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Review

New Parenteral Lipid Emulsions for Clinical Use

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ABSTRACT. Routine use of parenteral lipid emulsions (LE) in clinical practice began in 1961, with the development of soybean oil (SO) –based LE. Although clinically safe, experimental reports indicated that SO-based LE could exert a negative influence on immunological functions. Those findings were related to its absolute and relative excess of ω-6 polyunsaturated fatty acids (PUFA) and the low amount of ω-3 PUFA and also to its high PUFA content with an increased peroxidation risk. This motivated the development of new LE basically designed along the reduction of ω-6 PUFA and the ω-3 PUFA addition in order to obtain balanced levels of the ω-6/ω-3 ratio. The new LE for clinical use (available in Europe and South America) are differentiated by their content in polyunsaturated (ω-6 and ω-3), monounsaturated, and saturated fatty acids (FA), as well as FA source of their origin, including soy, coconut, olive, and fish oil. This article presents the new LE nutrition and energy functions but also its biochemical, metabolic, and immunomodulating aspects, according to their FA content. LE at 20% when infused from 1.0 to 2.0 g/kg body weight/day rates, either alone or in association with amino acids and glucose, are safe and well tolerated in routine clinical practice. LE combining SO with medium-chain triglycerides and/or olive oil have less ω-6 PUFA and are better metabolized, with less inflammatory and immunosuppressive effects than in relation to pure SO-based LE. The ω-3 PUFA used alone or as component of a new and complex LE (soy, MCT, olive and fish oil) has demonstrated anti-inflammatory and immunomodulatory effects. (*Journal of Parenteral and Enteral Nutrition* **30:**351–367, 2006)

Malnutrition depletion can lead to immunosuppression and damage to the body defense mechanisms, resulting in higher infection rates and mortality.[1,2] Improving the nutrition state can restore immunologic competence and reduce the frequency and severity of infectious complications in hospitalized patients.[3]

Intravenous (IV) nutrition therapy is indicated when the oral and enteral route is no longer available.[4] The standard use of parenteral nutrition (PN) in clinical practice started in 1968, after Dudrick and coworkers' original contribution.[4–7] These pioneers demonstrated that prolonged experimental and clinical parenteral administration of amino acids and glucose concentrated solutions, combined with minerals, vitamins and micronutrients, resulted in growth and body weight gain in children and adults.[4–7] PN therapy was incorporated in clinical practice in several morbid scenarios, with resulting changes in morbidity and mortality,[7–9] PN solutions were compounded mainly with amino acids and glucose.[7] However, the administration of concentrated glucose solutions may cause hyperglycemia, particularly in the more severely ill patients. Hyperglycemia in turn is associated with adverse effects, such as immunosuppression and a higher incidence of infectious complications.[10] To prevent hyperglycemia, attempts were made to reduce plasma glucose levels through insulin administration or partial substitution of infused glucose kcal by fats. The Solassol group in France was one of the first to describe the infusion of lipid emulsion (LE) in association with glucose and amino acids, constituting the so-called 3-in-1 PN.[11] This was then adopted in several countries and today may be considered standard practice.

Despite the experience with previous LE, the routine clinical use of parenteral fat in PN began in 1961 with the development, in Europe, of an LE based on soybean oil.[12] This LE became an important landmark in the history of nutrition therapy for patients under a parenteral regimen. The initial objective was to supply essential fatty acids (FA) and non–glucose-based energy, favoring mainly the nutrition treatment of patients with insulin resistance.[4,13] Essential ω-6 (linoleic) and ω-3 (α-linolenic) polyunsaturated fatty acids (PUFA) cannot be synthesized by the human organism and should be obtained specifically from the diet. The soybean oil–based LE, rich in ω-6 PUFA, proved to be clinically efficient in providing non–glucose-based energy and essential FA safely for the nutrition treatment of stable patients.[14] The establishment of a safe LE led to the first generation of LE development that included those rich in long-chain triglycerides mainly originating from soybean and safflower oil but also from corn and sunflower seed oils.[15,16]

However, since the 1970s there were experimental reports that LE based on soybean oil and rich in ω-6 PUFA appeared to negatively influence immunologic cell functions.[17–19] A better understanding of the

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TABLE I
Fatty acid composition of the commercially available parenteral lipid emulsions for clinical use

Fatty acid composition	Commercial parenteral lipid emulsions				
	Lipovenoes LCT 20%*	Lipovenoes MCT 20%*	ClinOleic 20%**	Omegaven 10%†	SMOFlipid 20%‡
Caproic	—	0.3	—	—	0.2
Caprylic	—	60.0	—	—	32.3
Capric	—	33.8	—	—	22.7
Lauric	—	0.4	—	—	0.3
Myristic	0.2	0.1	—	4.7	1.9
Palmitic	23.5	13.0	12.9	10.6	18.2
Palmitoleic	—	0.3	0.7	8.6	3.3
Stearic	8.0	5.2	3.5	2.1	5.5
Oleic	46.9	24.9	56.5	14.3	55.3
Linoleic	104.1	52.4	17.2	3.3	37.2
Stearidonic	—		—	3.8	0.9
Arachidonic	—		0.5	2.6	1.0
Alpha-Linolenic	13.5	7.5	2.3	1.2	4.7
Eicosapentaenoic	—	—	—	20.6	4.7
Docosapentaenoic	—	—	—	2.4	0.7
Docosahexaenoic	—	—	0.5	15.8	4.4

Data supplied by the manufacturers of the lipid emulsions (Fresenius Kabi and Baxter).
*Values expressed in g/L for 20% lipid emulsions (oil = 200 g/L, egg phosphatide = 12 g/L, glycerol = 25 g/L, and α-tocopherol = 0.1 g/L).
**Values expressed in g/L for 20% lipid emulsions (oil = 200 g/L, egg phosphatide = 12 g/L and glycerol = 22.5 g/L).
†Omegaven is available as lipid emulsion supplement only and has to be added to a standard lipid emulsion. Values expressed in g/L for 10% lipid emulsions (oil = 100 g/L, egg phosphatide = 12 g/L, glycerol = 25 g/L and α-tocopherol = 0.2 g/L).
‡Values expressed in g/L for 20% lipid emulsions (oil = 200 g/L, egg phosphatide = 12 g/L, glycerol = 25 g/L, and α-tocopherol = 0.2 g/L).

immunologic, inflammatory, and biomolecular functions of lipids led to the creation of new parenteral LE that were very different from the pioneering parenteral LE based on soybean oil. Nowadays, there are several LE available for clinical use (in Europe and South America) that vary in terms of their FA content and their sources of origin. The compositions of some commercially available LE are described in Table I.

