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CONSENSUS RECOMMENDATION

CE PODCAST ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations

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Abstract

Lipid injectable emulsions (ILEs) are complex pharmaceutical formulations intended as a source of energy and fatty acids for parenteral nutrition (PN) therapy. Part 1 of this series addressed issues associated with and safety recommendations pertaining to adult ILE use. Part 2 addresses ILE safety in neonatal and pediatric patients. Considerations for ILE use in the neonatal and pediatric populations differ from those of adults. For example, these patients often require higher doses compared with adult counterparts to support growth, development, and daily metabolic needs. ILE is also frequently administered as a separate infusion as opposed to in a total nutrient admixture owing to compatibility and stability issues and limitations to intravenous access in the neonatal and pediatric populations. ILE is the most frequent PN ingredient associated with PN errors occurring in the administration, prescribing, and transcribing processes. Concerns exist with use of in-line filters and repackaging of commercial products for infusion. ILE use in neonatal and pediatric patients has been associated with both minor and major adverse effects, which most often

occur with doses exceeding manufacturer recommendations. Gaps in ILE best practices for neonatal and pediatric patients predispose to errors in the PN use system. This paper describes safe-use considerations for ILE products available in the United States in neonatal and pediatric patients, including indications, prescribing, order review, preparation, administration, and monitoring. This paper has been approved by the American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors.

KEYWORDS
fatty acids, infant, lipid injectable emulsion, parenteral nutrition, pediatrics, safety

INTRODUCTION

Lipid injectable emulsions (ILEs) are complex pharmaceutical formulations intended as a source of energy and fatty acids (FAs) for parenteral nutrition (PN) therapy. Issues associated with adult ILE use and safety recommendations have been addressed in part 1 of this series.[1] Part 2 addresses the ILE safety issues in neonatal and pediatric patients. Considerations for ILE use in the neonatal and pediatric populations differ from those of adults. Neonatal and pediatric patients often require higher doses and receive ILE as a separate infusion as opposed to in a total nutrient admixture (TNA) owing to compatibility and stability issues.[2] It has been previously found that ILE is the most frequent PN ingredient associated with errors.[3] An evaluation of ILE errors specifically found that 38.8% of ILE errors occurred in neonates, infants, and children and were most often involved in the administration, prescribing, and transcribing processes.[4] Concerns exist with the use of in-line filters and repackaging of commercial products for infusion.[2] Because of the use of higher doses per kilogram of nutrients necessary to support growth, development, and daily metabolic needs, as well as limited intravenous access, issues with PN compatibility and stability within the PN or with other medications are common. ILE use in pediatric patients has been associated with both minor and major adverse effects, which most often occurred when using doses that exceed manufacturer recommendations.[5] The use of ILE as an energy source may be restricted in neonatal and pediatric patients related to elevated triglyceride (TG) levels or cholestatic liver disease.[2] With the recent availability of multiple ILE products, concerns for the choice, use, and safe practices of ILE in neonatal and pediatric patients have arisen. This paper describes safety considerations for ILE products available in the United States in neonatal and pediatric patients. The paper is organized into the following sections: ILE indications, prescribing, order review, preparation, administration, and monitoring. ILE products approved for use in the United States are provided in Table 1.[1] Those formulations containing more than one oil will be referred to as "Multi-oil ILE," whereas single-oil emulsions will be referred to as soybean oil ILE (SO-ILE) or fish oil ILE (FO-ILE) as applicable.

These recommendations do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the attending healthcare professional whose judgment is the primary component of quality medical care. The information presented is not a substitute for the judgment by the healthcare professional. Circumstances in clinical settings and patient indications may require actions different from those recommended in this document, and in those cases, the judgment of the treating professional should prevail. The American Society for Parenteral and Enteral Nutrition (ASPEN) does not endorse any particular brand of products mentioned herein. This paper has been approved by the ASPEN Board of Directors.

Overview of ILE FA composition

For PN-dependent patients, one of the original purposes for ILE was the provision of essential FAs (EFAs). Unlike FAs in the ω-5, ω-7, and ω-9 families, EFAs are those that cannot be synthesized in the body but are required from dietary sources.[11] In addition to serving as a dense source of nonprotein energy, EFAs provide substrate for cell membranes and serve as precursors to substances known as eicosanoids. Eicosanoids influence immune responses, contribute to pain perception, regulate cell growth, and modulate blood flow. The two major families of EFAs are the ω-3 and ω-6 FAs. EFAs draw from the same enzymatic pool to desaturate and elongate parent FAs to their biologically active downstream moieties. Traditionally, EFAs have been considered linoleic acid (LA), the primary

TABLE 1 Lipid injectable emulsion products, characteristics, abbreviations, and approval for use in the United States

Lipid injectable emulsion	Characteristic	Abbreviation	FDA-approved neonatal and pediatric indication
	Lipid injectable emulsion	ILE	
Intralipid (Baxter Healthcare Corporation, Deerfield, IL)	Soybean oil–based ILE	SO-ILE	A source of calories and EFAs for patients requiring PN for extended periods of time (usually for >5 days) and as a source of EFAs for prevention of EFAD syndrome[6]
Nutrilipid (B. Braun Medical, Inc, Bethlehem, PA)	Soybean oil–based ILE	SO-ILE	A source of calories and EFAs for PN and a source of FAs when a deficiency occurs for which oral or enteral nutrition is not possible, insufficient, or contraindicated[7]
SMOFlipid (Fresenius Kabi, Uppsala, Sweden)	Soybean, MCTs, olive, fish oil–based ILE	SO,MCT,OO,FO-ILE, Multi-oil	FDA approval not yet attained[8]
Omegaven (Fresenius Kabi, Uppsala, Sweden)	Fish oil–based ILE	FO-ILE	A source of calories and FAs in pediatric patients with PN-associated cholestasis[9],[a]
Clinolipid (Baxter Healthcare Corporation, Deerfield, IL)	Olive, soybean oil–based ILE	OO,SO-ILE, Multi-oil	FDA approval not yet attained[10]

Abbreviations: EFAD, essential FA deficiency; FA, fatty acid; FDA, US Food and Drug Administration; MCT, medium-chain triglyceride; PN, parenteral nutrition.
[a]For the purposes of this paper, intestinal failure–associated liver disease ("IFALD") is used in place of PN-associated cholestasis ("PNAC").

precursor of the ω-6 FA family, and alpha-linolenic acid (ALA), the main precursor of the ω-3 FA family. Recent evidence has shown that in the setting of inadequate LA and ALA, provision of their respective downstream metabolites, arachidonic acid (ARA) and docosahexaenoic acid (DHA), prevents EFA deficiency (EFAD) and supports adequate growth.[12,13]

The oil source(s) used in an ILE and its final percentage in the emulsion determine the different FA composition of each ILE product Table 2. Differences in FA composition account for the additional benefits or detrimental effects of specific ILEs. ILEs have been manufactured with one or more of these five types of oil: soybean, safflower, coconut (ie, medium-chain TGs [MCTs]), olive, and fish.

Soybean oil (SO) has been the most widely used oil source in ILEs. SO contains high concentrations of polyunsaturated FAs (PUFAs), with an ω-6:ω-3 ratio of LA to ALA of ~7:1.[14] Twenty-five percent of the FAs in SO come from oleic acid, a nonessential ω-9 FA.

Safflower oil has been used in ILE alone or in combination with SO in the United States. It was used as an alternative to SO in hopes of reducing the risk of fat overload syndrome.[15] Compared with SO, safflower-based ILE has higher concentrations of LA (77% vs 54%) and less ALA (0.5% vs 8%). When used as a sole oil source, safflower oil can predispose patients to ω-3 FA deficiency.[16] Currently, no commercially available ILE contains safflower oil.

