Lipids in the Intensive Care Unit: Recommendations from the ESPEN Expert Group*

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Summary

This article summarizes the presentations given at an ESPEN Workshop on “Lipids in the ICU” held in Tel Aviv, Israel in November 2014 and subsequent discussions and updates. Lipids are an important component of enteral and parenteral nutrition support and provide essential fatty acids, a concentrated source of calories and building blocks for cell membranes. Whilst linoleic acid-rich vegetable oil-based enteral and parenteral nutrition is still widely used, newer lipid components such as medium-chain triglycerides and olive oil are safe and well tolerated. Fish oil (FO)-enriched enteral and parenteral nutrition appears to be well tolerated and confers additional clinical benefits, particularly in surgical patients, due to its anti-inflammatory and immune-modulating effects. Whilst the evidence base is not conclusive, there appears to be a potential for FO-enriched nutrition, particularly administered peri-operatively, to reduce the rate of complications and intensive care unit (ICU) and hospital stay in surgical ICU patients. The evidence for FO-enriched nutrition in non-surgical ICU patients is less clear regarding its clinical benefits and additional, well-designed large-scale clinical trials need to be conducted in this area. The ESPEN Expert Group supports the use of olive oil and FO in nutrition support in surgical and non-surgical ICU patients but considers that further research is required to provide a more robust evidence base.

1. Nutrition support of the critically ill patient

Patients in an intensive care unit (ICU) are heterogeneous and include surgical and medical patients, mechanically-ventilated or non-ventilated, obese or undernourished, preterm infants to older adults, requiring either short-term or long-term intensive care [1]. Nutrition support is critical in maintaining homeostasis in the ICU patient and to provide nutrients for the maintenance of lean body mass as well as repair and maintenance of organ function and support of defense and healing processes.

Enteral nutrition (EN) comprises specialized liquid nutrition delivered through a nasogastric or post-pyloric feeding tube into the stomach or small intestine (duodenum/jejunum), respectively [2]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend that EN should be given to all ICU patients who are not expected to be taking a full oral diet within three days [3].

Whilst ESPEN acknowledges that there are no definitive data supporting the early use of EN in terms of clinical outcomes, its guidelines recommend that hemodynamically stable critically ill patients who have a functioning gastrointestinal tract should be fed early (< 24 hours) using an appropriate amount of feed [3]. Early initiation of EN is also recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Canadian Society of Critical Care Medicine (SCCM) [4], as well as the European Society of Intensive Care Medicine (ESICM) [5]. Administration of early EN in critically ill patients appears to also have a positive economic impact, with analysis suggesting that it is associated with significantly reduced costs relating to reduction in ICU stay and duration of mechanical ventilation compared with standard care [6].

There are a number of nutritional and non-nutritional benefits associated with early EN feeding. These include the maintenance of lean body mass, gut integrity, mucosal associated lymphoid tissue and muscle function, together with attenuation of oxidative stress [7]. Studies performed

after the publishing of ESPEN guidelines have demonstrated positive clinical outcomes with early EN administration, such as reduction in duration of mechanical ventilation, reduction in length of ICU stay and higher survival rates in critically ill mechanically-ventilated patients, compared with. delayed EN administration [8,9]. Furthermore, two meta-analyses investigating early EN (< 24 h) in critically ill and trauma patients reported a significant mortality reduction versus standard care and a significant reduction in incidence of pneumonia [10,11].

The macronutrient content of several EN formulas used in clinical practice or in experimental studies is detailed in Table 1; it is evident that these differ greatly in content of macronutrients and in individual bioactive nutrients including glutamine, arginine and omega-3 fatty acids. Hence the metabolic, physiologic and clinical impact of different EN formulas will differ.

Parenteral nutrition (PN) is nutrition support provided through intravenous administration of nutrients such as amino acids, glucose, lipids (as emulsions), electrolytes, vitamins and trace elements. PN can be provided through a central venous line or through a peripheral intravenous line [12]. The ESPEN Guidelines for Parenteral Nutrition in Intensive Care recommend that all patients who are not expected to be on normal nutrition within 3 days should receive PN within 24 to 48 hours, if EN is contraindicated or if they cannot tolerate EN [13]. Furthermore, supplementary PN may also be initiated alongside EN in critically ill patients to help achieve energy and protein targets.

In terms of the safety of PN compared with EN in critically ill patients, whilst PN is associated with a lower mortality risk, particularly when compared to late EN, it has an increased risk of infectious complications [14,15]. Compared to standard care (oral diet when tolerated plus iv dextrose) in malnourished patients, EN appears to be associated with a lower risk of infection, whilst PN confers a lower risk of mortality as well as infection [16]. Supplemental PN may have clinical benefits in addition to reaching nutritional targets earlier, such as reduced risk of

nosocomial infections when initiated on days 4 - 8 alongside EN compared to EN alone [17]. However, a recent large scale multi-center randomized controlled study compared EN to PN and found no significant difference in mortality and infectious complications [18]

2. Lipids in enteral and parenteral nutrition

Lipids are used in enteral and parenteral nutrition primarily due to their high caloric content and are thus a good concentrated source of energy. As such, they lower the amount of carbohydrate that needs to be provided as part of the nutrition support. Lipids also provide the building blocks for cell membranes and provide essential fatty acids, thereby preventing essential fatty acid deficiency. The two essential essential fatty acids are the omega-6 (n-6) polyunsaturated fatty acid (PUFA) linoleic acid (LA) and the omega-3 (n-3) PUFA α-linolenic acid (ALA). In the body these may be converted to longer chain, more unsaturated derivatives that have important biological functions [19]. LA is the metabolic precursor of arachidonic acid (ARA) while ALA is the metabolic precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The absence of lipids in artificial nutrition support regimens can result in the onset of essential fatty acid deficiency, especially in preterm infants, where there is insufficient synthesis of the omega-3 fatty acid DHA and the omega-6 fatty acid ARA from their essential precursors [20]. Lipids also allow for delivery of fat soluble vitamins.

Lipids used in nutrition support contain fats primarily in the form of triglycerides, with either medium-chain fatty acids (caprylic, capric, lauric and myristic acids), long-chain fatty acids (palmitic, oleic, linoleic and α-linolenic acids) or very long chain fatty acids (EPA and DHA) [19]. Table 2 details the nomenclature and sources of fatty acids commonly used as a component of nutrition support. Triglycerides rich in medium-chain fatty acids have been termed medium-chain triglycerides or MCTs. Soybean oil (SO) which is rich in linoleic acid, has been termed

138 long-chain triglycerides or LCTs, although strictly speaking any triglyceride composed of long-
139 chain fatty acids is a LCT. Fatty acid chain length, and the presence, number and position of
140 double bonds affect physical, physiological and functional properties of the fatty acid [19].
141 Hence, different fatty acids can influence, in different ways, a number of different physiological
142 processes such as metabolism, inflammation, immune response, oxidative stress, blood
143 coagulation, organ function and wound healing [19].

144 The blend of lipids used in nutrition support has evolved over time. This is well illustrated by
145 considering the lipid emulsions (LEs) used in PN (Figure 1). The first generation of such LEs
146 consisted purely of SO, with the second generation LEs including MCTs and structured lipids
147 and the third generation beginning with the inclusion of olive oil (OO). Most recently third
148 generation LEs containing fish oil (FO) have been introduced. Current commercially available
149 LEs used in PN are detailed in Table 3 and include: pure SO; a 50:50 mixture of SO and MCTs
150 (SO/MCT); inter-esterified SO and MCTs; a 20:80 mixture of soybean and olive oils (SO/OO;
151 this is referred to herein as olive oil-based); a 40:50:10 mixture of SO, MCTs and FO
152 (SO/MCT/FO); a 30:30:25:15 mixture of SO, MCTs, olive oil and FO (SO/MCT/OO/FO); and
153 pure FO [21]. Additional components of lipid PN formulations include varying amounts of
154 phytosterols (cholesterol-like structures that are present in plant oils); α-tocopherol and other
155 fat-soluble bioactives, depending on the fat source; and phospholipids, usually
156 phosphatidylcholine (sometimes called lecithin), as an emulsifer.

157 The major physiological effects of the key fatty acids found in different lipids are summarized
158 elsewhere [19,22,23]. SO is a source of the essential omega-6 PUFA LA, which comprises
159 about 50% of the fatty acids present and is the metabolic precursor of ARA. SO also contains
160 some (~7% of fatty acids) of the essential omega-3 PUFA ALA. Because it is a precursor of
161 ARA, an excess of LA is considered to promote inflammation, immunosuppression, coagulation,
162 and fatty liver (hepatic steatosis) [24], although conclusive evidence for this is lacking. However,

it is clear that high amounts of LA do impair synthesis of the omega-3 PUFAs EPA and DHA [25].

MCTs, a source of medium-chain saturated fatty acids usually from coconut oil, are a good energy source whilst not affecting blood triglyceride levels. They are ketogenic and protein sparing, and are relatively resistant to peroxidation [26,27]. MCTs do not appear to impair liver, immune or lung function [26,27]. However, rapid infusion of such a lipid emulsion in patients suffering from acute respiratory distress syndrome resulted in a deterioration of lung function and hemodynamics [28].

OO, a source of oleic acid, is relatively neutral in its physiological effects, for example on immune function, inflammation and blood coagulation [29]. Because of its high content of monounsaturated fatty acids, OO is more resistant to peroxidation and oxidative stress than SO. Importantly, OO also preserves hepatobiliary function [30].

