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ORIGINAL RESEARCH

Association between multioil intravenous lipid emulsion and cholestasis in infants with gastrointestinal disorders: A retrospective cohort study

Lauren J. Lee MD, MS[1,2] | Esther S. Kim MD[3] | Tahmineh Romero MS[4] | Kara L. Calkins MD, MS[3]

[1]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[2]Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts, USA

[3]Department of Pediatrics, Division of Neonatology and Developmental Biology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[4]Department of Medicine, Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

Correspondence
Kara L. Calkins, MD, MS, 10833 Le Conte Ave, Room B2-375 MDCC, Los Angeles, CA 90095, USA.
Email: Kcalkins@mednet.ucla.edu

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Abstract

Background: Infants with gastrointestinal (GI) disorders are at risk for parenteral nutrition–associated cholestasis. A multioil intravenous lipid emulsion (MO ILE) contains less phytosterols and more arachidonic and docosahexaenoic acid (DHA) than 100% soybean oil lipid emulsion (SO ILE). This study compares parenteral nutrition–associated cholestasis, growth, and fatty acids in infants with GI disorders who received MO ILE or SO ILE.

Methods: This retrospective cohort study included 48 infants with GI disorders born between 2014 and 2022 who received an intravenous lipid emulsion for ≥14 days. Cholestasis was defined as serum conjugated bilirubin ≥2 mg/dl; growth was assessed by z score changes. Gas chromatography and mass spectrometry was used to measure fatty acid content in the erythrocyte cell membrane.

Results: The incidence of parenteral nutrition–associated cholestasis was similar (MO ILE 30% vs SO ILE 29%, $P > 0.99$). However, compared with infants who received parenteral nutrition >28 days and SO ILE, infants who received parenteral nutrition >28 days and MO ILE experienced a slower rise in conjugated bilirubin (0.1 ± 0.03 vs 0.26 ± 0.38 mg/dl, P interaction < 0.001). Weight z score decline (discharge to birth) was less in the MO ILE group vs SO ILE group (−1.0 [−2.0, −0.4] vs −0.4 [−0.9, 0], $P = 0.04$). Although the MO ILE group demonstrated improved DHA status at weeks 1–3 ($P < 0.05$ for all), arachidonic acid and DHA decreased over time in both groups and there was no difference in the rate of change (P interaction > 0.3 for both).

Conclusion: In infants with GI disorders, MO ILE was associated with improved growth. MO ILE was well tolerated and hepatoprotective in infants who required prolonged parenteral nutrition.

Abbreviations: ARA, arachidonic acid; DHA, docosahexaenoic acid; GI, gastrointestinal; IF, intestinal failure; MO ILE, multioil intravenous lipid emulsion; SO ILE, 100% soybean oil intravenous lipid emulsion.

KEYWORDS
gastroenterology, life cycle, lipids, neonates, nutrition, parenteral nutrition, research and diseases, short bowel syndrome

CLINICAL RELEVANCY STATEMENT

Infants with gastrointestinal (GI) disorders are dependent on parenteral nutrition and lipid emulsions for non-protein calories and fatty acids. In this retrospective study, infants with GI disorders who received a multioil lipid emulsion with 15% fish oil demonstrated a slower rise in serum conjugated bilirubin and improved growth compared to their counterparts who received 100% soybean oil lipid emulsion. A multioil lipid emulsion with reduced soybean oil and some fish oil may offer some clinical benefits.

INTRODUCTION

Infants with gastrointestinal (GI) disorders require parenteral nutrition for hydration and growth during periods of intestinal recovery. Although some infants have a transient dependence on parenteral nutrition, a subset will develop intestinal failure (IF), defined as the inability of the gut to absorb nutrients, electrolytes, and fluid to sustain growth, resulting in parenteral nutrition dependence (>60 days in a 74-day period).[1] Infants who require prolonged parenteral nutrition are at risk for parenteral nutrition–associated cholestasis, defined as serum conjugated bilirubin of ≥2 mg/dl after 14 days of parenteral nutrition. Parenteral nutrition–associated cholestasis can progress to IF-associated liver disease, defined by hepatic injury in the setting of IF.[1,2] IF-associated liver disease can culminate in end-stage liver disease and is a common indication for multivisceral organ transplantation in children.[3]

Risk factors for parenteral nutrition–associated cholestasis and IF-associated liver disease are prolonged parenteral nutrition, intestinal injury, prematurity, infections, and the composition and dose of intravenous lipid emulsions. Lipids are a source of fatty acids and nonprotein energy. Historically, 100% soybean oil intravenous lipid emulsion (SO ILE) was the mainstay for infants with GI disorders.[4] SO ILE contains the essential fatty acids linoleic acid (ω-6) and α-linolenic acid (ω-3). However, SO ILE provides a high concentration of phytosterols, a skewed ω-6:ω-3 (7:1), and is devoid of the long-chain polyunsaturated fatty acids arachidonic acid (ARA, ω-6) and docosahexaenoic acid (DHA, ω-3). Phytosterols activate hepatic macrophages, stimulate cytokine production, and reduce the expression of genes associated with bile, bilirubin, and sterol secretion.[5] ARA and DHA play a critical role in infant development; they are metabolized to eicosanoids that regulate inflammation and immunity and serve as building blocks for neural and retinal tissue.[6–8]

