Intensive Care Med (2010) 36:735–749
DOI 10.1007/s00134-009-1744-5

REVIEW

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Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions

Received: 3 August 2009
Accepted: 28 December 2009
Published online: 14 January 2010

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Abstract *Background:* Energy deficit is a common and serious problem in intensive care units and is associated with increased rates of complications, length of stay, and mortality. Parenteral nutrition (PN), either alone or in combination with enteral nutrition, can improve nutrient delivery to critically ill patients. Lipids provide a key source of calories within PN formulations, preventing or correcting energy deficits and improving outcomes. *Discussion:* In this article, we review the role of parenteral lipid emulsions (LEs) in the management of critically ill patients and highlight important biologic activities associated with lipids. Soybean-oil-based LEs with high contents of polyunsaturated fatty acids (PUFA) were the first widely used formulations in the intensive care setting. However, they may be associated with increased rates of infection and lipid peroxidation, which can exacerbate oxidative stress. More recently developed parenteral LEs employ partial substitution of soybean oil with oils providing medium-chain triglycerides, ω-9 monounsaturated fatty acids or ω-3 PUFA. Many of these LEs have demonstrated reduced effects on oxidative stress, immune responses, and inflammation. However, the effects of these LEs on clinical outcomes have not been extensively evaluated. *Conclusions:* Ongoing research using adequately designed and well-controlled studies that characterize the biologic properties of LEs should assist clinicians in selecting LEs within the critical care setting. Prescription of PN containing LEs should be based on available clinical data, while considering the individual patient's physiologic profile and therapeutic requirements.

Keywords Energy deficit · Fatty acid · Intensive care · Lipid emulsion · Parenteral nutrition

Introduction

Many critically ill patients admitted to the intensive care unit (ICU) enter a state of negative energy balance during the first 3–4 days following admission [1, 2]. This energy deficit often progresses during their ICU stay and may result in malnutrition and adverse outcomes [1]. Multiple factors contribute to energy deficit, including increased

metabolism [3, 4], delays in the initiation of feeding, and inadequate caloric provision [1]. Indeed, a number of studies have demonstrated that target caloric intake is achieved in only 50–75% of ICU patients and that as many as 25% of patients receive only 1,000–1,500 kcal/day [5].

Prolonged negative energy balance within the ICU is associated with serious complications [1, 2]. In two separate studies, progressive negative energy balance was strongly correlated with increased numbers of infectious complications, particularly sepsis [1, 2]. In addition, cumulative total energy deficit has been correlated with increased length of mechanical ventilation, length of ICU stay, total number of complications, and duration of antibiotic use [1]. Delayed initiation of feeding and/or negative energy balance in critical care patients may also be associated with higher ICU and in-hospital mortality rates [5, 6], while early initiation of feeding results in improved caloric intake [7].

This article aims to review well-known papers that evaluate potential biologic effects of lipids when provided as a parenteral energy source and to provide future perspectives on the use of parenteral lipid emulsions (LEs) in critically ill patients.

Role of parenteral nutrition in the intensive care setting

Given the association between negative energy balance/malnutrition and both morbidity and mortality, ensuring that critically ill patients receive adequate caloric and nutrient intake should be a high priority for intensive care clinicians. Current guidelines recommend that all ICU patients who tolerate enteral nutrition (EN) should receive EN (approximately 25–30 kcal/kg per day) if they are not expected to be on a full oral diet within 3 days [8]. However, within the ICU setting EN may not be feasible or cannot be established at rates that provide adequate nutrition for a number of reasons. For example, EN may be frequently interrupted because of diagnostic investigations, surgery, diarrhea, vomiting, mechanical problems (e.g., tube displacement) or patient transfers [9]. EN may be contraindicated in patients with anatomic gastrointestinal disorders, severe diarrhea, and reduced intestinal blood flow [10]. Parenteral nutrition (PN) is therefore recommended under certain circumstances (Table 1) [11].

Despite these recommendations, PN is often underused. Although PN was once a popular means of administering nutrients, utilization has decreased in recent years because of concerns regarding metabolic complications associated with overfeeding [12, 13] and an increased risk of septic complications [8]. It has been suggested that EN is required in order to maintain gut function and is less likely to cause bacterial translocation than PN, although other perspectives exist [12, 14]. However, available literature suggests that supplementation of EN with PN enhances caloric intake and nutritional status [1, 15] and that PN is as safe as EN in critically ill patients [16, 17].

Individualizing nutrition in critically ill patients

The systemic inflammatory response is associated with metabolic stress in critically ill patients, including an overall increase in metabolic rate, production of reactive species, insulin resistance, and alterations in substrate utilization that result in hyperglycemia (partly because of increased gluconeogenesis), lipolysis, and increased proteolysis relative to protein synthesis, potentially resulting in negative nitrogen balance [3, 4, 11, 18, 19]. The nutrition provided to patients within the ICU setting should therefore aim to blunt this catabolic state and enhance anabolic activity during recovery while avoiding overfeeding. Administration of dextrose must often be balanced with infusion of insulin to maintain euglycemia and minimize increases in carbon dioxide (CO_2) production. Amino acids are required to promote nitrogen retention and support protein synthesis [10]. Lipids are generally administered to provide 30% of total calories, but dosage reduction should be considered when triglyceride concentrations are >400 mg/dL [15]. Nutritional requirements vary depending upon the level of metabolic stress; therefore, energy requirements, as well as blood glucose and electrolyte concentrations, should be monitored on a daily basis, and the composition of artificial nutrition adjusted as required [15].

