol (μ mol/L) ⁵	87	502	16	75	505	500

¹ SO, soybean oil; MCT, medium-chain triacylglycerol; SL, structured lipids; OO, olive oil; FO, fish oil; SMOF, soybean, coconut, olive, and fish oils.² Fresenius-Kabi, Bad Homburg, Germany.³ B Braun, Melsungen, Germany.⁴ Baxter, Maurepas, France.⁵ Data are from reference 28.

and that by Palmblad (72) were criticized because of its non-physiologic model, wherein lipids and streptococci were injected intraperitoneally in mice. SO-induced impairments in the function of the hepatic reticuloendothelial system (RES), and interference with lipopolysaccharide-induced cell stimulation, as was observed with HDLs, have been proposed as underlying mechanisms to explain the immunosuppressive effects of intravenous lipids (73, 74). However, the overall data regarding the effects of SO on immune responses have been disparate, because many investigators in numerous clinical and experimental settings found no evidence of an effect on a wide range of features and

functions of various immune cells, cellular signal transduction, or membrane characteristics (35, 74–83). Of note, these latter investigators, with the exception of some (81, 82), used lipids in a clinically relevant concentration range. Taken together, different experimental approaches in animal and human studies most probably play an important role in the ongoing controversy (77).

Physical mixtures of SO and medium-chain triacylglycerols

Saturated MCTs, present in coconut and palm kernel oils, have traditionally been regarded to be good sources of fuel calories but

TABLE 2Fatty acid composition of lipid emulsions¹

	Intralipid ²	Lipofundin ³	Structolipid ²	ClinOleic ⁴	Omegaven ²	SMOFlipid ²
	% by wt of total fatty acids					
Caproic acid (6:0)	—	0.5	0.1	—	—	0.2
Caprylic acid (8:0)	—	28.5	26	—	—	32.3
Capric acid (10:0)	—	20	10	—	—	22.7
Lauric acid (12:0)	—	1	0.2	—	—	0.3
Myristic acid (14:0)	—	—	—	0.2	5.1	1.9
Palmitic acid (16:0)	11	7.4	7	12.2	11.7	18.2
Palmitoleic acid (16:1n-7)	—	—	—	1.4	9.2	3.3
Stearic acid (18:0)	4	2	3	2.1	4.4	5.5
Oleic acid (18:1n-9)	24	11	14	62.3	15.1	55.3
Linoleic acid (18:2n-6)	53	29.1	35	18.7	4.4	37.2
α -Linolenic acid (18:3n-3)	8	4.5	5	2.3	1.8	4.7
Dihomo- γ -linolenic acid (20:3n-6)	—	—	—	—	0.6	—
Arachidonic acid (20:4n-6)	0.1	0.2	—	0.5	2.1	1.0
Eicosapentaenoic acid (20:5n-3)	—	—	—	—	19.2	4.7
Docosapentaenoic acid (22:5n-3)	—	—	—	—	2.1	0.7
Docosahexaenoic acid (22:6n-3)	—	—	—	0.5	12.1	4.4

¹ Data provided by the manufacturers.² Fresenius-Kabi, Bad Homburg, Germany.³ B Braun, Melsungen, Germany.⁴ Baxter, Maurepas, France.

to have with few other physiologic roles. Compared with SO, MCTs have biochemical properties that render them a superior source of energy in clinical situations of depletion, because of their easy accessibility for metabolic degradation (84). Compared with LCFAs, MCFAs are 100 times more soluble in water and can directly pass into cells without binding to FAs or transport proteins. Also, β -oxidation of MCFAs, in contrast with that of LCFAs, does not require carnitine for transport into mitochondria and also takes place in peroxisomes (85–87). Whereas LCFAs are incorporated into chylomicrons after absorption from the intestine and eventually reach the systemic circulation via the lymph system, MCFAs, on absorption, are directly transported to the liver via the portal vein (85).

In the mid-1980s, physical mixtures containing SO and MCTs, such as Lipofundin (B Braun, Melsungen, Germany), became available for TPN practice, reflecting the wish to decrease the high content of n-6 PUFAs in lipid emulsions. Besides their rapid metabolic breakdown, MCTs were also chosen because of their resistance to peroxidation (88, 89). The use of LCTs, however, remained necessary because humans do not tolerate pure MCTs, and MCTs are not a source of essential FAs. The special qualities of MCTs offer both benefits and risks, ie, positive effects on protein metabolism and on RES function but an increased risk of ketogenesis and acidosis (90, 91). Also important, the mix of SO and MCTs decreases glucose oxidation to a lesser extent than does pure SO (92). This finding is especially relevant because insulin resistance and hyperglycemia play a crucial role in the development of complications during critical illness (93). Glucose has also been found to decrease the oxidation of LCFAs, such as oleic acid, but not of MCFAs, such as octanoic acid, by affecting FA entry into mitochondria (94).