Besides their function as a source of nonglucose energy with high caloric density (≅ 9 kcal/g) and of essential FAs, it is now recognized that LE can influence immune functions in different ways, according to physicochemical characteristics of the FA pattern in their formula.[20]

Physicochemical Structure of the LE

The FA component of LE can be classified according to the size of their carbon chain (short: up to 4 carbon atoms; medium: 6–12 carbon atoms; and long: with >12 carbon atoms); their degree of unsaturation (no double bonds: saturated; 1 double bond: monounsaturated; 2 or more double bonds: polyunsaturated); and to the location of the first double bond, counted starting from their methyl end (first double bond in the ninth carbon atom: ω-9; first double bond in the sixth carbon atom: ω-6; and first double bond in the third carbon atom: ω-3).[21]

In the human organism, dietary FAs are transported in the bloodstream as chylomicrons. They are large triacylglycerol-rich lipoproteins, synthesized in the enterocyte after the digestion and absorption of dietary fat, which are covered by water-soluble proteins and phospholipids.[22] The LE are formed by artificial chylomicrons, structures similar to the chylomicron characterized by their spherical form (between 200 and 500 nm in diameter) and their particle size, which usually increases according to the oil amount in the emulsion.[23] The artificial chylomicrons present an hydrophobic entity, mainly constituted by triglycerides, and other traces of lipophilic substances, such as diacylglycerols, vegetable sterol esters, as well as liposoluble vitamins, including the tocopherol series.[23] Consequently, the presence of an emulsifier is needed for the oil dispersion in water and for the LE stability. In the artificial chylomicrons, the emulsifier fulfills the role of the phospholipids that envelop the natural chylomicrons.[24,25] The LE emulsifier, usually obtained from egg yolk or soybean, is formed by a single layer of phospholipid molecules with lipophilic and hydrophilic properties that allow the maintenance of the fats in aqueous phase in the emulsion.[23,24,26] All the commercially available LE, with 10%, 20%, and 30% oil concentration, contain a larger amount of emulsifier than necessary to totally cover the oil/water interface surface. The emulsifier excess forms particles with a diameter of <80 nm, called liposomes. Generally, the liposome content is greater in LE with a lower percentage of oil due to the higher phospholipid:oil ratio.[23,25]

Metabolism of the LE

In the circulating blood, the artificial chylomicrons and the liposomes originating from emulsifier excess enter in contact with circulating lipoproteins and cellular membranes. They are metabolized in a competitive manner during the lipolysis process, lipid and apolipoprotein transfer, and tissue internalization.[25,27]

Through the action of the lipoprotein lipase enzyme, the artificial chylomicrons triglycerides are hydrolyzed, releasing FAs and forming small particles or remnants that are quickly taken up by the liver.[23,25] The FAs are then transported to the tissues, in a similar manner to the natural chylomicrons, and are used by the cells mainly as an energy source.[23,25]

The liposomes, in turn, are of little interest in terms of energy and can present harmful effects in larger amounts. They inhibit lipolysis of artificial chylomicrons and, through the capture of endogenous cholesterol, they stimulate tissue cholesterol synthesis and become particles with ultrastructural and physiochemical characteristics of abnormal lipoproteins, called lipoprotein-X (LP-X). The LP-X is a vesicle measuring 30–70 nm in diameter, formed basically by a double layer of phospholipids and cholesterol (in an equimolar ratio). This abnormal lipoprotein is poor in apolipoproteins, presenting a similar density to that of low-density lipoprotein (LDL) and is clinically found in hepatic diseases with plasma lipid profile alterations (eg, obstructive jaundice).[23,27,28]

The LP-X formation corresponds to the final stage of the intravascular catabolism of liposomes, and its physicochemical characteristics make it a poor substrate for the action of lipolytic enzymes that, in turn, keep them stable in the circulation. LP-X can lead to cholesterol accumulation and hypercholesterolemia development or an increase in the cholesterol:plasma cholesterol ester ratio.[23,27,28]

The disturbances related to liposome metabolism in plasma depend on the speed and duration of parenteral infusion, as well as of the oil concentration in the LE. Slower and shorter parenteral fat infusion attenuates changes in the plasma lipids profile and limits the supply of liposomes. Furthermore, the liposome content is greater in LE with a low oil percentage. To provide the same amount of energy, 10% LE supplies around 3 times more liposomes than 20% LE, and 10 times >30% LE.[23] It has been demonstrated that 10% soybean oil–based LE leads to a larger accumulation of LP-X than its counterpart at 20%, which is less rich in liposomes.[29] Thus, it is now recommended that more concentrated parenteral LE be used and infused at a lower speed necessary to offer the total lipid requirements.

LE in Clinical Practice

In clinical practice, the parenteral LE can be infused separately or in mixed parenteral systems, with amino acids and glucose. Although usually infused by the central venous system, the LE can also be offered through peripheral veins in patients needing short-term PN and having moderate nutrition requirements and contraindication for central venous access.[30] However, the peripheral access can lead to vascular complications, such as phlebitis, thrombosis, and thrombophlebitis, depending on the LE composition, patient's sensitivity, quality of the intravascular catheter, and other factors.[31]

In clinical practice, depending on the patient's nutrition needs, it is recommended that the supply of LE be 25%–30% of the total caloric ingestion and about 50% of the total nonprotein energy consumption.[32] At an infusion rate of 0.8–1.5 g/kg bw this is equivalent to about 50–100 g of lipid a day, according to the patient's weight.[32,33] It is also recommended that the administration of LE not exceed the maximum of 2.5 g of lipid/kg body weight/d, or 60% of total calories value.[33] The initial supply of LE should be slow (≅0.05 g of lipid/kg of body weight/h) during the first 30 minutes, and then the infusion speed is increased gradually until about 0.1 g lipid/kg body weight/h.[34] In pediatric patients, LE infusions should begin at 0.5–1 g/kg per day and advance progressively at a rate of 0.5 g/kg per day to a maximum of 3 g/kg per day, except in the premature or septic infants, when LE infusion rates should be reduced.[35]

Excess LE administration should be avoided because it can lead to respiratory distress, coagulopathies, abnormal liver functions test, impaired reticuloendothelial system function, immunosuppression (result of fat overload), hypercholesterolemia (due to liposome excess), and hypertriglyceridemia.[36,37] Hence, monitoring levels of plasma triglycerides is mandatory during LE infusion.