Table 1 Potential indications for parenteral nutrition in intensive care patients [8–10]

Parenteral nutrition as a supplement to enteral nutrition	Parenteral nutrition alone
Enteral nutrition is insufficient to meet target caloric intake	Intolerance to enteral nutrition
Suppression of gastrointestinal activity (e.g., immediately following injury or surgery)	Major gut failure (e.g., extensive intestinal resection)
	Conditions preventing adequate nutrient absorption (e.g., inflammatory bowel disease, gastric outlet obstruction, intractable vomiting, severe diarrhea, paralytic ileus)

The role of lipid emulsions in parenteral nutrition

Early PN formulations consisted primarily of high concentrations of glucose and amino acids in order to provide adequate calories [20] and were often associated with a number of complications. Prolonged use of these formulations was associated with essential fatty acid (EFA) deficiency because they did not provide linoleic acid (LA; 18:2ω-6) or α-linolenic acid (ALA; 18:3ω-3), which are not synthesized by the body and must be obtained from the diet [20–22]. Furthermore, the high dextrose loads provided by early PN solutions were associated with a variety of other complications, such as excessive CO_2 production, metabolic stress (increased concentrations of cortisol, epinephrine, and glucagon), fever, and hepatic steatosis [20]. As critical illnesses can be associated with impaired glucose tolerance, overzealous infusion of hypertonic dextrose solutions was often also associated with hyperglycemia, which, if undetected and untreated, can progress to hyperosmolar nonketotic coma [23]. Hyperglycemia can also be associated with an increased incidence of complications in critically ill patients, such as severe infections, multiple organ failure, and increased mortality rates [24].

The incorporation of lipids into PN formulations has addressed many of these issues. Lipids provide a more energy-dense source of calories (approximately 9 kcal/g) than either amino acids (4 kcal/g) or dextrose monohydrate (3.4 kcal/g) [22]. Therefore, the fluid volume of PN required to achieve adequate caloric intake can be substantially reduced. The reduced fluid volume and increase in osmolarity of formulations incorporating LEs permit the safe administration of PN via the peripheral and central routes. Formulations with osmolarities $\leq$900 mOsm/L can be administered peripherally, while highly osmolar formulations can be administered via central veins, which may be of importance in critically ill patients requiring fluid restriction [10, 25]. Currently available parenteral LEs also contain sufficient LA and ALA to prevent EFA deficiency [21]. Perhaps most importantly, the use of LEs in PN is associated with a reduction in the metabolic complications related to excessive hypertonic glucose infusion because the dextrose load is correspondingly reduced. Results of a study involving critically ill patients with gastric carcinoma, sepsis, colitis or pancreatitis demonstrated that replacement of one-third of the total calories contained in a conventional glucose-amino acid PN formulation with a LE maintained or increased patients' body weight [26]. Plasma glucose concentrations were maintained or reduced, and no cases of hyperglycemia, hyperosmolar nonketotic coma or hypertriglyceridemia were observed [26]. Another study found that ICU patients receiving parenteral fluids unintentionally received 150–600 kcal/day dextrose as a constituent of various fluids and drugs [1]. Therefore, the administration of PN containing LEs may help to prevent hyperglycemia and its complications.

It should be noted that, despite the potential benefits of parenteral lipids, the use of LEs may be limited in some patients. Triglycerides and other components of LEs form artificial chylomicrons, which are hydrolyzed in the body into free fatty acids (FA) and small remnant particles taken up by the liver [22, 27, 28]; the presence of excess phospholipids can also form liposomes, which interfere with lipid metabolism and may result in hypercholesterolemia [21, 22, 28]. When parenteral lipids are given in excess of the liver's ability to process them, hyperlipidemia and hepatic steatosis may occur [21, 22, 28]. Parenteral LEs also commonly contain phytosterols, which may be present in the circulation in quantities large enough to induce cholestasis [28]. Although hepatic impairment is most common among patients on long-term PN [28, 29], critically ill patients are also at increased risk because plasma levels of FA increase with metabolic stress [27, 30]. Therefore, parenteral LEs should be used with caution in septic patients [27, 28, 30] and patients with other conditions known to impair hepatic clearance of FA [28, 30]. In addition to the duration and dose of parenteral LEs and the patient's level of metabolic stress, the oil source of the LE may also affect the relative risk of developing abnormal liver function [21, 22, 28, 31].

Evolution of parenteral lipid emulsions

Fatty acids

Although LEs contain numerous biologically active compounds, triacylglycerols providing FA are their primary component. Fatty acids are classified according to their structure, in terms of their hydrocarbon chain length (short, medium or long), degree of saturation (number of double bonds), and location of double bonds (counted from the methyl carbon of the hydrocarbon chain) (Table 2) [21, 22, 32]. Fatty acids play key roles in determining the structural integrity and fluidity of cell membranes and can give rise to several important bioactive mediators [21, 22, 33]. They can also regulate the expression of a variety of genes and modulate cell signaling pathways, such as those involved in apoptosis, inflammation, and cell-mediated immune responses. For example, longer-chain FA, such as arachidonic acid (AA; 20:4ω-6), eicosapentaenoic acid (EPA; 20:5ω-3), and docosahexaenoic acid (DHA; 22:6ω-3), are involved in the generation of pro- and anti-inflammatory lipid mediators [22].

