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Review: Lipid Formulations for the Adult and Pediatric Patient: Understanding the Differences

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Abstract

Intravenous lipid emulsions (IVLE) provide essential fatty acids (FA) and are a dense source of energy in parenteral nutrition (PN). Parenterally administered lipid was introduced in the 17th century but plagued with side effects. The formulation of lipid emulsions later on made it a relatively safe component for administration to patients. Many ingredients are common to all IVLE, yet the oil source(s) and its (their) percentage(s) makes them different from each other. The oil used dictates how IVLE are metabolized and cleared from the body. The FA present in each type of oil provide unique beneficial and detrimental properties. This review provides an overview of IVLE and discuss factors that would help clinicians choose the optimal product for their patients.

Elucidating the characteristics of each oil source over time has resulted in an evolution of the different formulations currently available. Emulsions have gone from being solely made with soybean oil, to being combined with medium-chain triglycerides (i.e., coconut oil), olive oil, and more recently, fish oil. Unfortunately, the lipid, among other constituents in PN formulations, has been associated with the development of liver disease. Lipid-sparing or lipid-reduction strategies have therefore been proposed to avoid these complications.

The ideal IVLE would reverse or prevent essential FA deficiency without leading to complications, while simultaneously providing energy to facilitate normal growth and development. Modifications in their ingredients, formulation, and dosing have made IVLE a relatively safe component alone or when added to PN formulations. The ideal emulsion, however, has yet to be developed.

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Overview of Lipid Emulsions

Intravenous lipid emulsions (IVLE) are a source of essential fatty acids (EFA) and serve as a complement to carbohydrates by providing a dense source of non-protein energy in parenteral nutrition (PN). Fatty acids are important sources of energy and structural components of cell membranes. They are also precursors to key modulators involved in cellular pathways of the immune response¹. Parenterally administered fat was first attempted in the 17th century when the English naturalist William Courten tried to infuse olive oil (OO) intravenously in dogs, which resulted in pulmonary emboli². Over time it was recognized that fat could be given intravenously only in the form of an emulsion. In the 1920s, Japanese investigators attempted to compound such an emulsion utilizing castor oil as the main ingredient. Numerous attempts were made between 1920 and 1960 to create a safe emulsion using a variety of oils and surfactants. A cottonseed oil-based emulsion (i.e., Lipomul® (15% cottonseed oil, 4% soy phospholipids, 0.3% poloxamer 188)) became the first IVLE approved in the United States in 1957². This was later withdrawn from the market due to severe adverse reactions, including fat overload syndrome²⁻⁴. A soybean oil-based lipid emulsion (SOLE) has been the predominant IVLE available to American practitioners since its introduction in Europe in 1961 and its subsequent approval in the United States in 1972. Other oil sources have been used outside the United States to create IVLE and may soon be available. This review aims to provide an overview of lipid emulsions and discuss factors that clinicians should consider when choosing the optimal product for their patients.

What is Common to All Lipid Emulsions?

All IVLE share many components. IVLE are suspensions of oil in an aqueous medium manufactured to possess properties similar to natural chylomicrons. These are the spherical forms of approximately 200–500 nm in diameter that the human body uses to transport hydrophobic fat in hydrophilic blood without causing embolic phenomena⁵.

Emulsions are unstable systems and undergo physical changes over time (e.g., aggregation, creaming, and increased droplet size). Manufacturing an emulsion requires an emulsifying agent to disperse the oil phase into the aqueous phase, resulting in a stable product. Numerous agents had been tried to serve as emulsifiers without success. Arvid Wretling developed the first safe IVLE for clinical use utilizing egg yolk phospholipid as an emulsifying agent². All currently available IVLE contain this emulsifying agent. Individuals with an egg allergy may be unable to receive them, although the egg lecithin currently used to manufacture IVLE is highly purified and unlikely to contain allergens thought to trigger hypersensitivity reactions. Given that such reactions have been described in the literature and noted in the package, this potential risk should be taken into consideration when prescribing IVLE to patients with egg allergy⁶. IVLE also contain sterile water for injection, sodium hydroxide to maintain a pH range between 6–9, and glycerol, which makes the emulsion isotonic and adds additional calories.

Manufacturing IVLE is difficult and requires very specific pH and temperatures under a nitrogen rich environment. Pharmacopeial specifications of IVLE help determine embolic risks, plasma clearance, and beyond-use dating of the formulation. The United States

Pharmacopeia (USP) chapter <729> has established value standards for globule size limits including a mean droplet diameter below 500 nm and a large globule content (percentage of fat globules >5 µm) no greater than 0.05% (PFAT5)^{7,8}. Other specifications include a pH between 6–9 and a free fatty acid content no greater than 0.07 mEq/g^{7,8}. Currently, all commercially available IVLE meet the USP standards.

Fatty Acids: An Overview

IVLE provide fatty acids, which are normally present as cholesterol esters in circulating lipoproteins, as phospholipids in cell membranes, and as triglycerides in adipose tissue, blood, liver, and muscle. Fatty acids are the monomers of lipids and consist of hydrocarbon chains that vary in length. They can be short (2–4 carbons), medium (6–12 carbons), long (14–21 carbons), or very long (>22 carbons) chains. Depending on the number of double bonds, they can also be classified as saturated (no double bonds), monounsaturated (one double bond), or polyunsaturated (more than one double bond). *Saturated fatty acids* (SFA) are often solid at room temperature and structurally have a straight carbon chain. A classic example of this type of fatty acid is butyric acid. *Monounsaturated fatty acids* (MUFA) are often liquid at room temperature and solid when cool. Palmitoleic and oleic acids are examples of MUFA abundant in OO. *Polyunsaturated fatty acids* (PUFA) are liquid at room temperature and include alpha-linolenic acid (ALA) and linoleic acid (LA). Lastly, *highly unsaturated fatty acids* have more than three double bonds. Examples include the very long chain fatty acids (20–22 carbon lengths) docosahexaenoic and eicosapentaenoic acids (DHA and EPA, respectively).