One of the latest generations of intravenous lipid emulsion is a multioil (MO) ILE that combines four oils. MO ILE comprises 30% SO, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil.[9] Compared with SO ILE, MO ILE contains less phytosterols, has a more balanced ω-6:ω-3 (2.5:1), and contains ARA, DHA, and eicosapentaenoic acid.[5,10] Alpha-tocopherol is added to MO ILE to prevent lipid peroxidation, and, in animal models, it promotes biliary secretion and reduces inflammation (Table 1).[10] In contrast, SO ILE contains ɣ-tocopherol, which is considered to be less biologically active.[14]

In an observational study, we demonstrated that preterm infants who received MO ILE are less likely to develop cholestasis, defined as a serum conjugated bilirubin ≥1 mg/dl (14% vs 37%, $P = 0.03$), and have lower maximum serum conjugated bilirubin concentrations (0.4 vs 0.8 mg/dl, $P = 0.001$) compared with preterm infants who received SO ILE. However, when days to reach full feeds was accounted for, the incidence of cholestasis was no longer statistically significant ($P = 0.059$).

TABLE 1 Intravenous lipid emulsions.

	SO ILE[4]	MO ILE[9]
Oil source (%)		
Soybean oil	100%	30%
MCT	0%	30%
Olive oil	0%	25%
Fish oil	0%	15%
Fatty acid (% by weight, mean value or range)		
Medium chain		
Caprylic	0	16.8 ± 0.23[11]
Capric	0	12.1 ± 0.17[11]
Long chain		
Linoleic (18:2n-6)	44–62[4]	17.5[9]
α-Linolenic (18:3n-3)	4–11[4]	2.25[9]
Arachidonic (20:4n-6)	0[12]	0.5[12]
Docosahexaenoic (22:6n-3)	0[13]	1–3.5[9]
Eicosapentaenoic (20:5n-3)	0[13]	1–3.5[9]
Oleic (18:1n-9)	19–30[4]	23–35[9]
ω-6: ω-3 Ratio	7:1[13]	2.5:1[13]
Phytosterols (mcg/ml)		
Sitosterol	243.26 ± 4.10[11]	131.58 ± 7.11[9]
Campesterol	37.19 ± 0.54[11]	20.45 ± 1.04[9]
Stigmasterol	49.57 ± 0.62[11]	18.51 ± 0.81[9]
Vitamin E (mg/L)		
α-Tocopherol	ND	163–225[9]

Abbreviations: ILE, intravenous lipid emulsion; MCT, medium-chain triglycerides; MO, multioil; ND, not determined; SO, soybean oil.

We speculated that this finding was because of the low incidence of intestinal injury and cholestasis, small sample size, and study design. In this study, the median parenteral nutrition duration was 29 and 23 days for the SO ILE group and the MO ILE group, respectively.[15]

These results lead us to the current study. The objectives of this study were to compare (1) cholestasis rates, (2) growth, and (3) fatty acid profiles in the red blood cell membrane in infants with GI disorders. We hypothesized that infants with GI disorders who received MO ILE would be less likely to develop cholestasis compared with infants with GI disorders who received SO ILE. This hypothesis was based on two observations: (1) infants with GI disorders require longer parenteral nutrition courses and are at higher risk for intestinal injury and gut dysmotility than preterm infants,[16,17] and (2) MO ILE contains less ω-6 fatty acids and phytosterols compared with SO ILE and is a source of ARA, DHA, eicosapentaenoic acid, and α-tocopherol.[9]

METHODS

Study design

This was a retrospective cohort study. Our primary outcome was cholestasis, defined as a serum conjugated bilirubin ≥2 mg/dl after 14 days of parenteral nutrition. Our secondary outcomes were change in weight z score (hospital discharge z score−birth z score), serum conjugated bilirubin ≥1 mg/dl after 14 days of parenteral nutrition, maximum serum conjugated bilirubin concentration, alanine transaminase and aspartate transaminase concentrations, changes in serum conjugated bilirubin concentration over time, and red blood cell membrane polyunsaturated fatty acid content. Our exposure of interest was MO ILE (SMOFlipid; Fresenius Kabi).[9] Our comparator was SO ILE (Intralipid; Fresenius Kabi).[4] Population means and SDs for anthropometrics were obtained from standardized growth charts.[18–22]

Eligibility criteria

Inclusion criteria for this study included infants with congenital and acquired GI disorders (defined as gastroschisis, omphalocele, intestinal atresia, Hirschsprung disease, pseudoobstruction, volvulus, intestinal perforation, or necrotizing enterocolitis stage II or III[23]) who were admitted to the neonatal intensive care units at the University of California Los Angeles (Mattel Children's Hospital and Santa Monica Medical Center), received ≥14 days of an ILE, survived to hospital discharge, and were born between 2014 and 2022. Exclusion criteria included infants transferred to another hospital prior to discharge and infants with major non-GI congenital disorders, genetic anomalies, and primary liver disorders other than cholestasis associated with parenteral nutrition.