Table 2 Fatty acid nomenclature and key dietary sources [22, 32]

Common name	Chemical name	Chemical structure [length of hydrocarbon chain (C atoms): number of double bonds and position of first double bond]	Dietary sources
Capric	Decanoic	10:0	Coconut oil
Lauric	Dodecanoic	12:0	Coconut oil
Myristic	Tetradecanoic	14:0	Milk
Palmitic	Hexadecanoic	16:0	Milk, eggs, animal fats, meat, cocoa butter, palm oil, fish and fish oils
Palmitoleic	9-Hexadecenoic	16:1ω-7	Fish and fish oils
Stearic	Octadecanoic	18:0	Milk, eggs, animal fats, meat, cocoa butter
Oleic	9-Octadecenoic	18:1ω-9	Milk, eggs, animal fats, meat, cocoa butter, olive oil
Linoleic	9,12-Octadecadienoic	18:2ω-6	Seeds, seed oils, eggs, animal fats, meat
Arachidonic	5,8,11,14-Eicosatetraenoic	20:4ω-6	Meat, egg lipids, algal oils
α-Linolenic	9,12,15-Octadecatrienoic	18:3ω-3	Seeds, seed oils, green leaves, nuts
Eicosapentaenoic	5,8,11,14,17-Eicosapentaenoic	20:5ω-3	Fish and fish oils
Docosapentaenoic	7,10,13,16,19-Docosapentaenoic	22:5ω-3	Fish and fish oils
Docosahexaenoic	4,7,10,13,16,19-Docosahexaenoic	22:6ω-3	Fish and fish oils, algal oils

Early parenteral lipid emulsions

The majority of early LEs, which were first included in PN during the 1960s, were derived from soybean oil, which contains a high concentration of both LA and ALA [21, 22, 33]. These early LEs were demonstrated to efficiently deliver nonglucose energy, thereby reducing the adverse effects associated with intake of high dextrose concentrations [21]. Furthermore, they provided EFA and the fat-soluble vitamins E and K [33]. However, studies published during the 1970s and 1980s found that soybean-oil- and cottonseed-oil-based LEs were associated with a number of adverse immunological effects, such as reduced migration and phagocytosis of granulocytes, which resulted in increased rates of infections, including sepsis [34–37]. The cottonseed-oil-based LE (Lipomul) had such adverse clinical effects (e.g., hemolytic anemia) that it has since been removed from the market.

Minimization of risks associated with parenteral lipids in critical care patients

In an effort to address concerns associated with the soybean-oil-based LEs, alternative sources of FA were investigated [21]. Much of this research focused on minimizing complications to which critically ill patients are particularly susceptible, including oxidative stress, alterations in cell-mediated immunity, inflammation, and thrombosis. Although these are important issues to consider, well-controlled clinical data in critically ill patients are limited, and discrepancies may be observed between studies because of the heterogeneity of the study designs, patient populations, and specific LEs used.

Oxidative stress

Reactive oxygen species (ROS) can react with and damage cell membranes, lipids, proteins, and DNA through oxidation. Under normal circumstances, ROS may be produced in increased amounts by cells such as neutrophils and macrophages as part of a natural immune response. Levels of ROS are balanced by the neutralizing activity of antioxidant molecules and enzymes, thereby preventing excessive damage to the host [38, 39].

Oxidative stress occurs when an imbalance develops because of high ROS levels and/or low antioxidant levels. During critical illness, increased ROS and inflammatory mediator production occurs against a background of compromised antioxidant activity, which is partly due to preexisting nutritional deficiencies and/or suboptimal provision of artificial nutrition. Depletion of the antioxidants selenium and zinc has been observed in trauma and burn patients, while surgery is associated with reductions in vitamins A, C, and E. This state of imbalance can cause tissue damage and may play an important role in the development of sepsis and multiple organ failure, among other complications (Table 3) [38, 39].

A key consequence of oxidative stress is lipid peroxidation, where ROS react with the double bond of unsaturated lipids, producing unstable lipid peroxides that may cause cell death [38, 39]. The high number of double bonds present in ω-6 and ω-3 polyunsaturated fatty acids (PUFA) provide targets for lipid peroxidation, and these FA may therefore be associated with an increased risk of oxidative stress [40]. For this reason, the antioxidant α-tocopherol (vitamin E) is sometimes added to PUFA-rich LEs in clinical practice.

Another approach to minimize oxidative stress is the partial replacement of PUFA-rich oils with alternative FA

Table 3 Diseases and intensive care unit states associated with reactive oxygen species-mediated tissue damage [39]

Septic shock
Acute respiratory distress syndrome
Systemic inflammatory response syndrome
Disseminated intravascular coagulation
Multiple organ dysfunction
Burns
Cardiovascular disease
Diabetes mellitus
Trauma
Reperfusion injury
Cancer

sources, such as oils rich in medium-chain triglycerides (MCT; derived from coconut oil containing medium-chain FA such as capric acid), which are more resistant to oxidative damage [41]. In one study of adults requiring PN, a 1:1 mixture of MCT (derived from coconut oil) and soybean oil (MCT/soybean oil LE) supplemented with α-tocopherol demonstrated a reduced propensity to lipid peroxidation when compared with a conventional soybean-oil-based LE (Table 4) [42]. However, a separate study comparing a soybean-oil-based LE with a MCT/soybean oil LE supplemented with α-tocopherol in patients undergoing abdominal surgery found no difference in lipid peroxidation between the two LEs [43].