Olive oil (OO) is rich in oleic acid, an ω-9 FA. Because OO does not contain precursors of eicosanoids, this monounsaturated FA is considered to be immune neutral. OO contains a small amount of LA and must be combined with another oil source rich in EFAs to prevent deficiencies. A currently available OO,SO-ILE is a blend of 80% OO and 20% SO, providing a mean concentration of LA of 35.8 mg/ml (range, 27.6–44.0 mg/ml) and ALA of 4.7 mg/ml (range, 1.0–8.4 mg/ml).[10]

Fish oil (FO) contains little LA and ALA but contains their downstream metabolites, ARA, eicosapentaenoic acid (EPA), and DHA.[13] The lower concentrations of LA and ALA have raised concerns about increasing the risk of EFAD when FO-ILE is used as monotherapy. However, in humans, when dosed at 1 g/kg/day, FO-ILE monotherapy has been shown to be effective in preventing EFAD development as well as reversing preexisting EFAD.[17]

MCT sources are derived from coconut and palm kernel oils and contain saturated FAs that are 6–12 carbons in length and include caprylic and capric acids.[18] MCT is devoid of EFA and thus cannot be used as the sole source of lipid.

ILE INDICATIONS

ILE is indicated in all neonates, infants, and pediatric patients requiring PN, as it is an essential component of nutrition that provides the energy, FAs, and substrate required for normal growth and development. For neonates, including those born prematurely prior to 37 weeks' gestational age (GA), PN with ILE is essential in providing energy and FAs to support growth and development until full enteral feedings can be established. Neonatal patients often develop surgically induced intestinal failure (IF) following conditions such as necrotizing

TABLE 2 Composition and properties of ILE products[1]

Category	Component[a]	OO,SO-ILE[10]	SO-ILE[6]	SO-ILE[7]	FO-ILE[9]	SO,MCT,OO,FO-ILE[8]
Source oil	SO, %	20	100	100	0	30
	FO, %	0	0	0	100	15
	MCT, %	0	0	0	0	30
	OO, %	80	0	0	0	25
Additives	Egg phospholipid, g/100 ml	1.2	1.2	1.2	1.2	1.2
	Glycerin, g/100 ml	2.25	2.25	2.5	2.5	2.5
	α-Tocopherol, mg/100 ml	3.2	0	0	15–30	16.3–22.5
	Sodium oleate, g/100 ml	0.03	0	0.03	0.03	0.03
ω-3	Linolenic acid, %	0.5–4.2	4–11	4–11	1.1 (mean)	1.5–3.5
	EPA, %	0	0	0	13–26	1–3.5
	DHA, %	0	0	0	14–27	1–3.5
ω-6	Linoleic acid, %	13.8–22	44–62	48–58	1.5 (mean)	14–25
	Arachidonic acid, %	0	0	0	0.2–2	NR
ω-7	Palmitoleic acid, %	0	0	0	4–10	NR
ω-9	Oleic acid, %	44.3–79.5	19–30	17–30	4–11	23–35
Saturatedfatty acids	Caprylic acid, %	0	0	0	0	13–24
	Capric acid, %	0	0	0	0	5–15
	Palmitic acid, %	7.6–19.3	7–14	9–13	4–12	7–12
	Stearic acid, %	0.7–5	1.4–5.5	2.5–5	0	1.5–4
	Myristic acid, %	0	0	0	2–7	NR
	ω-6:ω-3 ratio	9:1	7:1	7:1	1:8	2.5:1
	Phytosterols,[48] mg/L	208.8 ± 39.4	422.4 ± 130.5	NR	0	142.2 ± 15.3
Energy, kcal/ml		2	2[b]	2	1.12	2

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentanoic acid; FO-ILE, fish oil lipid injectable emulsion (Omegaven [Fresenius Kabi, Uppsala, Sweden]); NR, not reported; OO,SO-ILE, olive oil, soybean oil lipid injectable emulsion (Clinolipid [Baxter Healthcare Corporation, Deerfield, IL]); SO-ILE, soybean oil lipid injectable emulsion (Intralipid [Baxter Healthcare Corporation, Deerfield, IL]; Nutrilipid [B. Braun Medical Inc, Bethlehem, PA]); SO,MCT,OO,FO-ILE, soybean oil, medium-chain triglycerides, olive oil, fish oil lipid injectable emulsion (SMOFLipid [Fresenius Kabi, Uppsala, Sweden]).

[a]The "%" symbol in this column refers to the percent of total oil content of the product.

[b]This applies for the 20% product, whereas there is also a 30% product to be used for compounding purposes only, having an energy content of 3 kcal/ml.

[Correction added on December 7, 2021, after first online publication: The value in the OO,SO-ILE column for the component α-Tocopherol, mg/100 ml was corrected from '32' to '3.2'.]

enterocolitis (NEC), gastroschisis, and/or intestinal atresia or can present with congenital motility or intestinal mucosal disorders resulting in long-term dependence on PN.

Considerations for use

A recent systematic review of ILE use in preterm infants from the Cochrane Neonatal Group showed that regardless of ILE used, there were no statistically significant differences in clinically important outcomes.[19] The outcomes evaluated included growth, bronchopulmonary dysplasia (BPD), sepsis, retinopathy of prematurity (ROP) stage ≥3, IF-associated liver disease (IFALD), or death. However, there are special considerations that influence the choice of ILE product use based on oil sources and resultant FA composition. Considerations for use often apply long-term (ie, longer than a few days), in which the FA composition administered over time could potentially aggravate diseases to which neonates, infants, and pediatric patients are predisposed, especially those conditions that are associated with inflammation. Within the last 5 years, newer alternative ILE formulations have become available in the United States, permitting the use of ILEs other than pure SO-ILE. Currently, only SO-ILE and FO-ILE are US Food and Drug Administration (FDA) approved for use in neonatal and pediatric patient populations (Table 1). However, use of other ILE formulations containing various oil sources has been common internationally. With the familiarity of these products internationally, guidelines outside of the United States have suggested the use of ILEs other than pure SO-ILE as the primary ILE in neonatal and pediatric patient populations receiving PN for more than a few days.[20]

IFALD and ILE components

IFALD is a serious complication seen in infants and children with IF receiving long-term PN, primarily in infants with a history of prematurity and/or bowel resection resulting in short-bowel syndrome. Cholestasis, the typical presentation of neonatal and pediatric IFALD, is generally defined as an elevated serum direct bilirubin level ≥2 mg/dl (34.2 μmol/L) in the absence of infection or inflammation. If PN is unable to be discontinued, IFALD can either progress to end-stage liver disease or can be stabilized or possibly reversed if intestinal adaptation can occur. Recently, the term IFALD has replaced the old terminology of "PN-associated liver disease (PNALD)" or "PN-associated cholestasis (PNAC)" as the preferred terminology.[21]

The pathogenesis of IFALD is multifactorial.[21] IFALD may be partly due to the harmful components (such as phytosterols) within PN or a result of the pathophysiology of IF. ILEs made from oils containing high concentrations of the ω-6 PUFAs (eg, LA) and low concentrations of the ω-3 PUFAs (eg, ALA) have been linked to predisposing patients to IFALD. SO-ILE is rich in phytosterols. Phytosterols are naturally occurring compounds similar in structure to cholesterol found in plant cell membranes. Nghiem-Rao et al evaluated serial blood phytosterol concentrations in a group of 45 neonates and reported that higher sitosterol (the predominant phytosterol) levels were observed in very preterm infants receiving SO-ILE compared with those in controls (N = 9). This may lead to hepatoxicity in neonates.[22]

Vitamin E content in ILE may also limit the development of IFALD. One vitamin E isomer, alpha-tocopherol, may be involved in bile acid synthesis and prevent hepatic damage. Newer ILE products, such as OO,SO-ILE, FO-ILE, and SO,MCT,OO,FO-ILE, have alpha-tocopherol added (Table 2) to limit the amount of PUFA peroxidation,[23] whereas SO-ILE contains the less bioactive gamma-tocopherol. Lower plasma lipoprotein concentrations of alpha-tocopherol have been reported in patients receiving prolonged courses of SO-ILE, which may increase the risk of developing IFALD.[1]

With respect to choice of ILE in the setting of IFALD, balancing provision of calories, EFAs, and potentially protective α-tocopherol against the harmful effects of phytosterols is paramount to patient outcomes and safety. When choosing ILEs, consideration of prevention vs treatment of IFALD as well as populations studied and FDA approvals is necessary. Currently, only one ILE, an FO-ILE, has been FDA approved as a source of FAs and energy in infants and children with established IFALD. It was not approved as a means of preventing IFALD.