Modulation of Immune Functions by LE

LE can influence immunologic functions by different pathways. One of these is through their FA incorporation in the membrane phospholipids of immunologic cells, thereby altering its fluidity, structure, and function of various membrane-related receptors, transporters, enzymes, and ionic channels.[38–40] In addition, PUFA ω-3 and ω-6 participate directly in the inflammatory immune response, serving as a substrate for eicosanoid synthesis (lipid inflammatory mediators).[41]

Faced with an adequate stimulus, the membrane PUFA ω-6 arachidonic acid (AA) and ω-3 eicosapentaenoic acid (EPA) are mobilized from the cellular membrane phospholipids by the A2 phospholipase enzyme and compete for the same enzymatic paths (cyclooxygenase and lipoxygenase) for the eicosanoids formation. If there is a predominance of AA, then even class eicosanoids are released (prostaglandin E2, PGE2; leukotriene B4, LTB4; thromboxanes 2, TX2; and platelet aggregation factor, PAF, among others). If EPA predominates, then odd class eicosanoids are formed at a higher proportion (as prostaglandin E3, PGE3; leukotriene B5, LTB5; and thromboxane 3, TX3).[41,42]

The ability of ω-3 PUFA to compete with ω-6 PUFA for eicosanoid synthesis constitutes a key point in its anti-inflammatory properties.[41] Moreover, ω-3 PUFA exert other anti-inflammatory effects that seem to be, at least partly, independent from the modulation of eicosanoid production. Experimentally, ω-3 PUFA can indirectly influence the production of proinflammatory cytokines. The addition of these FAs into cell cultures of human osteoarthritic cartilage reduced the expression of proinflammatory genes (for example, inflammatory cytokines, cycloxygenase-2, 5-lipoxygenase, protein activator of 5-lipoxygenase) and prevented their activation mediated by cytokines.[43]

One of the mechanisms proposed to explain the ability of ω-3 PUFA to influence proinflammatory cytokine production at the gene level is through the peroxisome proliferator-activated receptors (PPAR) activation. PPARs bind proteins that participate in controlling the expression of broad arrays of genes also involved in immune and inflammatory response.[44] Among other functions, PPARs antagonize signaling pathways of

nuclear transcription factor κB (NFκB), responsible for the transcription of genes involved in the inflammatory response that include cytokines, adhesion molecules, and other proinflammatory signal mediators.[45] PPARs also control the expression of several genes involved in intra- and extracellular lipid metabolism and the duration and intensity of the inflammatory response because they induce the expression of genes that code proteins involved in the proinflammatory lipid mediators' catabolism.[44,46–48]

Indirectly, ω-3 PUFA can also suppress the signaling of T lymphocytes, probably due to a molecular structure modification of their lipid rafts after ω-3 PUFA incorporation. Membrane lipid rafts are specific regions within the plasma membrane, rich in cholesterol, sphingolipids, saturated FAs, and proteins, where signal transduction functions occur in T-cells.[49,50]

Although the anti-inflammatory effect of ω-3 PUFA is well established in the scientific literature, there is still controversy about whether these FA can impair immunologic functions such as phagocytosis, chemotaxis, and respiratory burst, thereby increasing susceptibility to infections. Although some *in vivo* and *in vitro* experimental studies have demonstrated maintenance or even improvement in the phagocytic and bactericidal capacity of mononuclear and polymorphonuclear leukocytes, others have reported impairment of these functions.[51–55] These differences could be attributed to variations in the biologic models and experimental protocols used by the researchers.

It is recognized that excess of either ω-6 or ω-3 PUFA in parenteral LE could be immunosuppressive, whereas maintenance of the immune response can be observed by LE infusion with an appropriate ω-6/ω-3 ratio.[56] According to clinical and experimental data, it has been suggested that the most favorable ω-6/ω-3 ratio is in the region of 2:1–4:1.[56–59]

Soybean oil–based LE has a high content of ω-6 PUFA and low amounts of ω-3 PUFA, presenting an ω-6/ω-3 ratio of 7:1. It has been demonstrated experimentally that this emulsion inhibits lymphocytes, macrophages, and neutrophil functions, besides impairing reticuloendothelial function and reducing the plasma lipid clearance.[18,37,60–64] These findings seem to be related with ω-6 PUFA excess and low amounts of ω-3 PUFA, as well as an increased oxidative stress related to the PUFA supply in the soybean-based LE.

Lipid peroxidation, the process involving incorporation of an oxygen molecule into the unsaturated FA carbon chain producing lipid peroxides, may occur under PUFA-rich LE parenteral infusion.[65] Lipid peroxides are unstable molecules that, by enzymatic or nonenzymatic decomposition, are converted to volatile malondialdehydes and hydrocarbons, pentane (produced by ω-6 PUFA peroxidation), and ethane (produced by ω-3 PUFA peroxidation).[66] These substances, in turn, can modulate or impair basal metabolism, as well as cell and organ function, because they can trigger chain reactions that inactivate enzymes, proteins, and other important elements necessary for cell survival.[65]

Soybean oil–based LE contain high amounts of γ-tocopherol but relatively small amounts of α-tocopherol which is the most potent fat-soluble antioxidant *in vivo*.[67] The oxidant effect of α-tocopherol through inhibition of lipid peroxidation by scavenging lipid peroxyl radicals is much faster than the reaction of the free radicals with FA chains, thus breaking the chain reaction.[68] However, during this process α-tocopherol is converted into a free radical (later recycled by specific reactions), and may lead to a pro-oxidant effect, as observed in certain experimental models.[69,70] These findings indicate an upper limit for α-tocopherol supplementation in LE; therefore, it is not necessary to exceed 200 mg/L.[71]

Besides PUFA content, temperature, light exposure, and storage bag material can also influence the intensity of lipid peroxidation. Hence, it is recommended that LE at high temperatures not be stored under bright conditions, or in packaging that allows penetration of oxygen, such as polypropylene:polyamide bags (7:3).[72]

The debate regarding the use of lipids as an energy source in PN solution was fueled after a meta-analysis published in 1998 that found higher rates of complications in surgical and critically ill patients receiving parenteral regimen with fat in comparison with those that received PN without fat.[73]

Taken together, these scientific observations promoted the search for a new alternative parenteral LE design. Contemporary nutrition planning should consider the nutrition and energy functions, as well as the biochemical, metabolic molecular, and immune-modulating characteristics of the FAs. The "ideal" LE should be readily metabolized, present a reduced risk of oxidative stress, not induce inflammation or have anti-inflammatory properties, and not have an immunosuppressive effect.[74] From this perspective, efforts are under way to develop new LE along 2 different ways, reduction of ω-6 PUFA and addition of ω-3 PUFA, to obtain more balanced ω-6/ω-3 ratios. In addition, to prevent damage arising from lipid peroxidation, the enrichment of LE with antioxidants is also required.