Infants with GI disorders who were enrolled in a prospective study that collected blood samples for analysis of polyunsaturated fatty acids in the red blood cell membrane were included in this study. Parents were provided with an informational sheet and provided verbal informed consent. Blood samples were collected on a weekly basis while on parenteral nutrition. To increase the sample size, retrospective data were collected on patients who satisfied inclusion and exclusion criteria but did not participate in this prospective study. Biospecimens were not available for these participants. Data were entered into a research electronic data capture database.[24] Data included information on demographics, nutrition, and common complications associated with GI disorders and IF. These studies were approved by the University of California Los Angeles Institutional Review Board.[15]

Nutrition exposures

Study participants received SO ILE[4,9] prior to the summer of 2017. After this date, MO ILE[9] was prescribed to infants with GI disorders. Infants received parenteral nutrition shortly after birth. Standard-of-care protocols were used to guide parenteral macronutrient dosing. Glucose infusion rates were initiated at 4–8 mg/kg/min and advanced by 1–2 mg/kg/min to a goal of 11–13 mg/kg/min. Parenteral amino acids were initiated at 1.5–2.5 g/kg/day and advanced by 0.5–1 g/kg/day to a target dose of 3–4 g/kg/day. Lipids were started at 0.5–1 g/kg/day in the first 12–48 h and advanced by 0.5–1 g/kg/day to a maximum dose of 3 g/kg/day. Lipids were decreased to 1.5 g/kg/day once the infant tolerated ~80–100 ml/kg/day of enteral feeds. The lipid dose was decreased by 50% if triglyceride concentrations were >150–250 mg/dl and discontinued if the triglyceride concentration was >250 mg/dl. Once bowel function was demonstrated, enteral feeds were started at 10–20 ml/kg/day and advanced by 10–20 ml/kg/day to a goal of 140–160 ml/kg/day. In general, if mother's own milk was not available, donor milk was provided for a brief period.

Red blood cell membrane fatty acids

Red blood cell membrane polyunsaturated fatty acid profiles were collected from participants enrolled in the prospective study. Biospecimens were collected at enrollment and then weekly while on parenteral nutrition. Agilent Technologies 5890A series II gas chromatography was used to measure the percentage of fatty acids in the red blood cell membrane. Quantification was based on the recovery of a known quantity of the internal standard (tridecanoic acid; NuChek Preparation) and on the response ratio of fatty acid standards purchased from NuChek Preparation. A pooled red blood cell membrane sample was used for quality control.[15] This analysis was completed at the University of California Los Angeles.

Statistical analysis

Categorial variables are summarized using counts and percentages. Continuous variables are summarized using medians and interquartile

ranges. Comparisons between groups (SO ILE vs MO ILE) for categorical variables were performed using Fisher exact test, whereas the Wilcoxon rank sum test was used for continuous variables. To account for repeated measures, generalized linear mixed models were used. These models included an interaction term between time and group to evaluate differences between the groups over time. The results of the mixed models were summarized using point estimates and their corresponding 95% CIs. All tests were two-sided, and a *P* value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 15.2. An ad hoc power analysis is presented in Supplement 1.

RESULTS

Twenty-two infants received SO ILE and 26 infants received MO ILE. When the SO ILE group was compared with the MO ILE group, median (IQR) birth weight (2.7 [1.8, 3.1] kg vs 2.3 [2.0, 2.8] kg, $P = 0.33$) was similar. Likewise, parenteral nutrition days (SO ILE 26 [18–59] days vs MO ILE 30.5 [20–44] days, $P = 0.67$) and ILE days (SO ILE 25 [16–57] days vs MO ILE 30 [20–46] days, $P = 0.63$) were comparable. Because of drug compatibility issues, infants in the MO ILE group occasionally received SO ILE. All patients who received any MO ILE were included in the MO ILE group. Thirty-four percent ($n = 9$) of the MO ILE group received some SO ILE. The participants in the MO ILE group who received some SO ILE received 24.5 (18–39) days of MO ILE, which was 64% (39%, 75%) of total ILE days (Table 2). No participants received other ILE products. Additional information for parenteral and enteral nutrition is provided in Table 3.