Prior to the availability of FO-ILE and other alternative ILE products, restriction of SO-ILE (also known as dose minimization) was the mainstay of therapy in preventing and treating IFALD. Prior to newer ILE formulations, the ASPEN guidelines for management of pediatric patients with IF suggest the limited use of pure SO-ILE, especially in infants at risk of developing IFALD.[24] Colomb et al showed a link between reduced SO-ILE doses and normalization of serum conjugated bilirubin.[25] Cober et al reported that severe SO-ILE restriction (ie, 1 g/kg/day twice weekly) was associated with a progressive decline in bilirubin levels in infants with IFALD, although there was a trend toward developing biochemical EFAD.[26] In those instances when EFAD was identified, the frequency of SO-ILE was increased from two to three times per week; if the patient continued to exhibit EFAD, the dosage was increased from 1 to 2 g/kg/day three times per week. Conversely, other studies did not demonstrate a benefit of ILE restriction on preventing IFALD. In 2016, Levit et al reported a multicenter randomized controlled trial of 136 premature neonates comparing SO-ILE at 1 g/kg/day with ~3 g/kg/day and found no difference in cholestasis rates.[27] Similarly, in 2017, a multicenter randomized controlled trial compared outcomes of 36 neonates with gastrointestinal disorders treated with low-dose SO-ILE (1 g/kg/day) or conventional dosing (3 g/kg/day). There was no difference in cholestasis, growth, and duration of PN. The authors reported that in the low-dose group, the rate of direct bilirubin rise was slower.[28]

Compared with SO-ILE, an alternative ILE containing SO,MCT,OO,FO demonstrated improvements in gamma-glutamyl transferase (GGT),[29] whereas others found no differences between the ILE products.[29,30] Infants in another study showed lower conjugated bilirubin levels with SO,MCT,OO,FO-ILE compared with SO-ILE.[31] Unfortunately, EFA status was not assessed in the majority of studies involving SO,MCT,OO,FO-ILE. One case series in which EFA status was assessed showed that doses <2.5 g/kg/day were associated with a trend toward EFAD, whereas higher doses increased the risk of IFALD.[32] Another case series followed a group of pediatric IF patients receiving SO,MCT,OO,FO-ILE at a median dose of 2 g/kg/day over 1.5 years.[33] ALA, LA, ARA, and DHA all significantly increased and remained normal within the reference range. Mead acid (MA), EPA, hepatic function, TGs, and the triene:tetraene ratio did not change significantly over time. Although retrospective in nature with a small sample size (N = 20), this case series suggests the SO,MCT,OO,FO-ILE can maintain EFA levels over prolonged periods of time.[33]

BPD and ROP

BPD occurs following premature birth resulting from underdeveloped lungs exposed to respiratory support, leading to a cycle of damage and repair of the lung. Besides the effects on the lungs, BPD results in long-term effects on growth and neurodevelopment.[34,35] In the neonatal population, the use of ILEs containing FO has been postulated to improve rates of BPD because it is a condition associated with inflammation and oxidative damage.[36] This is believed to be a result of the increased ratio of ω-3 to ω-6 FA and increased provision of vitamin E in these products. Results from studies examining the benefits of FO-containing ILEs on BPD have been mixed, with some showing decrease in BPD rates but not in overall BPD outcomes.[37] In a Cochrane meta-analysis by Kapoor et al, the use of FO-containing ILEs vs SO-ILEs failed to show an effect on BPD.[19]

Like BPD, ROP is a condition in premature neonates that is associated with inflammation and oxidative damage. ROP is a retinal vasoproliferative disease associated with premature birth and is a major cause of blindness in developed countries.[38] ROP consists of two phases: delayed retinal vascular growth and the resulting hypoxia within the developing retina due to insufficient vascularization. This hypoxia leads to the release of growth factors causing new and abnormal blood vessel growth.[39] DHA, which is present in FO-containing ILE products, is associated with retinal development.[37] Benefits in regard to ROP were shown in studies comparing non–FO-containing ILEs with FO-containing ILEs.[40,41] A meta-analysis by Vayalthrikkovil et al including four randomized controlled trials and two observational studies showed a reduction in the incidence of severe ROP or need for laser therapy among premature infants with the use of FO-containing ILE formulations.[42] However, another Cochrane meta-analysis by Kapoor et al did not show a statistically significant benefit of any ILE formulation with or without FO on the incidence of ROP.[43] Further research is needed in both areas to assess the benefits of newer ILE formulations in regard to BPD and ROP.

Although not FDA approved in pediatric patients, OO,SO-ILE and SO,MCT,OO,FO-ILE have been FDA approved in adults as a source of energy and EFAs for PN when oral or enteral nutrition is not possible, is insufficient, or is contraindicated. Although few studies demonstrate improved cholestasis or other improved health outcomes associated with OO,SO-ILE or SO,MCT,OO,FO-ILE use, interpretation of these studies is limited by use of differing dosages, short-term follow-up, small sample sizes, and reliance on proxy outcomes.[19,43,44] OO,SO-ILE and SO,MCT,OO,FO-ILE provide potential physiologic and nutrition benefits to patients receiving long-term PN, including the provision of EPA and DHA from ILEs containing FO. If a pure SO-ILE shortage was to occur in the United States, consideration of the use of newer alternative ILE should be given in order to provide essential calories and nutrients to neonatal and pediatric patients.

PRESCRIBING

Education of healthcare professionals with the responsibility of prescribing PN therapy can improve the ordering process and may reduce prescribing errors.[1,45] Organizations should have specific policies that address the competency required to prescribe PN therapy, including the ILE component.[46] The prescriber should place an appropriate order through a standardized electronic order (it is suggested that, ideally, this should be via a computerized prescriber order entry [CPOE] system with decision support directly or as a link from the standardized electronic order) and be consistent with current guidance documents on PN prescribing.[1,47]

Because of the number of ILE products available with unique characteristics[1] (Table 2), the standardized order should include the brand name of the ILE product.[1] ILE product shortages must be communicated to the prescriber with a plan for allocation and use of therapeutic alternative(s). Any product outage should be addressed in the electronic PN order template.

The dose of ILE is ordered as the amount per day (ie, grams per kilogram per day).[1] The dose should be based on patient characteristics and other sources of nutrition. A recent ILE survey with gap analysis revealed 57.1% of ILEs are administered as a separate infusion in pediatric patients and 88.8% infused ILE separately in neonates.[2] If the total daily dose of ILE (as a TNA or administered separately) is being infused over a duration of <24 h, then the rate of infusion should not exceed the maximum rate. The maximum rate for SO-ILE is 0.15 g/kg/h.[49,50] Contact the manufacturer for the maximum rate of ILE infusion for their products. The recommended daily dose for ILE in neonates and pediatrics is provided in Table 3. SO-ILE and FO-ILE are indicated for pediatric use in the United States. Of note, the use of SO,MCT,OO,FO-ILE and OO,SO-ILE in pediatrics is currently off-label in the United States.

ILE selection and dosing considerations are important in pediatric patients at risk of or diagnosed with IFALD. ILE dose minimization of SO-ILE is a strategy that was introduced prior to alternative ILE formulations being approved and/or available for use within the United States.

TABLE 3 Published pediatric dosage for ILE products

	OO,SO-ILE, g/kg/day[50,51]	SO-ILE, g/kg/day [6,7]	FO-ILE, g/kg/day [9]	SO,MCT,OO,FO-ILE, g/kg/day [31]
Preterm neonate	3[a]	3	1[a]	3[a]
Term neonate, infant (0–12 months)	3[a]	2.5–3	1[a]	3[a]
Pediatric (1–10 years)	3[a]	2.5	1[a]	2.5–3[a]
Adolescent (11–17 years)	2.5[a]	2–2.5	1[a]	2–2.5[a]

Abbreviations: FO-ILE, fish oil lipid injectable emulsion (Omegaven [Fresenius Kabi, Uppsala, Sweden]); OO,SO-ILE, olive oil, soybean oil lipid injectable emulsion (Clinolipid [Baxter Healthcare Corporation, Deerfield, IL]); SO-ILE, soybean oil lipid injectable emulsion (Intralipid [Baxter Healthcare Corporation, Deerfield, IL]; Nutrilipid [B. Braun Medical Inc, Bethlehem, PA]); SO,MCT,OO,FO-ILE, soybean oil, medium-chain triglycerides, olive oil, fish oil lipid injectable emulsion (SMOFLipid [Fresenius Kabi, Uppsala, Sweden]).