LE With Low Ω-6 PUFA Content

With the objective of diluting the high ω-6 PUFA content present in conventional soybean oil–based LE, new LE based on soybean oil mixture with medium-chain triglycerides (MCT) or olive oil (rich in monounsaturated FA) were developed.

LE Based on a Mixture of MCT and Soybean Oils

The first LE formulated to reduce the ω-6 PUFA content was a physical mixture of 50% MCT obtained from coconut oil and 50% soybean oil (MCT/LCT), Table I. This MCT/LCT LE has 50% less ω-6 PUFA content than the conventional LE based only on soybean oil.

Due to the fact that they are easily metabolized, the addition of MCT confers biochemical and metabolic advantages to the MCT/LCT LE.[75] MCT metabolism is at least partially independent from carnitine transport into the mitochondria, thereby representing a rapid

source of lipid energy. In addition, they promote better plasma clearance and do not accumulate in the liver.[75]

Since its development, MCT/LCT parenteral lipid emulsion has been indicated for critically ill patients due to the fact that MCT is less susceptible to lipid peroxidation and does not participate in eicosanoid synthesis, thereby reducing the impact on the reticuloendothelial system and on the systemic inflammatory response in relation to ω-6 PUFA.[76,77]

However, it has been demonstrated experimentally that a MCT/LCT LE in physical mixture may selectively change leukocyte function. MCT/LCT LE increased neutrophil β-2 integrin, adhesion molecule expression, and degranulation but decreased killing of *Candida albicans* by human neutrophils compared with soybean oil–based LE.[78,79] In addition, MCT have an inhibitory effect on long-chain triglycerides oxidation when both are mixed together, and high MCT doses may have a ketogenic effect, thereby limiting their use in patients with diabetes mellitus or other clinical conditions aggravated by acidosis and ketosis.[75]

Despite the experimental controversial findings, the use of MCT/LCT LE in a physical mixture has proven to be clinically safe for supplementation in surgical patients[80–83]; patients with respiratory failure,[84] hepatic disease,[85] and liver transplant[86]; critically ill patients[87,88]; and sepsis,[76,89] decreasing incidence of abdominal abscess, weight loss, infection, and mortality rates and improving parameters such as nitrogen balance and pulmonary/liver functions compared with soybean oil–based LE. In relation to immunologic parameters, clinical use of MCT/LCT had positive effect by maintaining or improving leukocytes and reticuloendothelial system function.[76,80–89] Data from clinical studies with the use of MCT/LCT in physical mixture supporting this information are shown in Table II.

To improve the safety and efficacy of MCT/LCT parenteral LE and at the same time to decrease the disadvantages of the physical mixture, a new LE containing triglycerides synthesized from several combinations of LCT from soybean oil and MCT from coconut oil was developed. These structured triglycerides are composed of a random chemical grouping of triglycerides containing various medium- and long-chain FAs on the same glycerol backbone.[90]

Experimentally, MCT/LCT in a physical mixture but not in a structured form increased the early respiratory burst with oxygen radical production of isolated nonstimulated human neutrophils.[91] The increased oxygen radical production after MCT/LCT LE incubation may be due to an inadequate activation of the respiratory burst that is probably detrimental for phagocyte function.[91]

Structured MCT/LCT LE infusion was well tolerated by critically ill patients[92] and by those submitted to surgical procedures,[93–96] improving nitrogen balance and maintaining laboratory routine clinical biochemistry, in relation to MCT/LCT physical mixture.[92–96] Data from clinical studies with the use of MCT/LCT parenteral LE in structured form supporting this information are shown in Table II.

LE Based on Olive Oil

Another alternative to reduce the high content of ω-6 PUFA is the dilution with olive oil rich in monounsaturated fatty acids (MUFA). Olive oil–based LE contain approximately 20% of ω-6 PUFA, enough to supply or correct the essential FA requirements, and are rich in vitamin E, important to prevent lipid peroxidation cell damage (Table I).[97–99]

MUFA have been frequently regarded as having a neutral effect on immune function.[100] Olive oil–based LE may avoid the impairment of the immune response associated with ω-6 PUFA and may achieve an immunologically neutral effect.

However, MUFA seem to exert some immunomodulating functions similar to the FA present in fish oil (EPA and DHA). In patients with rheumatoid arthritis, MUFA decreased the neutrophil LTB4 and macrophages interleukin-1 (IL-1) production, and increased lymphocyte proliferation.[101] In a case-controlled observational study, olive oil ingestion was related to greater protection from the development and/or complication of rheumatoid arthritis.[102] These observations suggest that olive oil exerts an immune modulatory effect, fueling the discussion regarding its neutrality on the immune system and its use as placebo.

The modulatory effect of olive oil–based LE on immune function has been evaluated experimentally. Olive oil–based LE reduced the production of TNF-α and IL-1β to a similar extent as soybean oil–based LE, without modifying the proliferative capacity of human lymphocytes or the expression of CD25 or HLA-DR surface molecules.[103] In human mononuclear cells, culture with olive oil–based LE was associated with a smaller inhibitory effect on the *in vitro* proinflammatory cytokines IL-1β and TNF-α release in comparison to soybean oil–based LE and also to MCT/LCT LE.[104]

It has been demonstrated that parenteral infusion of olive oil–based LE, either in isolation or combined with glucose and amino acids, is clinically safe, well tolerated, and may preserve liver function.[105,106] Moreover, it maintains normal levels of essential FAs in adult and pediatric patients, even when used for 2–3 months with home PN.[98,99] Consequently, olive oil–based LE may represent a safe alternative for parenteral fat supply, with less potential impact on the immune and inflammatory response, as well as on the lipid peroxidation, than LE with higher ω-6 PUFA content. Data from clinical studies with the new olive oil–based LE use supporting this information are shown in Table III.

LE Rich in ω-3 PUFA

LE based on fish oil. The biologic properties of ω-3 PUFA, particularly EPA and DHA contained in fish oil, support its potential use for various clinical conditions. A common factor among some of these diseases is endothelial inflammation, underscoring the role of ω-3 PUFA as an anti-inflammatory agent.