Metabolism of MCT differs from that of long-chain triglycerides (LCT). Unlike longer-chain FA, MCT require little carnitine for mitochondrial entry, and it has been suggested that their more rapid breakdown may impart an increased production of ketones in critically ill patients [44]. However, this is thought to be a transient phenomenon that is reversible upon discontinuation of MCT infusion and rarely causes clinical problems. However, formulations containing MCT should not be used in patients who develop ketosis or acidosis in the ICU setting [41].

It has been suggested that monounsaturated FA (MUFA; often derived from olive oil, which also provides antioxidants) with only one double bond, such as oleic acid (OA; 18:1ω-9), may be less susceptible to lipid peroxidation than ω-6 and ω-3 PUFA with several double bonds. In vitro studies indicated that cells treated with OA or olive oil were associated with less mitochondrial ROS production than cells treated with certain PUFA (e.g., DHA) or a soybean-oil-based LE [45, 46]. In a preclinical rodent study, lipid peroxidation was lower among mice administered OA or olive oil by gavage than among mice administered PUFA (i.e., LA or DHA) or fish oil [47]. In children requiring PN, a LE containing 80% olive oil led to lower concentrations of certain lipid peroxides than a soybean-oil-based LE (Table 4) [48]. In a separate study involving preterm infants, peroxidation markers were similar between an olive-oil-rich LE supplemented with α-tocopherol and a conventional soybean-oil-based LE, whereas vitamin E status was enhanced with olive-oil-rich LE [49].

Cell-mediated immunity

Fatty acids have been shown to modulate the immune system in a number of ways, influencing cell signaling, gene expression, and apoptosis. In particular, ω-6 PUFA have been associated with reduced migration and phagocytic activity of neutrophils and macrophages, decreased lymphocyte reactivity to microbial antigens, and inhibition of antibody-dependent cellular cytotoxicity [34, 35, 50–52]. The consequences of these immunosuppressive actions have been demonstrated within the ICU setting. When compared with PN containing no lipids administered to trauma patients, PN containing a soybean-oil-based LE was associated with higher rates of infection and significantly longer durations of mechanical ventilation, longer ICU stays, and longer hospital stays (Table 4) [53]. In patients with septic shock, those receiving a soybean-oil-based LE showed increased leukocyte counts and reduced neutrophil cytotoxic activity, while those receiving a fish-oil-based LE experienced opposite effects [54]. However, excessive (hypercaloric) feeding may also have contributed to immunosuppression observed in some older studies.

Among surgical patients receiving PN, a soybean-oil-based LE supplemented with fish oil was associated with a shorter ICU and overall hospital stay when compared with a LE that did not contain fish oil; however, the rates of infection were similar between groups (Table 4) [55]. When a soybean-oil-based LE was supplemented with fish oil, higher doses were associated with a reduction in the length of ICU and overall hospital stay, significantly reduced antibiotic requirement, and significantly increased survival [56].

In comparison with soybean oil, MCT are generally described as immune neutral; however, effects upon certain components of the immune system have been described. In two ex vivo studies, MCT and MCT/soybean oil LEs increased monocyte activation and neutrophil adhesion and degranulation [57, 58]. In contrast, another ex vivo study reported that MCT and MCT/soybean oil LEs were both associated with impaired neutrophil killing of *Candida albicans* [59]. An in vitro study showed that a MCT/soybean oil LE inhibited the proliferation of T-lymphocytes but not lymphokine-activated killer cells [60].

There are few clinical data evaluating the effect of MCT on immune function. In a study involving healthy volunteers, administration of an MCT/soybean oil LE was associated with increased total leukocyte and neutrophil counts and significantly decreased lymphocyte counts [61]. A second study of healthy subjects found that, in contrast to intermittent infusion of soybean-oil-based LE,

Table 4 Key clinical studies evaluating biological and clinical effects of lipid emulsions

