Lipid emulsions in parenteral nutrition: does it matter?

Krista Haines*, Braylee Grisel, Laura Gorenshtein and Paul E. Wischmeyer*#

Purpose of review
Recently, clinicians have shown interest in switching patients to nonsoybean-based intravenous lipid emulsion (ILE) formulas for parental nutrition (PN) due to adverse outcomes related to high Omega-6 content in soybean oil (SO) ILE’s. This review summarizes recent literature on improved clinical outcomes with new Omega-6 lipid-sparing ILE’s in PN management.

Recent findings
Although there is a paucity of large-scale studies directly comparing Omega-6 lipid sparing ILE’s with SO-based lipid emulsion use in PN in ICU patients, there is strong translational and meta-analysis evidence to suggest that lipid formulations containing fish oil (FO) and/or olive oil (OO) have favorable effects on immune function and improve clinical outcomes in ICU populations.

Summary
More research is needed to directly compare omega-6-sparing PN formulas with FO and/or OO versus traditional SO ILE’s. However, current evidence is promising for improved outcomes using newer ILE’s including reduced infections, shorter lengths of stay, and reduced costs.

Keywords
critical care, ICU, lipid emulsion, nutrition, parenteral nutrition, total parenteral nutrition

Parenteral nutrition (PN) is critical when oral intake or enteral nutrition (EN) delivery is not possible, such as in cases of bowel obstruction, recent abdominal surgery, short bowel syndrome, and other conditions [1–3]. However, PN historically has been thought to be associated with increased risks due to its association with elevated liver enzymes, parenteral nutrition-associated liver disease (PNALD), increased inflammation, infection risk, and complex formulations that can lead to prescription errors [4*,5]. However, recent evidence from multiple level I randomized controlled trials has shown that PN is no longer associated with increased risk of infection in ICU patients versus EN [6–9]. Further, there is increasing evidence that implicates the make-up of specific intravenous lipid emulsion (ILE) formulations in a range of the traditionally-believed adverse effects of PN [4*,10**,11]. ILE’s function in PN as artificial chylomicrons, allowing nutrition to bypass normal routes of absorption, bile emulsification, and pancreatic degradation [11]. Fatty acids (FAs) or triglycerides that make up PN-ILEs are classified by degrees of saturation, carbon length, and location of double bonds. Each of these classifications have effects on biochemical functioning and may influence clinical outcomes in critically ill patients [10**]. Medium-chain fatty acids (MCFAs), long-chain fatty acids (LCFAs), and polyunsaturated fatty acids (PUFAs) are the major components currently used in ILE formulations. Additionally, ILE’s contain emulsifiers, phytosterols, and alpha tocopherols that help mediate some of the adverse cholestatic and oxidative stress effects of LE [12].

*Division of Trauma and Critical Care and Acute Care Surgery, Department of Surgery, Duke University Medical Center and #Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA

Correspondence to Paul E. Wischmeyer, MD, EDIC, FASPEN, FCCM, Professor of Anesthesiology and Surgery, Duke University School of Medicine, DUMC, Box 3094 Mail # 41, 2301 Erwin Road, 5692 HAFS, Durham, NC 27710, USA. Tel: +1 919 681 6648; fax: +1 919 681 2923; e-mail: Paul.Wischmeyer@Duke.edu

Curr Opin Crit Care 2023, 29:000–000
DOI:10.1097/MCC.0000000000001058

1070-5295 Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved. www.co-criticalcare.com

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.
Metabolic support

KEY POINTS

- Recent international clinical guidelines and expert consensus panels have begun to make recommendations for a switch to newer generation intravenous lipid emulsions (ILEs) containing fish oil (FO) and/or olive oil (OO) to reduce patient exposure to Omega-6 soybean oil (SO) in parenteral nutrition (PN).

- Omega-6 soybean oil (SO) intravenous lipid emulsions (ILEs) have been implicated in adverse clinical outcomes in PN patients, thought to be due to SO-mediated increases in oxidative stress and inflammatory response, suppression of cell-mediated immunity, and promotion of PN-associated liver disease (PNALD).