Recently, fish oil–based LE has become available for IV infusion in clinical practice. The possibility of infusing ω-3 PUFA by venous access can optimize its biologic effects because this pathway enables rapid cellu-

TABLE II
Clinical results of LE containing 50% medium-chain triglycerides and 50% soybean oil treatment

Reference	Type of study	Population (*n*)	Groups	Treatment	Main results
Smirniotis et al (1998)[89]	Prospective randomized open	Surgical ICU patients with sepsis and ARDS (n = 21)	PN + SO PN + MCT/LCT	12 g fat/hour (8 h)	MCT/LCT increased O_2 consumption SO increase pulmonary venous administered and mean pulmonary artery pressure
Grau et al (2003)[80]	Prospective randomized double-blind	Severely undernourished patients with laparotomy, with or without cancer (n = 72)	PN + SO PN + MCT/LCT	550 kcal of lipid (≅58 g fat/d) (2 Preoperative days and 3 postoperative days)	MCT/LCT reduced incidence of infection and abdominal abscesses in surgical patients MCT/LCT reduced the incidence of abdominal abscess and mortality of patients without cancer
Lai & Chen (2000)[81]	Randomized open	Children submitted to surgery (n = 38)	PN + SO PN + MCT/LCT	1.5 g fat/kg bw/d (14 Postoperative days)	MCT/LCT increased percentage of lymphocytes MCT/LCT reduced serum aspartate aminotransferase and bilirubin after 14 days of infusion MCT/LCT decreased respiratory quotient after 14 days of infusion MCT/LCT improved nitrogen balance MCT/LCT increased oxidation of fat and decreased use of carbohydrate
Waitzberg et al (1997)[82]	Prospective crossover blind trial	Malnourished patients with gastric cancer (n = 10)	PN + SO PN + MCT/LCT	0.08 g fat/kg bw/h (2 Preoperative days)	MCT/LCT did not change chemotaxis, phagocytosis, bacterial death, or oxidative metabolism of monocytes and neutrophils SO reduced bacterial death by neutrophils
Jiang et al (1993)[83]	Randomized open	Major abdominal surgery patients (n = 12) and volunteers (n = 6)	PN + SO PN + MCT/LCT	1.55 g fat/kg bw/d (For 2 preoperative days and for 7 postoperative days)	MCT/LCT increased muscle use MCT/LCT tending to less loss of nitrogen MCT/LCT reduced weight loss in postoperative period MCT/LCT increased concentration of ketones
Smyrniotis et al (2001)[84]	Prospective randomized open	Patients with acute pancreatitis and ARDS (n = 9)	PN + SO PN + MCT/LCT	50% of calories from lipid (2 d)	SO increased the mean pulmonary artery pressure and decreased arterial PO_2/fractional inspired oxygen MCT/LCT increased O_2 consumption, cardiac output, and CO_2 production
Kuse et al (2002)[86]	Prospective randomized double-blind	Patients with liver transplant (n = 22)	PN + SO PN + MCT/LCT	0.5–1 g fat/kg bw/d (second postoperative day) 1–2 g fat/kg bw/d (3rd through 10th postoperative days)	MCT/LCT and SO groups showed significant increases in hepatic RES activity MCT/LCT improved functioning of hepatic RES after 7 days of parenteral nutrition
Jeevanandam et al (1995)[87]	Multicenter prospective double-blind	Critically ill patients (n = 10)	PN + SO + PN + MCT/LCT (75%/25%)	9 kcal/kg bw/d (≅1 g fat/kg bw/d) (7 d)	MCT/LCT increased plasmatic concentration of metabolites, indicating rapid hydrolysis and efficient use of this LE MCT/LCT increased body lipolysis MCT/LCT increased oxidation and reduced esterification of fatty acids MCT/LCT and SO led to similar concentration of plasma albumin, total protein, prealbumin, transferring, cholesterol, and lactate MCT/LCT and SO plus glucose induced no increase in ketone concentration, suggesting decreased hepatic disposal of triglycerides by β-oxidation

Ball (1993)[88]	Randomized open	Critically ill patients (n = 20)	PN + SO PN + MCT	100 g fat/d (mean of 8 days)	MCT/LCT no adverse effects presented MCT/LCT had higher number of neutrophil counts (2 patients had very high counts); MCT/LCT greater concentration of ketone and plasmatic glycerol MCT/LCT lower negative nitrogen balance on days 6 and 9 MCT/LCT and SO had a high urinary carnitine excretion
Lindgren et al (2001)[92]	Randomized double-blind parallel study	ICU patients with sepsis or multiple injury (n = 30)	PN + structured MCT/LCT PN + SO	1.5 g fat/kg bw/d (5 d)	In the structured MCT/LCT group, the nitrogen balance and the cumulative nitrogen balance were significantly better on day 3 The structured MCT/LCT was well tolerated, and no difference was found compared to the LCT emulsion regarding respiratory quotient, energy expenditure, glucose, or triglyceride levels during infusion
Kruimel et al (2001) [93]	Randomized double-blind parallel study	Patients with aortic prosthesis (n = 25)	PN + structured MCT/LCT PN + MCT/LCT	26% of total energy requirement calculated by Harris-Benedict equation in kcal/d (5 postoperative days)	Structured MCT/LCT had better nitrogen balance Structured MCT/LCT had lower increase in serum triglyceride and plasma medium-chain free fatty acid levels on the first postoperative day
Bellantone et al (1999)[94]	Randomized blind	Colorectal surgery patients with anastomosis (n = 19)	PN + structured MCT/LCT PN + SO	11.2 kcal from lipid/kg bw/d (≅1.29 g fat/kg bw/d) (5 postoperative days)	Structured MCT/LCT and SO had a positive nitrogen balance The excretion of 3-methylhistidine was higher in the SO but decreased in the following days and was similar to the structured MCT/LCT on day 5
Chambrier et al (1999)[95]	Randomized double-blind	Major elective abdominal surgery patients (n = 40)	PN + structured MCT/LCT PN + MCT/LCT	50% of calories from lipid (Structured MCT/LCT ≅0.85 ± 0.15 g fat/kg bw/d) (MCT/LCT ≅0.86 ± 0.12 g fat/kg bw/d) (5 postoperative days)	Physical MCT/LCT mixture increased aspartate transaminase (ASAT), alanine transaminase (ALAT), and triacylglycerol plasma levels in routine clinical biochemistry Structured MCT/LCT is as efficacious as physical mixture to maintain a better nitrogen balance in postoperative patients
Sandstrom et al (1995)[96]	Randomized double-blind crossover	Elective abdominal surgery patients (n = 37)	PN + structured MCT/LCT PN + SO	1.0 g/kg bw/d (part 1) 1.5 g/kg bw/d (part 2) (6 postoperative days)	Both LE were well tolerated in parts 1 and 2 of the study Structured MCT/LCT were not associated with any side effects, were rapidly cleared from the plasma compartment, and were rapidly oxidized without any significant hyperlipidemia or ketosis Structured MCT in the presence of excess of nonprotein calories (part 2) caused a significantly higher whole body fat oxidation