MCT-containing emulsions are not yet commercially available in the United States, despite their proven tolerability and rapid clearance in severely ill malnourished patients (90, 95–99). Of note, these data come from small (≤ 20 patients) short-term (≤ 10 d of lipid administration) studies that were not designed to evaluate clinical endpoints such as infectious complications and patient survival. One larger study, by Garnacho-Montero et al (99), included 72 septic patients, but it has only been published in Spanish. The only larger prospective randomized trial to report on a clinical endpoint (infectious complications), by Grau et al (100), was a short-term (5 d of lipid administration) study that has only been published in Spanish. These investigators compared SO-MCTs and SO given for 2 d preoperatively and 3 d postoperatively to 72 severely malnourished patients who underwent a laparotomy because of suspected malignancy (100). Overall, it was found that SO-MCTs significantly reduced the incidence of intraabdominal abscesses when compared with SO-based TPN, without an effect on other infections. In addition, in the subgroup of patients without cancer, SO-MCTs decreased mortality (100).

With respect to the mechanisms behind the effects of MCTs on outcome, it has been shown that infusion of SO-MCTs impairs lung function and aggravates tissue inflammation in patients with acute respiratory distress syndrome, but not in healthy subjects (101). On the other hand, this might also represent a nonspecific lipid effect, as was suggested by the finding that pure SO induced similar abnormalities (102). As with SO, and probably because of similar flaws in experimental design, numerous investigations have failed to produce a uniform picture of the immunologic effects of SO-MCTs (103). In the experimental setting, when

compared with other lipids, MCTs at clinically relevant concentrations up to 5 mmol/L, increase β_2 -integrin-mediated human phagocyte adhesion and cell membrane fluidity but decrease motility and the capacity of these cells to kill fungal pathogens (104–107). MCFAs also increase the expression of PPAR- γ and other transcription factors in adipocytes (108). In addition, SO-MCTs and pure MCTs distinctly modulate calcium- and protein kinase C-mediated cell signaling of human neutrophils (49, 50). Taken together, these findings suggest that MCTs activate isolated immune cells, but at the same time impair several cell functions. Also important, these data challenge the view that immunologic effects of lipids are essentially determined by their ratio of n-6 to n-3 PUFAs because SO-MCTs and pure SO are equivalent in this respect (109). The relevance of these findings in clinical practice, however, remains to be established.

Structured lipids

The considerations on metabolism and immunology regarding SO and MCTs in the 1990s resulted in the development of synthetic SLs, such as contained in Structolipid (Fresenius-Kabi). These SL are made by hydrolysis of SO and MCTs with subsequent random reesterification of MCFAs and LCFAs in the 1, 2, or 3 positions to glycerol (110–112). The type of core material influences the circulation time of lipids, because emulsions with MCFAs in the 1,3 position are removed more slowly from the circulation than are those with LCFAs in these positions (112).

No long-term clinical trials have yet been conducted that have evaluated SL effects on infectious complications and patient survival, although data from several short-term investigations suggest that SLs are well tolerated and are more rapidly oxidized and cleared from the plasma when compared with SO and SO-MCTs (22, 110, 113). Studies in humans and animals indicate that the use of SLs in catabolic subjects improves nitrogen balance, preserves the function of the RES, and disturbs liver function to a lesser extent than do SO and SO-MCTs (114, 115).

Only few data are available regarding the immunologic characteristics of SLs. Experimental work indicates that SL exposure at concentrations up to 5 mmol/L does not significantly influence phagocyte functions or cell signaling (49, 104, 106, 107). This is intriguing, given the presence of MCFAs in these triacylglycerols and the significant effects of MCTs on leukocyte function (*see* “Soybean oil–based lipid emulsions” above). The preferential localization of MCTs at the surface of lipid droplets in physical SO-MCT mixtures is probably crucial, because MCFAs in SLs are evenly distributed within the lipid droplets (22). Finally, SLs and SO have shown beneficial effects on liver morphology in TPN-induced hepatosteatosis in rodents, with fewer fatty changes when compared with lipid-free or MCT-based formulations (116).