Clinical outcomes and growth are displayed in Table 4. The incidences of cholestasis (SO ILE 29% vs MO ILE 30%, $P > 0.99$) and serum conjugated bilirubin ≥1 mg/d (SO ILE 57% vs MO ILE 52%, $P = 0.8$) were comparable. There was no difference in between the groups for median maximum serum conjugated bilirubin (1.2 [0.5, 2.5] mg/dl vs 1.2 [0.3, 2.1] mg/dl, $P = 0.7$) and liver function tests when the SO ILE group was compared with the MO ILE group (Table 4). There was no difference in the rate of change of conjugated bilirubin between the groups (SO ILE 0.29 ± 0.07 per week, MO ILE 0.14 ± 0.06 per week, $P = 0.13$). When compared with the SO ILE group, MO ILE's weight *z* score change was significantly less (SO ILE −1.0 [−2.0, −0.4] vs MOLE −0.4 [−0.9, 00], $P = 0.04$). The mean difference between the two groups was significantly different favoring MO ILE (−0.59 [−1.16, −0.02] $P = 0.04$).

As expected, infants who received >28 days of parenteral nutrition had a higher rate of cholestasis compared with infants who received ≤28 days of parenteral nutrition (50% vs 5%, $P = 0.002$). Because parenteral nutrition duration is associated with cholestasis, we investigated hepatic injury in infants who received parenteral nutrition for >28 days.[16,25] Sixty percent of infants who received SO ILE, compared with 43% of infants who received MO ILE, developed cholestasis (OR 0.5 [95% CI 0.10–3.18], $P = 0.41$). The rate of change of conjugated bilirubin was 0.26 ± 0.38 mg/dl in the SO ILE group ($P < 0.001$) and 0.1 ± 0.03 mg/dl in the MO ILE group ($P = 0.002$, difference in rate of change, −0.16 ± 0.05 mg/dl, *P* interaction <0.001) (Table 5).

Polyunsaturated fatty acids in the red blood cell membrane in the SO ILE and MO ILE groups are depicted in Figure 1. When compared with the SO ILE group, the MO ILE group's red blood cell membrane contained less linoleic acid ($P = 0.002$ at week 2 and $P = 0.01$ at week 3) and more DHA and eicosapentaenoic acid ($P < 0.05$ for weeks 1–3). Linoleic acid increased over time in the SO ILE group (2.02 ± 0.24%/week, $P < 0.001$) and in the MO ILE group (1.70 ± 0.46%/week $P = 0.002$, *P* interaction = 0.4). The rate of change for α-linolenic acid in the SO ILE group was 0.04 ± 0.01% per week ($P = 0.005$) and in the MO ILE group was 0.06 ± 0.05% per week ($P = 0.5$) with no difference between groups (*P* interaction = 0.5).

Although the MO ILE group demonstrated significantly improved DHA status compared with the SO ILE group during weeks 1–3 ($P < 0.05$ for all), DHA decreased in both groups (SO ILE −0.30 ± 0.05%/week $P < 0.001$ vs MO ILE −0.31 ± 0.07% per week, $P = 0.0008$) and there was no difference in the rates between the two groups (*P* interaction = 0.9). Eicosapentaenoic acid increased significantly in both groups (SO ILE 0.04 ± 0.009% per week, $P < 0.001$ and MO ILE 0.18 ± 0.08% per week, $P = 0.045$) with a significant difference between the two groups ($P = 0.006$). ARA showed a significant decrease in the SO ILE group (−1.24 ± 0.13% per week, $P < 0.001$) and MO ILE group (−1.50 ± 0.15%, $P < 0.001$) with no difference over time between groups (*P* interaction = 0.45) (Figure 1).

DISCUSSION

In this single-site study of 48 with with GI disorders, there was no difference in the rate of parenteral nutrition–associated cholestasis based on lipid type. Despite this finding, infants who received MO ILE demonstrated improved growth. Moreover, infants who received MO ILE and >28 days of parenteral nutrition demonstrated a slower rise in serum conjugated bilirubin compared with infants who received SO ILE and >28 days of parenteral nutrition. Infants diagnosed with surgical GI disorders, particularly infants with complex gastroschisis, jejunal atresia, and surgical necrotizing enterocolitis, are at high risk for IF-associated liver disease.[2] In this study, gestational age, birth weight, GI diagnosis, infection rate, lipid dose, and duration of parenteral nutrition were comparable between the two groups. Therefore, it can be concluded that MO ILE is safe, well tolerated, and shows a trend toward improved rates of cholestasis for infants with GI disorders who require prolonged parenteral nutrition. Because it is challenging to predict who will require prolonged parenteral nutrition at birth, some experts recommend that these infants should receive an intravenous lipid emulsion with a reduced amount of soybean oil– or a fish oil–containing lipid.[26,27] Because MO ILE contains a reduced amount of soybean oil along with some fish oil, medium-chain triglycerides, and olive oil, it remains to be determined which oil and which constituents in the oil (ie, the type and amount of fatty acids, phytosterols, and antioxidants) protect against hepatic injury.