Essential Fatty Acids (EFA)

One of the original indications for the use of IVLE in patients requiring PN was the provision of EFA. These are fatty acids that cannot be synthesized in the body but rather need to be obtained from the diet^{9,10}. In contrast, fatty acids from the omega-5, omega-7, and omega-9 families are non-essential. EFA serve as an energy source, provide structural support to cell membranes, and are precursors to important cellular metabolites. The omega-3 fatty acids (O3FA) and omega-6 fatty acids (O6FA) are the two families of EFA. They both compete for space within the cell membrane and are processed by the same enzymes (i.e., elongases and desaturases) to generate their more active downstream products. Fatty acids from these families differ structurally depending on where the first double bond from the terminal methyl group is located. The first double bond thus occurs at the third carbon in O3FA, and at the sixth carbon in O6FA. Historically, ALA and LA have been considered the main members of the O3FA and O6FA families, respectively. Recently, the true essentiality of ALA and LA has been questioned. Provision of their main downstream products (i.e., DHA and arachidonic acid (ARA), respectively) is just as effective at preventing the development of biochemical essential fatty acid deficiency (EFAD)¹⁰.

What is Different Between Lipid Emulsions?

Despite sharing several common properties, the oil source used and its percentage dictate the key differences between IVLE. These differences account for their additional benefits or detrimental effects, especially when used for prolonged periods (Table 1). Typically, IVLE are manufactured with one of five types of oil: soybean, safflower, coconut, olive, or fish. Each has unique inflammatory properties and may even confer different pharmaceutical and therapeutic benefits.

Soybean oil

SOLE have been widely used for decades. Soybean oil (SO) contains high concentrations of PUFA with a ratio of LA (O6FA) to ALA (O3FA) of approximately 7:1¹¹. Additionally, 25% of the fatty acids in SO come from the non-essential family of omega-9 fatty acids (O9FA) in the form of oleic acid. SO is naturally rich in phytosterols and has high levels of gamma-tocopherol but low amounts of alpha-tocopherol (bioactive form of vitamin E)¹¹. Evidence from *ex vivo*, animal, and clinical studies suggest that the type of IVLE used may influence immune functions. For instance, emulsions with high content of O6FAs have been linked with immunosuppressive effects^{12–14}. One study evaluated the effect of lipid intake on the postoperative stress response and cell-mediated immune function of patients subjected to gastric or colorectal surgery¹⁵. Higher postoperative concentrations of interleukin-6 and C-reactive protein were seen in patients receiving a SOLE (20% of the energy intake in extremely high non-protein calorie intake of 40 kcal/kg daily) compared to those receiving lipid-free PN. This is the reason why many centers do not administer 100% SOLE to critically ill patients, which is discussed in greater detail below.

The phytosterols present in SO are plant sterols thought to contribute to the development of intestinal failure-associated liver disease (IFALD)¹⁶. Phytosterols, including campesterol, sitosterol, and stigmasterol, are typically absorbed only in small amounts in the gastrointestinal tract¹⁷. These plant sterols decrease blood cholesterol levels by interfering with its gastrointestinal absorption. This makes them beneficial agents when taken orally in patients with hypercholesterolemia and atherosclerosis^{18,19}. However, phytosterols accumulate in the liver when given intravenously where they inhibit the enzyme 7 α -hydroxylase, the rate-limiting enzyme in bile acid synthesis^{16,20,21}. Unlike SOLE, fish oil (FO)-based lipid emulsions (FOLE) contain very little phytosterols. This difference may partially explain the potential benefit of FOLE as a lipid source in PN-dependent patients with IFALD. Levels of plasma phytosterols were measured in preterm infants receiving different IVLE in a randomized controlled trial²². Phytosterol concentrations were higher in infants receiving 100% SOLE. Cholestasis did not develop in this group and is not surprising given the short duration of the study. The role of phytosterols in hepatocyte damage has been demonstrated by their antagonizing effect on the farnesoid X nuclear receptor, which is critical in regulating the level of intrahepatic bile acids²³. Additionally, the incorporation of phytosterols in erythrocyte membranes accelerates the breakdown of these cells and increases the bilirubin load to the liver²¹. Phytosterols can also increase the risk of sepsis by altering the migratory and phagocytic function of neutrophils as shown in animal models^{21,24,25}.

Safflower Oil

Safflower oil had been used in IVLE alone or in combination with SO in the United States since 1980. It was developed as an alternative to SO and was hypothesized to decrease the risk of fat overload syndrome²⁶. In comparison to SO, safflower-based IVLE had higher concentrations of LA (77% versus 54%), although less ALA (0.5% versus 8%). The use of safflower oil predisposed patients to develop O3FA deficiency when used as a sole source of fat in IVLE²⁷. For this reason, it was later reformulated as a 50/50 blend with SO. Safflower oil-based emulsions are not currently available due to raw material issues.

Coconut Oil (Medium-chain triglycerides (MCT))

After the introduction of SOLE, a second-generation emulsion was introduced in Europe that contained a 50/50 mixture of SO and MCT derived from coconut oil¹¹. These emulsions reduce the O6FA content by 50%. MCT are SFA that are 6–12 carbons long and include caprylic and capric acids²⁸. They are easily metabolized and lack pro-inflammatory properties, both characteristics unique to this fat source. MCT are resistant to peroxidation and have protein-sparing effects not inferior to the ones seen with long-chain triglycerides (LCT). Additionally, MCT do not accumulate in the liver and consequently do not impair hepatic function^{28,29}. However, MCT oils are devoid of EFA and thus cannot be used as a sole source of fat. They may have a unique pharmaceutical benefit in that MCT added to certain total nutrient admixtures (TNA) results in a more stable lipid emulsion than those containing an abundance of LCT. The shorter chain length (6–12 carbons versus 18 carbons in SO) exerts less stress on the emulsifying agent and allows the lipid phase to remain miscible with the aqueous phase of the emulsions for longer periods of time³⁰.