ARDS, acute respiratory distress syndrome; bw, body weight; ICU, intensive care unit; LE, lipid emulsion; MCT/LCT, lipid emulsion containing 50% of medium-chain triglycerides and 50% of soybean oil; SO, soybean oil–based lipid emulsion; RES, reticuloendothelial system; PN, parenteral nutrition.

lar incorporation and reduces losses from the digestion and absorption of oral ω-3 PUFA. Due to the increased number of double bonds in their carbon chain, ω-3 PUFA are more susceptible to lipid peroxidation than ω-6 PUFA, but the oxidative risk by fish oil LE is efficiently counteracted by α-tocopherol enrichment.[107]

Current data indicate that diseases with an inflammatory character can be sensitive to LE rich in ω-3 PUFA and that an increase in these FA can optimize the treatment of patients with respiratory disorders, cystic fibrosis, rheumatoid arthritis, arteriosclerosis, acute cardiac diseases, sepsis, and cancer associated with cachexia, under PN.[108–113] Specifically regarding cancer, ω-3 PUFA have been associated with beneficial effects in clinical and experimental studies, with reduction of weight loss and maintenance of fat and muscle tissues, as well as inhibition of angiogenesis, progression of the acute phase response, and of tumor growth.[114–117]

Experimentally, the triglycerides that comprise ω-3 PUFA-rich LE are poorly hydrolyzed by lipoprotein lipase. However, the plasma clearance of their FA is faster than in soybean oil–based LE.[118] The plasma clearance of soybean oil–based LE involves intravascular lipases, apolipoprotein E (Apo E), and the receptor for LDL (r-LDL). However, this mechanism seems to be significantly less important for the clearance of chylomicrons in ω-3 PUFA rich LE, depending on a diminished participation of lipase lipoproteins and independent of Apo E, r-LDL, and pathways sensitive to lactoferrin.[118]

Pure parenteral fish oil LE was well tolerated by healthy volunteers. When infused in a mixture with soybean oil–based LE in short-term postoperative patients, no side effects were reported.[119–121] In surgical patients, the fish oil–based LE increased the phospholipid incorporation of ω-3 PUFA in cell membranes, and did not impair coagulation and platelet functions. It also seems to preserve immune function and to prevent some aspects of the inflammatory response. Fish oil–based LE was related to shorter hospital and intensive care unit length of stay and, in a recent retrospective study, decreased morbidity and mortality rates in this patient population.[122–127] In sepsis and other inflammatory conditions, the use of fish oil LE is associated with an increase in odd series eicosanoid production and a decrease of proinflammatory cytokine release.[113,128] The decrease of inflammatory eicosanoid production after fish oil LE infusion was also observed in other inflammatory diseases, such as psoriasis, with an improvement of the inflammatory skin lesions.[129,130] In addition, fish oil LE use in cystic fibrosis was safe and did not impair pulmonary function.[109] Data from clinical studies with the new fish oil LE use supporting this information are shown in Table IV.

LE based on a mixture of soy oil, MCTs, olive oil, and fish oil. A new LE commercially available in Europe combines the 2 concepts initially proposed for the development of an "ideal" LE. It contains reduced amounts of ω-6 PUFA, through the addition of MCT and olive oil, as well as fish oil. This new LE is based on a physical mixture of 30% soybean oil (essential FA supply), 30% medium-chain FAs (fast source of energy with a satisfactory metabolic profile), 25% olive oil (less immunologic influence and reduced lipid peroxidation), and 15% fish oil (anti-inflammatory effect). This product is characterized by presenting a balanced content of FA and ω-6:ω-3 ratio, within the range considered to be optimal in the current literature (approximately 2.5:1) for critical care patients. Furthermore, this LE is supplemented with appropriate amounts of the antioxidant α-tocopherol (200 mg/L).[131]

This new parenteral LE was well metabolized and tolerated by healthy volunteers and from a clinical standpoint seems to present a better metabolic profile in relation to triglyceride elimination in patients with PN regimens of 7–14 days, compared with soybean oil LE.[131,132] Furthermore, it may be associated with less hepatic dysfunction and preserved antioxidant capacity of patients in the intensive care unit and had a favorable effect on the hospital length of stay of surgical patients.[133,134] During parenteral supply of the new LE based on a mixture of 4 different oils, ω-3 PUFA (EPA and DHA) were quickly incorporated into the plasma phospholipids and cell membranes of leukocytes and platelets, resulting in the favorable modulation of immunologic and inflammatory variables and pointing out its potential indication in hyperinflammatory conditions and suppression of the immune response.[134] Data from clinical studies with the new LE based on a mixture of 4 different oils that support this information are shown in Table V.

Final Considerations

The experience acquired in clinical practice has led to new concepts regarding the LE composition, storage, and supply. These have contributed to promoting its safe use as a source of essential FA and non–glucose-based energy. In relation to LE composition, the development of improved formulations is characterized by 3 distinct generations: LE rich in ω-6 PUFA, LE with reduced ω-6 PUFA content, and LE rich in ω-3 PUFA.

We are now closer to full exploitation of the nutrition properties of lipids and to better use of their capacity to modulate inflammation and the immune response. There may be a real possibility, in the near future, that a specific LE will be indicated for a specific patient's disease, opening a new horizon where LE will be offered not only for nutrition support but as true immuno-PN. In that sense, the use of LE containing ω-3 PUFA already stands out for the treatment of diseases with an inflammatory nature.

In the future, we should expect new LE explorations, including the genetic impact of different FAs. For instance, there is evidence that points out the different modulating properties at the gene level among the members of the ω-3 family (EPA and DHA).[135] Further studies in this field, focusing on EPA and DHA effects on gene modulation of cytokines and their receptors and on signal transduction pathways, transcription factors, cell cycle, and apoptosis-related genes, will generate new knowledge that potentially will contribute to the improvement of LE containing EPA and/or DHA in concentrations adjusted to the patient's needs.