TABLE 2 Demographics and nutrition data.

	All patients (*n* = 48)	SO ILE (*n* = 22)	MO ILE (*n* = 26)	*P* value
Maternal race, *n* (%)				0.01
White	28 (58)	17 (77)	11 (42)	
Black	3 (6)	0 (0)	3 (12)	
Asian	1 (2)	1 (5)	0 (0)	
Other	8 (17)	0 (0)	8 (31)	
Unknown	8 (17)	4 (18)	4 (15)	
Maternal ethnicity: Hispanic, *n* (%)	21 (46)	11 (55)	10 (38)	0.6
Gravida status, median (IQR)	2 (1–3)	2 (2–3)	2 (1–3)	0.4
Para status, median (IQR)	1 (1–2)	2 (1–2)	1 (1–2)	0.08
Multiple gestation, median (IQR)	3 (6)	2 (9)	1 (4)	0.6
Maternal antenatal steroids, *n* (%)	14 (29)	8 (36)	6 (19)	0.03
Antibiotics prior to delivery, *n* (%)	21 (44)	8 (36)	12 (49)	0.3
Male sex, *n* (%)	27 (56)	14 (63)	13 (50)	0.4
Gestational age (weeks), median (IQR)	36.7 (34.9, 37.4)	36.9 (35, 37.4)	36.5 (34.9, 37.4)	0.6
Cesarean delivery, *n* (%)	21 (44)	7 (32)	14 (54)	0.2
Apgar, 1 min, median (IQR)	8 (6–9)	8 (5–9)	8 (6, 9)	0.7
Apgar, 5 min, median (IQR)	9 (8–9)	9 (7–9)	9 (8, 9)	0.7
Birth weight, kg, median (IQR)	2.5 (2.0–3.0)	2.7 (1.8, 3.1)	2.3 (2.0, 2.8)	0.3
Birth length, cm, median (IQR)	46 (44–48)	46 (43, 48)	46 (44, 49)	0.1
Head circumference, cm, median (IQR)	31 (30–33)	31 (30, 32)	31 (30, 33)	0.7
Small for gestational age: yes, *n* (%)	10 (22)	4 (26)	6 (23)	>0.99
First feed: human milk, *n* (%)	41 (85)	19 (86)	22 (85)	-
Day of life of first enteral feed, median (IQR)	14 (11, 21)	14 (10, 17)	14 (11, 22)	0.7
Parenteral nutrition days, median (IQR)	28 (19, 44)	26 (18, 59)	31 (20, 46)	0.08
Intravenous lipids days, median (IQR)	27 (19, 46)	25 (16, 57)	26 (19, 39)	
Full feeds, day of life, median (IQR)	25 (18, 39)	25 (15, 56)	26 (19, 38)	0.9
GI diagnosis, *n* (%)				0.3
Gastroschisis	29 (60)	13 (59)	16 (62)	
Omphalocele	3 (6)	0	3 (12)	
Atresia	11 (23)	4 (18)	7 (27)	
Volvulus	1 (2)	1 (5)	0	
Necrotizing enterocolitis	1 (2)	1 (5)	0	
Perforation	1 (2)	1 (5)	0	
Other	2 (4)	2 (9)	0	
Length of stay, median (IQR)	40 (26, 67)	32 (24, 72)	42 (26, 69)	0.8

Note: Small for gestational age as defined as a birth weight less than the 10th percentile. Full enteral nutrition was defined as 100 kcal/kg/day of enteral nutrition or ad libitum feeding, whichever came first. The Apgar score is a standardized scoring system for neonates immediately after birth, with components including color, heart rate, respirations, reflexes, and muscle tone.

Abbreviations: ILE, intravenous lipid emulsion; MO, multioil; NEC, necrotizing enterocolitis; SO, soybean oil.

TABLE 3 Parenteral and enteral nutrition.