FO, a good source of EPA and DHA, is anti-inflammatory and may promote immune function and improve hepatic metabolism and liver function, including reversal of intestinal failure-induced fatty liver and cholestasis [19,23,31]. EPA and DHA also have anti-coagulation and anti-arrhythmic effects, and oppose the actions of omega-6 PUFAs [19,23]. However, being very long chain, highly unsaturated fatty acids, both EPA and DHA are prone to peroxidation.

Lipids provided in EN are subject to the normal intestinal processes of digestion and absorption, with the products appearing in the bloodstream as triglyceride components of chylomicrons. LEs in PN bypass intestinal processes and so may be metabolized differently from lipoproteins originating from the gut. Once infused, the LEs, comprising triglycerides stabilized with a shell of phospholipids, acquire endogenous apoproteins that enable binding to and activation of lipoprotein lipase [32]. The structure of LEs (i.e., their fatty acid composition) appears to affect their rate of plasma clearance and hence tissue uptake. Animal studies have demonstrated that synthetic triglycerides comprising two medium chain and one long chain fatty acid clear faster

than either MCTs or LCTs alone [33,34], an effect which is also observed in humans [35]. The addition of FO to an SO/MCT emulsion (SO:MCT:FO 40:50:10) resulted in faster plasma clearance than SO/MCT in both mice and humans [36,37].

The hydrolysis of circulating triglycerides arising from either enteral or parenteral lipid, yields free fatty acids that may enter adjacent tissues or remain in the circulation. The essential omega-3 PUFA ALA is not well incorporated into membrane phospholipids. However, the essential omega-6 PUFA LA, its metabolite ARA, and the metabolites of ALA EPA and DHA are incorporated into cell membrane phospholipids and into membrane lipid raft regions, thereby affecting the structure and function of membrane-bound proteins [19,21]. Thus these different PUFAs play a key role in cell membrane structure and function, regulation of gene expression and cell signaling pathways involved in apoptosis, metabolism, inflammation, cell-mediated immunity, blood clotting and organ function as well as synthesis of bioactive lipid mediators such as eicosanoids and docosanoids [19,21,22]. Eicosanoids are signaling molecules synthesized from 20-carbon PUFAs and include the prostaglandins (PGs), thromoboxanes (TXs) and leukotrienes (LTs) produced from ARA and EPA. Lipoxins produced from ARA and resolvins produced from EPA are also eicosanoids. Docosanoids are signaling molecules synthesized from 22-carbon PUFAs and include the resolvins, protections and maresins produced from DHA.

Once incorporated into cell membranes, the metabolism of omega-6 and omega-3 PUFAs results in the production of eicosanoids and docosanoids that have differing roles in inflammation and immune response, platelet aggregation smooth-muscle contraction and so on [19]. The omega-6 PUFA ARA is metabolized to pro-inflammatory lipid mediators such as the 2-series PGs and TXs and the 4-series LTs [38,39]. It also gives rise to anti-inflammatory and inflammation resolving lipoxins [40]. Preclinical studies have highlighted the importance of lipid mediators produced from ARA in sepsis. Direct inhibition of cyclooxygenase-2 and 5-

lipoxygenase, enzymes involved in the synthesis of ARA-derived pro-inflammatory mediators (PGs, TXs, LTs), results in increased lipoxins which attenuate the inflammatory response and protect from sepsis [41]. Furthermore, administration of ARA-derived lipoxin A_4 in a mouse model of sepsis increased survival through reduction of systemic inflammation and blood bacterial load [42]. The omega-3 PUFAs EPA and DHA compete with ARA and result in synthesis of weaker pro-inflammatory 3-series PGs and TXs and 5-series LTs [43]. EPA and DHA also give rise to resolvins (both EPA and DHA), protectins and maresins (DHA only), which play a key role in resolution of inflammation, reduction of tissue injury and promotion of wound healing [44]. Resolvins reduce the inflammatory response via decreasing neutrophil invasion, reduction of synthesis of pro-inflammatory cytokines via inhibition of NF-kB, recruitment of monocytes, increased phagocytosis of apoptotic neutrophils and facilitation of removal of macrophages via the lymphatic system [44,45]. Rodent models have demonstrated that the inflammation-resolving effect of DHA-derived resolvin D2 is associated with increased survival in bacterial sepsis [46]. Resolvin D2 was able to decrease local and systemic bacterial burden, excessive cytokine production and neutrophil recruitment, whilst increasing macrophage phagocytosis [46]. EPA and DHA also exert an anti-inflammatory effect acting through other mechanistic pathways, including suppression of nuclear factor kappa B signaling via activation of the cell surface GPR120 protein and the intracellular receptor peroxisome proliferator activated receptor γ, and thus inhibition of production of a range of pro-inflammatory cytokines, adhesion molecules, cyclooxygease-2, inducible nitric oxide synthase and matrix metalloproteinases [19,43].

It is evident from the forgoing discussion that individual fatty acids have unique functional properties and that different members of the same fatty acid family (saturated, omega-6, omega-3) do not share the same properties [19]. For this reason, it is important that discussion of the role of the fatty acid composition of lipids to be used in nutritional support of patients in

238 the ICU (or elsewhere) should focus on individual fatty acids rather than on fatty acid families.
239 Therefore, discussion of compositional properties such as the omega-6 to omega-3 ratio is not
240 valuable. This is because this ratio can be altered in many different ways that may not have the
241 same functional or clinical impact. For example, the omega-3 fatty acid component may be
242 altered by using more ALA or by using more EPA+DHA and the outcome from those two
243 scenarios is likely to be different. This is discussed further elsewhere [47,48].

244

245 ## 3. Fish oil-enriched EN in critically ill patients

246 ESPEN guidelines state that an immune-modulating EN formula enriched with arginine,
247 nucleotides and omega-3 fatty acids is superior to standard enteral formula in certain groups of
248 patients, i.e. upper gastrointestinal surgical patients, trauma patients and patients with mild
249 sepsis [3]. No benefit has been established in patients with severe sepsis, in whom an immune-
250 modulating formula may be harmful and is therefore not recommended [3]. ASPEN and SCCM
251 have previously issued similar guidelines [4], but these have been modified recently and
252 suggest that immune-modulating enteral formulations (containing arginine with other agents,
253 including omega-3 fatty acids, glutamine and nucleic acids) should not be used routinely in the
254 medical ICU [49]. Consideration for these formulations should be reserved for patients with
255 traumatic brain injury and perioperative patients in the surgical ICU [49].

256 Regarding critically ill patients with acute respiratory distress syndrome (ARDS) and severe
257 acute lung injury (ALI), ESPEN guidelines state that such patients should receive an enteral
258 formulation characterized by an anti-inflammatory lipid profile (i.e. omega-3 rich FO, borage oil)
259 and antioxidants [3], a guideline previously supported by ASPEN and SCCM [4]. However, in
260 2013, the Canadian Clinical Practice Guidelines reviewed new study data investigating the
261 effect of such EN formulas in critically ill patients with ALI/ARDS and downgraded the

recommendation to “should be considered” from “recommended” due to a diminished effect on mortality risk [50]. Furthermore, ASPEN in 2016 decided not to make any recommendation in this area [49]. Details of the studies discussed in the following sections may be found in Table 4.

3.1 ALI/ARDS

ARDS is characterized by diffuse pulmonary inflammation, increased vascular permeability and oedema [51,52]. Whilst a previous definition separated ALI from ARDS as a non-severe form (old definition [53]) and the term is still used in preclinical models, ALI is now defined as mild ARDS (Berlin Definition). Evidence from preclinical models of ALI/ARDS suggests that nutritional supplementation of EN with omega-3 fatty acids may improve vascular leakage, pulmonary inflammation and improve gas exchange and oxygenation [54,55].

Several clinical studies in patients with ALI/ARDS have shown that continuously-administered EN enriched with EPA, DHA, γ-linolenic acid (GLA, an omega-6 fatty acid present in borage oil) and anti-oxidants, resulted in improved oxygenation [56–59] and reduced duration of ventilation [56–58], decreased new organ failure [56,58,59] and shortened ICU stay [56,58–60] compared with standard EN. There is little evidence supporting the use of this formulation in mortality reduction in this patient population, apart from one study in patients with ARDS secondary to sepsis [58].

In contrast to these positive findings, two studies that utilized bolus administration of enteral FO in patients with ALI, found no clinical benefit compared with standard EN [61,62], with one trial being stopped early due to futility and reporting fewer ventilator- and ICU-free days, and a non-significant increase in the 60-day mortality in the FO group [61]. Compared to continuous administration, bolus delivery may not not enable sufficient incorporation of EPA and DHA into cell membranes, which may have played a role in these negative findings. Furthermore, in one trial, whilst underfeeding occurred in both intervention and control groups, a five-fold higher

protein intake was reported in the control group, which is likely also to have contributed to the lack of effect seen in the study group [61,63].

A meta-analysis of 955 patients with ARDS/ALI concluded that FO-enriched EN had no effect on 28-day mortality [64]. However, a sensitivity analysis demonstrated that, on exclusion of the two studies delivering a bolus of FO, there is evidence that supports the use of continuous administration of EN containing FO in decreasing mortality in critically ill patients, including patients with ALI/ARDS [65]. However, ASPEN decided to make no recommendation at this time regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (i.e. omega-3 rich FO, borage oil and antioxidants) in patients with ARDS and severe ALI, given the conflicting data [49].

3.2 Sepsis

Sepsis is associated with a hyper-inflammatory response which directly and indirectly causes widespread tissue damage, through the release of pro-inflammatory mediators, proteases and oxidants from activated macrophages, as well as vasodilators such as nitric oxide, which acts as a key mediator in septic shock [66,67].