[a]1.5 g/kg/day has been used off-label for FO[51] doses for OO,SO-ILE, and SO,MCT,OO,FO-ILEs are also considered to be off-label.

Dosing of SO-ILE at 1 g/kg/day has been employed in infants at risk of IFALD.[52] The SO-ILE dose minimization strategy carries the risk of patients developing EFAD.[53] SO,MCT,OO,FO-ILE has been reported in pediatrics as an alternative to SO-ILE formulations as a lipid source associated with less hepatotoxicity.[54,55] A multicenter phase 3 study to determine the role of SO,MCT,OO,FO-ILE vs SO-ILE in preventing IFALD should provide greater clarity as to the role of SO,MCT,OO,FO-ILE within the neonatal and infant population.[56] Development of EFAD has been reported after inappropriate lipid minimization with SO,MCT,OO,FO-ILE.[57] Prescribers should be aware that SO,MCT,OO,FO-ILE and OO,SO-ILE have considerably lower levels of EFAs than SO-ILE formulations, and therefore, the same lipid minimization strategies used with SO-ILE should not be extrapolated for use with these ILE products. Labeled dosing recommendations for FO-ILE is 1 g/kg/day. FO-ILE has strong evidence supporting its use in IFALD patients and has been associated with reduction of bilirubin levels. There have been reports of FO-ILE doses of up to 1.5 g/kg/day when additional calories are necessary and unable to be provided by higher dextrose loads.[51] Although FO contains minimal ALA and LA, patients receiving FO-ILE at recommended doses have not developed clinical EFAD, because of DHA and EPA content within FO-ILE.[58]

ORDER REVIEW

The PN process should involve a knowledgeable pharmacist reviewing the PN and ILE orders to optimize patient safety and efficacy.[59] Breaches in the review process may lead to errors and patient harm, including insufficient or excessive dosing, as well as infusion rates exceeding maximum recommendations. Healthcare organizations should have written policies and procedures outlining PN order review by the pharmacist.[45] A national survey revealed 23% of organizations did not dedicate any pharmacy staff to this critical step.[60] Specifically, in regards to neonatal and pediatric patients, dosing requirements, recognition of potential allergy considerations, and administration via potentially limited vascular access are essential to ensure safe provision of PN and ILE in these patient populations. The review process is provided in Table 4.

A checklist is recommended to ensure all elements of review are addressed.

ILE should be ordered as an amount per kilogram per day in neonatal and pediatric patients. Additionally, the ILE order should be evaluated to determine whether the prescribed amount is pharmaceutically stable and compatible with other components of the PN admixture at the ordered doses/volumes, as well as other medications.[45] Patients with a history of anaphylactic allergic reactions to eggs, fish, peanuts, soybean, or any of the active ingredients or excipients should be evaluated for suitability prior to receiving ILE containing the offending ingredient(s). Pharmacists should evaluate all documented allergies for any contraindications to ILE. For patients with either a soybean or fish allergy, ILE formulation selection is critical in order to avoid the offending oil source. However, patients with egg allergies are unable to utilize any of the currently available ILE formulations because egg serves as the emulsifying agent in all ILE products. Regardless of allergy history, patients should be monitored carefully during the first 15 min of the initial infusion for symptoms of allergic reaction or intolerance.

PREPARATION

As part of the ASPEN ILE national survey, the use of TNAs was evaluated. Of those responding, TNAs were used in 42% of adults, 27% of pediatric patients, and 8% of neonates, indicating most neonatal and pediatric patients receive ILEs as a separate infusion.[2] At the time of the survey, only 22% of institutions responding had access to a Multi-oil ILE product

TABLE 4 Parenteral nutrition order review process[45,61]

Order topic	Content to review
Patient	• Identifiers—name, medical record number, or other unique identifiers; location • Birth date and/or age • Allergies and associated reactions • Height and dosing weight in metric units
Parenteral nutrition	• Indication(s) • Administration route (peripheral vs central)/vascular access device • Volume and infusion rate • Infusion schedule (continuous or cycle) • Type of formulation (dextrose/amino acids with separate infusion of ILE or TNA)
Order review and problem resolution[a]	• Date and time order submitted • Administration date and time • Laboratory values • Other medications/fluids the patient is receiving as a separate infusion • Additional non-intravenous medications the patient is receiving • Contact information for the prescriber

Abbreviations: ILE, lipid injectable emulsion; TNA, total nutrient admixture.

[a]Each parenteral nutrition order is to be reviewed for appropriate dose based on age and clinical condition as well as stability and compatibility throughout the beyond-use date. Issues and problems should be resolved with the prescriber prior to parenteral nutrition compounding.

(ie, SO,MCT,OO,FO-ILE); most continued to compound with SO-ILE. Currently, all ILE formulations are only commercially available in package sizes that are not appropriate for neonatal patients, who typically receive doses in the range of 10–20 ml/day. When the original manufacturer's containers are used in a neonate, the potential for administration errors exists. ILE infusion errors are a leading cause of medication errors among pediatric patients. Although the 2014 ASPEN PN Safety Consensus Recommendations[45] strongly recommend against the practice, it is for the above-mentioned safety reasons that ILEs are commonly repackaged into smaller volumes using syringes and infused via a syringe pump in the neonatal and infant population. According to the ASPEN ILE survey, ILE was repackaged into syringes (56% pediatric, 81% neonate) most commonly, followed by the drawdown method (31% pediatric, 9% neonate).[2] Repackaging into syringes is often done to decrease waste, especially if there are concurrent product shortages, but has the potential for microbial contamination and requires stability data for the use of product in a different container. Both the drawdown method, in which excess ILE is removed and the dose is dispensed in the manufacturer's original container, and repackaged syringes reduce the risk of administering excessive lipid volume from a large commercial container. If ILEs are not repackaged or manipulated but instead supplied directly from the commercially available container, safety parameters should be in place to prevent medication errors related to incorrect programming of the infusion pump. With the increased safety checks within newer infusion systems, dose limits and minimum infusion times can be hardwired into the process to minimize these type of errors. Additionally, utilization of CPOE integration with the infusion pumps is another mechanism to prevent human error. However, categorizing PN or ILE as a titratable medication may reduce the safety-net functionality, as dosing in an acceptable range that could apply to multiple patient populations may be required.

ILE repackaging

Stucki et al evaluated the influence of environmental cleanliness and risk manipulations on hospital-filled syringes.[62] They reported that syringes prepared in the operating room and on the nursing unit had contamination rates of 6% and 16%, respectively ($P < .0001$); only those prepared in an ISO class 5 laminar airflow hood within an ISO class 7 drug preparation area remained sterile. Studies investigating the impact of ILE repackaging did not determine the point at which the contamination of the syringe occurred: at the time of compounding or during the administration process.[63,64] Contamination of ILEs and subsequent nosocomial infections have been well described.[65–70] Because in the neonatal and pediatric patient, ILEs tend to infuse separately from the amino acids–dextrose solutions and the ILE may not be infused from the primary ILE container, there is more potential for infectious complications. Typical contaminants that are known to thrive in ILEs include *Escherichia coli*, *Staphylococcus epidermidis*, diptheroids, micrococci, *Malassezia furfur*, and *Candida*

albicans.[65,66] Obayashi et al demonstrated that single-use packages of ILEs inoculated with opportunistic bacteria *Serratia marcescens* and *Burkholderia cepacia* had considerable microbial proliferation.[66] Contaminated intravenous admixtures administered through a central venous catheter are a rare cause of catheter-related bloodstream infections (CRBSIs) but are one of the most readily identifiable causes of epidemic nosocomial bacteremia. In most instances, the outbreak involves a single organism. However, it is not common practice to culture infusate specimens as part of diagnostic evaluation for a CRBSI unless there is strong epidemiologic evidence to do so. It is possible that many instances of infusate contamination–related infection may go undetected. In 2007, in response to nosocomial infusate infections, the US Pharmacopeial Convention (USP) revised its standards for the preparation of sterile products that addressed the environmental conditions, storage requirements, and training of staff involved in the intravenous admixture process.[71]

If a syringe pump is utilized to infuse the ILE, repackaging should occur daily using strict aseptic technique. If two syringes are needed, the unused syringe should be refrigerated until the time of administration and then allowed to come to room temperature prior to infusion, for patient comfort.[72,73] Enough volume of ILE should be dispensed to allow for priming of the intravenous tubing (ie, 10–25 ml depending on infusion set). The use of non-DEHP infusion sets and containers is recommended.