Clinical study	Population	Design	Treatment groups	Key findings
Lipid peroxidation/antioxidant activity				
Gobel et al. [49]	Premature infants (28–37 weeks gestation; $N = 45$)	Prospective, randomized, double-blind trial	Intralipid vs. ClinOleic for 7 days, starting ≤72 h after birth	Urinary malondialdehyde excretion at day 7: no difference between groups (data not provided)
Goulet et al. [48]	Children with gastrointestinal disorders (at home; $N = 18$)	Prospective, randomized trial	Intralipid vs. ClinOleic for 2 months	LDL peroxidation index at day 60: 55.1 (ClinOleic) vs. 63.3 μmol/L (Intralipid; NS) LDL + VLDL peroxidation index at day 60: 83.7 (ClinOleic) vs. 104.6 μmol/L (Intralipid; $P = 0.0027$)
Linseisen et al. [43]	Adults undergoing abdominal surgery ($N = 33$)	Prospective, randomized, double-blind trial	Intralipid vs. Lipoplus for 5 days	Total plasma cholesterol oxidation products concentration at day 6: 45.5 (Lipoplus) vs. 40.9 μmol/L (Intralipid; NS) Total antioxidant capacity at day 6: 153 (Lipoplus) vs. 129 μmol/L (Intralipid; NS)
Manuel-y-Keenoy et al. [42]	Adults requiring total PN ($N = 24$)	Prospective, randomized, double-blind trial	Intralipid vs. Lipofundin MCT + α-tocopherol (200 mg/dL) for 11 days	Serum concentrations of α-tocopherol at day 11: significantly higher for Lipofundin MCT vs. Intralipid ($P = 0.006$) Malondialdehyde/mg LDL- and VLDL-cholesterol at day 11: significantly reduced for Lipofundin MCT vs. Intralipid ($P = 0.022$)
Immunosuppression/infection rates				
Battistella et al. [53]	Adult trauma patients ($N = 60$)	Prospective, randomized, double-blind trial	Intralipid vs. PN containing no lipids for 10 days	Mean duration of mechanical ventilation: 27 (Intralipid) vs. 15 days (no lipids; $P = 0.01$) Mean ICU stay: 29 (Intralipid) vs. 18 days (no lipids; $P = 0.02$) Mean hospital stay: 39 (Intralipid) vs. 27 days (no lipids; $P = 0.03$) Total number of infectious complications: 72 (Intralipid) vs. 39 (no lipids; $P < 0.05$) Number of patients with pneumonia: 22 (Intralipid) vs. 13 (no lipids; $P = 0.05$) Number of patients with sepsis: 13 (Intralipid) vs. 5 (no lipids; $P = 0.04$)
Weiss et al. [55]	Adults undergoing abdominal surgery ($N = 24$)	Prospective, randomized trial	Lipoven + Omegaven vs. Lipoven for 5 days	Mean ICU stay: 4.1 (Lipoven + Omegaven) vs. 9.1 days (Lipoven; NS) Mean hospital stay: 17.8 (Lipoven + Omegaven) vs. 23.5 days (Lipoven; NS) Number of infectious complications: 5 in each group
Grau et al. [64]	Adults undergoing laparotomy ($N = 72$)	Prospective, randomized, double-blind trial	Intralipid vs. Lipofundin-MCT	Incidence of intra-abdominal abscesses: 32% (Intralipid) vs. 8% (Lipofundin-MCT; $P < 0.05$) Incidence of in-hospital mortality: 36% (Intralipid) vs. 15% (Lipofundin-MCT; NS)
Garcia-de-Lorenzo et al. [31]	Adults with severe burns ($N = 22$)	Prospective, randomized, double-blind trial	ClinOleic vs. Lipofundin-MCT for 6 days	Mean ICU stay: 32.9 (ClinOleic) vs. 41.8 days (Lipofundin-MCT; NS) Mean hospital stay: 57.0 (ClinOleic) vs. 64.9 days (Lipofundin-MCT; NS) Incidence of infections: 6 patients in each group Incidence of in-ICU mortality: 36% (ClinOleic) vs. 27% (Lipofundin-MCT)

Table 4 continued

Clinical study	Population	Design	Treatment groups	Key findings
Huschak et al. [88]	Adult multiple trauma patients ($N = 33$)	Prospective, randomized, open-label study	ClinOleic (lipid-to-glucose ratio = 3:1) vs. Lipofundin-MCT (lipid-to-glucose ratio = 1:3) for 6 days	Mean duration of mechanical ventilation: 13 (ClinOleic/low glucose) vs. 24 days (Lipofundin-MCT/high glucose; $P = 0.01$) Mean ICU stay: 18 (ClinOleic/low glucose) vs. 25 days (Lipofundin-MCT/high glucose; $P = 0.04$) Mean hospital stay: 80 (ClinOleic/low glucose) vs. 85 days (Lipofundin-MCT/high glucose; NS) Mean sepsis score significantly lower for ClinOleic/low glucose vs. Lipofundin-MCT/high glucose on days 5–14 ($P < 0.05$)
Wichmann et al. [70]	Adults undergoing abdominal surgery ($N = 256$)	Prospective, randomized study	Intralipid vs. Lipoplus for 5 days	Mean ICU stay: 6.3 (Intralipid) vs. 4.1 days (Lipoplus; NS) Mean hospital stay: 21.9 (Intralipid) vs. 17.2 days (Lipoplus; $P = 0.0061$) Incidence of pyrexia: 24.0% (Intralipid) vs. 17.3% (Lipoplus; NS) Incidence of catheter-related sepsis: 3.9% (Intralipid) vs. 3.1% (Lipoplus; NS) Incidence of pneumonia: 3.9% (Intralipid) vs. 0.8% (Lipoplus; NS) Incidence of mortality: 1.6% (Intralipid) vs. 4.7% (Lipoplus; NS)
Mateu-de Antonio et al. [74]	Adults requiring PN ($N = 42$)	Retrospective, observational study	Intralipid vs. ClinOleic	Mean ICU stay: 31.3 (Intralipid) vs. 25.2 days (ClinOleic; NS) Mean hospital stay: 46.5 (Intralipid) vs 45.4 days (ClinOleic; NS) Incidence of sepsis: 50% (Intralipid) vs. 43.5% (ClinOleic; NS) Incidence of mortality: 44% (Intralipid) vs. 47.8% (ClinOleic; NS)
Heller et al. [56]	Adults requiring total PN ($N = 661$)	Prospective, open-label study	Intralipid + Omegaven for ≥3 days	Mean ICU stay: significantly decreased at Omegaven doses >0.05 g/kg per day ($P < 0.001$) Mean hospital stay: significantly decreased at Omegaven doses >0.05 g/kg per day ($P < 0.001$) Requirement for antibiotics: significantly higher at Omegaven doses <0.05 vs. 0.15–0.2 g/kg per day ($P < 0.001$) Survival rate: significantly lower at Omegaven doses <0.05 vs. 0.1–0.2 g/kg per day ($P < 0.001$)
Inflammation				
Gogos et al. [68]	Severely ill adults ($N = 20$)	Prospective, randomized study	Lipofundin-S vs. Lipofundin-MCT for 30 days	Circulating TNF-α concentrations: no differences between groups Endotoxin-induced TNF-α release at day 30 vs. baseline: 185.4 vs. 95.3 pg/mL (Lipofundin-S; $P < 0.01$); 90.7 vs. 103.8 pg/mL (Lipofundin-MCT; NS)