- Multiple recent meta-analysis publications in adult patients, as well as recent U.S. pre/post comparison studies in adult and pediatric patients, consistently show that the use of newer generation, SO-sparing ILE’s containing FO and/or OO reduce infection risk and hospital/ICU length of stay in patients receiving PN.

- Recent clinical trial data shows that use of newer generation, SO-sparing ILE’s containing FO and/or OO reduces liver injury and PNALD in adults and children on PN, and use of pure FO ILE’s can reverse cholestasis and PNALD in pediatric and neonatal patients.

- Recent cost-effectiveness analysis show that FO-containing ILE’s are associated with significant cost savings in the United States and multiple other countries worldwide versus standard PN with SO ILEs.

EFFECT OF PARENTAL NUTRITION-LIPID intravenous LIPID EMULSION’S BEYOND CALORIE DELIVERY: ROLE IN IMMUNE AND LIVER FUNCTION

ILE’s as a component of PN, are key to deliver essential fatty acids and energy [13*,14*]. However, the optimal form of ILE in PN is controversial and has undergone further study recently [4**,10**]. The addition of ILE’s to PN has been found to modulate cell signaling and immune function [15]. Soybean oil (SO) was the first LE used commercially in 1961 and has continued to be predominantly used in the United States. As discussed previously, its high Omega-6 content has been implicated in adverse outcomes, leading to increased oxidative stress burden in critically ill patients [16–18]. Increased rates of Omega-6 lipid peroxidation is thought to contribute to this oxidative stress. Additionally, soybean oil-based LEs are thought to increase bacteremia and infection risks by promoting inflammation and suppressing cell-mediated immunity [4**,18–21] (Fig. 1). Omega-6 FAs, commonly found in SO-based formulas, metabolize into prostaglandin, leukotriene, and thromboxane precursors, implicating them in the increased inflammation and decreased cell-mediated immunity [22,23]. Conversely, Omega-3 FA’s metabolize into DHA and EPA – precursors of anti-inflammatory molecules [12,22,23]. PUFAs compete with the same metabolic enzymes, meaning that the ratio of omega-6 and omega-3 fatty acids will affect the ratio of pro-inflammatory and anti-inflammatory precursors of the lipid in the body [23]. Initial PN formulas had up to 50% composition of n-6 linoleic acid, which is associated with increased oxidative stress as compared to other FA structures [11]. A small number of studies have shown reduced inflammation and improved cell-mediated immune function with new alternative ILEs, which have reduced Omega-6 lipid content [22–24]. Finally, FO can be metabolized into key resolution mediators (i.e., resolvins, protectins) essential for the resolution of inflammation [25]. Combination lipids such as soy/MCT/olive/fish oil have demonstrated decreased inflammatory properties, increased antioxidant content, and decreased cholestasis [5**]. The relative pro-inflammatory/anti-inflammatory properties of the ILE’s components are shown in Fig. 2.

One of the common concerns with PN use is the development of PNALD [5**]. This is more common in pediatric patients but is known to be a concern in the critically ill population. The mechanisms responsible for PNALD are hypothesized to be hepatic steatosis brought on by dysregulation of lipoproteins via bypassing regular bile emulsification routes, composition of phytosterols, and dosing of dextrose contributing to insulin dysregulation. [5**,26] Further, there is increasing evidence that PNALD can be prevented or reversed with the use of FO-based ILEs, which are composed of PUFAs with lower phytosterol content [5**,22]. Newer generation ILE’s associated with decreased inflammation and PNALD (likely due to lower phytosterol concentrations) include pure FO ILEs, olive oil ILE’s and combinations of fish oil, olive oil, soybean oil, and medium chain fatty acids together [5**,22].

IMPACT OF LIPID FORMULATION ON CLINICAL OUTCOMES: DOES IT MATTER?