Whilst no definitive study demonstrates that the use of EN enriched with omega-3 fatty acids results in improved outcomes for critically ill patients with sepsis, there does appear to be clinical benefit when administered in early-stage sepsis. Specifically, in patients without any sepsis-associated organ failure, administration of FO-enriched EN resulted in reduction in the progression of sepsis as well as in respiratory and cardiac failure and a reduced length of ICU stay compared with a lower lipid-containing EN [68].

3.3 Major abdominal surgery

There is evidence supporting the use of FO-enriched EN in major abdominal surgery. Peri-operative administration of EN containing arginine, omega-3 fatty acids and RNA was reported to reduce post-operative complications and hospital length of stay in malnourished cancer patients undergoing major abdominal surgery versus standard post-operative EN [69]. Furthermore, immune-modulating EN (containing omega-3 fatty acids, arginine and glutamine) administered post-operatively to malnourished patients undergoing resection for pancreatic/gastric cancer resulted in a shorter hospital stay, fewer infectious complications and reduced morbidity and mortality compared to post-operative standard oligopeptide EN [70].

3.4 Severe trauma

There are few studies assessing the effect of FO-enriched EN specifically on trauma patients. One study administered pre-emptively FO-enriched EN (containing EPA, DHA, GLA and anti-oxidants) to severe trauma patients to assess its effect on the development of respiratory complications, but found no difference in the level of oxygenation (PaO_2/FiO_2 ratio), incidence of ARDS/ALI, duration of ventilation, length of ICU stay or 28-day mortality compared with a high fat/low carbohydrate EN formulation [71]. However, whilst red blood cell EPA, GLA and omega-3 index (the sum of EPA plus DHA) increased significantly in the study group, the optimal omega-3 index required for clinical efficacy failed to be reached, and this may have contributed to the study's negative findings. This raises the importance of omega-3 fatty acid baseline measurement in ICU patients, to determine the extent of incorporation during supplementation; ultimately such measurements could be used as a predictor of therapeutic efficacy [72].

3.5 Benefit versus harm of immune-modulating EN in ICU patients

The ESPEN guidelines recommend the use of FO-enriched EN in subgroups of critically ill patients and there are a number of studies (discussed above) that show clinical benefit of such EN. However, a recent study has raised questions concerning the benefit and harm of immune-

modulating EN. Van Zanten et al. conducted a multi-centre trial in 301 mechanically ventilated critically ill patients, and found that high protein EN enriched with immune-modulating nutrients (glutamine, omega-3 PUFAs, selenium and anti-oxidants) had no effect on infections and other clinical endpoints (mortality, organ failure, duration of mechanical ventilation, length of stay) compared with standard high protein EN [73]. The study population comprised medical, surgical and trauma ICU patients. Sub-group analysis found that medical ICU patients had increased 6-month mortality rates in the enriched EN group suggesting that in this particular medical population, immune modulating EN should not be used. Specifically, these results, together with the increased mortality observed in the REDOXS trial [74] raise concerns over the safety of the glutamine component of the enteral feed in certain ICU patients.

4. Clinical and biochemical effects of different lipid emulsions in PN used in critically ill patients

ESPEN guidelines recommend that lipids should be an essential part of PN for energy and to ensure essential fatty acid provision, and that intravenous LEs can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 h [13]. However, the choice of lipid used in PN may have an effect on clinical outcomes in the critically ill patient.

4.1 Soybean oil-based lipid emulsions

As discussed in Section 2, pure SO may have a number of less desirable effects on physiological processes, such as promoting inflammation and suppressing immune function due to its high LA content, and a tendency for peroxidation due to its relatively low α-tocopherol content. Pure SO has also been associated with a number of complications including hyperbilirubinemia and intestinal failure associated liver disease (IFALD). SO intake may

355 increase the lung flow of lymph and pulmonary pressure, and decrease the partial pressure of
356 oxygen in arterial blood (PaO_2) resulting in respiratory acidosis, and modify lipid metabolism
357 when compared to second and third generation lipids [75,76].

358 There is evidence that SO-based PN might exacerbate the post-surgical inflammatory response
359 in gastrointestinal surgery patients with severe surgical-related stress, and impair immune
360 function when compared to standard glucose-containing PN [77]. The pro-inflammatory effect of
361 the SO emulsion was not so pronounced in patients with moderate surgery-related stress. An
362 immunosuppressive effect was also seen in polytrauma patients receiving early SO-containing
363 PN, which was associated with higher rates of infection, reduced T cell function and lowered
364 natural killer cell activity [78]. This was linked to longer duration of mechanical ventilation and
365 longer ICU and hospital stay, compared to standard glucose-containing PN [78]. However,
366 neither of these studies examined the impact of other lipids to which the effects of SO could be
367 compared.

368 The accumulating evidence base has resulted in a recommendation from the German Society
369 for Nutritional Medicine (DGEM) that pure SO LEs should no longer be used in PN support of
370 critically ill patients [79]. DGEM will further refine its recommendation in its updated guidelines
371 and will advise that ICU patients should receive second or third generation LEs with reduced
372 content of omega-6 fatty acids (M. Adolph and K. Mayer, personal communication; [80]).
373 ASPEN suggest withholding SO-based LEs during the first week following initiation of PN in the
374 critically ill patient or limiting this to a maximum of 100 g/wk (often divided into 2 doses/wk) if
375 there is concern about essential fatty acid deficiency [49].

376 **4.2 Olive oil-based lipid emulsions**

377 OO-based LEs appear to be a safe alternative to pure SO-based LEs, which is reflected in the
378 ESPEN guidance that OO-based PN is well tolerated in critically ill patients [13]. Using OO-

based PN in adult surgical patients results in better fatty acid status, increased blood vitamin E concentration, decreased lipid peroxidation and decreased inflammatory variables [81–83]. However, the evidence base for the potential for OO-based LEs to improve clinical outcomes is not consistent. In surgical ICU patients administered OO-based PN for up to 28 days post-surgery, there was no difference in glycemic control, immune function, or inflammatory or oxidative stress markers compared to SO-based PN [84]. Mortality rate, incidence of nosocomial infections and acute renal failure, as well as length of stay, were all reported to be similar between the two groups. Mateu-de Antonio et al. also found no difference in the number or type of infections, length of ICU or hospital stay or mortality following an average duration of 19 days of post-operative OO-based PN compared to SO in surgical ICU patients [85].

4.3 SO/MCT-based lipid emulsions

There is good evidence that supports the use of SO/MCT LEs instead of pure SO in critically ill patients. A study in severely malnourished surgical patients receiving peri-operative total PN reported a significantly lower incidence of intra-abdominal abscesses with SO/MCT versus SO [86]. There was no reported difference in other infection rates or mortality. SO/MCT is also associated with a shorter period of mechanical ventilation in critically ill patients with COPD compared to SO [87].

4.4 Fish oil-containing lipid emulsions

ESPEN guidelines state that addition of EPA and DHA to LEs has demonstrable effects on cell membranes and inflammatory processes, and that FO-enriched lipid emulsions probably decrease length of stay in critically ill patients [13]. DGEM will also state that specific LEs enriched with omega-3 fatty acids may be considered for administration in critically ill patients (M. Adolph and K. Mayer, personal communication). There have been a number of studies

investigating the effect of FO-enriched PN in critically ill patients (see Tables 5, 6 and 7 for more details about the studies included in the following sections).

4.4.1 Fish oil-enriched PN in surgical ICU patients

Administration of FO-enriched PN in patients undergoing major surgical procedures appears to be effective in lowering the post-operative inflammatory response. For example, suppression of the pro-inflammatory cytokine IL-6 was reported following parenteral FO administration in elderly patients undergoing hip surgery compared to the absence of intravenous FO administration [88]. Furthermore, perioperative infusion of FO in cardiac surgery patients significantly increased platelet EPA and DHA and atrial tissue EPA together with a decrease in IL-6 concentrations, with no adverse effects reported compared with the saline control [89]. Compared to SO, perioperative FO-enriched PN in surgical ICU patients decreased post-operative serum IL-6 and whole blood tumor necrosis factor (TNF)-α production, and increased monocyte expression of human leukocyte antigen-DR (a marker of immune competence) [90]. This effect was associated with a shorter hospital stay in the FO-enriched PN group, but there was no difference in infection rate or mortality. Administration of FO-enriched PN (FO + SO) for 7 d post-gastrointestinal surgery resulted in significantly fewer incidences of systemic inflammatory response syndrome (SIRS) and significantly shorter hospital stay compared with SO alone [91]. There was also a trend towards fewer infectious complications in the FO-enriched PN group. Similar results were reported for short-term (3 d) pre-operative infusion of FO alone in gastrointestinal cancer patients awaiting surgery [92]. Administration of FO improved the post-operative immune response (decreased interleukin (IL)-6 and IL-10, decreased leukocyte oxidative burst, maintenance of monocyte percentage expressing human leukocyte antigen-DR and CD32, and increased neutrophil CD32 expression) but had no effect on post-operative infections or length of ICU or hospital stay [92].