Table 4 continued

Clinical study	Population	Design	Treatment groups	Key findings
Koller et al. [71]	Adults undergoing abdominal surgery ($N = 30$)	Prospective, randomized, double-blind study	Intralipid vs. Lipoplus for 5 days	Day 6: significant increase in LTB_5 release vs. baseline with Lipoplus but not Intralipid ($P = 0.0104$) No difference between groups for LTC_5 release Day 6 LTB_5/LTB_4 ratio: significant increase vs. baseline with Lipoplus but not Intralipid ($P < 0.02$)
Wichmann et al. [70]	Adults undergoing abdominal surgery ($N = 256$)	Prospective, randomized study	Intralipid vs. Lipoplus for 5 days	Day 6: significant increase in LTB_5 release vs. day 1 in both groups ($P < 0.01$) Day 6 LTB_5/LTB_4 ratio: significant increase vs. day 1 with Lipoplus ($P = 0.002$) but not Intralipid
Mayer et al. [73]	Adults with sepsis ($N = 21$)	Prospective, randomized study	Lipoven vs. Omegaven for 5 days	Endotoxin-induced TNF-α, IL-1β, IL-6, IL-8 release (days 1-18): significant increase from baseline with Lipoven; significant decrease from baseline with Omegaven
Mateu-de Antonio et al. [74]	Adults requiring PN ($N = 42$)	Retrospective, observational study	Intralipid vs. ClinOleic	Mean concentrations of C-reactive protein at end of PN: 8.4 (Intralipid) vs. 11.0 mg/L (ClinOleic; NS)
Thrombosis				
Porta et al. [78]	Adult critically ill patients ($N = 23$)	Prospective, randomized, open-label study	Intralipid vs. Lipofundin-MCT for 7 days	No significant changes in platelet aggregation in either treatment group
Roulet et al. [78]	Adults undergoing total esophagectomy ($N = 19$)	Prospective, randomized study	Lipoven vs. Lipoven + Omegaven for 7 days	Mean bleeding time: 3.1 (Lipoven) vs. 3.3 min (Lipoven + Omegaven; NS) Mean maximal collagen-induced platelet aggregation: 91% (Lipoven) vs. 87% (Lipoven + Omegaven; NS) Mean maximal adenosine diphosphate-induced platelet aggregation: 78% (Lipoven) vs. 77% (Lipoven + Omegaven; NS)

All lipid emulsions administered as part of total parenteral nutrition within the ICU setting, unless otherwise stated

LDL low-density lipoprotein, *NS* not significant, *VLDL* very low-density lipoprotein, *PN* parenteral nutrition, *ICU* intensive care unit, *MCT* medium-chain triglycerides, *TNF* tumor necrosis factor, *LT* leukotriene, *IL* interleukin

infusion of PN containing MCT/soybean oil LE did not impair the clearance of 99Tc-sulfur colloid by the reticuloendothelial system [62]. In pediatric surgical patients receiving PN, an MCT/soybean oil LE was associated with a significantly increased lymphocyte count when compared with a soybean-oil-based LE [63]. Another study compared an MCT/soybean oil LE with a soybean-oil-based LE in severely undernourished patients undergoing laparotomy [64]. In that study, the incidence of intra-abdominal abscesses was significantly lower in the MCT/soybean oil group than the soybean oil group, but there were no significant differences between the groups for other infections (Table 4) [64].

Lipid emulsions containing high concentrations of olive oil may have less impact on the host immune response than soybean-oil-based or MCT/soybean oil LEs, with little effect on lymphocytes, natural killer cells, and neutrophils. In an in vitro study, the percentage of lymphocytes undergoing apoptosis or necrosis was higher following incubation with 200 μM LA (77%) than with 200 μM OA (23%); both were higher than the control group (3%) [65]. Another study showed that lymphocyte activation was dose-dependently inhibited by soybean-oil-based LEs but not an olive-oil-rich LE [66]. In contrast to a MCT/soybean oil LE, an olive-oil-rich LE had little effect on neutrophil activation, phagocytosis, generation of ROS or chemotaxis [67]. The immunosupportive effects of an olive-oil-rich emulsion may be reflected clinically by the low incidence of infectious complications reported in severely burned patients receiving PN in the ICU: in a study evaluating this patient population, the incidences of sepsis and multiple organ failure and the duration of mechanical ventilation, ICU stay, and hospital stay were comparable for patients receiving olive-oil-rich and MCT/soybean oil LEs (Table 4) [31].

Inflammation

Administration of soybean-oil-based LEs is associated with high blood levels of the ω-6 PUFA LA and its metabolite AA, the further metabolism of which may produce proinflammatory eicosanoids [e.g., prostaglandins, thromboxanes, and leukotrienes (LT)] that can regulate additional inflammatory mediators [e.g., tumor necrosis factor (TNF)-α] [32]. This hypothesis is supported by a study reporting that malnourished, severely ill patients experienced significantly increased total production of TNF-α when receiving PN with a soybean-oil-based LE but not an MCT/soybean oil LE [68]. Although there has been much focus on the proinflammatory effects of AA-derived eicosanoids, lipoxins derived from AA have potent inflammation-resolving effects [69].