Olive Oil

OO is rich in O9FA (i.e., oleic acid), a type of MUFA that is not considered essential, as they are not precursors of eicosanoids. OO-based emulsions were introduced in Europe in the 1990s. The relatively small amount of LA (approximately 5%) explains why this oil source requires blending with an oil containing EFA. OO has a lower content of phytosterols and abundant alpha-tocopherol. One OO-based IVLE (e.g. Clinolipid®, Baxter Healthcare Corporation, Deerfield, IL) is comprised of four parts OO: one part SO. The mean concentration of LA is 35.8 mg/mL (range 27.6 – 44.0 mg/mL) and ALA is 4.7 mg/mL (range 1.0 – 8.4 mg/mL)³¹. This product provides 30% of the PUFA content of standard SOLE. In comparison to SO, OO is rich in MUFA that possess less pro-inflammatory properties and are more resistant to oxidative stress injuries from free radicals. This type of mixed oil emulsion has replaced SOLE as the standard IVLE in many countries³². In one randomized controlled trial, an OO-containing IVLE (4:1 OO/SO) was compared to SOLE in preterm infants less than 28 weeks' gestational age³³. OO-containing IVLE was found to be safe and well tolerated. Long-chain PUFA concentrations were similar in infants receiving OO IVLE in comparison to the SOLE group despite the significantly lower amount of PUFA in the OO/SO IVLE. Moreover, no difference in lipid peroxidation was observed. Similar results were reported in several other randomized controlled trials involving neonates receiving OO/SO IVLE, with none showing any significant difference in oxidative stress in comparison to SOLE monotherapy^{34,35}. In another investigation,

triglyceride, cholesterol, high- and low-density lipoprotein (HDL and LDL, respectively) concentrations, and liver function tests were similar between the two groups. Very low-density lipoprotein (VLDL) concentrations were statistically lower in neonates receiving SOLE in comparison to those receiving the OO blend³⁶. Another potential benefit of using OO-containing IVLE is improved glucose tolerance. SO appears to enhance glucose production by means of glycogenolysis and gluconeogenesis. Infants receiving OO-containing IVLE have been demonstrated to tolerate higher carbohydrate intake without developing hyperglycemia³⁷. Unlike SO and FO, OO is considered immune neutral³⁸. The high content of O6FA in SOLE serve as precursors to cytokines and pro-inflammatory prostaglandin E2 and leukotriene B4³⁸. A study comparing the inflammatory effects between SOLE and OO-rich IVLE in preterm neonates demonstrated that pro-inflammatory cytokine concentrations were significantly higher in those receiving SOLE³⁹. One potential downside for the use of an OO-containing IVLE is the greater risk of extraction compared to other IVLE of the plasticizer di (2-ethylhexyl) phthalate (DEHP) if it is infused using a polyvinylchloride (PVC) administration set. DEHP exposure could potentially increase the risk of developing IFALD⁴⁰. For these reasons, regardless of oil source, when compounding admixtures containing IVLE, PVC or DEHP coated containers should not be used.

Fish Oil

Like OO, FO-containing IVLE are less pro-inflammatory than conventional SOLE³⁸. The eicosanoids produced from O3FAs in FO are generally less inflammatory in comparison to those originating from O6FAs contained in SO. FO is rich in the antioxidant alpha-tocopherol, which is added to prevent the oxidation of its fatty acids. Alpha-tocopherol is the form of vitamin E that is preferentially absorbed and accumulated in humans. In comparison, SO is rich in gamma-tocopherol, which must be methylated to the preferred bioactive alpha-tocopherol. FOLE was originally developed to supplement conventional SOLE and not intended for use as monotherapy¹¹. Unlike SOLE, FOLE contain little LA and ALA but contain their downstream metabolites, ARA, EPA, and DHA¹¹. The paucity of O6FA has raised concerns about the development of EFAD when FOLE is used as monotherapy. However, in humans, 100% FOLE has been shown to effectively reverse preexisting EFAD and to prevent its development when dosed at 1 g/kg/day^{41,42}. Subsequent work in animal models has confirmed this concept. In studies involving a murine model, the provision of only the downstream metabolites of LA and ALA (i.e., ARA and DHA, respectively) and no other EFA was shown to prevent EFAD and hepatic steatosis without negatively impacting growth or fertility⁴³. O3FA present in FO are also natural ligands to some receptors of the G-protein-coupled receptors (GPR) family. Recent evidence demonstrates that the interaction with these receptors mediate some of the therapeutic benefits of O3FA in tissues such as the liver, brain, and bones^{44–47}.

Do Oil Sources Determine the Inflammatory Characteristics of IVLE?

Each emulsion has its own inflammatory characteristic based on the different oil sources and their predominant fatty acid. The EPA present in FO is a precursor to the series 5-leukotrienes and series 3-prostanoids, molecules with anti-inflammatory properties. O3FA also affect eicosanoid metabolism and the epoxigenation pathways by decreasing the

hepatic levels of the enzyme soluble epoxide hydrolase⁴⁸. By doing this, O3FA decrease the degradation of anti-inflammatory molecules. Additionally, O3FA serve as precursors to pro-resolving molecules that aid in the resolution of the inflammatory response^{48,49}. In contrast, ARA present in SO leads to the formation of series 2-prostanoids and series 4-leukotrienes, molecules known to be generally more pro-inflammatory⁵⁰. ARA has also been shown to have anti-inflammatory and pro-resolving properties by serving as the precursor to lipoxins and prostaglandin-mediated lipoxins⁴⁹. Thus the fat source in IVLE and its resulting inflammatory profile has dictated the evolution of the different formulations over time. Emulsions have evolved from being solely made with SO in the 1960s, to being combined with MCT in the 1980s, OO in the 1990s, and more recently, with FO⁵¹ (Figure 1).

Oil Sources: Impact on Clearance

Triglycerides in IVLE are hydrolyzed by lipoprotein lipase (LPL). This enzyme is located on the endothelial surface of extrahepatic tissues, which end up utilizing the released fatty acids^{52,53}. The remaining lipid particles are either hydrolyzed by hepatic lipases, or cleared intact by other tissues^{54,55}. The oil source in IVLE strongly determines how the body clears them from the circulation. Brouwer et al compared the elimination of intravenous OO and SO lipid emulsions⁵⁶. Although SOLE had a higher rate of elimination than OO-containing IVLE, the hepatic lipase activity was more important in the elimination of OO. These findings suggested the presence of additional clearance pathways beyond the enzymatic ones that have been mentioned. The reticulo-endothelial system (RES) and other tissues also play a role in the metabolism and clearance pathways of IVLE. The phospholipid concentration also seems to have an effect on clearance of IVLE. Depending on their concentration (i.e., 10% and 20%) IVLE differ in their phospholipid/triglyceride ratio (0.12 and 0.06, respectively). A study comparing the effects on plasma lipid and lipoproteins in 10% and 20% SOLE in low birth weight neonates demonstrated that 10% emulsions led to higher concentrations of plasma triglycerides, accumulation of cholesterol and phospholipids in LDL, and the appearance of lipoprotein X-like particles⁵⁷. These particles decrease the rate of hydrolysis by competing for LPL with other lipoproteins rich in triglycerides. Altogether, these changes impact the hepatic clearance of LDL and chylomicron remnants, and delay the hydrolysis of circulating triglycerides^{57,58}. For this reason, 20% SOLE is preferred over 10% SOLE as an IVLE source in low birth weight infants. Similar differences were seen in a study comparing different concentrations of SOLE in critically ill adults⁵⁹. Patients who received a 30% emulsion had lower plasma levels of triglycerides, phospholipids and free-cholesterol than those who received the 10% SOLE. The 10% group also showed an increase in levels of lipoprotein X-like particles. MCT oils bind poorly to albumin and are cleared more rapidly from the plasma. Several properties in the metabolism and clearance of MCT make them potentially a more beneficial source of fat in septic or critically ill patients. First, they do not accumulate in tissues, including the RES. Accumulation of lipids in macrophages from the RES has proven to negatively affect their immunologic function in both human and animal models following administration of LCT emulsions^{60,61}. Second, they undergo rapid oxidation and their entry into the mitochondria is mediated by a carnitine-independent fatty acid transport (although carnitine may still be required for their oxidation)^{28,62,63}. Unfortunately, the blood-brain barrier is permeable to highly soluble