There is also evidence supporting the post-operative administration of FO-containing PN in gastric surgery patients in improving post-surgical immune competence, lowering infection rate and shortening hospital stay. In elderly patients following colorectal cancer surgery, administration of PN containing FO + SO for 7 d resulted in lowered levels of IL-6 and TNF-α and fewer CD8 positive cells in the bloodstream, fewer infectious complications and incidences of SIRS, and shorter length of hospital stay compared with SO alone [93]. Furthermore, a study in gastric carcinoma patients undergoing major abdominal surgery reported that post-operative PN enriched with FO resulted in fewer infectious complications and a shorter hospital stay compared with standard PN [94]. A reduced infection rate was also found in gastrointestinal surgery patients following 5 days of post-operative PN containing OO/SO enriched with FO compared to OO/SO alone [95], whilst another study found a shorter length of hospital stay was associated with FO-enriched SO/MCT compared to SO alone in gastrointestinal surgery patients [96]. Decreased length of hospital stay was found to be associated with 5 days of post-operative administration of SO/MCT/OO/FO-containing PN compared to SO-based PN in gastrointestinal surgery patients [97]. Furthermore, in liver transplantation patients, FO-enriched PN given for 7 days post-surgery resulted in a decreased length of hospital stay compared to SO/MCT [98]. Perioperative administration of FO-enriched PN in surgical patients appears to have a beneficial effect on clinical outcomes as suggested by Heidt et al. from a study in coronary artery bypass graft patients which resulted in a shortened ICU stay compared to SO-based PN [99] and Tsekos et al.'s study in gastrointestinal surgery patients which resulted in decreased mortality, decreased requirement for mechanical ventilation and decreased hospital stay compared to SO/MCT-containing PN [100].

These findings are supported by a meta-analysis of 23 studies including 1,502 surgical and ICU patients which investigated the effects of FO-enriched PN compared with other LEs (SO, SO/MCT, OO/SO) on various clinical outcomes [101]. Whilst the authors found no effect on

mortality, FO-enriched PN resulted in a clinically and statistically significant reductions in infection rate and in length of ICU and hospital stay. A smaller meta-analysis of 7 RCTs also concluded that post-operative administration of FO-enriched PN in major abdominal surgery patients has a beneficial effect on post-operative infection rates and length of ICU and hospital stay [102]. Furthermore, a meta-analysis of five trials performed by Manzanares et al. found that FO administered either parenterally or enterally resulted in a non-statistically significant trend towards reduced duration of mechanical ventilation [103].

In addition to its positive effects on inflammation and immune function, FO-enriched PN may help to preserve liver function in critically ill surgical patients. Decreased total bilirubin as well as serum IL-6, TNF-α and nuclear factor kappa B was reported in gastrointestinal surgical patients following post-operative administration of FO-enriched PN compared with SO/MCT [104]. Rates of infectious complications and SIRS were comparable between the two groups. A similar study also utilizing FO-enriched PN versus SO/MCT in post-operative patients, found similar results, although statistical significance was not reached for the reductions in liver dysfunction, infection rate and serum pro-inflammatory cytokines [105]. In comparison with pure SO, FO/SO (20:80) administered post-operatively to major abdominal surgery patients resulted in significantly decreased markers of liver dysfunction (ALT and AST), bilirubin and lipase [106]. Weight was maintained in the FO-enriched PN group, as well as a tendency towards shorter ICU stay in those patients at risk of sepsis [106]. Hence FO-enriched PN improved liver and pancreas function in this patient population, and may have been a factor in reducing ICU stay for patients at risk of sepsis. The newer composite SO/MCT/OO/FO (30:30:25:15) LE has also shown a liver-protecting effect in post-operative patients requiring PN, resulting in significantly lower ALT, AST and α-GST compared with OO/SO [107].

This liver-protective effect has also been demonstrated in liver transplantation patients, whereby post-operative FO-enriched PN lowered ALT and prothrombin time as well as length of hospital

476 stay compared with PN containing SO/MCT [98]. Improvement in liver injury and a reduction in
477 the number of infectious morbidities was also reported for the FO-enriched PN group.

478 It is important to note that not all clinical studies in surgical ICU patients have been positive.
479 Parenteral SO/MCT/OO/FO administered to gastric cancer surgical patients resulted in no
480 difference in efficacy, safety, tolerance or clinical outcomes (including post-operative
481 complications) compared with SO/MCT [108]. Metry et al. also found no difference in ventilation
482 requirement, duration of ICU or hospital stay or mortality following 7 days of post-operative
483 administration of parenteral SO/MCT/OO/FO compared to SO alone [109]. Furthermore, Wu et
484 al.'s study in gastrointestinal surgery patients found no difference in inflammatory markers (C-
485 reactive protein, IL-6, IL-10, TNF-α and transforming growth factor β1) or markers of oxidative
486 stress compared with SO/MCT [110].

487 A meta-analysis of 6 RCTs (306 surgical patients) did conclude that SO/MCT/OO/FO was
488 associated with lower hepatic enzymes, low-density lipoprotein, triglycerides and C-reactive
489 protein following post-operative administration compared with SO, but found no statistically
490 significant changes compared with SO/MCT [111]. There was no difference in adverse events or
491 length of hospital stay compared with either SO or SO/MCT.

492 Eicosanoids are involved in the control of platelet aggregation and so influence blood clotting
493 and bleeding time. TXA_2 and prostacyclin (PGI_2) are both produced from the omega-6 PUFA
494 ARA. TXA_2 is pro-aggregatory and PGI_2 is anti-aggregatory. EPA from FO decreases the ARA
495 content of the platelet membrane [112], so decreasing production of both TXA_2 and PGI_2 [112].
496 Instead, production of the EPA-derived eicosanoids TXA_3, which is a weak platelet aggregator,
497 and PGI_3 which is a potent inhibitor of platelet aggregation occurs [112]. Thus, FO results in
498 decreased platelet aggregation [112], which can increase bleeding and time to clotting. With
499 regard to this theoretical increased risk of bleeding with FO-based PN, studies to date have

shown that FO is safe to include in PN regimens and does not increase risk of bleeding. Acute pretreatment with omega-3 PUFAs in coronary artery bypass graft patients non-significantly affected the activity of platelets and did not influence postoperative blood loss [113].

Based on the evidence available and according to the new ESPEN guidelines on clinical nutrition in surgery, postoperative PN including omega-3-fatty acids should be started only in malnourished patients who cannot be adequately fed enterally and, therefore, require PN [114]. If PN is required post-operatively in the ICU, 2nd or 3rd generation lipid emulsions may be administered, and in the case of surgical complications, FO-containing PN is recommended.

4.4.2 Fish oil-enriched PN in non-surgical ICU patients

Compared to SO and SO/MCT, FO-enriched PN may provide clinical benefits for a wide range of ICU patients. In mechanically ventilated critically ill patients, FO-enriched PN resulted in a shorter duration of mechanical ventilation and a faster time to ICU discharge compared to lipid-free or SO-based PN [115]. In patients with acute pancreatitis, administration of FO-supplemented PN resulted in significantly decreased CRP in addition to better oxygenation index and fewer days of continuous renal replacement therapy compared with SO alone [116].

Clinical studies in patients with sepsis have shown that parenteral administration of either omega-6 or omega-3 fatty acids results in elevated concentrations of the respective free fatty acids several-fold, as well as appearance of the respective eicosanoids [117]. Hence PN containing FO should theoretically lead to increased levels of inflammation-resolving resolvins and associated clinical benefits. The latter is supported by some trials. Compared to standard care, FO administered to patients with sepsis resulted in a significant reduction in new organ dysfunction and lower maximum C-reactive protein concentrations [118]. A significant reduction in mortality was observed for patients with less severe sepsis. Furthermore, FO-enriched PN (SO/MCT/FO 50:40:10) administered to patients with sepsis or SIRS for 5 days increased

plasma EPA levels, decreased plasma IL-6, improved oxygenation (PO_2/FiO_2 ratio) and reduced length of hospital stay compared to SO/MCT [119]. However, several studies have failed to show any clinical benefit of FO-enriched PN in cases of sepsis or septic shock compared to either standard care, saline or SO-based PN [117,120–122], although one of these studies did find a non-statistically significant trend towards shorter ventilation time [117].

FO-enriched PN administered to critically ill medical and surgical patients may result in a significant reduction in the number of nosocomial infections compared to SO/MCT [123]. Time free of infection was also significantly longer in the FO-supplemented group, although there was no effect reported for ICU or hospital stay or 6-month mortality rate.

This lack of effect of FO-enriched PN on mortality rate compared to standard PN is confirmed by meta-analyses of 6 RCTs [124] and of 8 RCTs [125] in critically ill adults, the latter also finding no difference in infectious complications or ICU length of stay. There was weak evidence of a reduction of hospital length of stay associated with FO-enriched PN, but this was strongly influenced by one small study [125].

Not all trials investigating the use of FO-enriched PN in critically ill patients report positive outcomes. Administration of FO-enriched PN to medical ICU patients (with and without SIRS) had no effect on inflammatory markers (IL-6), incidence of infection, duration of mechanical ventilation, length of ICU stay or 28-day mortality compared with SO/MCT [126]. The study included severely ill patients that were at different stages of the inflammation/inflammation resolution cycle; hence the intervention may have been administered after termination of the initial inflammatory process in some patients. Timing of omega-3 fatty acid administration is important if hyper-inflammation is to be prevented, and from previously discussed studies, administration prior to commencement of inflammation is likely optimal. Furthermore, dosage levels of the administered FO also play a critical role in whether the intervention provides clinical

benefit. A study investigating the dose-dependent effects of FO-enriched PN in a range of ICU patients found that the most favorable effects on survival, infection rates and length of hospital stay occurred when parenteral FO was administered between 0.1 and 0.2 g/kg/d. A 26% lower antibiotic demand was associated with parenteral administration of FO between 0.15 and 0.20 g/kg/d [127].

5. Lipids and PN in pediatric patients

The joint European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and ESPEN guidelines on PN in pediatrics recommend that in small preterm infants, when EN is not possible, PN including lipids should be initiated as soon as possible after birth [128]. Intolerance to full EN is common in preterm infants, and results in a high incidence of postnatal growth failure.