OO-based lipid emulsions

In the OO-based emulsion (Clinoleic; Baxter) that became available for use in TPN in the late 1990s, 80% of SO has been replaced by OO, which is rich in the long-chain n-9 MUFA oleic acid (18:1n-9). This results in MUFA and PUFA contents of 65% and 20%, respectively, with an n-6 to n-3 PUFA ratio of 9:1 (117).

The few small, short-term clinical trials that have been performed with OO should merely be considered as safety and tolerance studies that provide no insight into the immunomodulating effects of OO-based emulsions. A randomized



double-blind trial in 19 children, with an SO emulsion as control, showed that prolonged (60 d) administration of OO was well tolerated and decreased the accumulation of toxic lipid peroxidation products (118). The safe use of OO, with beneficial effects on TPN-induced liver dysfunction and no side effects or altered inflammatory markers, has been confirmed in several small (≤ 14 subjects) studies in stable home TPN patients (117, 119, 120). Accordingly, a recent trial that unfortunately included a control group that received a lower dose of a different lipid (SO-MCT), reported good tolerance and an absence of side effects from OO-based TPN in 33 critically ill trauma patients (121).

Previous research has shed some light on the immunologic properties of OO. An increase in the dietary intake of oleic acid by healthy volunteers for 2 mo was found to decrease the expression of adhesion molecules of human mononuclear cells without affecting lymphocyte proliferation and natural killer cell activity (122). Similar immune-neutral effects have been observed with parenteral OO, eg, in an *in vitro* study that compared OO with 2 SO emulsions. Although both the latter suppressed lymphocyte proliferation and the production of interleukin (IL)-2, OO showed no deleterious effects (123). When the effects of lipid emulsions at concentrations up to 2.5 mmol/L on calcium signaling in human neutrophils were studied, it was found that all evoked a prompt attenuation of the cell stimulation by a bacterial tripeptide. However, OO and SO were by far less potent in this respect when compared with SO-MCT and FO (50). Olive oil has also been found to inhibit the production of proinflammatory cytokines by isolated human mononuclear cells at concentrations up to 1% (≈ 10 mmol/L), significantly less than SO and SO-MCT (124). Similarly, the expression of activation markers (CD11b, CD66b) on human neutrophils and mononuclear cells in whole blood did not change after exposure to OO at a concentration of 5 mmol/L, whereas SO-MCT elicited cell activation as evidenced by a significantly increased marker expression (105). Another recent study in this field also reported less of an effect of OO at concentrations from 0.03 to 3 mmol/L on human neutrophil functions (oxidative burst, chemotaxis, and elastase release) *in vitro* and on rat neutrophil adhesion *ex vivo* than of SO and SO-MCT (125). Two *in vivo* animal studies in rats are available to corroborate the immune-neutral effects of OO on leukocyte functions (spleen lymphocyte proliferation, IL-2 receptor expression, and bacterial clearance) in comparison with the deleterious effects observed for SO and SO-MCT (126, 127). Finally, somewhat more circumstantial evidence of an immune-neutral effect of OO is provided by a recent study that showed no evidence of oxidative damage or altered oxidant-antioxidant balances in a considerable portion (40%) of the Dutch home TPN population, most of whom (75%) were using an OO-based TPN formulation (128). In conclusion, there is not much evidence that OO directly influences immune function, although indirect effects may result from competition for incorporation with *n*-6 and *n*-3 PUFA into membrane phospholipids (35).

FO-based lipid emulsions

There is currently one emulsion available for parenteral use that contains FO as the single lipid source (Omegaven; Fresenius-Kabi). This 10% emulsion contains 100 g lipid/L, of which 27–59 g is EPA plus DHA, and has a very low ratio (1:8) of *n*-6 to *n*-3 PUFAs (Table 1). It is recommended to combine this fish-oil emulsion with others (eg, SO or SO-MCT) in such a

manner that FO contributes 10–20% of infused emulsion. Another emulsion that includes FO is Lipoplus (B Braun), also known as Lipidm in some countries. This is a 20% lipid emulsion with the lipid being a mix of 50% MCT, 40% SO, and 10% FO. Each liter of Lipoplus contains 9–17 g EPA plus DHA. Studies in animal models show that inclusion of *n*-3 PUFAs in mixed lipid emulsions increases blood clearance and extrahepatic tissue uptake of lipid, despite the fact that FO is a poor substrate for lipoprotein lipase (89, 129, 130).