MCT. This makes MCT potentially toxic to the central nervous system when present in high concentrations⁶⁴. Moreover, as previously discussed, MCT oils cannot be used as a sole source of fat in IVLE as they are devoid of EFA; they must be administered in combination with a LCT.

In vivo animal studies by Qi et al⁵⁴ demonstrated that FOLE undergo faster clearance from the blood than SOLE. *In vitro* studies have shown that omega-3 triglycerides are relatively resistant to the hepatic and lipoprotein lipases, with much lower lipolytic activities than those seen with O6FA-rich emulsions⁶⁵. For this reason, the faster clearance of FOLE relative to SOLE seems to be mediated by their tissue uptake rather than by the activity of the aforementioned lipases. FOLE also accelerate triglyceride clearance and inhibit the synthesis of endogenous triglycerides and VLDL. These effects are not mediated by enzymatic actions, but rather by clearance enhancement^{54,66,67}.

The presence of heparin affects the clearance of IVLE. Heparin stimulates intravascular lipolysis by promoting the release of LPL and hepatic lipases into the circulation⁶⁸. Addition of heparin is helpful when clearance of IVLE is compromised, such as in premature neonates^{69,70}.

The combination of oil sources in the newer IVLE aims to take advantage of the beneficial properties of each of the available fat options. For example, the combination of MCT with FO allows for MCT to release their readily oxidizable fatty acids while preventing O3FA from entering oxidative pathways. Bypassing oxidative pathways allows O3FA to exert their beneficial effects on different targets⁷¹.

Clinical Considerations

Lipid emulsions were initially brought to the market based on their ability to provide energy and EFA (i.e., a nutritional indication). Studies used to support the approval process were statistically underpowered to show meaningful differences in clinical outcomes. As a result, it has been post-marketing studies that describe clinical differences in the various commercially available IVLE. The addition of IVLE to TNAs is also a common practice in certain settings. The use of these admixtures is controversial, however, given concern for the potentially unstable emulsions, incompatibility of medications with the IVLE, microbial growth, occlusion, and a reduced lifespan of intravenous catheters used for infusion^{72,73}. Due to their high requirements for calcium and phosphorus that can impact the stability of the admixture, TNAs are not recommended to be used in neonates and children⁷³.

Prevention of Essential Fatty Acid Deficiency

The main beneficiaries of IVLE are those patients that are not able to tolerate or adequately absorb nutrients administered through the oral and/or enteral route. IVLE serve as a dense source of non-protein energy and when dosed properly provide the EFA that avoid the development of EFAD. This condition occurs when less than 1–2% of the total energy consumed comes from the EFA ALA and LA. EFAD is rare in the general population, and more commonly develops in patients with malabsorption syndromes and in those that are PN-dependent⁷⁴. Clinically, EFAD most typically leads to growth retardation, eczematous

dermatitis, and alopecia^{74–76}. As the content of ARA, a tetraenoic acid, decreases in tissues, the content of non-essential fatty acids (i.e., mead acid (MA), a trienoic acid synthesized from oleic acid) increases⁷⁷. MA is produced in states of EFAD and is created from the elongation and desaturation of oleic acid when there is insufficient O6FA and O3FA. The Holman Index is used to diagnose EFAD. It is comprised of the triene (i.e., MA)(i.e., ARA) ratio and can be easily calculated. Values greater than 0.2 are indicative of EFAD⁷⁷. The biochemical signs of EFAD usually precede those seen clinically and appear in as little as 7–10 days following EFA restriction. The isolated deficiency of O3FA and/or O6FA is even more rare. Animals fed O3FA-deficient diets showed impaired vision and visual evoked potentials, polydipsia, and changes in stereotyped behavior^{78–80}. Some of these findings have also been shown in humans, including visual impairment in pre-term infants yet more variable results in those at term⁸¹. Clinical manifestations in humans are seen especially when O3FA is not adequately supplied in critical periods of brain and retinal development⁸¹. O3FA deficiency also leads to similar skin changes seen in patients with EFAD, plus hair loss, impaired growth, and depressive symptoms⁸². Similarly, O6FA deficiency leads to the aforementioned dermatologic and hair changes in addition to dry eyes, dysrhythmias, and impaired growth⁹. Table 2 summarizes the differences between O3FA and O6FA deficiencies.

IVLE as Therapeutic Modalities

In critically ill adults, lipid-PN may be given to individuals with prolonged suppression of gastrointestinal activity following severe trauma or surgery and in conditions associated with malabsorption such as prolonged ileus, gastric outlet obstruction, diarrhea, and vomiting⁸³. This is different from circumstances that lead to PN dependency in premature infants and children that include intestinal motility disorders and conditions resulting from major intestinal resections such as necrotizing enterocolitis, malrotation, and/or intestinal atresia⁸⁴.