Surveys of current practice in neonatal ICUs in Europe and the US show that there is a wide range in the timing and initial dose of lipid administration [129]. In the UK and Ireland, whilst a greater proportion of preterm infants start PN within 48 h, around one quarter of preterm infants still are not given PN until or after day 3 [130]. When considering a role for PN and lipids in preterm infants, the potential to improve neurodevelopmental outcomes should not be overlooked: DHA is critical in neurodevelopment with the brain comprising 60% of lipid, and with > 80% of brain DHA accumulating between 26-40 weeks gestation [131].

In preterm infants, there is concern regarding early lipid-containing PN and the risk of complications such as sepsis, bronchopulmonary dysplasia (BPD), hyperbilirubinemia, liver disease, persistent pulmonary hypertension of the newborn (PPHN) and thrombocytopenia. However, a meta-analysis of 14 studies investigating the effect of early (≤ 2 d) parenteral lipid in very low birth weight (VLBW) infants, found no difference in sepsis, BPD, growth or mortality rates compared to later (≥ 2 d) administration [132]. This is supported by a later RCT comparing

lipid-containing PN administered from birth to VLBW infants with standard PN from birth with lipids administered 2 d later, which reported no difference in growth, biochemical or clinical outcomes between the groups [133,134].

There is also a risk of hypertriglyceridemia associated with lipid administration in preterm infants, due to limited fat and muscle mass and thus decreased hydrolytic capacity from lipoprotein lipase. Whilst there is no specific indicator of lipid tolerance, as plasma triglyceride levels indicate plasma clearance, monitoring of plasma triglycerides is recommended. ESPGHAN recommends a safe triglyceride level of 2.85 mmol/l (250 mg/dl) in preterm infants and newborns [128], whilst ASPEN recommends 2.26 mmol/l (200 mg/dl) [135]. However, in one trial, hypertriglyceridemia of >3 mmol/l (>265 mg/dl) was not associated with neonatal morbidities [133].

IFALD is associated with chronic (>14 d) total PN (TPN), and incidence is directly related to TPN duration. Short bowel syndrome (SBS) accounts for 1.4% of all deaths for children under 4 y and is primarily related to the development of IFALD which is identified through biochemical parameters such as direct bilirubin levels >2 mg/dl (34 μmol/l), increased GGT, ALT, and serum bile acids [136,137]. Some 40-60% of patients with short bowel syndrome on TPN develop cholestasis, and a study published in 2005 reported that the mortality rate is approximately 78% if bilirubin remains > 3 mg/dl for 3 months, and increases to 90% if cholestasis is diagnosed and there is no weaning off TPN within a year of diagnosis, or failure to receive a liver transplant [138]. A Pediatric Intestinal Failure Consortium (PIFCon) retrospective analysis of clinical outcome data for infants with intestinal failure reported that of a cohort of 272 infants (< 1 y old and on prolonged TPN for > 2 months), the mortality rate was 27% and intestinal transplantation rate was 26% [139].

595 Besides prematurity and prolonged TPN use, other risk factors for IFALD include lack of enteral
596 nutrition, multiple operative procedures, sepsis or inflammation, and possibly also nutrient
597 deficiencies or toxicities associated with other components in lipid PN [140,141].
598 Preventative/treatment measures for IFALD may include cycling PN, feed advancement,
599 prevention and aggressive treatment of sepsis, lipid reduction to ≤ 1 g/kg/d, altering the lipid
600 being used in PN (see below), elimination of hepatotoxic medications, reduction of bacterial
601 overgrowth, use of the bile acid ursodiol, reduction of transfusions and minimizing surgical
602 procedures if possible [137,142–151], although the evidence in favour of some of these is weak
603 [152]. Whilst IFALD/cholestasis may be reversed with elimination/reduction of lipids, cholestasis
604 may be progressive whilst on PN. It may lead to liver cirrhosis, liver failure, liver transplant or
605 death [153].

606 Regarding the choice of LE in PN for pediatric patients, it is suggested that high levels of
607 omega-6 PUFAs and phytosterols found in SO can be hepatotoxic and lead to IFALD [154].
608 Phytosterols have been shown to antagonize the farnesoid-X-receptor (FXR) [155] which
609 normally acts to suppress hepatic lipogenesis and bile acid synthesis. Thus, in the presence of
610 phytosterols, those processes continue uncontrolled leading to both fatty liver and cholestasis.
611 FO-containing PN may have a protective effect against IFALD due to the lower phytosterol
612 content, higher omega-3 PUFA content, and higher α-tocopherol content, and to direct
613 regulation of bile flow through eicosanoid-mediated mechanisms [156]. In pediatric patients with
614 IFALD whose cholestasis was resolved with use of FO, decreased direct bilirubin levels and
615 markers of liver injury were reported together with improvement in hepatic function [156,157].
616 However, some of these studies compared a group of infants receiving FO-based PN with an
617 historic control group. Furthermore, some studies used pure FO LE rather than a lipid mix.
618 Finally, many studies have lowered the lipid dose being used (generally to 1 g/kg/d) at the same

time as introducing FO-containing PN. Thus, it is difficult to disentangle the effects of the lower lipid dose from those of an alternative lipid mixture.

With regard to other potential clinical benefits of FO-enriched PN in preterm infants, an RCT in VLBW infants administered SO/MCT/OO/FO reported a significant increase in weight gain and increased plasma EPA and DHA (but no difference in ARA) compared to SO-based PN [134,158]. However, there were no differences in morbidity, mortality or biochemical outcomes between the two groups. Several studies concur regarding these outcomes with multi-component lipid PN versus other LEs [158–164].

FO-enriched PN given to infants undergoing major cardiac surgery may help ameliorate the post-operative inflammatory response. A study investigating the effects of parenteral SO/MCT/FO (40:50:10) given pre- and post-operatively to infants undergoing open heart surgery reported a lower inflammatory response post-surgery compared with SO alone [165]. Specifically the FO containing LE resulted in higher plasma phospholipid EPA and decreased plasma LTB_4 and lymphocytes. An earlier trial also found significantly lower TNF-α concentrations and a positive association with length of hospital stay in the SO/MCT/FO group compared with SO when given perioperatively in infants undergoing cardiac surgery [166].

In summary, for preterm infants, lipids given directly following birth at 2 g/kg/d appear safe according to short term studies. Emulsions with a mix of lipid sources including FO may offer benefits over SO alone, although long-lasting positive effects need to be proven.

6. Economic considerations for fish oil-enriched lipids in the ICU

Pradelli et al. performed an analysis of the cost-effectiveness of SO/MCT/OO/FO in surgical and ICU patients in four European countries (Italy, Germany, France and the UK) [167]. The

642 analysis considered costs associated with nutritional treatment, ICU stay, general ward stay and
643 nosocomial infections as well as the benefits of FO-containing PN on infection rates and length
644 of stay. The study concluded that the treatment costs associated with FO-enriched PN were
645 completely offset by the savings made from the subsequent reduction in hospital stay and
646 reduced antibiotic costs. Hence, FO-containing PN is cost-effective and beneficial for both ICU
647 and non-ICU patients in hospitals in Italy, Germany, France and the UK compared with standard
648 PN.

649 **7. Future directions**

650 **7.1 Effects of omega-3 fatty acids in preclinical models of acute neurological injury**

651 Spinal cord injury (SCI) is associated with significant social and healthcare burden [168]. In the
652 acute phase following SCI, the initial lesion expands and results in a secondary injury wave,
653 reflected in the progressive loss of grey matter within the spinal cord [169,170]. Secondary
654 injury pathophysiology is characterized by activation of inflammatory pathways, increased
655 glutamate release and vascular damage leading to ischaemia [171]. Preclinical studies involving
656 rodent compression and hemisection SCI models, at thoracic and cervical levels, have
657 demonstrated that acute DHA injection in the range of 250–500 nmol/kg body weight, with or
658 without sustained dietary supplementation, has a neuroprotective effect and improves
659 neurological outcomes [172–177]. Specifically, DHA administration results in a reduced lesion
660 size and less inflammation (including TNF-α expression), reduced neuronal, oligodendrocyte
661 and neurofilament loss, reduced macrophage/microglia recruitment and activation, and less
662 apoptotic death, and this is correlated with an improved locomotor recovery [172–176]. DHA
663 appears to enhance motor function recovery via its effect on the serotonin fiber input on motor
664 neurons [177]. DHA also has a positive effect on synaptic remodeling and may enhance
665 synaptogenesis. Immunoreactivity of synaptophysin, a synaptic vesicle protein, was found to be

666 less reduced after injury in DHA-treated animals compared with controls, in a rat model of
667 cervical SCI [177].

668 With regard to traumatic brain injury (TBI), in the US there are 1.5-2 million new cases per year,
669 accounting for 30% of injury-related deaths, with an annual cost of $25 billion [178]. TBI,
670 particularly repetitive, increases susceptibility to Alzheimer's disease, as evidenced in murine
671 models, where repetitive TBI resulted in increased amyloid β-deposition, isoprostanes and
672 cognitive impairment [179]. However, acute DHA administration (500 nmol/kg body weight) 30
673 minutes after controlled cortical impact can improve spatial memory [180]. In terms of the
674 mechanisms involved, TBI and SCI are both associated with glutamate overflow which may be
675 controlled via omega-3 PUFA through inhibition of voltage-sensitive Na^+ and Ca^{2+} channels and
676 activation of K^+ channels [181].

677 DHA may also be a future treatment option for patients with stroke. In rodent ischaemic stroke
678 models, DHA administration, acting via biosynthesis of neuroprotectin D1 (aka protectin D1),
679 reduces astrocyte and neuronal cell death and promotes cell survival, resulting in significantly
680 reduced total infarct volume [182,183].