Because of the increased requirements for calcium and phosphorus, neonatal and pediatric PN poses compatibility and stability issues for TNA. These electrolytes require lower pH for best solubility, which has the potential to destabilize the emulsion. Therefore, it is often unsafe to compound a TNA for most neonatal and pediatric patients unless utilized in a home care setting with specific limitations. Some programs use multichamber bags (MCBs) to help improve stability of the TNA because the contact time between the ILE and the rest of the PN components is limited. In the survey of those centers using commercially manufactured MCB PN, nearly 5% add separate ILEs to their two-chambered PN.[2] The reviewing pharmacist must still evaluate the prescribed formulation for compatibility of each ingredient with all other ingredients and the stability of the final TNA emulsion; once the ILE has been added to the MCB, it is no longer a two-in-one formulation.[61]

Unstable or incompatible TNA is rarely obvious to the unaided eye.[74] Among other factors, pH and electrolyte concentrations can impact TNA stability. A nonacidic pH is necessary to maintain emulsion stability, which limits calcium-phosphate compatibility. The zeta-potential maintains the homogeneous dispersion of sub-micrometer fat droplets in water.[1] The high concentration of cationic electrolytes (especially of divalent cations) in a TNA reduces the zeta-potential, which can destabilize the lipid emulsion. When the final concentration of the ILE is reduced upon addition to a TNA, the admixture may become less stable. It has been previously recommended that to ensure TNA stability, the final concentration should be at least 2% SO-ILE, 4% AA, and 10% dextrose.[45]

Most TNA compatibility information is derived from admixtures containing only SO-ILE. Multi-oil ILEs containing other oil sources, such as MCTs, may improve overall TNA stability by decreasing the stress on the emulsifier.[74] ILEs containing OO may also be more stable than those with SO alone or with safflower oil.[75]

ADMINISTRATION

In the majority of neonatal and pediatric patients, ILE is typically being administered separate from the amino acids–dextrose solution. ILE infusion is usually via a Y-site into the same catheter as the PN. ILE is infused using a 1.2-μm in-line filter located below the bifurcation of the tubing, closest to the catheter hub.[76] When ILE is infused separate from PN, utilizing a different intravenous vascular access device (VAD), each infusion line (PN and ILE) should include a 1.2-μm filter between the infusion container and the intravenous catheter.

Between January 1, 2000, and December 31, 2005, 54 of 173 hospitals (30%) participating in MEDMARX reported errors involving ILE.[77,78] Oftentimes, errors are a result of human error, infusion pump programming errors (eg, switching the infusion rate of the PN and the ILE), misconnection of tubing, or infusion device failure. In such cases, patients may simply experience hypertriglyceridemia that resolves upon discontinuation of the ILE. In other cases, more-serious complications such as respiratory failure, metabolic acidosis, and even death have been linked to very rapid infusion of ILE.[79–81]

Ideally, ILEs should be infused directly from the original manufacturer's container, but as mentioned previously, concerns exist regarding the volume provided in these commercially available preparations. The source container, whether it is the original container or a repackaged bag or syringe, should be changed 12 h after its initial entry.[79] In pediatric patients, ILE is commonly infused over 24 h. This can be accomplished by dividing the total daily dose into two containers that are replaced after 12 h. A vented spike should be used to infuse an ILE contained in a glass bottle; nonvented spikes can be used when infusing ILE from a bag.[9]

ILEs are susceptible to light oxidation and formation of free radicals, lipid peroxides, or other degradation products.[82] Infants receiving non-photoprotected PN have higher levels of urinary peroxides compared with infants

receiving photoprotected PN.[83] Photoprotection can be either partial (bag only) or complete (ie, protecting the PN admixture, the administration sets, and the pharmacy preparation process). Complete photoprotection is associated with lower amounts of peroxides. In preterm infants, complete photoprotection has been associated with an improved enteral intake.[84] ILEs, because they are rich in PUFAs and vitamin E, may be more prone to the effects of photooxidation. Neuzil et al demonstrated that when SO-ILE was exposed to phototherapy light for 24 h, the concentrations of hydroperoxides in the ILE increased 60-fold (from a baseline of ~10 μmol/L).[85] In comparison, at the end of a 24-h SO-ILE infusion period, the ILE for infants in the neonatal intensive care unit who did not receive phototherapy contained a mean of 40 μmol/L hydroperoxides as compared with 97 μmol/L for infants who received phototherapy.[85] The authors recommend protecting ILEs from ambient light and phototherapy. ASPEN recommends photoprotection of PN admixtures and ILEs for neonates.[86] Insufficient information exists for advising photoprotection of PN admixtures and ILEs administered to older children and adults.[86]

Whenever an ILE is infused separately from the amino acids–dextrose solution, there is a risk of an inadvertent rapid infusion of the ILE. Depending upon the oil source, patients may experience hypertriglyceridemia that resolves upon discontinuation of the infusion; in other cases, complications such as fat overload syndrome can occur. Fat overload syndrome is characterized by hepatosplenomegaly, respiratory distress, headaches, jaundice, and spontaneous hemorrhage.[87] Adverse effects associated with fat overload syndrome are due, in part, to increases in serum TG levels that occur when infusion rates exceed the rate of lipid hydrolysis. This is seen when the recommended maximum ILE infusion rate (in grams per kilogram per hour) is exceeded. Furthermore, the plasma concentrations of FA increase if the rate of lipid hydrolysis exceeds the rate of uptake and oxidation of free FAs.[88] Management options are limited to stopping the infusion and the use of supportive care to avoid the aforementioned complications, although plasma exchange has also been used.[89] Most published case reports of rapid infusions of ILE have been limited to those involving SO-ILE.[80] Rapid infusion of FO-ILE resulted in transient hypertriglyceridemia, which resolved within 14 h without complications of fat overload.[90]

In the event of a rapid infusion of ILE, regardless of oil type, management should consist of supportive care, with serum TG levels checked 4 h after the discontinuation of the infusion; the expectation is that levels will return to baseline during that time. In the event TG levels continue to remain elevated, serial TG levels should be rechecked at 4-h intervals until they normalize. Strategies to avoid rapid ILE infusion include independent double checks, checklists, and completion of the entire setup including pump programming prior to setting up the second infusion.[45]

Coadministration of medications with ILE is always a challenge, given limited vascular access and risks for incompatibility. When evaluating compatibility and stability of a medication with ILE based on either the manufacturer's recommendations or primary literature sources, it is important to focus on the methodology of testing, specific ILE formulation utilized, other medications or components also infused with the products, and the concentration of the medications infused. The manifestation of physical instability of ILE includes increases in the mean droplet size of ILE and growing proportions of large lipid particles, which include peroxide formation and pH change without necessarily impacting the physical stability of the emulsion.[91] ILE physical instability may occur not only in a TNA but also with Y-site administration.[92] Compatibility data from one type of ILE should not be applied to another. In some cases, it may be necessary to place a peripheral catheter and infuse an ILE formulation separately. ILEs are isotonic and may be infused through peripheral catheters, alone or co-infused with a dextrose-containing carrier fluid. In the rare cases that the ILE infusion must be interrupted to administer a medication, the entire prescribed daily ILE dose must be administered to help prevent an EFAD.[93] For FO monotherapy or Multi-oil ILEs, this requires the calculation of the maximum safe ILE infusion rate, so rate adjustments may be made to allow for the total daily dose that is ordered to be infused. When using SO-ILE, this approach may not be applicable, because of the higher content of EFAs and the potential to exceed the maximum safe SO-ILE administration rate.