Adult Considerations—The initiation of IVLE therapy in the critically ill adult should not be undertaken lightly. The Canadian Clinical Practice Guidelines recommend withholding the addition of pure SOLE for the first 10 days of PN therapy in patients that are otherwise not malnourished, are able to tolerate (at least partially) enterally administered nutrients, or in those where a short-term course of PN is expected⁸⁵. The basis of this recommendation lies on the detrimental inflammatory properties of emulsions rich in O6FA, and on SO being an important component in most commercially available IVLE⁸⁶. Similarly, recent recommendations from the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N), and the Society of Critical Care Medicine (S.C.C.M)⁸⁷ suggest withholding or limiting the use of SOLE during the first week of PN administration to a maximum of 100 grams per week if there is concern for EFAD. A meta-analysis of two randomized studies evaluating the early addition of lipids in PN found no difference in mortality rates, but a large reduction in infectious complications when SOLE were held⁸⁵. In this population, there are minimal concerns regarding withholding lipids (i.e. hypocaloric nutrition and EFAD) if the patient is tolerating some enteral nutrition and requires a short course of PN (<10 days). The availability of alternative IVLE containing different oils in addition to SOLE may explain why practice guidelines are different in other countries, where such products are considered “an integral part of PN for energy and to ensure fatty

acid provision.”⁸⁸ Although current Canadian guidelines recommend the use of SO-sparing strategies when the addition of IVLE to PN is indicated, A.S.P.E.N and S.C.C.M refrain from making recommendations about the use of alternatives to SOLE as they are not currently available in the United States^{87,89}.

Given these recommendations, many studies have attempted to determine which combination of oil sources translates into better outcomes for critically ill, PN-dependent patients. Manzanares et al^{90,91} summarize the findings from different trials in a recent systematic review and meta-analysis that have compared different alternatives to SOLE monotherapy in this setting (Table 3). There is a trend towards significance of alternatives to SOLE alone being associated with important reductions in mortality, duration of mechanical ventilation, and intensive care unit (ICU) length of stay. Edmunds et al⁸⁶ reviewed data from a prospective international multicenter study to determine the effects of different IVLE on clinical outcomes in 451 critically ill patients. Inclusion criteria included adult patients in the ICU for more than 72 hours, mechanically ventilated within 48 hours, and receiving PN without prior/concurrent EN for 5 or more days. Patients who did not receive any form of IVLE had the longest duration of mechanical ventilation. Those that received either OO- or FO-containing IVLE were extubated and discharged sooner from the ICU alive than those receiving SOLE. SOLE monotherapy was associated with a longer ICU stay. In summary, although SOLE-sparing alternatives are recommended, evidence is still lacking regarding which optimal blend of oil sources is the most suitable in critically ill patients.

Pediatric Considerations—In children and preterm infants, the search for alternatives to SOLE has failed to find an ideal option for its replacement. Results from 15 studies were pooled in a recent systematic review from the Cochrane Neonatal Group and included the use of MCT/LCT, MCT/OO/FO, MCT/FO, OO/SO, and borage/SO IVLE (either in total or partial parenteral nutrition) in preterm neonates⁹². None of the measured primary outcomes, mortality, growth rate, or days to regain birth weight, reached statistically significant differences. Secondary outcomes (i.e., sepsis, IFALD, duration of ventilation, necrotizing enterocolitis (equal or greater than stage 2), intraventricular hemorrhage (grade III and IV), periventricular leukomalacia, patent ductus arteriosus, hyperglycemia, and hypertriglyceridemia) also failed to show any significant differences. Neither EFA status nor neurodevelopmental outcomes were considered. The guidelines for the management of pediatric patients with intestinal failure from the A.S.P.E.N. are similar to the adult recommendations, also suggesting the limited use of SOLE, especially in infants at risk of developing IFALD⁹³. The use of lipid reduction strategies or finding alternatives to SOLE are also recommended.

Complications Associated with IVLE

The IVLE component in PN can cause several metabolic and physiological adverse effects (AEs). Hypertriglyceridemia is one of the most common AEs and can predispose patients to elevations in hepatic enzymes, hemolysis, and respiratory distress. Other potential consequences of prolonged administration of IVLE include hematologic abnormalities with recurrent thrombocytopenia and hyperactivation of the monocyte-macrophage system⁹⁴. Worsening of respiratory function may be due to increased pulmonary vascular

constriction⁹⁵. Changes in the alveolar–arteriolar oxygen gradient can lead to decreased gas exchange and may be due to diminished bioavailability of endothelial-derived vascular relaxants⁹⁶. In one report, IVLE was shown to worsen bronchopulmonary dysplasia in premature infants⁹⁷. The use of IVLE has also been known to cause vasoconstriction leading to hypertension⁹⁸. The rapid infusion of SOLE may negatively affect pulmonary gas diffusion and alter hemodynamic stability in adults with respiratory distress syndrome. Rapid infusion rates (i.e., 100 g over 5 hours) were linked with vasoconstriction, while significant vasodilation was observed with slower infusion rates (i.e., 100 g over 10 hours)⁹⁹.

Fat Overload Syndrome—Fat overload syndrome is a well-known complication of IVLE therapy. It is characterized by headaches, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous hemorrhage¹⁰⁰. It has been described in several case reports in the presence of rapid infusion and/or high doses of IVLE. AEs are due to elevations in plasma triglyceride levels that occur when the infusion rate exceeds the rate of hydrolysis. Whenever the rate of hydrolysis exceeds the rate of uptake and oxidation of free fatty acids, plasma concentrations of fatty acids increase¹⁰¹. Other symptoms seen with fat overload syndrome include anemia, leukopenia, thrombocytopenia, low fibrinogen levels, and depressed levels of coagulation factor V. Oftentimes these will simply reverse by stopping the IVLE infusion⁹⁶. In addition to discontinuing the IVLE, supportive care is the mainstay of therapy. In one instance, plasma exchange was utilized¹⁰². The majority of published case reports of rapid infusions of IVLE involve SOLE or safflower IVLE. In one case report, a 10-month-old infant developed fat overload syndrome while receiving a SOLE at a dose of 5 g/kg/d for 5 weeks. The patient had many of the symptoms of fat overload syndrome, including fever, jaundice, and bruising¹⁰³. In a study evaluating a safflower IVLE, 15 neonates were given 1 g/kg/d dose and were evaluated for triglyceride and free fatty acid clearance¹⁰⁴. The dose was infused over 4 hours (0.25 g/kg/h), which exceeded the recommended 0.17 g/kg/h limit. Peak serum triglyceride levels averaged 592 mg/dL for appropriate gestational age newborns and slightly higher for those small for gestational age (606 mg/dL). Hyperbilirubinemia, coagulopathies, and elevations in transaminases were also observed. Treatment included discontinuing both the PN and IVLE for 72 hours and reintroducing the IVLE at a lower dose. Based upon these findings, the authors recommended that IVLE doses should not exceed 4 g/kg/d, considerably higher than what is currently used in clinical practice. Guidelines from the European Society of Parenteral and Enteral Nutrition (E.S.P.E.N) recommend that IVLE can be safely administered at a rate 0.7–1.5 g/kg over 12–24 hours⁸⁸.