	Baseline		Week 1		Week 2	
	SO ILE	MO ILE	SO ILE	MO ILE	SO ILE	MO ILE
GIR, mg/kg/min	7.7 (6.9, 9.1)	8 (7, 9)	12.4 (11, 13.7)	12.1 (10.9, 13.8)	12.1 (9.9, 13.5)	12.3 (7.6, 12.9)
AA, g/kg/day	2.2 (2, 3)	2.9 (2.3, 3.2)	3.5 (3.1, 3.9)	3.5 (3.1, 3.7)	3.2 (2.9, 3.6)	3 2 (2.2, 3.7)
ILE, g/kg/day	1 (1, 2)	1 (1, 1)	3 (2.9, 3.1)	3 (2.9, 3)	3 (2.7, 3.0)	2.8 (1.5, 2.9)
EN kcal/kg/day	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 32)	0 (0, 18.7)
	Week 3		Week 4		Rate of change within groups	
	SO ILE	MO ILE	SO ILE	MO ILE	SO ILE	MO ILE
GIR, mg/kg/min	9.2 (6.7, 11.6)	11.6 (8.4, 13.2)	10.2 (6.9, 11.7)	11 (6, 13.2)	−1.39 ± 0.25/week*	−0.89 ± 0.3/week*
AA, g/kg/day	2.6 (2, 3.3)	3 (1.9, 3.8)	2.9 (2.2, 3.6)	3.4 (1.7, 3.8)	−0.34 ± 0.07/week*	−0.36 ± 0.19/week
ILE, g/kg/day	2.7 (1.1, 2.9)	2.9 (2.7, 3)	2.1 (1, 2.9)	2.8 (1, 3)	−0.35 ± 0.09/week*	−0.18 ± 0.11/week
EN, kcal/kg/day	10.3 (0, 30.9)	13 (0, 35)	16.8 (0, 53.8)	6 (0, 48.8)	9.54 ± 1.69/week*	7.44 ± 1.88/week*

Note: Data are represented as a median (interquartile range).

Abbreviations: AA, amino acid; EN, enteral nutrition; GIR, glucose infusion rate; ILE, intravenous lipid emulsion; MO, multioil; SO, soybean oil.

*Significant difference in rate of change within group. There was no significant difference in rate of change between groups.

Our results replicate the findings of a pilot study that randomly assigned 24 infants with GI disorders to SO ILE dosed at 1 g/kg/day (SO ILE min) or MO ILE dosed at 3 g/kg/day. This prospective cohort was then compared with 24 historical controls who required an abdominal surgery and received SO ILE dosed at 2–3 g/kg/day (SO ILE historic). Infants who received MO ILE demonstrated a slower rise in serum conjugated bilirubin (SO ILE historic, +0.293 mg/dl/week vs MO ILE, $P < 0.001$; SO ILE min +0.242 mg/dl/week vs MO ILE, $P < 0.001$) and had a lower conjugated bilirubin at study completion (SO ILE historic, 1.7 ± 1.7 mg/dl; SO ILE min, 1.6 ± 1.4 mg/dl; MO ILE, 0.4 ± 0.4 mg/dl; $P = 0.002$) compared with infants who received SO ILE, regardless of dose. Like our study, there was no difference in the incidence of cholestasis between groups.[28] Our study and the aforementioned study are single-site studies with limited sample sizes. As a result, they are not powered to detect a difference in IF-associated liver disease. Because IF-associated liver disease is a rare disease that unfolds with time, it remains unclear if an adequately powered study comparing SO ILE to MO ILE after birth in this population can be performed (Supplement 1).[1,16,29]

In our study, infants who required >28 days on parenteral nutrition were more likely to develop cholestasis compared with infants who required ≤28 days. Studies that have followed infants requiring prolonged parenteral nutrition and have received MO ILE have shown a trend toward a decreased incidence of cholestasis and improved markers of cholestasis.[9,30–32] In a retrospective cohort study of 37 infants with IF who required parenteral nutrition over a 12-month period, the MO ILE group was less likely to develop IF-associated liver disease (24% vs 55%, $P = 0.05$) and had a lower median peak conjugated bilirubin (2.16 vs 3.68 mg/dl, $P = 0.056$) when compared with the SO ILE group.[31] Similarly, in a cohort of 50 infants who received parenteral nutrition for ≥6 weeks, rates of liver disease decreased from 54% to 20% in MO ILE recipients but remained stable at 7% for SO ILE recipients. Of note, in this study, infants receiving MO ILE received a longer duration of parenteral nutrition and had a higher baseline serum conjugated bilirubin than those who received SO ILE.[32] This trend was again demonstrated in a multicenter, randomized controlled study in 161 infants with GI disorders who were expected to require parenteral nutrition for at least 28 days. There was no difference in cholestasis. However, in infants who received parenteral nutrition >28 days, only two infants who received MO ILE developed cholestasis, whereas nine infants who received SO ILE developed cholestasis.[33]

In animal studies, fish oil has been shown to be hepatoprotective when compared to SO ILE.[5,10] In a mouse model of intestinal disease, mice who received SO ILE had more liver damage and hepatic macrophage activation when compared with mice who received a fish oil–based lipid emulsion.[5] At equivalent doses, SO ILE contains a higher concentration of phytosterols and lower concentration of vitamin E, and no DHA, eicosapentaenoic acid, and ARA compared with MO ILE. In children with IF, intestinal serum phytosterol concentrations are positively associated with histological liver damage, including liver fibrosis, which can progress to cirrhosis and liver failure.[34]

It has been proposed that the increased delivery of DHA and eicosapentaenoic acid and decreased delivery of proinflammatory fatty acids in MO ILE may play a role in cholestasis. As DHA and eicosapentaenoic acid concentrations increase in the red blood cell membrane, ARA and other fatty acid concentrations decrease. ARA-derived eicosanoids are more proinflammatory and promote platelet aggregation, whereas DHA and eicosapentaenoic acid are more anti-inflammatory. In our study, the red blood cell membrane fatty acid profile reflected the lipid type. DHA status was higher in the MO ILE group at most time points, although DHA status still declined. ARA declined with no difference between groups. In a

TABLE 4 Growth and clinical outcomes.