With regard to effects on outcome in animal studies, FO has been shown to improve survival in models of endotoxemia (131–135). FO also decreased endotoxin-induced metabolic perturbations in guinea pigs and rats and improved heart and lung function and decreased lung edema in endotoxic rats and pigs (134, 136–143). Compared with linoleic acid-rich vegetable oils, FO fed to rats before exposure to live bacteria (either as a result of cecal ligation and puncture or intravenous administration of live Group B *Streptococcus*, respectively) resulted in increased survival, which was associated with decreased production of prostaglandin E_2 (144, 145). Infusion of FO after induction of sepsis by cecal ligation and puncture decreased mortality (and prostaglandin E_2 production) compared with vegetable oil (146). Intragastic administration of FO into chow-fed rats before cecal ligation and puncture improved survival more than did saline or vegetable oil infusion (147).

At least one aspect of the pathophysiologic background behind these effects of FO on outcome appears to be an altered production of bioactive mediators in the form of diminished circulating concentrations of inflammatory eicosanoids (131–135, 144, 145). Feeding FO to mice decreased the *ex vivo* production of TNF- α , IL-1 β , and IL-6 by endotoxin-stimulated macrophages (148–150). Several studies in healthy human volunteers involving supplementation of the diet with FO also have shown a decreased production of TNF- α , IL-1 β , and IL-6 by endotoxin-stimulated monocytes or mononuclear cells (151–156). Besides the effects on eicosanoid and cytokine production, another important aspect of FO may be its positive effect of FO on bacterial killing by the host's immune system, because infusion of FO into rats also receiving low-dose endotoxin decreased the number of viable bacteria in mesenteric lymph nodes and liver (157). FO did not decrease bacterial translocation across the gut and so the authors concluded that it must have improved bacterial killing.

Studies with parenteral FO in surgical patients

Intravenous infusion of FO into patients for 5 d after gastrointestinal surgery has been shown to alter the FA composition of leukocytes in that the EPA content was increased 2.5-fold (152). This would be expected to affect the profile of eicosanoids produced from AA and EPA. Indeed, several studies have shown that the infusion of FO into such postoperative patients lowers the production of AA-derived leukotrienes (eg, leukotriene B_4 and leukotriene C_4) and thromboxanes (eg, thromboxane A_2) and increases the production of EPA-derived leukotrienes (eg, leukotriene B_5 , leukotriene B_5 isomers, and leukotriene C_5) by blood leukocytes stimulated *ex vivo* (158–161).

Several studies have focused on clinical outcomes in response to the influence of parenteral FO in surgical patients. Importantly, no deleterious immunologic effects of FO infusion were observed in these patients. Furthermore, the only one of these fairly small studies to have examined hard endpoints, such as length of hospital stay, suggests real clinical benefits of fish-oil