681 Preclinical rodent models have also shown that the improved neurological outcome following
682 acute DHA injection is not only associated with neuronal survival. Indeed, controlled cortical
683 impact models in mice have demonstrated that ablation of astrocytes resulted in decreased
684 neuronal survival, and increased neuroinflammation [184]. Hence, a subset of astrocytes appear
685 to have a role in aiding neuronal survival and reducing inflammation after brain injury [185]. It
686 has also been demonstrated that after mild compression injury in mice, heterogeneity of
687 microglia at the site develops alongside a coordinated microglial response [186]. Following TBI,
688 there is upregulation of a sub-population of microglia that express galectin-3/MAC-2 lectins that
689 are involved in myelin degradation [187]. Hence the acute DHA administration appears to play a

role in modulating this complex glial response, e.g. by increasing these new and proliferating microglia and astrocytes, and ultimately resulting in decreased lesion volume.

In humans, following a single TBI, there is evidence of persistent neuroinflammation and microglial activation for up to 17 years afterwards [188,189]. This suggests that interventions using DHA may be appropriate for a longer time period following TBI rather than just in the acute phase.

In summary, preclinical models of SCI and TBI suggest that DHA, if administered in the acute phase and for some time afterwards, may help to limit progression of neurological injury and improve neurological outcomes.

7.2 Effects of omega-3 fatty acids in preclinical models of sepsis and tissue injury

Omega-3 fatty acids have been shown to have a protective effect against oedema formation in a model of septic lung failure due to the increased generation of LTB_5. In perfused rabbit lung treated with *E. coli* hemolysin, EPA suppressed vascular permeability and shifted leukotriene formation from the 4-series to the 5-series compared to ARA [190]. Hence, the composition of LEs used in PN may influence microvascular changes induced by bacterial toxins.

The favorable lipid mediators formed from EPA may also have a beneficial effect on pulmonary hypertension compared to those formed from ARA. In a rabbit lung model of acute pulmonary hypertension investigating the pulmonary vasoconstrictor potencies of EPA and ARA, EPA resulted in an almost 2-fold decrease in pulmonary hypertension compared to ARA [191]. EPA is metabolized to PGI_3 and TXA_3 and it may be that the dominant presence of TXA_3 mediates EPA's weaker pulmonary vasoconstrictor effects, compared with ARA and ARA-derived TXA_2.

In inflammatory conditions, particularly systemic inflammation with sepsis and multi-organ failure, the transmigration of monocytes through the vascular endothelium is an important

713 contributing factor to the pathogenesis of the condition. In an *in vitro* experiment investigating
714 the effect of different free fatty acids on TNF-α activated human umbilical vein endothelial cells,
715 EPA and DHA (but not ARA), resulted in markedly suppressed platelet-activating factor (PAF),
716 resulting in reduced monocyte rolling and adherence, with DHA being more potent than EPA
717 [192]. Previous work has suggested that the binding of endothelial PAF and the PAF receptor
718 on leukocytes are responsible for the adhesive interactions of monocytes followed by their
719 activation [193]. This mechanism involving PAF may be one factor responsible for the
720 inflammation-dampening effect of EPA and DHA.

721 In a murine model of acute inflammation, pre-infusion of FO-rich LE resulted in reduced
722 leukocyte invasion and reduced TNF-α production in the alveolar space following intra-tracheal
723 LPS challenge, compared with SO or saline [194]. In PAF-receptor knock-out mice, the different
724 effects of FO and SO were far less marked. This supports the hypothesis that the anti-
725 inflammatory effect of FO is dependent on PAF/PAF-receptor linked signaling. Similarly, in a
726 murine model of ARDS, pre-infusion with FO-containing LE resulted in greater reduction of
727 leukocyte invasion and protein leakage into the alveolar space than either SO or SO/MCT [195].
728 These results suggest that the reduction in the proportion of omega-6 PUFA administered may
729 help improve lung injury.

730 Extensive lymphocytic apoptosis is a hallmark feature of late-stage sepsis, and can be clearly
731 seen in the spleen as well as other organs [196]. In a murine model of endotoxin-induced ALI,
732 OO pre-infusion resulted in less mortality compared with SO pre-infusion [197]. Fewer
733 lymphocytes were observed in the spleen in the SO group which appeared to be due to
734 increased apoptosis and necrotic cell death, although both LEs resulted in increased
735 lymphocytic apoptosis via intrinsic pathways. Hence, OO-based LEs may have fewer
736 deleterious immunological effects than SO, at least in murine models of ALI.

In critically ill patients, a reduced flow of blood to the gut can lead to intestinal ischaemia, decreased barrier function and increased bacterial translocation. A rat endotoxin model investigating the effects of different lipid pre-infusions on microcirculation and intestinal barrier function reported improved blood flow to the intestine and less viable bacteria detected in the mesenteric lymph nodes and liver following endotoxin challenge with FO-supplemented SO/MCT compared with SO/MCT or SO alone [198]. The reduction in viable bacteria is thought to be related to improved killing of translocated bacteria rather than a reduction in translocation.

In healthy human volunteers, infusion of FO blunted the endotoxin-induced inflammatory response including suppression of monocyte generation of pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8), and inhibition of monocyte-endothelium adhesion and transendothelial monocyte migration compared to SO [199]. Decreased fever in response to LPS, reduced TNF-α synthesis and a reduced LPS-induced neuroendocrine response (ACTH and noradrenaline) have also been observed with FO infusion in humans [200]. Similar protective results have been found after pre-infusion of either SO- or FO-based lipid emulsions and subsequent LPS-inhalation [201]

In summary, from preclinical models, different lipids may impact the inflammatory response of critically ill patients. SO LEs may exert negative effects in terms of increased pro-inflammatory cytokines and immune depression, such as lymphocyte destruction, whereas FO appears to dampen the inflammatory response and improve pre-clinical outcomes.

8. Conclusion

Lipids are an important component of enteral and parenteral nutrition and provide essential fatty acids, a concentrated source of calories and building blocks for cell membranes. Whilst LA-rich vegetable oil-based enteral and parenteral nutrition is still widely used, newer lipid components such as MCTs and OO appear to be safer and better tolerated than pure SO. FO-enriched

761 enteral and parenteral nutrition appears to be well tolerated and confers additional clinical
762 benefits, particularly in surgical ICU patients, due to its anti-inflammatory and immune-
763 modulating effects. Whilst the evidence base is not conclusive, there appears to be a potential
764 for FO-enriched nutrition, particularly administered peri-operatively, to reduce the rate of
765 complications and ICU and hospital stay in surgical ICU patients, as well as to improve
766 complications such as IFALD associated with SO-based LEs. The evidence for FO-based
767 nutrition in non-surgical ICU patients is less clear regarding its clinical benefits and additional,
768 well-designed large-scale clinical trials need to be conducted in this area.

769 Whilst FO-based PN can be more expensive than other available LEs, cost-benefit analysis has
770 shown that the treatment costs for ICU patients are completely offset by the savings made from
771 the subsequent reduction in hospital stay and reduced antibiotic costs.

772 Future directions regarding FO-based enteral and parenteral nutrition may include its use in TBI
773 and SCI, as well as in complications relating to sepsis and tissue injury, following the success of
774 such interventions in preclinical models.

775

776 **Conflicts of Interest**

777 P.C.C. has received speaking and advisory honoraria from Fresenius-Kabi, B. Braun,
778 Baxter Healthcare, Abbott Nutrition and Danone/Nutricia. M.A. has received speaking
779 honoraria from B. Braun, Cosmed and Danone/Nutricia. N.E.D. has received speaking
780 and advisory honoraria from Abbott Nutrition. T.G. has received speaking honoraria
781 from B. Braun and Fresenius-Kabi. S.K. has received speaking honoraria from
782 Fresenius-Kabi, B. Braun, Baxter Healthcare, Nutricia Poland, Nestle and Shire. S.L has
783 received speaking honoraria from Fresenius-Kabi, Baxter Healthcare and Abbott

784 Nutrition ,K.M. has received speaking honoraria from Fresenius-Kabi, B. Braun, Baxter
785 Healthcare, Abbott Nutrition, and Nestlé. A.M-T. has received grant funding from B.
786 Braun. L.P. has received speaking honoraria and grants from Fresenius-Kabi, Amgen,
787 CSL Behring, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Novartis, Roche, Sorin
788 Group, and Viiv Healthcare. M.P. holds an issued patent on the treatment of parenteral
789 nutrition-associated liver disease: a license agreement for the use of Omegaven has
790 been signed by Boston Children's Hospital and Fresenius Kabi. P.S. has received
791 speaking honoraria and grants from Fresenius-Kabi, B. Braun, Baxter Healthcare and
792 Abbott Nutrition. J.K.I. and H.V. have no conflicts to declare.

793

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Figure caption

Figure 1. Evolution of lipid emulsions for use in parenteral nutrition.

Table 1. Macronutrient composition of EN formulas commonly used in research studies

	Oxepa[1]	Pulmocare[1]	Ensure Plus HN[2]	Impact[3]	Reconvan[4]
Protein (g/l)	63	63	63	56	55
Carbohydrate (g/l)	105	105	204	132	120
Fat (g/l)	93 (MCT, canola oil, fish oil, borage oil)	93 (MCT, canola oil, corn oil, high oleic safflower oil)	49 (MCT, canola oil, corn oil)	28 (Palm kernel oil, high oleic sunflower oil, high oleic safflower oil, fish oil)	33 (MCT, safflower oil, flaxseed oil, fish oil)
Omega-6 PUFAs (g/l)	18.4	18.4	7.7	5.8	6.9
Of which GLA (g/l)	4.3	0	0	0	0
Omega-3 PUFAs (g/l)	10	4.8	1.5	3.3	3.4
Of which EPA + DHA (g/l)	6.5	0	0	1.7	2.5
Also contains	Taurine, carnitine, vitamin C, α-tocopherol, β-carotene	Taurine, carnitine, vitamin C, α-tocopherol, β-carotene	Vitamin C, α-tocopherol	Arginine, nucleotides, vitamin C, α-tocopherol, β-carotene	Arginine, glutamine, vitamin C, α-tocopherol, β-carotene

Source: [1]Abbott Nutrition company website; [2]Taken from [68]; [3]Taken from [202] and Nestlé Health Science company website; [4]Fresenius Kabi company website.