	SO ILE (*n* = 22)	MO ILE (*n* = 26)	*P* value
Cholestasis: CB ≥ 2 mg/dl, *n* (%)	6 (29)	7 (30)	>0.9
Cholestasis: CB ≥ 1 mg/dl, *n* (%)	12 (57)	12 (52)	0.8
Maximum CB after 14 days of age, mg/day, median (IQR)	1.2 (0.5, 2.5)	1.2 (0.3, 2.1)	0.7
Weight *z* scores, median (IQR)			
Birth	−0.1 (−0.8, 0.1)	−0.4 (−0.9, 0.2)	0.5
Discharge	−0.9 (−1.8, −0.4)	−0.9 (−1.7, −0.4)	>0.9
Δ*z* Discharge–Birth	−1.0 (−2.0, −0.4)	−0.4 (−0.9, 0)	0.04
Length *z* scores, median (IQR)			
Birth	−0.8 (−1.2, 0)	−0.1 (−1.0, 0.3)	0.15
Discharge	−0.6 (−1.3, 0.2)	−0.5 (−1.2, 0.5)	0.7
Δ*z* Discharge–Birth	−0.1 (−1.0, 0)	−0.2 (−0.8, 0.6)	0.5
Head circumference *z* scores, median (IQR)			
Birth	−1.1 (−1.4, −0.3)	−0.4 (−1.4, 0.4)	0.3
Discharge	−0.8 (−1.4, −0.1)	−0.6 (−1.6, 0.2)	0.4
Δ*z* discharge–birth	−0.1 (−0.7, 0.3)	−0.3 (−0.9, 0.3)	0.5
Late onset sepsis, *n* (%)	1 (5)	2 (8)	>0.9
Number of surgeries, *n* (%)	2 (1, 2)	2 (1, 2)	0.2
Maximum AST IU/L, median (IQR)	40.5 (32.5, 70.5)	52 (31, 99)	0.7
AST > 40 IU/L, median (IQR), *n* (%)	10 (50)	10 (53)	>0.9
Maximum ALT IU/L, median (IQR)	22 (13, 50.5)	44 (14, 76)	0.4
ALT > 40 IU/L, *n* (%)	7 (35)	9 (47)	0.5
Maximum triglycerides, mg/dl, median (IQR)	140 (102, 158)	122.5 (89, 140.5)	0.5
Triglycerides > 250 mg/dl, *n* (%)	1 (6)	0 (0)	0.5

Note: Late onset sepsis was defined as a positive blood culture after 72 h of life and >5 days of intravenous/intramuscular antibiotics.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CB, conjugated bilirubin; CGA, corrected gestational age; ILE, intravenous lipid emulsion; IQR, interquartile range; MO, multioil; SO, soybean oil.

TABLE 5 Cholestasis and rate of rise of conjugated bilirubin stratified by parenteral nutrition days.

	PN ≤ 28 days		PN > 28 days	
	SO ILE *n* = 12	MO ILE *n* = 12	SO ILE *n* = 10	MO ILE *n* = 14
CB ≥2 mg/dl, *n* (%)	0	1 (11)	6 (60)	6 (43)
	OR not estimable		OR 0.5 (0.1–2.6) *P* = 0.4	
Rate of change of CB, mg/dl	0.17 ± 0.05	0.07 ± 0.03	0.26 ± 0.38	0.10 ± 0.03
	Interaction term *P* = 0.14		Interaction term *P* < 0.001	

Note: Cholestasis, defined as conjugated bilirubin (CB) ≥2 mg/dl, data represented as *n* (%). Odds ratio (OR) comparing the two groups, SO ILE (soybean oil intravenous lipid emulsion) and MO ILE (multioil intravenous lipid emulsion), in infants who received parenteral nutrition (PN) ≤28 days and infants who received PN >28 days. Rate of change data are shown as mean (±SE). Interaction term *P* value between the two groups (SO ILE vs MO ILE) in infants who received PN ≤28 days and infants who received PN >28 days.

larger sample size, we speculate that the rate of change for DHA may be significant. It remains to be determined what the optimal fatty acid profile should be in intravenous lipid emulsions, and if "target" fatty acids concentrations are associated with specific clinical outcomes.