Since the invention of the first commercially available SO ILEs, multiple generations of ILEs have been developed. The second generation of ILEs included safflower oil and MCT-based oils with SO, the third generation of ILEs a mix of OO (80%) and SO (20%), and the fourth generation of ILEs includes any formulation including FO [12]. In many countries worldwide, newer generation ILE’s containing OO or FO are used widely and endorsed/recommended by societal guidelines [12,15,27,28]. In the United
States, there are currently 4 ILE products with an adult indication available, including a standard SO emulsion (Intralipid, Nutralipid), a third-generation SO/OO-based emulsion (ClinOleic) and a fourth-generation product with SO/MCT/OO/FO (SMOFli-pid). In Europe, there are more alternatives with regard to third and fourth-generation ILEs, e.g., mixtures of SO/MCT (Lipofundin), SO/MCT/FO

**FIGURE 1.** Molecular/cellular immune and inflammatory effects of soy ILE [3,15,23,25,45]. ILE, intravenous lipid emulsion.

**FIGURE 2.** Comparison of pre-inflammatory effects of different intravenous lipid emulsions [3,22]. Note: relative (not absolute) figurative scale to demonstrate relative inflammatory activity.
Metabolic support

(Listed in Table 1 for Composition of Key Commonly Used ILE’s worldwide)

Key new data show the newer generation ILEs appear to demonstrate clinical benefit over standard SO-ILE use. In a key 2022 systematic review by Notz et al., results showed that ‘omega-6 sparing’ strategies decreased infections and ICU LOS, with a trend to reduced 1-month mortality ($P = 0.06$) (see Table 2). Specific newer-generation lipids may provide unique clinical benefits. For instance, OO-based ILEs contain immunomodulatory properties that appear to be associated with lower infection rates [29,30]. Newer 4th generation FO ILEs contain anti-inflammatory and immunomodulatory effects, which may be beneficial for critically ill patients who often have hyperinflammation and immune dysfunction (Fig. 2). A range of meta-analyses have found compelling clinical benefits for the use of FO in PN from multiple RCTs, which includes the recently published Canadian Critical Care Nutrition guidelines [4*,31*,32] (see Table 2 for summary of recent meta-analysis publications on omega-3 ILE sparing trials). To exemplify this, results of the largest meta-analysis [39**], including 49 RCTs and 3641 patients, showed the use of n-3 PUFAs was associated with 40% fewer infections ($P < 0.00001$), approximately 2 days’ shorter hospital stay ($P < 0.00001$), about 2 days shorter ICU stay ($P = 0.01$), and sepsis was reduced by 56% ($P = 0.0004$) [33]. Further cost-effectiveness evaluation using data from this meta-analysis demonstrated that FO-containing ILE reduced costs in the United States and a range of European countries (see data summarized in Figs. 3 and 4) [34]. This group has recently published (2023) an updated meta-analysis looking at outcomes examining the use of all newer generation lipid formulations versus SO-ILE. The results of this analysis of 47 studies showed that FO ILEs demonstrated a significant reduction in infection risk and hospital LOS versus SO-ILEs and MCT/SO-ILEs [10**]. Finally, in a recently published study, we found that after a switch to 4-OLE from SO-ILE at Duke University Hospital, there was a reduction in hospital LOS, urinary tract infection (UTI) risk, and hepatic dysfunction in all hospitalized adult patients and adult ICU patients [35**]. Similar findings were observed in all pediatric inpatients, as well as pediatric ICU patients postswitch to 4-OLE from SO-ILE. In this first-of-its-kind study of 4-OLE in a pediatric population, significant reductions in hospital LOS, UTIs, and hepatic dysfunction were observed in both all hospitalized pediatric patients and pediatric ICU patients [36**]. Favorable effects were also observed in a small cohort of longer-term HPN patients when using 4-OLE compared with previous use of a pure SO-ILE [37]. An added benefit of the omega-3 fatty acid ILEs found in FO is that they increase learning, memory, cognitive well being, and blood flow to the brain [38*]. It is also clearly proven that pure FO-ILE in PN reduce, and in fact can reverse, the occurrence of cholestasis in very low birth weight and preterm infants [5**,39**,40*,41].

A final important factor to consider when determining ILE composition in PN is the risk of allergic reaction. Although infrequent, ILEs in PN may contain ingredients from common allergens such as egg, soybean, and fish and may lead to reactions anywhere from a mild local reaction to anaphylaxis [42,43].