Likewise, a medication may be compatible with an ILE when given via Y-site but not when coadministered into a TNA or vice versa. If there are no compatibility data, the ILE infusion should be stopped, the VAD flushed with either 0.9% sodium chloride or 5% dextrose in water (if the medication is not compatible with 0.9% sodium chloride), and the medication administered, followed by a second flushing of the VAD and resumption of the ILE infusion. In the case of a medication being coadministered into a VAD in which a TNA is infusing, it may be necessary to taper the TNA off prior to administering the medication and restarting the TNA when the medication infusion is complete or to co-infuse a similar dextrose-containing intravenous fluid. Flushing of the VAD per policy will also be necessary. The most recent review of VAD flushing for neonatal and pediatric patients focuses on preventing catheter occlusion but includes heparin in many of the recommendations. VAD flushing policies are evolving away

from the use of heparin in favor of 0.9% sodium chloride flushes.[94]

Transitions of care

There is very little literature that describes the process for a safe transition of nutrition care in the pediatric patient. There are, however, numerous issues to consider when the use of any ILE is involved. Whenever possible, the use of a TNA product can minimize issues for the caregivers. This minimizes preparation time and decreases the number of infusion devices the caregiver will need to set up as well as provides some cost savings.[95] Using a TNA may not always be possible, because of the lack of appropriate compatibility and stability information. Compatibility and stability of ILEs are different for each product.[96] The type of ILE utilized can affect the stability of the PN and should be taken into consideration if the use of a TNA is contemplated.[97]

Pediatric patients occasionally require supplemental intravenous medications or fluids. Relative lack of intravenous access necessitates the use of the PN catheter to administer these medications. Co-infusion of intravenous medications or fluids should be done with caution and include careful assessment of compatibility with the PN, TNA, and/or ILE. Safeguards should also be put into place to ensure the multiple intravenous fluids are administered via the correct VAD as well as at the correct rate.

Small pediatric patients who require long-term PN may only need small volumes of ILE. These volumes may not be stable enough to use in a TNA. Strategies that have been employed include providing a 7-day total volume of ILE in fewer days per week or the use of an MCB with the ILE being added just prior to administration. However, when administering ILE in a two-chambered bag, TNA compatibility guidelines still must be adhered to. These compounds, despite being combined immediately before administration, should not be considered the same as a two-in-one with the ILE coadministered.

There may be third parties (ie, compounding pharmacies) that restrict the type of ILE they will dispense, which can affect stability and compatibility. The lack of specificity by the discharging prescriber of the ILE to be utilized can lead to the home care agency substituting another ILE or changing the amino acid source, which could also affect stability and safety.[98] To minimize this risk, prescribers should note "do no interchange" if they feel it is necessary that specific brands of ILE or amino acids must be used to safely compound the admixture. Similarly, home care companies should have evidence to ensure the stability of substituted ILE or amino acid products.

MONITORING

Patients receiving ILE should be monitored to ensure the dose of ILE is appropriate and that the infusion and content are well tolerated. Appropriate monitoring includes consideration of the following issues.

Serum TG concentration

Hypertriglyceridemia is defined in the pediatric patient as a serum TG level >200 mg/dl.[99] It develops from a variety of risk factors, including infection, inflammation, hypothyroidism, renal and liver failure, insulin resistance, diet, or medications.[99] Nutrition factors linked with hypertriglyceridemia include macronutrient excess (either as carbohydrate or fat), poor glycemic control, and carnitine deficiency.[100] If left untreated, severe hypertriglyceridemia may predispose patients to complications such as pancreatitis, lipid pneumonitis, and neurologic changes, including kernicterus.

Hypertriglyceridemia is a common complication in patients receiving PN, occurring in up to 33% of adult patients receiving PN.[100] In most cases, the treatment for PN-induced hypertriglyceridemia is to reduce the dose or discontinue the ILE infusion for 4–6 h to allow for TG clearance. Inclusion of carnitine within the PN solution has also been utilized to assist with patients with hypertriglyceridemia. Carnitine is essential for the transport of long-chain FAs into the mitochondria and for appropriate metabolism.[101] Without enteral nutrition or the inclusion in PN solution, carnitine deficiency will develop within 2 weeks. Neonatal patients are naturally carnitine deficient if born prior to 32–34 weeks' GA, as carnitine accrual primarily occurs during the third trimester. Addition of carnitine in PN solutions has been shown to mobilize fat stores and prevent steatosis in neonatal patients.[102]

Influence of oil source on TG clearance/fat overload syndrome

SO-ILE

ILEs containing long-chain TGs (LCTs) from SO tend to clear more slowly than those containing MCTs or FOs.[103] Interestingly, in animal studies, most ILEs, regardless of oil source, will be cleared from the blood within the first 2 min of being infused.[104]

SO-ILE can predispose patients to hypertriglyceridemia. In addition to oil, ILEs contain excipients that provide

~10% of their calories as glycerin (glycerol) and egg emulsifier. These emulsions contain long-chain FAs suspended in a superficial layer of phospholipids. Depending upon the ILE's concentration (10%, 20%, or 30%) and the volume of ILE infused, the amount of phospholipids will vary dramatically. The high free phospholipid content found in a lower-percentage (10%) ILE may interfere with ILE-TG clearance.[5] For this reason, the use of 10% SO-ILE has been discouraged in neonates because of its high phospholipid content per gram of fat.[105] Furthermore, SO-ILE infusion rates >0.15 g/kg/h may exceed the rate of metabolism and can lead to accumulation and further increase in serum TG.[106] The clearance of TGs from the administration of SO-ILE varies with GA and weight for GA, which is particularly noticeable with 4-h infusions of 1 g/kg/day despite maintaining a serum TG level ≤250 mg/dl.[107]

Serum TGs were evaluated in a prospective observational study of extremely low-birth-weight (LBW) infants receiving a PN regimen including 20% SO-ILE up to 2 g/kg/day.[108] Twenty of the 75 patients had a TG level >200 mg/dl, which, upon multivariate analysis, was associated with lower birth weight, but there was no significant difference in ILE dose or age at the time of elevated TG concentration.[108]

In a prospective cohort of 162 neonates receiving PN with 20% SO-ILE dosed at up to 2–3 g/kg/day for at least 2 weeks, hypertriglyceridemia (≥150 mg/dl) was seen in 32 patients (20%).[109] TG concentrations did not differ significantly between those with an infection or without, but those with hypertriglyceridemia were more likely to have hepatic dysfunction (35% vs 12%, $P < .01$) and growth retardation (47% vs 12%, $P < .001$).[109]

Interestingly, in a study of nearly 200 neonates, when the same dose of a SO-ILE formulation was administered from commercial plastic containers, hypertriglyceridemia was more common than in those receiving ILE in the previously available glass bottles (26% vs 6%, $P = .004$).[110] This likely reflected the coarser emulsion found initially in plastic containers with higher content of large fat globules that are more difficult to clear. Additionally, the same dose of SO-ILE administered using a 10% ILE is more likely to be associated with hypertriglyceridemia than a 20% SO-ILE is.[105]

In 30 LBW infants receiving 10% SO-ILE at 2–3 g/kg daily infused over 24 h, serum TG concentrations were higher in those with sepsis (maximum mean TG concentration of 2.02 mmol/L [179 mg/dl] vs 1.15 mmol/L [102 mg/dl], $P < .02$).[111] Daily check of serum TGs and dose reduction to 2 g/kg/day in septic LBW infants are recommended.[111] Otherwise, LBW and very LBW infants (VLBW) can tolerate high doses of ILE in the first week of life. In a randomized, controlled trial in 100 VLBW infants appropriate for GA, the administration of 20% SO-ILE (as a TNA) starting at either 0.5 g/kg or 2 g/kg/day resulted in higher mean serum TG concentrations initially, but only 15% of infants in the high-dose group exceeded 200 mg/dl.[112] While receiving greater energy intake and experiencing less weight loss in that week, the high-dose ILE group also experienced statistically less NEC and ROP.[112]