Table 2. Fatty acids of importance in parenteral nutrition

Fatty acid	Shorthand nomenclature	Oil source
Caprylic acid	8:0	Coconut oil or palm kernel oil
Capric acid	10:0	Coconut oil or palm kernel oil
Lauric acid	12:0	Coconut oil or palm kernel oil
Myristic acid	14:0	
Palmitic acid	16:0	
Oleic acid	18:1n-9	Olive oil
Linoleic acid	18:2n-6	Vegetable seed oils e.g. soybean oil
α-Linolenic acid	18:3n-3	Vegetable seed oils e.g. soybean oil
Eicosapentaenoic acid	20:5n-3	Fish oil
Docosahexaenoic acid	22:6n-3	Fish oil

Table 3. Oil and typical fatty acid compositions (% of total) of commercially available lipid emulsions for use in parenteral nutrition

	Intralipid®	Lipofundin® MCT/LCT	Structolipid®	Omegaven®	ClinOleic®	Lipoplus® (also known as Lipidem®)	SMOFlipid®
Oil source	100% soybean	50% MCT + 50% soybean	36% MCT + 64% soybean	100% fish***	80% olive + 20% soybean	50% MCT + 40% soybean + 10% fish***	30% MCT + 30% soybean + 25% olive + 15% fish***
SFA	15	58	46	21	14	49	37
MUFA*	24	11	14	23	64	14	33
PUFA	61	31	40	56	22	37	30
n-3 PUFA	8	4	5	48	3	10	7
ALA	8	4	5	1	3	4	2
EPA	-	-	-	20	-	3.5	3
DHA	-	-	-	19	-	2.5	2
n-6 PUFA**	53	27	35	5	19	27	23

Information taken from [203], [204] and [205].

SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

*mainly oleic acid

**mainly linoleic acid

***the fatty acid composition of fish oil is more variable than that of vegetable oils so that the precise contribution of different fatty acids may differ in different batches

Note that the fish oil used in Lipolus® is more concentrated in EPA and DHA than that used in SMOFLipid® so that 10% fish oil in Lipoplus® provides more EPA and DHA than 15% fish oil in SMOFLipid®

Table 4. Clinically relevant outcomes of studies using fish oil-enriched EN in critically ill patients

Study	Population (Number enrolled/included in analysis)	Intervention	EPA (g/d)	DHA (g/d)	GLA (g/d)	Control	Outcome in intervention group
Braga et al. 2002 [69]	Major abdominal surgery for GI malignancy (196/150)	Peri- & post-operative IMPACT®	~ 2.9 EPA + DHA		0	Post-operative standard EN	↓ Number of complications ↓ Hospital length of stay
Elamin et al. 2012 [59]	ARDS (22/17)	Oxepa®	N/A	N/A	N/A	Pulmocare®	↑ Oxygenation ↓ Lung injury ↓ Organ dysfunction ↓ ICU stay
Gadek et al. 1999 [56]	ARDS (146/98)	Oxepa®	6.9	2.9	5.8	Pulmocare®	↑ Oxygenation ↓ Ventilator days ↓ New organ failure ↓ ICU stay
Grau-Carmona et al. 2011 [60]	Septic patients with ALI/ARDS (160/132)	Oxepa®	5.4	2.3	4.9	Ensure Plus HN®	↑ Oxygenation ↓ New organ failure ↓ ICU stay
Kagan et al. 2015 [71]	Severe trauma (120/99)	Oxepa®	5.5	2.3	4.7	Pulmocare®	No effect on oxygenation, incidence of ARDS/ALI, length of ventilation time, length of ICU stay or 28-day mortality
Klek et al. 2011 [70]	Major abdominal surgery for GI malignancy (341/305)	Post-operative Reconvan®	~ 5 EPA + DHA		0	Post-operative Peptisorb®	↓ Hospital stay ↓ Infectious complications ↓ Overall morbidity ↓ Overall mortality
Pontes-Arruda et al. 2006 [58]	ARDS secondary to sepsis/septic shock (165/103)	Oxepa®	4.9	2.2	4.6	Pulmocare®	↑ Oxygenation ↓ New organ failure ↓ Ventilator days ↓ ICU stay ↓ Mortality

Pontes-Arruda et al. 2011 [68]	Early stage sepsis (115/106)	Oxepa®	4.6	2.0	4.4	Ensure Plus HN®	↓ Progression of sepsis ↓ Respiratory and cardiac failure ↓ ICU stay
Rice et al. 2011 [61]	ARDS/ALI (272/272)	Bolus FO + GLA	6.8	3.4	5.9	Equivalent with no FO or GLA	No clinical benefit. Trial stopped early due to fewer ventilator-free and ICU-free days, and greater 60-day mortality in FO group
Singer et al. 2006 [57]	ALI (100/95)	Oxepa®	5.4	2.5	5.1	Pulmocare®	↑ Oxygenation ↓ Ventilator duration
Stapleton et al. 2011 [62]	ALI (90/85)	Bolus FO	9.8	6.8	0	Equivalent with no FO	No effect on SOFA, ventilator free days or mortality
Van Zanten et al. 2014 [73]	Medical/surgical/ trauma ICU patients	Experimental high protein feed enriched with glutamine, omega-3 fatty acids & antioxidants	~ 4.5 EPA + DHA		0	Protison (high protein feed)	No effect on infections, mortality, organ failure, duration of mechanical ventilation or length of stay. Increased 6-month mortality rate reported in medical sub-group.

SOFA, Sequential Organ Failure Assessment score.

Table 5. Clinically relevant outcomes from including different lipid emulsions in PN in surgical patients

Study	Population	Intervention	Duration	Control	Outcome in intervention group
Badía-Tahull et al. 2010 [95]	Gastrointestinal surgery	OO/SO + FO (ClinOleic® + Omegaven®) (n=13)	5 d	OO/SO (ClinOleic®) (n=14)	↓ Number of infections. Trend towards lower mortality and fewer incidences of sepsis. No effect on length of hospital stay
Berger et al. 2008 [206]	Abdominal aorta aneurysm surgery	SO/MCT/FO (Lipoplus®) (n=12)	4 d	SO/MCT (Lipofundin®) (n=12)	Trend towards shorter ICU and hospital stay
Berger et al. 2013 [89]	Cardiac surgery	FO (Omegaven®) (n=14)	3 infusions: 12 h and 2 h before surgery and immediately after surgery	Saline (n=14)	Trend towards shorter length of mechanical ventilation and shorter ICU stay
Grimm et al. 2006 [97]	Gastrointestinal surgery	SO/MCT/OO/FO (SMOFlipid®) (n=19)	5 d	SO (Lipovenoes®) (n=14)	↓ Length of hospital stay
Han et al. 2012 [105]	Major surgery	SO/MCT + FO (Lipofundin® + Omegaven®) (n=18)	7 d post-surgery	SO/MCT (Lipofundin®) (n=12)	Trend towards less liver dysfunction and fewer infections
Heidt et al. 2009 [99]	Coronary artery bypass surgery	FO (Omegaven®) (n=52)	~12 h prior to surgery until ward transfer	SO (Lipovenoes®) (n=50)	↓ Post-operative atrial fibrillation ↓ ICU stay
Heller et al. 2004 [106]	Gastrointestinal surgery	SO + FO (Lipovenoes® + Omegaven®) (n=24)	5 d post-surgery	SO (Lipovenoes®) (n=20)	↓ Markers of liver dysfunction
Jiang et al. 2010 [91]	Gastrointestinal surgery	SO + FO (Intralipid® + Omegaven®) (n=100)	7 d post-surgery	SO (Intralipid®) (n=103)	↓ SIRS ↓ Length of hospital stay Trend towards fewer

					infectious complications.
Klek et al. 2005 [94]	Gastrointestinal surgery	Post-operative FO (Omegaven®) (n=30)	Mean duration 9 d	SO/MCT (Lipofundin®) (n=30) SO/MCT + glutamine (Lipofundin®+ Dipeptiven®) (n=30)	↓ Infectious complications ↓ Hospital stay
Ma et al. 2012 [108]	Gastrointestinal surgery	SO/MCT/OO/FO (SMOFlipid®) (n=20)	5 d post-surgery	SO/MCT (Lipovenoes®) (n=20)	No difference in post-operative complications, infections or duration of hospital stay
Mateu-de Antonio et al. 2008 [85]	Surgery patients	OO/SO (ClinOleic®) (n=23)	Mean duration 19 d	SO (Intralipid®) (n=16)	No difference in number and type of infections, ICU stay, hospital stay or mortality.
Metry et al. 2014 [109]	Gastrointestinal surgery	SO/MCT/OO/FO (SMOFlipid®) (n=41)	7 d post-surgery	SO (Intralipid®) (n=42)	No difference in ventilation, duration of ICU or hospital stay or mortality
Piper et al. 2009 [107]	Surgery	SO/MCT/OO/FO (SMOFlipid®) (n=22)	5 d post-surgery	OO/SO (ClinOleic®) (n=22)	↓ Markers of liver dysfunction
de Miranda Torrinhas et al. 2013 [92]	Gastrointestinal surgery	Pre-operative FO (Omegaven®) (n=31)	3 d pre-surgery	SO/MCT (Lipovenoes®) (n=32)	No effect on post-operative infections, length of ICU or hospital stay.
Tsekos et al. 2004 [100]	Gastrointestinal surgery	Perioperative SO/MCT + FO (Omegaven®) (n=53) vs Post-operative SO/MCT + FO (Omegaven®) (n=86)	2-3 d pre-surgery followed by 5 d post-surgery	SO/MCT (brand un-disclosed) (n=110)	Perioperative: ↓ Mortality ↓ Number of patients requiring ventilation ↓ Hospital stay No change in length of ICU stay
Umpierrez et al. 2012 [84]	Surgery	OO/SO (ClinOleic®) (n=51)	28 d post-surgery	SO (Intralipid®) (n=49)	No difference in mortality, infections or length of stay