TABLE III
Clinical results of olive oil–based LE treatment, according to the literature

Reference	Type of study	Population (n)	Groups	Treatment	Main Results
Reimund et al (2005)[98]	Prospective open	Stable adults with home parenteral nutrition (n = 14)	PN + OO	21%–47% fat (90 days)	OO did not alter nutrition, clinical, and inflammatory markers between day 0 and end of month 3 OO did not present deficiency in essential fatty acids
Goulet et al (1999)[99]	Randomized double-blind	Children with short-bowel syndrome, intractable diarrhea, and chronic intestinal pseudo-obstruction (n = 18)	PN + OO PN + SO	1.8 g fat/kg bw/d (60 days)	OO and SO did not alter levels of triglycerols, apolipoprotein A1 and B, and cholesterol (HDL) SO increased LDL OO and SO did not modify the concentration of ω-6 in erythrocyte membrane and the ω-9/ω-6 ratio (20:3ω-9/20:4ω-6) OO increased level of oleic acid (18:1ω-9) on day 60 and presented lower index of lipid peroxidation.
Garcia-de-Lorenzo et al (2005)[105]	Prospective, double-blind, randomized	Severely burned patients (n = 22)	PN + OO/SO PN + MCT/LCT	1.3 g fat/kg bw/d (6 days)	Abnormalities of liver function tests occurred more frequently in the MCT group than in the OO group Fatty acid metabolism and PN tolerability were similar with both lipid emulsions Seven patients died from multiple-organ failure after PN infusion. Compared with surviving patients, those who died were older and hyperglycemic at baseline, and their plasma IL-6 levels continued to increase.
Gobel et al (2003)[106]	Randomized double-blind	Premature children (n = 33)	PN + OO PN + SO	0.5, 1, and 2 g fat/kg bw/d (3 consecutive days) 2 g fat/kg bw/d (next 4 days) (7days)	OO and LCT did not differ in plasma phospholipids AA concentration and total ω-6 PUFA and ω-3 PUFA metabolites OO increased the intermediaries of PUFA (C18:3ω-6 and C20:3ω-6) OO increased and SO decreased the plasmatic α-tocopherol/lipids ratio and α-tocopherol/cholesterol ratio OO and SO did not differ between baseline and study end and between groups for plasma triglycerides, biochemical indicators of liver function, integrity, and differential blood counts. There was no significant difference between groups in the occurrence of clinical adverse events (bradycardia, gastroesophageal reflux, hyperbilirubinemia and apnea)

AA, arachidonic acid; bw, body weight; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCT/LCT, lipid emulsion containing 50% of medium-chain triglycerides and 50% of soybean oil; OO, olive oil–based lipid emulsion; PUFA, polyunsaturated fatty acids; SO, soybean oil–based lipid emulsion; PN, parenteral nutrition.

TABLE IV
Clinical results of fish oil–based LE treatment, according to the literature

Reference	Type of study	Population (n)	Groups	Treatment	Main Results
Katz et al (1996)[109]	Prospective randomized double-blind	Patients with cystic fibrosis (n = 18)	PN + SO PN + FO	0.15 g fat/kg bw/d (120 days)	FO was well tolerated and did not lead to allergic or toxic reactions, abnormalities in liver function tests, or coagulation parameters FO increased plasma EPA and DHA FO had a tendency toward improved pulmonary function
Mayer et al (2003)[113]	Prospective randomized open-label	Patients with severe sepsis or septic shock (n = 21) Control group: healthy volunteers (n = 6)	PN + SO PN + FO	35 g fat/d (5 days)	FO increased plasma free ω-3 fatty acids and ω-3 fatty acids incorporation in mononuclear leukocyte membrane after 2 days of infusion FO reduced the release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8) by mononuclear leukocytes that was increased by SO
Mayer et al (2003)[120]	Prospective randomized crossover double-blind	Healthy volunteers (n = 12)	SO FO	35 g fat/d (2 infusions of 2 days with an interval of 3 months between them)	FO was well tolerated and did not lead to adverse events FO did not change the expression of adhesion molecules CD11b, CD18, CD49, CCR2 and CCR5 FO inhibited monocytes' endothelium adhesion and transendothelial monocytes' migration FO decreased monocyte proinflammatory cytokine (TNF-α, IL-1, IL-6, and IL-8) and did not change IL-10 generation in response to endotoxin FO increased ω-3/ω-6 ratio in the plasma free fatty acids fraction and in monocyte membrane lipid pool
Heller et al (2002)[121]	Prospective randomized double-blind	Surgical patients with gastrointestinal or pancreas carcinoma (n = 44)	PN + SO PN + SO + FO	1 g fat/kg bw/d (Up to 0.2 g/kg bw/d of FO) (5 postoperative days)	FO was safe and did not change thromboplastin time, activated partial thromboplastin time, fibrinogen, antithrombin III coagulation factor, and platelet number and function compared to control group
Morlion et al (1996)[122]	Prospective randomized controlled	Patients with major abdominal surgeries (n = 30)	PN + SO PN + SO + FO, 85:15 (SO:FO)	1 g fat/kg bw/d (5 postoperative days)	FO increased EPA and DHA concentration in the plasma phospholipids and leukocytes membranes FO showed an increased trend to enhance LTB5 and LTC5 release FO did not impair laboratory tests and did not lead to side effects or complaints

Schauder et al (2002)[123]	Prospective randomized double-blind	Patients with large-bowel surgery (n = 60)	PN + SO PN + SO + FO, 5:1 (SO:FO) PN without fat	0.6 g/kg bw/d (1 preoperative day) 1.2 g/kg bw/d (5 postoperative days) (6 days)	FO did not affect lymphocytes' subset distribution and proliferation FO prevented the drop in INF-γ release observed in the other groups FO increased IL-2 in the postoperative day 6 FO increased IL-2R only in postoperative day 3 FO increased TNF-α postoperative day 6
Roulet et al (1997)[124]	Prospective randomized	Surgical patients with esophageal epidermoid carcinoma (n = 19)	PN + SO PN + SO + FO, 9:1 (SO:FO)	1.45 g fat/kg bw/d (7 postoperative days)	FO was safe and did not impair postoperative bleeding or hepatic and renal function FO increased EPA in platelet phosphatides FO doubled EPA/AA ratios in platelet phosphatides FO decreased maximal reaction speed and increased latency, with collagen as aggregating factor
Weiss et al (2002)[125]	Prospective randomized	Patients with major abdominal surgeries (n = 24)	SO + PN* FO + PN* (*In post-operative days 4 and 5)	10 g fat/d* (* + 50 g SO in PN) (1 preoperative day and 5 postoperative days)	FO showed a tendency to lower TNF-α release in postoperative day 5 FO reduced IL-6 in the postoperative days 0, 1, and 3 FO preserved expression of leukocyte antigen HLA-DR that decreased in control group FO did not alter infection rates FO did not alter mortality rates FO reduced stay in ICU FO reduced length of hospital stay
Heller (2004)[126] (based on the same data as Heller [2002])	Prospective, randomized, double-blind	Surgical patients with gastrointestinal or pancreas carcinoma (n = 44)	PN + SO PN + SO + FO	1 g fat/kg bw/d (Up to 0.2 g/kg bw/d of FO) (5 postoperative days)	FO decreased ALAT, ASAT, LDH, and lipase FO prevents weight loss (that was absent in the FO group), in relation to control group FO did not change length of stay but showed a tendency to shorter ICU stay in patients with increased risk of sepsis (IL-6/IL-10 ratio >8) FO also decreased ICU stay in patients at risk of sepsis after gastrectomies and Whipple procedures FO was similar to control group in relation to gastrointestinal function (bowel sounds and movements and the possibility of starting enteral feeding)