Conversely, the long-chain ω-3 PUFAs EPA and DHA found in fish oils are thought to possess anti-inflammatory properties because they are readily incorporated into cell membranes and thereby impact AA metabolism [18, 32], because the metabolism of EPA is associated with production of less biologically potent eicosanoids than those produced from AA [18, 32], and because EPA and DHA are precursors of resolvins with powerful inflammation-resolving properties [18, 69]. Indeed, when soybean oil was partially replaced with fish oil (3:1 ratio) in surgical patients receiving PN, LT synthesis was shifted from the proinflammatory LTB_4 (produced from AA) to the less potent LTB_5 (produced from EPA) (Table 4) [70, 71]. This change was associated with significantly reduced concentrations of the inflammatory mediators interleukin (IL)-6 and TNF-α [72]. In patients with sepsis, concentrations of IL-1β, IL-6, IL-8, and TNF-α released from mononuclear leukocytes were significantly increased following administration of a soybean-oil-based LE compared with a decrease of approximately 30% following administration of a fish-oil-based LE [73].

Lipid emulsions rich in olive oil have not been well studied with regard to their effect on inflammation; however, a few studies have demonstrated that OA has relatively few effects on the production of inflammatory mediators. In a preclinical study, lipopolysaccharide-induced production of IL-1β, IL-6, IL-8, and TNF-α by neutrophils was not altered by an olive-oil-rich LE, compared with significant reductions in IL-1β with soybean-oil-based and MCT/soybean oil LEs [67]. In another study, infectious complication rates, mortality rates, and length of ICU stay were similar among critically ill patients receiving PN containing soybean-oil-based and olive-oil-rich LEs [74].

Thrombosis

Thrombosis is a common and serious complication for many critically ill, surgical, and trauma patients, as these states may be associated with changes in the availability of clotting factors and alterations in the fibrinolytic pathway, resulting in intravascular coagulation [75]. However, the effects of LEs on coagulation have not been extensively assessed. In one study, platelet aggregation was inhibited immediately following intravenous infusion of a fish-oil-based LE to healthy volunteers, but had returned to normal at 24 h [76]. In surgical patients receiving PN, the latency to collagen-induced platelet aggregation and time to maximal platelet aggregation were significantly longer for a soybean-oil-based LE than for a fish-oil-enriched LE; however, adenosine-diphosphate-induced platelet aggregation and bleeding time were unchanged [77]. Another study found no change in platelet aggregation for critically ill patients receiving either soybean-oil-based or MCT/soybean oil LEs [78].

The effects of parenteral olive-oil-rich LEs on thrombosis have not been systematically evaluated.

Table 5 Key characteristics of widely available parenteral lipid emulsions [22, 43, 73, 89]

	Intralipid	Lipoven	Lipofundin-MCT	Structolipid	Omegaven	Lipoplus	ClinOleic	SMOFLipid
Manufacturer	Fresenius-Kabi, Germany	Fresenius-Kabi, Germany	B. Braun, Germany	Fresenius-Kabi, Germany	Fresenius-Kabi, Germany	B. Braun, Germany	Baxter, France	Fresenius-Kabi, Germany
Oil source (% by weight)	Soybean	Soybean	Coconut (50%), soybean (50%)	Coconut (36%), soybean (64%)	Fish (100%)	Coconut (50%), soybean (40%), fish (10%)	Olive (80%), soybean (20%)	Coconut (30%), soybean (30%), olive (25%), fish (15%)
Typical FA composition (% of total FA)								
Caproic			0.5	Trace				Trace
Caprylic			28.5	26		30		10
Capric			20	10		19.5		11
Lauric			1	Trace				Trace
Myristic					5	0.5	Trace	1
Palmitic	11	12	7.5	7	12	6	12	10
Stearic	4	5	2	3	4.5	2.5	2	3.5
Palmitoleic					9	0.5	1.5	1.5
Oleic	24	24	11	14	15	8	62	31
Linoleic	53	53	29	35	4.5	24.5	19	20
α-Linolenic	8	8	4.5	4	1.8	3.5	2.5	2
Arachidonic					2			
Eicosapentaenoic					20	3.5		3
Docosapentaenoic					2	3		Trace
Docosahexaenoic					12	2.5		2
α-Tocopherol (μmol/L)	87	132	502	16	505	562	75	500

FA fatty acids

However, in one study of patients undergoing hemodialysis, the need to change hemofilters due to blood coagulation was significantly reduced among patients receiving PN containing an olive-oil-rich LE compared with a soybean-oil-based LE [79].

Choosing a parenteral lipid emulsion for the critically ill patient

Components of commercially available lipid emulsions

A summary of the key characteristics of available parenteral LEs is presented in Table 5; in some countries (i.e., the USA) only soybean-oil-based LEs are available [8]. The choice of parenteral LE should be based upon several considerations. It has been suggested that the ratio of LA to ALA is important because of competition between these FA for a number of enzymes, thereby potentially influencing the production of eicosanoid and eicosanoid-like inflammatory mediators [80]. However, a number of studies have suggested that the absolute concentrations of certain PUFA are more important than their ratio in determining their biologic effects [80, 81]. In addition, the FA content of LEs can vary depending upon the specific source of oil (e.g., EPA and DHA within different fish oils) [80].