FOLE does not appear to exhibit similar complications when infused rapidly. In one case series, 6 children received FOLE at an infusion rate that exceeded 0.17 g/kg/h¹⁰⁵. Infusion rates as high as 5 g/kg/h were accidentally administered (range 0.2–5 g/kg/h) without evidence of fat overload syndrome. In these patients, vital signs remained stable and none showed manifestations of respiratory distress, fever, or hemorrhage. Transient elevations in serum triglyceride levels were observed but promptly returned to acceptable levels. The authors suggested that the reason for the apparent absence of fat overload syndrome in patients receiving rapid infusions of FOLE may be related to their clearance and also the small number of patients in this case series. Unlike SOLE, FOLE appear to be cleared more

rapidly from the intravascular space¹⁰⁶. Lipid clearance follows a biphasic pattern, with an initial rapid clearance occurring within 10 minutes followed by a slower clearance phase of 10–25 minutes. Most IVLE clearance from the blood occurs within the first 2 minutes of an infusion in animal models. IVLE containing SO tend to clear more slowly than those containing MCT or FO¹⁰⁶. Despite being cleared more efficiently, FOLE undergo less catabolism than SOLE. The mechanisms involved in the hydrolysis of FOLE and the hydrolysis of SOLE are very different. LPL, apolipoprotein E, LDL receptor, and lactoferrin-sensitive pathways modulate the removal of chylomicron-sized O6FA-rich IVLE. In contrast, clearance of chylomicron-sized FOLE is independent of these pathways⁵⁴. In one study, FO was shown to accelerate triglyceride clearance by facilitating LPL-mediated lipolysis. The DHA and EPA in particular significantly reduce chylomicron triglyceride half-lives and particle sizes and increase the activity of pre-heparin LPL¹⁰⁷. Taken together, these findings suggest that FO does not reduce production of triglycerides, but rather enhances the clearance of emulsion particles. This suggests that FOLE do not remain in the systemic circulation long enough and may not predispose patients to the complications associated with rapid infusion of SOLE. Interestingly, the presence of FOLE in combination with SOLE did not prevent the development of fat overload syndrome. In one case report, a 2-year-old girl developed fat overload syndrome as a result of accidental, very rapid infusion of a SO/MCT/OO/FO IVLE that showed the same complications seen with SOLE monotherapy¹⁰⁸. The child was successfully treated with supportive care combining fluid infusion, transfusion of platelets, and substitution of serum albumin (0.5 g/kg/d) and fresh-frozen plasma (10 mL/kg). In addition, she received extra platelets, erythrocyte transfusion, and filgrastim due to a very low leukocyte count. These complications perhaps were due to the relatively low FOLE content of the SO/MCT/OO/FO IVLE (15%) in comparison to its SOLE content (30%). To date, there have been no published reports of fat overload syndrome involving SO/OO or SO/MCT IVLE. Regardless of the oil source, triglyceride levels should be monitored for any IVLE being rapidly infused.

Hepatic Complications—The hepatic abnormalities induced by PN administration manifest differently depending on whether they occur in adults or children. In adults, fat accumulation more often leads to benign, asymptomatic steatosis, with mild to moderate (and reversible) transaminitis and hyperbilirubinemia^{109,110}. In contrast, children more commonly develop intrahepatic cholestasis with resulting direct hyperbilirubinemia and hepatocellular injury, both of which can lead to potentially irreversible changes such as fibrosis and cirrhosis if prolonged. Risk factors for the development of IFALD include prematurity in infants, and prolonged PN administration, sepsis, frequent surgical procedures, and lack of enteral intake both in children and adults^{111,112}.

Until recently, the discontinuation of PN therapy and re-institution of enteral nutrition were the only known measures that prevented and/or treated IFALD. Unfortunately, this alternative is not feasible in those patients that are unable to be weaned from PN and achieve full enteral autonomy. The potential role of IVLE in the pathogenesis of IFALD has been recognized. For this reason, current strategies focus on changing the fat source and reducing the lipid dose. The use of FOLE to prevent and reverse the steatosis developed in a murine model of non-alcoholic fatty liver disease was first described by Alwayn et al¹¹³. Based on

findings from these experiments, Gura et al¹¹⁴ reported the reversal of cholestasis in two infants that had developed IFALD. Subsequently, Gura et al⁸⁴ proved the safety and efficacy of FOLE for the treatment of IFALD in a larger cohort of patients compared with a historical cohort that had been treated with SOLE. A recent prospective double-blind randomized controlled trial by Lam et al¹¹⁵ assigned infants with IFALD to receive either SOLE or FOLE. The study was terminated prematurely due to enrollment challenges, but preliminary results showed that infants in the FOLE group had a significantly slower increase in levels of direct hyperbilirubinemia and alanine aminotransferase (ALT) in comparison to those in the SOLE group. Additionally, infants receiving FOLE were able to increase their intake of enteral nutrition. This was associated with a significant clinical improvement although it may have also served as a confounder contributing to this effect. Results from this study continue to suggest the role of FOLE as a potentially safe and effective alternative for the treatment of IFALD. Although readily available in Europe and Asia, FOLE has yet to be approved by the United States Food and Drug Administration (FDA). Until then, use of FOLE in children with IFALD in the US may only be done as part of a compassionate use protocol. The mechanism of action by which FOLE reverses IFALD is yet to be fully elucidated, but the combination of low levels of phytosterols, high levels of alpha-tocopherol, and a relative abundance of O3FA to O6FA in FO may play an important role¹¹². More recently, Nandivada et al¹¹⁶ reported the long-term effects of FOLE therapy and showed no increases in the risk of mortality, need for intestinal transplantation, or development of EFAD. In this cohort, biochemical markers of liver disease returned to normal levels within the first year of FOLE therapy.