Table 1. Composition of commonly available parenteral nutrition lipid formulas [3,22,25,29,47,48]

<table>
<thead>
<tr>
<th>Product name used in paper</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Lipid source</th>
<th>Linoleic (% by weight)</th>
<th>α-Linolenic (% by weight)</th>
<th>EPA</th>
<th>DHA</th>
<th>ARA</th>
<th>n-6/n-3 ratio</th>
<th>Phytosterols (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO, MCT, FO ILE</td>
<td>Lipidem/Lipoplus B. Braun</td>
<td>40% soybean oil 50% (MCT) coconut oil 10% fish oil</td>
<td>24.5</td>
<td>3.5</td>
<td>3.5</td>
<td>2.5</td>
<td>0</td>
<td>2.7:1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>SO, MCT, OO, FO ILE</td>
<td>SMOFLipid Fresenius Kabi</td>
<td>30% soybean oil 30% coconut oil 25% olive oil 15% fish oil</td>
<td>21.4</td>
<td>2.5</td>
<td>3</td>
<td>2</td>
<td>0.15-0.6</td>
<td>2.5:1</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>OO, SO-ILE</td>
<td>ClinoLipid/ ClinOleic Baxter</td>
<td>80% olive oil 20% soybean oil</td>
<td>18.5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>9.1</td>
<td>274 ± 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FO-ILE</td>
<td>Omegaven Fresenius Kabi</td>
<td>100% fish oil</td>
<td>4.4</td>
<td>1.8</td>
<td>19.2</td>
<td>12.1</td>
<td>1-4</td>
<td>1.8</td>
<td>3.66</td>
<td></td>
</tr>
</tbody>
</table>
Lipid emulsions in parenteral nutrition: does it matter? Haines et al.

**Table 2.** Key recent meta-analyses comparing new generation LEs use to standard soybean oil-based LE in PN

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients Description</th>
<th>Number of RCTs/ Patients</th>
<th>Comparison Details</th>
<th>Main results (clinical outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradelli 2023 [10**]</td>
<td>Adult hospitalized patients</td>
<td>47 studies (patient number varied by outcome studied)</td>
<td>PN with ILE’s covering at least 70% of total energy provision. Included: ILEs: FO-ILEs, OO-ILEs, MCT/SO ILE, and pure SO-ILEs.</td>
<td>FO-ILE reduced risk in infection versus SO-ILEs [odds ratio (OR) = 0.43 [90% credibility interval (CrI) 0.29–0.63]]</td>
</tr>
<tr>
<td>Notz 2022 [4**]</td>
<td>Adult critically ill patients</td>
<td>26 studies N = 1733 patients</td>
<td>Omega-6 reduction strategy in PN (SO/MCT, SO/OO, FO containing PN) versus Standard PN</td>
<td>FO-ILE reduced hospital length of stay versus SO-ILEs [mean difference (MD) = –2.31 (–3.14 to –1.59) days]</td>
</tr>
<tr>
<td>Compher 2022 [46*]</td>
<td>Adult critically ill patients*</td>
<td>10 studies N = 919 patients</td>
<td>FO-containing ILE versus non-FO-containing ILE as a component of PN</td>
<td>Decreased pneumonia incidence ~5% versus ~9% (P = 0.03). No differences in other outcomes, including catheter-related infections, length of ICU stay, days on mechanical ventilation, hospital mortality, and one-month mortality.</td>
</tr>
<tr>
<td>Pradelli 2020 [33]</td>
<td>Adult hospitalized patients</td>
<td>49 studies N = 3641 patients</td>
<td>PN with n-3 PUFAs versus standard PN. Covering ≥70% of energy requirements</td>
<td>Reduced infection risk by 40% (P &lt; 0.00001). Reduced sepsis risk by 56% (P = 0.0004). Reduced mean length of ICU stay by 1.95 days (P = 0.01). Reduced length of hospital stay by 2.14 days (P &lt; 0.0001). Trend to reduced mortality rate by 16% (P = 0.15).</td>
</tr>
<tr>
<td>Pradelli 2020 [49]</td>
<td>Adult hospitalized ICU patients (subgroup of [39**] with cost-effectiveness analysis)</td>
<td>24 studies N = 1421 patients</td>
<td>PN with n-3 PUFAs versus standard PN. Covering ≥70% of energy requirements</td>
<td>Reduced infection risk by 38% (P &lt; 0.0004). Reduced mean length of ICU stay by 1.89 days (P = 0.01). Reduced length of hospital stay by 3.05 days (P = 0.003). Trend towards a reduced risk of sepsis by 43% (P = 0.13). No differences in days on mechanical ventilation and one-month mortality.</td>
</tr>
</tbody>
</table>