In 18 LBW infants receiving 10% SO-ILE at 2 g/kg/day infused at 0.084 g/kg/h, serum TG concentrations did not exceed a mean value of 1 mmol/L (85 mg/dl) in the first week of PN therapy.[113] A retrospective review of 356 neonates evaluated serum TG concentrations obtained during ILE administration across four intensive care units.[114] Peak TG values were compared with patient characteristics and clinical outcome. Five percent of levels exceeded 400 mg/dl, and all were in infants weighing <1500 g. Even those with TG 180–400 mg/dl were more likely to be LBW and premature and require ventilator support compared with those below 180 mg/dl.[114] Hypertriglyceridemia was associated with higher mortality (odds ratio = 4.4, $P = .045$) on multivariate logistic regression.[114]

A study assessing tolerance of ILE infusion in 45 neonates (820–1550 g, >27 weeks' GA) evaluated three SO-ILE regimens for up to 8 days, in which the patients were randomized to (1) a stepwise increase from 1 to 4 g/kg/day infused over 24 h, (2) starting at 4 g/kg/day infused over 24 h, and (3) a stepwise increase from 1 to 4 g/kg/day but infused over 16 h with an 8-h break.[115] Although group 3 did not receive the highest dose of ILE, they experienced the highest mean TG concentrations, which were significantly greater than those in the other two groups. The hypertriglyceridemia was associated with ILE infusion rates exceeding 0.16 g/kg/h.[115]

The infusion of SO-ILE (1–3 g/kg/day) in premature infants results in increases in unbound free FAs.[116] Although values are greater than for term infants, the values are elevated at baseline prior to the ILE infusion.[116] Whether the elevation adversely influences binding of other circulating substances (eg, bilirubin, calcium) to albumin has not always been clear in the literature. This study did not evaluate serum bilirubin or calcium concentrations. When bilirubin concentrations have been evaluated in premature infants, the data suggest that the risk for ILE-induced hyperbilirubinemia may be overestimated.[117]

Multi-oil ILE

A retrospective review of 195 VLBW infants <29 weeks' GA receiving 1–3 g/kg/day of ILE (OO,SO-ILE or SO,MCT,OO,FO-ILE) reported that most were able to maintain serum TG levels ≤2.8 mmol/L (~250 mg/dl), but 38 did experience higher concentrations, including 11 with severe hypertriglyceridemia (>4.5 mmol/L [~400

mg/dl]).[118] The latter was more likely to occur in those ≤25 weeks' GA.[118]

It has been common to reduce ILE dosing to 0.5–1.5 g/kg/day in neonates when serum TG levels exceed 250 mg/dl.[119] In a randomized controlled trial comparing SO,MCT,OO,FO-ILE with MCT:LCT-ILE in infants of at least 34 weeks' GA, the standard doses resulted in significantly different proportions of patients experiencing serum TG levels ≥250 mg/dl (9.1% vs 37%, $P = .024$) but similar rates of cholestasis, defined as conjugated bilirubin level >1 mg/dl (18.2% vs 14.8%, not significant).[117] In a retrospective study comparing LCT:MCT-ILE (63%:37%) with LCT-ILE (SO + OO) in adult intensive care unit patients, the change in serum TG levels from baseline was approximately +0.2 mmol/L (~18 mg/dl) with the latter ILE but negligible with the former ($P = .01297$).[120]

Guidelines for pediatric patients receiving specialized nutrition support offer recommendations for the management of hypertriglyceridemia in patients requiring SO-ILE or Multi-oil–ILE, avoiding the use of 10% SO-ILE and overfeeding.[121] Infants and children who exhibit elevated TG levels (ie, >200 mg/dl) while the ILE is infusing over 24 h should have TG levels reassessed by infusing the next dose over 20 h with a repeat TG level obtained after 4 h without the ILE infusing. This ensures the initial elevated TG level was not the result of the ILE actively being infused into the patient. If the TG levels remain elevated, the infusion should continue to be held another 4 h and the TG level rechecked; the infusion should resume when the TG levels are <200 mg/dl.[122]

FO-ILE

Laboratory monitoring for patients receiving FO-ILE is similar to monitoring used for any other ILE. FO enhances the clearance of emulsion particles.[123] The manner in which FO is cleared may account for the apparent absence of fat overload syndrome and its complications in patients receiving rapid infusions of FO-ILE and thus the lack of the black box warning in the package insert for FO-ILE.[50] Unlike SO-containing ILE, FO-ILE appears to be cleared more rapidly from the intravascular space. Fat clearance follows a biphasic pattern, with an initial rapid clearance phase occurring within 10 min, followed by a slower phase of 10–25 min. The mechanisms involved in the hydrolysis of FO-ILE and SO-ILE are different. Removal of chylomicron-sized ω-6 predominate emulsions (ie, SO) is modulated by lipoprotein lipase (LPL), apolipoprotein E (ApoE), low-density lipoprotein receptor (LDL-R), and lactoferrin-sensitive pathways.[90,104] The clearance of chylomicron-sized ω-3 predominate ILEs, such as FO, is independent of ApoE, LDL-R, and lactoferrin-sensitive pathways.[124] According to Park and Harris, FOs accelerate TG clearance by assisting LPL-mediated lipolysis and by reducing chylomicron TG half-lives and particle sizes.[125] For example, in an adolescent patient experiencing chronic hypertriglyceridemia (peak of 628 mg/dl) while receiving intermittent courses of SO-ILE, a switch to FO-ILE allowed reduction of serum TG levels to 183 mg/dl within 3 weeks.[124]

In a case series describing the outcomes of six patients whose FO-ILE was infused at rates exceeding 0.17 g/kg/h, infusion rates as high as 5 g/kg/h were accidentally administered (range, 0.2–5 g/kg/h) without evidence of fat overload syndrome.[90] Brief elevations in serum TG levels were reported but returned to acceptable levels in 12–14 h. Despite studies utilizing higher infusion rates, the manufacturer's package insert should be consulted for recommended maximum ILE infusion rates.

In the event of a rapid infusion of FO-ILE, patients should still be considered at risk for hypertriglyceridemia. The FO-ILE should be stopped immediately, and serum TGs should be checked 4 h later. In general, when TG levels < 250 mg/dl in monitored infants (<400 mg/dl in older children), the infusion of FO-ILE may be resumed.

EFAD

In the general population, EFAD is rare and occurs in patients with malabsorption or who are receiving PN with inadequate fat intake.[126] The clinical signs and symptoms of EFAD include alopecia, eczematous dermatitis, poor wound healing, and growth retardation.[127] One of the original indications for an ILE was to serve as a source of EFAs to avoid the development of EFAD. This deficiency state can occur if <1%–2% of the total energy consumed comes from the ALA and LA. Monitoring of EFA status should be considered in patients who are malnourished, those with signs/symptoms of EFAD, or those patients for whom it is believed they received less than the recommended dose of ILE.

As the concentrations of ARA, a tetraenoic acid, decreases in tissues, the concentration of nonessential FA (ie, MA, a trienoic acid synthesized from oleic acid) increases.[128] MA is produced in states of EFAD and is created from the elongation and desaturation of oleic acid when there is insufficient ω-6 and ω-3 FAs. The Holman index is used to diagnose biochemical EFAD.[128] It comprises the triene (ie, MA) to tetraene (ie, ARA) ratio and can be easily calculated. Values >0.2 are indicative of biochemical EFAD, with clinically observed EFAD not occurring until >0.4.[128] Use of the triene-tetraene ratio should be balanced with the patient's serum values for ALA, LA, ARA, and FA.[129]