infusion in these patients (162). In this study, Omegaven was infused, providing 10 g FO/d, on the day before abdominal surgery and for 5 d after abdominal surgery (162). On days 4 and 5, the patients also received standard TPN, which included 50 g fat/d as SO. No differences in infection rates or mortality were observed. However, the postoperative stay in intensive medical wards was significantly shorter in the fish-oil group as was the total hospital stay. The postoperative stay on medical wards was significantly shorter in the fish-oil group. A more recent report from a larger cohort of patients receiving parenteral nutrition after surgery does indicate a benefit of including FO in the regimen (163). There were no differences between the control group (50%:50% SO-MCT) and the patients receiving FO (a mix of Omegaven with the 50%:50% SO-MCT mix, in which a maximum of one-third of the mix was as FO) with respect to the proportion of patients who developed wound infections or who died or in the length of hospital stay. However the proportion of patients in the fish-oil group who were readmitted to intensive care was significantly lower than in the control group. A group of patients also received the FO-containing emulsion for 2 d after surgery. Here there were a number of very significant benefits. This group had a decreased need for mechanical ventilation, a shorter length of hospital stay, less of a need for readmission to intensive care, and lower mortality (163). Another study showed that intravenous infusion of a lipid emulsion containing SO and FO (80%:20%, by vol) into patients for 5 d after major gastrointestinal surgery accelerated the normalization of liver and pancreatic function compared with soybean oil alone. Overall, there was no difference between the groups with respect to length of stay in the intensive care unit or in the hospital. However, in a subgroup of patients at risk of sepsis, there was a reduced intensive care unit stay in the patients who received FO (164). In a recently published study, a mixed group of >650 patients, including ≈230 postsurgical patients, received parenteral nutrition including FO at 0.11 g/kg per day for ≥3 d; there were significantly lower rates of infections, fewer complications, and shorter hospital stays in postsurgical patients who received FO than in those who received the control emulsion (165). These authors identified that infusion of ≈0.15 g FO/kg per day decreased the mean intensive care unit stay and hospital stay. In postsurgical patients who received SO or a mix of SO and FO (80:20, by vol) for 5 d, sepsis incidence, deaths in the intensive care unit, length of intensive care unit stay, and length of hospital stay all tended to decrease in the patients receiving FO, although none of these differences was significant (160). Another group reported a significantly lower length of hospital stay in patients who received a mix of MCT, SO, and FO (50:40:10; Lipoplus) after gastrointestinal surgery than in patients who received SO alone (166). Although some of these studies have been published only in abstract form and further details are required for them to be evaluated more fully, the findings from published studies in gastrointestinal surgical patients clearly show a clinical benefit of the inclusion of long-chain n-3 PUFAs in parenteral nutrition regimens (162–165). However, the study by Tsekos et al (163) also showed a much greater benefit when FAs were additionally provided before surgery, which, of course, is only possible in elective surgery. The greater benefit of preoperative infusion of long-chain n-3 PUFAs may relate to better incorporation of the FAs into leukocytes and other tissues.

As previously mentioned, FO-induced modulation of the production of inflammatory mediators appears to play a crucial role

in its beneficial clinical effects. Plasma TNF- α concentrations were lower (day 6), whereas plasma IL-6 concentrations were lower (day 10) after surgery in patients who had undergone major gastrointestinal surgery and then received a mix of SO, MCT, and FO (30%:50%:20% by vol) for 5 days after surgery compared with those who received SO-MCT (50%:50% by vol) (159). In a more recent study, Omegaven was infused on the day before abdominal surgery and for 5 d after abdominal surgery (162). On days 4 and 5, the patients also received standard TPN, which included 50 g fat/d as SO. TNF- α production by endotoxin-stimulated whole blood tended to be lower (day 5) in the fish-oil group, but not significantly so. Postoperative serum IL-6 concentrations were significantly lower in the fish-oil group than in the control group. Monocyte expression of human leukocyte class II antigens of the DR type was preserved in the fish-oil group, but declined after surgery in the control group. Another study compared the effects of lipid-free TPN or lipid-based TPN including SO or a mix of 83% SO and 17% FO (Omegaven) for 5 d after large-bowel surgery (167). There were no differences between the groups with respect to the numbers of circulating lymphocyte populations before or after surgery. Also, there were no differences between groups with respect to T lymphocyte proliferation, but IL-2 production increased in the fish-oil group, and FO prevented the postsurgery decline in interferon γ production. Taken together, these studies indicate that inclusion of FO in TPN regimens for gastrointestinal surgical patients modulates the generation of inflammatory eicosanoids and cytokines and may help to counter the surgery-induced decline in antigen presenting cell activity and T lymphocyte cytokine production (158, 159, 161, 162, 167).

Studies with parenteral FO in patients with sepsis

It has been shown that fish-oil infusion in patients with sepsis might be associated with clinical improvements. Grecu et al (168) reported significantly lower reoperation rates, intensive care unit stays, and hospital stays in patients who received parenteral FO (as a 66% SO and 33% FO mix) than in those who received SO, but there was no difference in mortality between the 2 groups. Heller et al (165) included 268 patients with abdominal sepsis in their study of parenteral n-3 PUFA infusion. They found a significantly lower rate of infection and shorter lengths of intensive care unit and hospital stay in those patients receiving >0.05 g FO/kg per day than in those receiving less than this. Mortality was significantly decreased in those patients who received >1 g FO/kg per day. Thus, these recent data are also strongly suggestive of genuine clinical benefit from the inclusion of long-chain n-3 PUFAs in parenteral nutrition regimens given to patients with sepsis.