Wachtler et al. 1997 [207]	Gastrointestinal surgery	SO/MCT/FO (Prototype of Lipoplus®) (n=19)	5 d post-surgery	SO/MCT (brand un-disclosed) (n=21)	Trend towards fewer infections and shorter ICU stay. No effect on length of hospital stay
Wang et al. 2012 [104]	Gastrointestinal surgery	SO/MCT/FO (Lipoplus®) (n=32)	5 d post-surgery	SO/MCT (Lipofundin®) (n=31)	↓ Total bilirubin
Weiss et al. 2002 [90]	Surgery (n=24)	Peri-operative FO (Omegaven®)	d-1 to d 5	SO (Lipovenoes®)	↓ Length of hospital stay. No effect on infection rate or mortality.
Wichmann et al. 2007 [96]	Gastrointestinal surgery	SO/MCT/FO (Lipoplus®) (n=127)	5 d post-surgery	SO (Intralipid®) (n=129)	↓ Length of hospital stay. Trend towards fewer infections and decreased length of ICU stay. No effect on mortality
Wu et al. 2014 [110]	Gastrointestinal surgery	SO/MCT/OO/FO (SMOFlipid®) (n=20)	5 d post surgery	MCT/SO (Lipovenoes®) (n=15)	No difference in infections, duration of hospital stay or mortality
Zhu et al. 2012 [93]	Elderly gastrointestinal surgery	SO + FO (Intralipid® + Omegaven®) (n=29)	7 d post-surgery	SO (Intralipid®) (n=28)	↓ Infectious complications ↓ SIRS ↓ Length of hospital stay

Table 6. Clinically relevant outcomes from including different lipid emulsions in PN in critically ill medical patients

Study	Population	Intervention	Duration	Control	Outcome
Barbosa et al. 2010 [119]	Critically ill with sepsis/SIRS	SO/MCT/FO (Lipoplus®) (n=13)	5 d	SO/MCT (part of LipidSpecial®) (n=10)	↑ PO_2/FiO_2 ratio ↓ Length of hospital stay for surviving patient sub-group. No difference in ventilation days, length of ICU stay or mortality
Barros et al. 2013, 2014 [208,209]	Elderly ICU patients on EN	Supplementary FO (Omegaven®) (n=15)	6 h infusions / d for 3 d	No supplementary PN (n=25)	↑ Gas exchange Trend towards shorter length of mechanical ventilation and decreased mortality. No effect on liver function
Burkhart et al. 2014 [120]	Sepsis	FO (Omegaven®) (n=25)	7 d	Standard care (n=25)	No difference in duration of ICU stay or mortality
Edmunds et al. 2014 [115]	Mechanically ventilated critically ill	FO-enriched lipids (SMOFlipid®, Lipoplus® or Omegaven®) (n=19) OO/SO (ClinOleic®) (n=74)	≥ 5 d	SO-based lipids (various brands) (n=223) Lipid-free (n=70) SO/MCT (various brands) (n = 65)	For FO-enriched lipids: ↓ Duration of mechanical ventilation ↓ Length of ICU stay ↓ Mortality
Friesecke et al. 2008 [126]	Medical ICU	SO/MCT + FO (Lipofundin® + Omegaven®) (n=63)	≥ 6 d	SO/MCT (Lipofundin®) (n=60)	No effect on infection, duration of mechanical ventilation, length of ICU stay or 28-day mortality
García-de-Lorenzo et al. 2005 [210]	Severe burns	OO/SO (ClinOleic®) (n=11)	6 d	SO/MCT (Lipofundin®) (n=11)	No effect on organ dysfunction, requirement for ventilation, number of infections, length of ICU or hospital stay or mortality
Grau-Carmona et al. 2015 [123]	Medical and surgical ICU	SO/MCT/FO (Lipoplus®) (n=58)	≥ 5 d	SO/MCT (Lipofundin®) (n=59)	↓ Nosocomial infections No difference in duration of ventilation, length of ICU or hospital stay or 6-month

					mortality
Gupta et al. 2011 [211]	ARDS on EN	Supplemental FO (Omegaven®) (n=31)	14 d	Standard EN (n=30)	No difference in duration of ventilation, ICU stay or hospital stay or mortality
Hall et al. 2014 [118]	Critically ill with sepsis	FO (Omegaven®) (n=30)	14 d or to discharge	Standard care (N=30)	↓ SOFA ↓ Mortality in less severe sepsis subgroup No effect on length of stay
Khor et al. 2011 [121]	Severe sepsis	FO (Omegaven®) (n=14)	5 d	Saline (n=13)	No effect on length of ICU or hospital stay
Mayer et al. 2003 [122]	Septic shock	FO (Omegaven®) (n=10)	5 d	SO (Lipoven®) (n=11)	No effect on mortality or length of mechanical ventilation
Mayer et al. 2003 [117]	Septic shock	FO (Omegaven®) (n=5)	10 d	SO (Lipoven®) (n=5)	Trend towards shorter ventilation time. No mortality in either group
Sabater et al. 2008 [212]	ARDS	SO/MCT/FO (Lipoplus®) (n=8)	12 h	SO (Intralipid®) (n=8)	No effect on gas exchange or mortality
Wang et al. 2008 [116]	Acute pancreatitis	SO + FO (Lipovenoes® + Omegaven®) (n=20)	5 d	SO (Lipovenoes®) (n=20)	↓ Requirement for renal replacement therapy ↑ Oxygenation index Trend towards fewer infections and shorter length of ICU and hospital stay
Zhu et al. 2012 [98]	Liver transplantation	FO (Omegaven®) (n=33)	7 d post-surgery	SO/MCT (20% emulsion with a 1:1 ratio) (n=33)	↓ Length of hospital stay

SOFA, Sequential Organ Failure Assessment.

Table 7

Clinical and biochemical outcomes from including different lipid emulsions in PN in pediatric patients

Study	Population	Intervention	Duration	Control	Outcome in intervention group
Beken et al. 2014 [159]	Very low birth weight preterm infants	SO/MCT/OO/FO (SMOFlipid®) (n=40)	Mean: 14 d	SO (Intralipid®) (n=40)	↓ Retinopathy of prematurity No difference in morbidity or mortality outcomes
D'Ascenzo et al. 2014 [160]	Very low birth weight preterm infants	SO/MCT/OO/FO (SMOFlipid®) (n=30)	7 d following birth	SO (Intralipid®) (n=32)	↑ Plasma EPA and DHA ↓ Plasma ARA ↑ Serum triglycerides, plasma phospholipids, free cholesterol No difference in weight.
Deshpande et al. 2014 [161]	Preterm neonates	SO/MCT/OO/FO (SMOFlipid®) (n=17)	7 d	OO/SO (ClinOleic®) (n=17)	↑ RBC EPA ↑ Vitamin E ↓ F_2 isoprostanes
Larsen et al. 2012 [166]	Infants undergoing open heart surgery	SO/MCT/FO (Lipoplus®) (n=16)	1-4 d before and 10 d post-surgery	SO (Intralipid®) (n=16)	↓ TNF-α No difference in clinical outcomes
Larsen et al. 2015 [165]	Infants undergoing open heart surgery	SO/MCT/FO (Lipoplus®) (n=16)	3 d pre-op and 5 d post-op	SO (Intralipid®) (n=16)	↑ Plasma phospholipid EPA ↓ Plasma LTB_4 and lymphocytes
Pawlik et al. 2013 [162]	Very low birthweight preterm infants	OO/SO+FO (ClinOleic® + Omegaven®) (n=60)	28 d	OO/SO (ClinOleic®) (n=70)	↑ Plasma DHA ↓ Cholestasis
Savini et al. 2013 [163]	Very low birthweight preterm infants	SO (Intralipid®) (n=30) vs SO/MCT (Lipofundin®)(n=30) vs SO/MCT/FO	21 d	--	Lowest plasma phytosterols in SMOFlipid® group No difference in liver function

		(Lipidem®) (n=27) vs OO/SO (ClinOleic®) (n=29) vs SO/MCT/OO/FO (SMOFlipid®) (n=28)			
Vlaardingerbroek et al. 2014 [158], Roelands et al. 2016 [134]	Very low birth weight infants	SO/MCT/OO/FO (SMOFlipid®) (n=48)	Median: 11 d	SO (Intralipid®) (n=48)	↑ Plasma EPA and DHA ↑ Weight gain No difference in ARA. No differences in morbidity, mortality or other biochemical outcomes No difference in neurodevelopmental outcome
Wang et al. 2016 [164]	Preterm infants	OO/SO (ClinOleic®) (n=50)	14 d	SO (Intralipid®) (n=50)	↓ Direct bilirubin Differences in bile acid composition No difference in clinical outcome