Many factors other than IVLE have also been implicated in the development of hepatic complications in PN-dependent patients. For example, recent findings from a retrospective review in preterm infants showed that PN-associated cholestasis was more common in those receiving higher daily doses of dextrose after adjusting for daily lipid and protein intake¹¹⁷. Other etiologic factors in PN that may contribute to the development of IFALD include excessive administration of calories from overfeeding, aluminum contamination, toxicity/deficiency of amino acids, among others¹¹⁰. The details of how these cause liver disease go beyond the scope of this review article.

Restriction of SOLE: In addition to FOLE monotherapy, modifications in the amount and combinations of oil sources have been proposed for the treatment and prevention of IFALD in children. In a prospective study, Cober et al¹¹⁸ showed that reducing the dose of SOLE to neonates with IFALD from 3 g/kg/day to 1 g/kg/day led to a decline in bilirubin levels compared with a historical control cohort group. Rollins et al¹¹⁹ tested the same strategy in preventing the development of IFALD in high-risk neonates. Findings showed a slower rate of rise of markers of cholestasis (i.e., direct bilirubin and total bile acids) in the SOLE-restricted patients. Close monitoring of EFA status is encouraged when adopting lipid-reduction strategies given the marked reduction in fatty acids being administered. In the Cober study, provisions were made to increase SOLE intake if trends towards EFAD developed. Similarly, Sanchez et al¹²⁰ reported the results of implementing a lipid reduction strategy in high-risk surgical infants and compared them with a historical control cohort. The incidence of IFALD dropped significantly following the adoption of this approach. Patients

from the historical cohort were almost twice as likely to develop IFALD in comparison to those that were lipid-restricted. The efficacy of lipid reduction strategies in preventing IFALD did not hold true in a more recent multicenter randomized controlled trial in preterm neonates¹²¹. Neonates younger than 2 days of life received SOLE at rates of 1 or 3 g/kg/day. No differences in the development of cholestasis or growth were observed.

Other Approaches: Combining other oil sources with FOLE has been shown to be somewhat effective in comparison to SOLE alone for the treatment of IFALD. Diamond et al¹²² administered both SOLE and FOLE (1 g/kg/day each) to 12 patients with short bowel syndrome who developed IFALD. Overall, complete resolution of IFALD occurred in 9 patients. Five of these patients showed resolution of IFALD only once SOLE therapy was discontinued and FOLE monotherapy was used.

Newer preparations such as SMOFlipidTM (Fresenius-Kabi, Uppsala, Sweden) combine multiple oil sources (MCT, FO, OO, and SO) and have proven to be of benefit in patients with IFALD. Muhammed et al¹²³ reported results from a case series of children with IFALD treated with SMOFlipidTM compared to those that remained on SOLE. After 6 months of treatment, 5 out of 8 patients on SMOFlipidTM showed resolution of jaundice, compared to only 2 out of 9 patients in the SOLE group. Interestingly, apart from the 2 patients that failed treatment (1 died, 1 listed for transplant), the remaining 6 patients in the SMOFlipidTM group showed a sudden and sustained fall in bilirubin levels as early as 1 month after switching from SOLE. Another group in Australia has shown similar results when comparing SMOFlipidTM to SOLE in preterm infants with IFALD, with significant reduction in the rate of increase, and then reversal, of direct bilirubin levels¹²⁴.

The Ideal Lipid Emulsion

The ideal emulsion would be one that reversed or prevented EFAD without leading to hepatic steatosis, hypertriglyceridemia, or the elevation of liver enzymes, while simultaneously facilitating normal growth and development. Modifications in their ingredients, formulation, and dosing have made IVLE a relatively safe component alone or added to PN formulations. The ideal IVLE, however, has yet to be developed.

Common abbreviations (in alphabetical order)

ALA	Alpha-linolenic acid
ARA	Arachidonic acid
DHA	Docosahexaenoic acid
EFA	Essential fatty acids
EFAD	Essential fatty acid deficiency
EPA	Eicosapentaenoic acid
FO	Fish oil

FOLE	Fish oil-based lipid emulsion
HDL	High-density lipoprotein
IFALD	Intestinal failure-associated liver disease
IVLE	Intravenous lipid emulsion
LA	Linoleic acid
LCT	Long-chain triglycerides
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
MA	Mead acid
MCT	Medium-chain triglycerides
MUFA	Monounsaturated fatty acids
O3FA	Omega-3 fatty acids
O6FA	Omega-6 fatty acids
O9FA	Omega-9 fatty acids
OO	Olive oil
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acids
RES	Reticulo-endothelial system
SFA	Saturated fatty acids
SO	Soybean oil
SOLE	Soybean oil-based lipid emulsion
TNA	Total nutrient admixtures
VLDL	Very low-density lipoprotein

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Figure 1.
Evolution of fat sources in IVLE and their corresponding changes in inflammatory profile

Attributes of widely available IVLE. Abbreviations: LA, linoleic acid; ALA, α -linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ARA, arachidonic acid.

Table 1

Component	Intralipid	Omegaven	Clinolipid/ClinOleic	SMOFlipid	Lipidem/Lipoplus®
Soybean Oil (%)	100		20	30	40
Medium-chain triglycerides (%)				30	50
Olive Oil (%)			80	25	
Fish Oil (%)		100		15	10
Glycerol (g/100 mL)	2.25	2.5	2.25	2.5	2.5
Egg Phospholipid (g/100 mL)	1.2	1.2	1.2	1.2	1.2
Phytosterols (mg/L)	439 $\pm$ 5.7	3.66	274 $\pm$ 2.6	207	N/A ¹²⁵
Vitamin E (mg/100 mL)	3.8	15–30	3.2	16–23	24.2
LA (%)	50	4.4	18.5	21.4	24.5
ALA (%)	9	1.8	2	2.5	3.5
EPA (%)	0	19.2	0	3	3.5 2.5
DHA (%)	0	12.1	0	2	
ARA (%)	0	1–4	0	0.15–0.6	0 ⁸³

Table 2

Clinical differences most commonly seen in omega-3 and omega-6 fatty acid deficiency (data from animal and human studies).