Several studies establish that infusion of long-chain n-3 PUFAs into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes. Infusion of a mix of SO and FO (66%:33%, by vol) over 5 d significantly decreased serum C-reactive protein (CRP) concentrations by an average of ≈88% in patients with abdominal sepsis; parenteral SO alone did not significantly alter the CRP concentration (168). Septic patients who were intolerant of enteral nutrition received an SO-based emulsion or an emulsion containing FO for 5 or 10 d (169, 170). Blood leukocyte counts and serum CRP concentrations tended to be lower and the production of leukotriene B₅ by stimulated neutrophils was significantly higher in patients who received FO (169). Production of TNF- α , IL-1 β ,



IL-6, IL-8, and IL-10 by endotoxin-stimulated mononuclear cells did not increase during infusion of FO, whereas the production of the 4 proinflammatory cytokines was markedly elevated during the first 2 d of SO infusion (170).

Complex mixed-type emulsions including SO, MCT, OO, and FO

It has been argued that the ratio of n-6 to n-3 PUFAs in parenteral lipids, to support the immune system, should mirror the nutritional environment in which human evolution took place (8, 171). This view is bolstered by observations in an animal transplant model in which the infusion of an emulsion with a ratio of n-6 to n-3 PUFAs of $\approx 2:1$ showed immune-neutral characteristics, in the form of a maximally reduced graft organ survival, whereas graft survival gradually increased with both lower or higher ratios of n-6 to n-3 PUFAs (171, 172). In line with these findings, a novel emulsion has been developed. This so-called SMOFlipid (Fresenius-Kabi) is a 20% lipid emulsion with the lipid being a mix of 30% MCT, 30% SO, 25% OO, and 15% FO, resulting in a ratio of n-6 to n-3 PUFAs of 2.5:1. A recent phase I study reported that a short infusion (6 h) of SMOF at a rate of 0.125 g fat/kg body weight per hour in healthy male volunteers, when compared with pure SO (Lipovenoes; Fresenius-Kabi), was well tolerated and increased plasma elimination, as evidenced by a less marked increase in serum triacylglycerol concentration and, at the end of infusion, lower serum triacylglycerol concentrations (173). Effects of SMOF and SO on liver function and oxidative stress have been compared in metabolically stressed patients, with SMOF showing slightly dampened liver enzyme abnormalities and increased plasma concentrations of antioxidants (174). A double-blind, randomized study compared TPN based on SMOF or on SO in patients for 5 d after major abdominal surgery (175). Again, SMOF, administered at a dose of 1.5 g fat/kg body weight per day, was well tolerated and increased plasma n-3 FA concentrations and decreased n-6 FA concentrations. SMOF also increased plasma EPA and DHA concentrations but had no effect on AA. Neutrophil leukotriene B₅ release was enhanced on day 6 with SMOF, and the length of hospital stay decreased by 7 d (13 compared with 20 d). These data corroborate findings in an earlier study, in which the length of hospital stay in postgastrointestinal surgery patients decreased more with SMOF than with SO (13 compared with 20 d) (176). A recent trial randomly assigned 200 patients after elective abdominal or thoracic surgery to receive TPN based on either SMOF or SO for 5 d postoperatively (177). Although both emulsions were well tolerated and relevant laboratory variables were not different between groups, a trend toward a reduced length of hospital stay was observed with SMOF (16 compared with 18 d). The specific immunologic characteristics of SMOF remain to be characterized.

CONCLUSION

Patients with severe intestinal failure can be successfully treated with TPN for long periods. The foremost threats to patient survival are the underlying condition leading to gut malfunction and infectious complications. Lipids are an established component of TPN, and the lipid component of TPN solutions has traditionally been in the form of SO. There is a view that SO represents an imbalanced FA supply, with an overabundance of n-6 PUFAs. Hard evidence that SO-based lipid emulsions have

adverse immunologic effects is lacking. Nevertheless, alternatives to using pure SO have been developed and are in use in some countries. Emulsions that include MCT, OO, and FO as a partial replacement for SO are available. Evidence to date is that these emulsions all offer some advantages over the use of SO alone, although there is a lack of sufficient data on the immunologic consequences and on clinical endpoints. However, promising results in recent studies, especially in those that used FO-based lipids, are encouraging. Clearly, more work to evaluate these emulsions in various clinical settings and to understand the mechanisms of action for their effects are needed. 

The author's responsibilities were as follows—GJAW: provided the idea for the study; GJAW and PCC: reviewed the manuscript. The authors had no conflicts of interest to report.

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