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 LEs, 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 00 (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