Manifestation	Omega 3 Fatty Acids	Omega 6 Fatty Acids
<i>Constitutional Symptoms</i>	<i>Impaired growth. Dermatologic and hair changes</i>	
<i>Visual Symptoms</i>	Impaired vision and visual evoked potentials	Dry eyes
<i>Neurologic Symptoms</i>	Changes in stereotyped behavior, depression	None
<i>Other</i>	Polydipsia	Dysrhythmias

Table 3

Summary of findings from randomized trials evaluating strategies and alternatives to soybean oil-based emulsions in adult, critically ill patients (adapted from Manzanares et al⁹¹). Abbreviations: ICU, intensive care unit; PN, parenteral nutrition; LCT, long-chain triglycerides; MCT, medium-chain triglycerides; FO, fish oil; OO, olive oil; LFT, liver function tests; TG, triglycerides; FFA, free fatty acids; LOS, length of stay; RBP, retinol-binding protein; COPD, chronic obstructive pulmonary disease; IL, interleukin; HLA, human leukocyte antigen; SIRS (systemic inflammatory response syndrome); LPS, lipopolysaccharide; CRP, C-reactive protein.

Authors (year)	Inclusion Criteria (n)	Oil sources compared	Measured outcomes	Conclusions
<i>Nijveldt RJ et al</i> ²⁶ (1998)	Patients in the surgical ICU with at least 5 days of ventilator support, on total PN, and septic (n=20)	LCT (Intralipid®) vs LCT/MCT (50/50, Lipofundin®)	Metabolic and biochemical differences with special focus on liver enzymes	No differences in energy expenditure, nitrogen balance, LFT, carnitine, transferrin, pre-albumin, albumin, cholesterol, TG, and FFA. Trend towards higher total bilirubin levels in the LCT group
<i>Lindgren et al</i> ²⁷ (2001)	Patients in ICU anticipated to require total PN for at least 5 days (n=30)	LCT (Intralipid®) vs LCT/MCT (36/64, Structolipid®)	Nitrogen balance, energy metabolism and safety	Better 3-day cumulative nitrogen in the LCT/MCT group. No differences in tolerance, energy expenditure, glucose or TG levels during infusion
<i>Garnacho-Montero et al</i> ²⁸ (2002)	Patients in ICU likely to require at least 10 days of total PN (n=72)	LCT (Intralipid®) vs LCT/MCT (50/50, Lipofundin®)	Metabolic and clinical effects	No differences in ICU LOS, ICU mortality, or in-hospital mortality. The rise in RBP and recovery of nitrogen balance was greater in those receiving MCT/LCT
<i>Greco et al</i> ²⁹ (2003)	Patients in ICU with abdominal sepsis (n=54)	FO (Omegaven®)+LCT vs LCT	Daily serum lipids, CRP levels, reoperation rate, ICU and hospital LOS, and mortality	Decreased reoperation rate, ICU and hospital LOS in those receiving parenteral FO. No differences in mortality
<i>Huschak et al</i> ³⁰ (2005)	Patients in ICU following major trauma requiring mechanical ventilation (n=33)	LCT/OO (20/80, ClinOleic TM) vs LCT/MCT (50/50, Lipofundin®)	Energy expenditure, energy intake/energy expenditure ratio, duration of mechanical ventilation, and ICU LOS	No difference in energy expenditure or energy intake/energy expenditure ratio between groups. OO group showed shorter duration of mechanical ventilation and ICU LOS (of note, lipid/glucose ratio in PN was different in experimental groups: 75/25 in LCT/OO vs 37/63 in LCT/MCT)
<i>Iovinelli et al</i> ³¹ (2007)	Patients in ICU with COPD requiring mechanical ventilation (n=24)	LCT (Intralipid®) vs LCT/MCT (50/50, Lipofundin®)	Nutritional status, metabolic rate, time of ventilatory support and weaning	No difference in duration of mechanical ventilation, but weaning was shorter in those receiving LCT/MCT
<i>Garcia-de-Lorenzo et al</i> ³² (2007)	Patients in ICU with severe burns requiring total PN for 5–7 days (n=22)	LCT/OO (20/80, ClinOleic TM) vs LCT/MCT (50/50, Lipofundin®)	Adverse events, clinical outcomes and biochemical parameters	No difference in mortality and infection rate between groups. Patients in LCT/MCT showed a higher number of liver function abnormalities
<i>Friesecke et al</i> ³³ (2008)	Patients in ICU expected to require PN for at least 6 days, with less than 25% calories provided by enteral nutrition (n=166)	LCT/MCT (50/50, Lipofundin®) alone vs LCT/MCT (50/50, Lipofundin®) + FO (Omegaven®)	Changes in IL-6 and HLA-DR expression. Secondary outcomes included nosocomial infections, duration of mechanical ventilation, ICU LOS, and 28-day mortality	No difference seen in all of the measured outcomes between groups

Authors (year)	Inclusion Criteria (n)	Oil sources compared	Measured outcomes	Conclusions
<i>Wang et al</i> ³⁴ (2009)	Patients in ICU with severe acute pancreatitis (n=56)	LCT (Lipovenos®) alone vs LCT (Lipovenos®) + FO (Omegaven®)	Changes in IL-10, HLA-DR, CD4+/CD8+ ratio, infection and need for surgery	The group treated with FO showed a significant increase in interleukin 10 and HLA-DR. No differences seen in CD4+/CD8+ ratio, infection rate and need for surgery
<i>Barbosa et al</i> ³⁵ (2010)	Patients in medical ICU with SIRS or sepsis (n=25)	LCT/MCT (50–50, Nutriflex® Lipid special) vs MCT/LCT/FO (50/40/10, Lipolus®)	Plasma levels of eicosanoids and cytokines, and in LPS-stimulated whole blood culture supernatants. Secondary measures included days of ventilation, ICU LOS, hospital LOS, and mortality	The FO group showed a greater decrease in levels of IL-6, and a smaller decrease in levels of IL-10. There was no difference in days of ventilation, ICU LOS, and mortality. Surviving patients had a shorter hospital LOS in the FO group
<i>Umpierrez et al</i> ³⁶ (2012)	Patients in medical and surgical ICU requiring PN for more than 5 days (n=100)	LCT (Intralipid®) vs LCT/OO (20/80, ClinOleic TM)	Clinical outcomes, hospital LOS, glycemic control, inflammatory and oxidative stress markers, and granulocyte and monocyte functions	No differences noted in any of the measured outcomes between groups
<i>Pontes-Arruda et al</i> ³⁷ (2012)	Patients in ICU requiring PN (n=406)	LCT/OO (20/80, ClinOleic TM) vs LCT/MCT (not specified)	The main objective of the study was to compare PN-delivery systems (multi-chamber bag vs compounded) in incidence of BSI. Secondary outcomes included development of sepsis/shock, ICU LOS, and 28-day mortality	No differences in secondary outcomes between groups