TABLE IV
(Continued)

Reference	Type of study	Population (n)	Groups	Treatment	Main Results
Tsekos et al (2003)[127]	Retrospective	ICU patients with major abdominal surgery (n = 256)	PO PN PN + MCT + FO, 8:2 (MCT:FO) - PO PN + MCT + FO, 8:2 (MCT:FO) Pre- + PO	0.6 g fat/kg bw/d (2–3 preoperative days)	FO was well tolerated and complaints were not reported FO offered in both pre- and postoperative period decreased mortality rates, and the absolute number of deaths tended to be lower when FO was given only postoperatively (nonsignificant) FO offered in both pre- and postoperative period decreased the number of patients requiring mechanical ventilation and hospital length of stay FO offered in both pre- and postoperative or only in postoperative period decreased the absolute number of patients with wound infections and the readmission to ICU
Mayer et al (2003)[128]	Prospective randomized open-label pilot	Patients with sepsis shock (n = 10) Healthy volunteers (n = 8)	PN + FO PN + SO	40 g fat/d (10 days)	FO increased free ω-3 fatty acids in plasma (EPA and DHA) FO improved neutrophil function (increased LTB5 and PAF release) FO increased TXA3/TXA2 ratios FO decreased leukocytes counts FO slightly increased fMLP-induced neutrophil superoxide generation on day 7 FO tended to decrease C-reactive protein levels and to have a shorter ventilation time
Mayser et al (1998)[129]	Prospective randomized double-blind multicentric	Patients with chronic plaque-type psoriasis (n = 83)	SO FO	20 g fat/d (14 days)	FO and SO decreased psoriasis area and severity index, whereas FO was superior to the SO group with respect to change in severity of psoriasis per body area, changes in overall erythema, overall scaling, and infiltration FO increased plasma free EPA concentration, neutrophil leukotriene B5, and platelet thromboxane B3 generation
Grimminger et al (1993)[130]	Prospective randomized controlled	Patients with acute psoriasis (n = 20)	SO FO	10 g fat/d (10 days)	FO markedly decreased the disease severity FO increased >10-fold neutrophil EPA-derived 5-lipoxygenase product formation FO decreased neutrophil PAF generation

ALAT, alanine amino-transferase; ASAT, aspartate amino-transferase; bw, body weight; CRP, c-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; fMLP, formyl-methionyl-leucyl-phenylalanine; FO, fish oil–based lipid emulsion; ICU, intensive care unit; IL, interleukin; INF, interferon; LDH, lactate dehydrogenase; LT, leukotriene; PAF, platelet-activating factor; PO, postoperative; PUFA, polyunsaturated fatty acids; SO, soybean oil–based lipid emulsion; TNF, tumor necrosis factor; PN, parenteral nutrition; TX, thromboxane.

TABLE V
Clinical results of multiple-oil-based LE treatment, according to the literature

Reference	Type of study	Population (n)	Groups	Treatment	Main results
Schlotzer et al (2004)[131]	Prospective randomized two-way crossover double-blind	Healthy male volunteers (n = 12)	SO SMOF	0.75 g fat/kg bw/d (2 infusions of 6 h with an interval of 6 d between them)	SMOF did not alter vital signs or laboratory parameters and was well tolerated locally SMOF only presented adverse events with mild intensity and that were completely reversible Lipid metabolism/routine biochemistry parameters, compared to control group: SMOF reduced serum concentrations of triglycerides after a 6-h infusion SMOF reduced half-life of serum triglycerides SMOF led to a faster steady state (after the start of infusion) and to faster baseline values (after the end of infusion) of serum triglyceride concentration
Genton (2004)[132]	Prospective randomized double-blind	Surgical patients (n = 32)	PN + SO PN + SMOF	2 g fat/kg bw/d (max) (7–14 days)	Lipid metabolism/routine biochemistry parameters, compared to control group: SMOF did not alter plasma triglycerides SMOF did not alter total cholesterol SMOF did not alter plasma glucose levels SMOF did not alter hepatic enzymes
Antebi (2004)[133]	Prospective randomized double-blind	Adult ICU patients with major surgery (n = 20)	PN + SO PN + SMOF	1.5 g fat/kg bw/d (At least 5 postoperative days)	SMOF was as safe and tolerable as the control group Routine biochemistry/lipid metabolism parameters: SMOF led to a lower increase of hepatic enzymes, CRP and PL/APO A1 levels Antioxidant status: SMOF improved plasma α-tocopherol, retinol, and LDL α-tocopherol levels
Grimm et al (2005)[134]	Prospective randomized double-blind multicentric	Patients with major abdominal surgery (n = 33)	PN + SO PN + SMOF	1.5 g fat/kg bw/d (5 postoperative days)	Phospholipid and leukotriene profile on postoperative day 6: SMOF increased plasma phospholipids content derived from total ω-3 FA, EPA, and DHA and decreased that derived from total ω-6 FA, LA, and AA compared with initial values, leading to an elevation of ω-3/ω-6 FA and EPA/AA ratios SMOF increased LTB5 and decreased LTB4 release compared to initial values, leading to an elevation of LTB5/LTB4 ratios Antioxidant status on postoperative day 6: SMOF increased plasma α-tocopherol compared to the control group Clinical outcomes: SMOF was well tolerated, and undesirable clinical effects were not recorded SMOF reduced length of hospital stay

AA, arachidonic acid; ALT, alanine amino-transferase; AP, alkaline phosphatase; APO, apoprotein; bw, body weight; CRP, C reactive protein; EPA, eicosapentaenoic acid; FA, fatty acids; γ-GT, γ-glutamyl transferase; ICU, intensive care unit; LA, linoleic acid; LDL, low-density lipoprotein; LT, leukotriene; MCT, olive oil– and fish oil–based lipid emulsion; PL, phospholipids; SMOF, soybean oil, medium-chain trigylcerides, olive oil, fish oil; SO, soybean oil–based lipid emulsion; PN, parenteral nutrition.

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