FO, fish oil; ILE, intravenous lipid emulsion; LOS, length of stay; MCT, medium-chain triglyceride; OO, olive oil; PUFAs, polyunsaturated fatty acid; SO, soybean oil; **Only studies reporting clinical outcomes. 

**CONCLUSION**

A growing body of literature is beginning to clearly demonstrate that the choice clinicians make when choosing an ILE for their PN patients does matter. ‘Omega-6 sparing’ or ‘SO-sparing’ ILE strategies continue to be recommended by most international guidelines and expert consensus panels for critically ill patients requiring PN [31**,32,44,45]. Undoubtedly, there is a need for further large-scale multicenter studies to determine which formulation will provide the greatest benefit to critically ill patients [46*]. However, key recent meta-analyses and other newer clinical studies continue to demonstrate benefits and cost-savings associated with...
the use of FO-ILEs, OO-ILEs, and 4-OLEs over SO-ILEs [4,10,33,34,36]. Unfortunately, a majority of US centers continue to utilize SO-ILE for PN patients (personal communication, P.E. Wischmeyer). We hope the data presented here will be considered by US and worldwide hospitals to inspire a switch to a SO-sparing ILE for their PN patients.

Acknowledgements
None.

Financial support and sponsorship
None.

Conflicts of interest
Dr P.E. Wischmeyer reports receiving investigator-initiated grant funding related to this work from National Institutes of Health, Department of Defense, Abbott, Baxter, and Fresenius. Dr Wischmeyer has served as a consultant to Abbott, Fresenius, Baxter, Cardinal Health, and Nutricia, for research related to this work. Dr Wischmeyer has received unrestricted gift donation for nutrition research from Musclesound and DSM. Dr Wischmeyer has received honoraria or travel expenses for CME lectures on improving nutrition care from Abbott, Baxter, Fresenius, Danone-Nutricia, DSM, and Nestle. Dr Haines has received investigator-initiated grant funding from American Society for Parenteral and Enteral Nutrition, National Institutes of Health, and Abbott. Dr Haines has received honoraria for CME lectures from Fresenius.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

   Key new review of role of PN-lipid emulsions in parenteral nutrition-associated liver disease.
Lipid emulsions in parenteral nutrition: does it matter? Haines et al.


Recent review article giving a thorough overview of parenteral nutrition practice in hospital and home setting.


New key review article on key pharmacy and compounding issues related to parenteral nutrition practice.


Recent meta-analysis of new generation lipids versus soybean oil lipid emulsions showing clinical benefits of newer generation lipid emulsions versus soybean oil lipid emulsions in parenteral nutrition in ICU patients.


Pre/Postcomparative study showing after a switch to 4-OLE from SO-ILE at Duke University Hospital, there was a reduction in hospital LOS, urinary tract infection (UTI) risk and hepatic dysfunction in all hospitalized adult patients and adult ICU patients.


Recent review on the effects of Omega-3 fatty acid on brain function.


New meta-analysis of FO-containing lipid emulsions vs. non-FO-containing lipid emulsions on parenteral nutrition-associated cholestasis in very low birth weight infants. Analysis showed fish oil-containing lipid emulsions can reduce the occurrence of PNAC in VLBW infants based on the available original randomized controlled trial studies, especially for patients with parenteral nutrition duration exceeding 14 days and extremely low birth weight infants.


Retrospective cohort trial in premature infants, showing PN with mixed fish oil-based (given as 4-Oil LE) lipid emulsions is associated with a lower incidence of PN-associated cholestasis compared with soybean oil-based lipid emulsions.


Recent review article on key pharmacy and compounding issues related to parenteral nutrition practice.