The stability of LEs, with respect to phase separation and presence of large globules, is also an important issue in clinical settings in which the final concentrations of lipid components and emulsifiers are of key importance. All LEs eventually become unstable when diluted above a certain threshold within the PN formulation. Current regulations in the USA require that globules >5 μm do not exceed 0.05% (weight/volume) of the emulsion [82]. In general, MCT/soybean oil and olive-oil-rich LEs have demonstrated greater stability when compared with soybean-oil- and safflower-oil-based LEs, although stability may vary between manufacturers [82, 83]. The stability of MCT/soybean oil LEs may be due to the inclusion of shorter-chain lipids, which exhibit a lower free energy when dispersed in water, resulting in greater miscibility between phases and reduced physicochemical stress on emulsifying agents compared with LEs containing predominantly longer-chain triglycerides [83]. Olive-oil-rich LEs contain sodium oleate, which acts as an additional emulsifying agent and thereby augments stability [83]. In addition, the stability of PN formulations that contain LEs may be affected by interactions between FA and other commonly administered compounds, such as carnitine, heparin, and some vitamins [84–86].

Potential therapeutic roles for lipid emulsions

Lipid emulsions demonstrate different biologic effects depending upon their specific FA content, which may translate into beneficial effects for selected patients (Table 6). The biologic effects associated with LEs are likely to benefit a majority of patients receiving parenteral LEs, including those on long-term total PN, but may have the greatest importance for patients under metabolic stress. Therefore, physicians need to consider several issues when selecting an LE as part of a PN regimen.

All currently available LEs provide sufficient ω-6 and ω-3 EFA, with the exception of 100% fish oil LE, which should generally only be used as a pharmacological agent or as a supplement to other LEs [21, 22]. Although there are conflicting views regarding the comparative utility of different LE formulations in critically ill patients, there is growing consensus that LEs based entirely on soybean oil should be avoided in favor of emulsions in which the LA and ALA content is partially replaced by MCT, olive oil providing MUFA or fish oil providing EPA and DHA. This is particularly true for patients with highly proinflammatory states, such as surgical, trauma, burn, and septic patients [8, 87]. In addition, the clinical use of LEs should not exacerbate oxidative stress in critically ill patients. Unfortunately, evidence on the differential effects of LEs in critically ill patients remains limited. Furthermore, inconsistencies of findings between studies have suggested that the biologic effects of FA may vary with the medical condition and level of metabolic stress; therefore, further clinical trials exploring the effects of FA in different subpopulations of critically ill patients are highly desirable.

Table 6 Potential therapeutic applications of lipid emulsions

Cell function and proliferation
Provide sufficient fatty acids
Improve metabolism and limit/reverse energy deficit
Oxidative stress
Limit the contribution of lipid peroxidation to oxidative stress
Maintain or increase antioxidant concentrations
Intrinsic immune function
Support the immune system and limit immunosuppression
Reduce the incidence of infectious complications
Inflammation
Prevent/regulate hyperinflammation, especially important for patients with pre-existing inflammation (e.g., surgery, sepsis, chronic inflammatory diseases)

Conclusions

Energy deficit is a major problem among ICU patients and is associated with an increased incidence of complications, length of stay, and mortality. PN, either alone or in combination with EN, can improve caloric delivery to critically ill patients, preventing or correcting energy deficits and improving outcomes. Lipids are an important source of calories in artificial nutrition, and they have demonstrated a wide range of biologic activities that may benefit a variety of patients receiving PN, as well as those receiving EN with or without PN supplementation.

Parenteral lipid emulsions derived from soybean oil are the most extensively evaluated formulations in preclinical and clinical studies and have demonstrated efficacy and safety in delivering vital nutrition to critically ill patients. Newer LEs that utilize partial substitution of soybean oil with MCT, olive oil or fish oil either alone or in combination have demonstrated potential benefits in terms of reduced impacts on oxidative stress and differential effects on cell-mediated immunity and inflammation. However, few published studies have evaluated the biologic effects of newer parenteral LEs, and data assessing the clinical benefits of these newer formulations are limited and sometimes inconsistent because of the heterogeneity of the study designs and patient populations. Ongoing research to further characterize and compare the biologic properties of lipids given parenterally, as well as enterally, will be an important resource for physicians, especially those managing critically ill patients, who are often under metabolic stress. These studies must be adequately designed and well controlled. Until then, the prescription of LEs should be based upon the limited clinical data available, the range of available LEs, cost implications, and an understanding of the potential biologic effects of their components, bearing in mind the situation and therapeutic goals of the individual patient.

Acknowledgments Editorial assistance was provided by Kimberly Brooks, PhD, of MedErgy (Yardley, PA).

Conflict of interest statement The writing of this manuscript was financially supported by a grant from Baxter Healthcare, Deerfield, IL, USA to MedErgy, Yardley, PA. All authors were financially supported by Baxter Healthcare to attend a workshop on lipid emulsions held in May 2008 in Rome, Italy. P.C.C. has received speaking honoraria from B. Braun, Baxter Healthcare, Fresenius-Kabi, and Abbott Nutrition and has received research funding from B. Braun. B.V.K. has received speaking honoraria and research funding from B. Braun, Baxter Healthcare, and Fresenius-Kabi. P.S. has received speaking honoraria from Abbott Nutrition, Baxter Healthcare, and Fresenius-Kabi and research funding from B. Braun and Fresenius-Kabi. G.J.A.W. has received speaking honoraria from Baxter Healthcare and Fresenius-Kabi. G.L.J. has received speaking honoraria and/or consulting fees from Baxter Healthcare, Nestle Nutrition, and Abbott Nutrition.

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