TABLE 5 Summary of recommendations for ILE use in neonates and pediatrics

Section	Content summary
Introduction	ILE is more often used as an energy source and administered separate from PN. There are concerns about in-line filtration, compatibility of TNA and medications coadministered with PN, and repackaging of commercial products for infusion.
Indication	As in adults, ILE is used for energy and as a source of EFAs with a necessity to dose for adequate growth and development. Choice of ILE is dependent on the risk of IFALD, BPD, and ROP.
Prescribing	Dose ILE in grams per kilogram per day. The infusion rate of ILE as either TNA or infusion separate from PN should not exceed the maximum rate based on the oil source. Dose minimization to reduce the risk of IFALD may predispose to EFAD.
Order review	The ILE order is reviewed for dose (based on use, ie, as an energy source or to prevent EFAD), allergy status, compatibility, and stability and ensuring ALL the elements of review are addressed.
Preparation	There is a risk of contamination when repackaging ILE for adult, pediatric, or neonatal use unless proper procedures are followed. It is often not possible to compound TNA for most pediatric patients because of the increased requirements for calcium and phosphorus. Traditional TNA compatibility is derived from SO-ILE. Consult manufacturers for compatibility and stability information for other ILE products.
Administration	For infusions longer than 24 h, divide the daily dose into two containers that are changed every 12 h. ILE is filtered using a 1.2-μm filter whether coadministered or infused with PN. Photoprotection reduces free radical and lipid peroxides. Light protection is recommended when ILE is used in neonates. There is a risk of inadvertent rapid infusion of ILE when administered separate from PN, which may lead to hypertriglyceridemia and/or fat overload syndrome, especially when the maximum recommended rate is exceeded (>0.15 g/kg/h for SO-ILE). Contact manufacturers for the maximum rate for other ILE. Implement safeguards such as double checks, checklists, and completely setting up the ILE infusion prior to other intravenous fluids including programming to avoid infusion rate errors with PN and other fluids. Coadministration of medications with ILE is a challenge. Compatibility of medications for SO-ILE should not be applied to other oils in ILE unless there is evidence to support it. Consult the ILE manufacturer for ILE compatibility with medications.
Transfer of care	Whenever possible, use of a TNA product can minimize issues for the caregiver. This minimizes preparation time and number of infusion devices. Because of access issues, supplemental fluids or medications may need to be administered concomitant with PN. The type of ILE used can affect compatibility and stability. Prescribers may need to note "do not interchange," as specific brands of ILEs or amino acids must be used to safely compound the PN.
Monitoring	Hypertriglyceridemia is defined as a TG level >200 mg/dl. Avoid exceeding maximum doses and infusion rates of ILE. Monitor for EFAs in the malnourished, in patients with signs and symptoms of EFAD, or in those receiving a SO-ILE dose <1 g/kg/day or when using lipid minimization dosing for any ILE. Liver function tests should be monitored for those at risk of IFALD.

Abbreviations: BPD, bronchopulmonary dysplasia; EFA, essential fatty acid; EFAD, EFA deficiency; IFALD, intestinal failure–associated liver disease; ILE, lipid injectable emulsion; PN, parenteral nutrition; ROP, retinopathy of prematurity; SO-ILE, soybean oil–based ILE; TG, triglyceride; TNA, total nutrient admixture.

The biochemical signs of EFAD usually precede those seen clinically and appear in as little as 2–3 days in the preterm infant.[130,131] The isolated deficiency of either ω-3 or ω-6 FAs is rare and has been seen in animals fed artificial diets devoid of specific EFAs.[13,132]

The triene-tetraene ratio does not specifically address ω-3 status. If the MA remains low, it suggests that there are adequate ω-3 stores, as the body employs the same enzymes to metabolize ω-3 and ω-6 FAs, only producing ω-9 FAs when there are inadequate stores of the other FAs. Although the ratio of 0.2 is the classic definition of EFAD, others have suggested lower triene-tetraene ratio cutoffs because values are altered by the age of the patient and method used to extract and quantify FA.[133] If the ratio is >0.4, clinical signs and symptoms of an EFAD may be seen.[134] FA (including EFA) profiles will reflect the FA composition of the oil source of the ILE; therefore, FA profiles are best obtained when an ILE is not infusing.[129]

Platelet function/bleeding

Severe lipemia from fat overload syndrome following short infusion periods has been associated with bleeding disorders and presumed to be related to altered platelet function.[135] The theoretical risk of decreased platelet adhesion from reduction of ARA available for thromboxane production may not be significant enough, even with FO-ILE monotherapy, to increase bleeding risk. FO-ILE supplementing SO-ILE for 7 days increased EPA content of platelet membrane phosphatidylcholine and phosphatidylethanolamine, with slower aggregation but no postoperative bleeding.[136] No clinically significant postprocedural bleeding was observed in a cohort of 183 pediatric patients receiving FO-ILE monotherapy compared with rates in the general population.[137] However, the thromboelastography findings from a neonatal animal model receiving FO-ILE monotherapy still suggest close monitoring.[138]

Liver function test elevations

Liver function tests (LFTs) include bilirubin (total and direct), ALT, AST, and GGT. ILEs made from SO and safflower oil contain high concentrations of the proinflammatory ω-6 PUFAs (ie, LA) and low concentrations of the less inflammatory ω-3 PUFAs (eg, ALA). Plant-derived ILEs also contain high phytosterol concentrations, which have long been implicated in the pathogenesis of IFALD.[139] When ingested enterally, <5% of phytosterols are absorbed in the gut and ultimately undergo biliary excretion.[137] However, when phytosterols are infused intravenously, as in the case of ILEs, they become fully bioavailable and accumulate in the liver and inhibit bile acid transport.[139] One specific phytosterol, stigmasterol, downregulates the gene expression of bile acid transporters and inhibits the farsenoid X receptor.[140] It has been suggested that bloodstream concentration of phytosterols correlates with bilirubin levels. Reduction in SO-ILE intake has been linked with a decrease in phytosterol and bilirubin levels.[141] In contrast, FO-ILEs contain high concentrations of ω-3 PUFA and low concentrations of both ω-6 PUFA and phytosterols.

Overall, values for TGs and LFTs should be determined at baseline and periodically thereafter, depending on clinical and nutrition status, as well as following a dosage change. EFA should be monitored after 1 month for EFAD if low-dose SO-ILE or a Multi-oil ILE is prescribed. If the patient is malnourished, more-frequent monitoring is warranted. Monitor for fat overload syndrome when the ILE dose is >3 g/kg/day, infusion exceeds the maximum recommended rate (in grams per kilogram per hour), or inadvertent rapid infusion occurs during administration.

SUMMARY

A summation of ILE recommendations for neonates and pediatrics is provided in Table 5. ILE is used for energy and as a source of EFAs. Choice and dose of ILE also impact the risk of IFALD, BPD, and ROP in some studies. In contrast to ILE use in adults, ILE is often administered separate from PN, which may lead to safety issues such as inadvertent rapid infusion, issues with filtration, and contamination risks from commercial product repackaging as well as intravenous line access and care. Because of limited venous access, lower volumes and higher normal doses of calcium and phosphorus and ILE compatibility and stability create challenges for admixture such as TNA and co-infusion with medications. Adverse events related to ILEs are more likely to cause harm in neonatal and pediatric patients. It is imperative that institutional protocols for ILE use in neonatal and pediatric patients be carefully developed and evaluated using the considerations for safe practices presented in this paper.

CONFLICT OF INTEREST

M. Petrea Cober is a consultant at B. Braun, Fresenius Kabi, and Baxter Healthcare. Kathleen M. Gura is a consultant and on the speakers bureau of Fresenius Kabi and the advisory board of B. Braun. Jay M. Mirtallo is a consultant and on the speakers bureau of Fresenius Kabi. Phil Ayers is a consultant and on the speakers bureau of Fresenius Kabi. Joseph Boullata is a consultant and on the speakers bureau of Fresenius Kabi. Collin R. Anderson and Steven Plogsted have no conflict of interest.

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AUTHOR CONTRIBUTIONS

P. Cober, K. Gura, J. Mirtallo, P. Ayers equally contributed to the conception and design of the research; P. Cober, K. Gura, J. Mirtallo, P. Ayers and J. Boullata contributed to the design of the research; P. Cober, K. Gura, J. Mirtallo, P. Ayers , J. Boullata, S. Plogsted and C. Anderson contributed to the acquisition and analysis of the data; P. Cober, K. Gura, J. Mirtallo, P. Ayers, J. Boullata, S. Plogsted, and C. Anderson contributed to the interpretation of the data; and P. Cober, K. Gura, J. Mirtallo, P. Ayers , J. Boullata, S. Plogsted, and C. Anderson, drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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