In this study and in our previous study of preterm infants, we found a difference in growth between infants who received SO ILE and those who received MO ILE.[15] However, in two studies in pediatric patients with IF who were dependent on

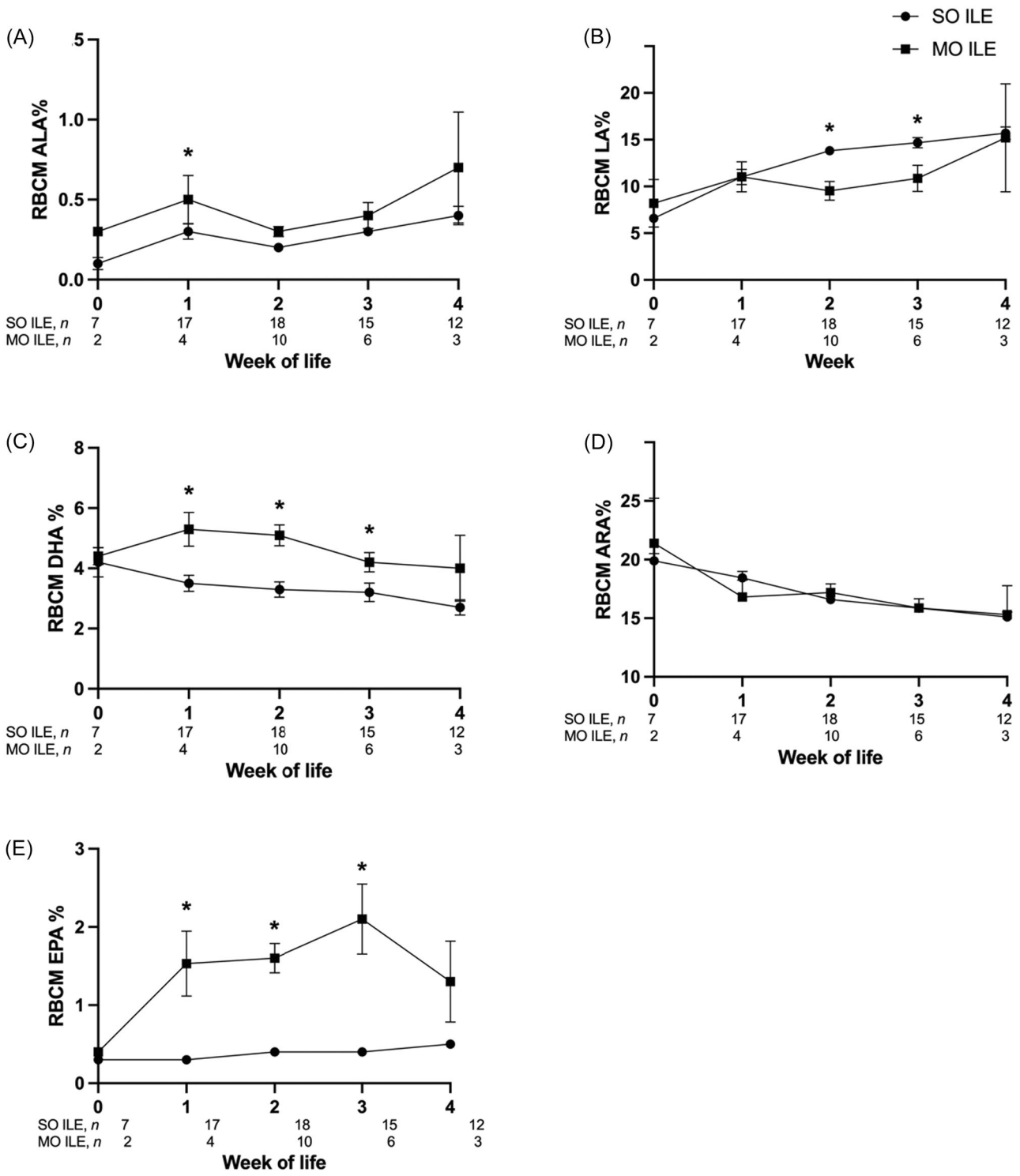

FIGURE 1 Red blood cell membrane (RBCM) polyunsaturated fatty acids over time. (A) a-linolenic acid (ALA), (B) linoleic acid (LA), (C) docosahexaenoic acid (DHA), (D) arachidonic acid (ARA), (E) eicosapentaenoic acid (EPA). Solid circles signify soybean oil intravenous lipid emulsion (SO ILE). Solid squares signify multioil intravenous lipid emulsion (MO ILE). Data are represented as a mean (SE). *$P < 0.05$ between groups at specific time points. There was a significant difference when rates were compared between groups using generalized mixed linear models for EPA (SO ILE 0.04 ± 0.009% per week vs MO ILE 0.18 ± 0.08% per week, $P = 0.006$).

long-term parenteral nutrition, there was no change in growth seen in patients who received MO ILE compared with those who received SO ILE.[35,36] It remains unclear if these results can be replicated in a larger study and if this growth trajectory is related to less inflammation and translates to a healthier body composition.

This study has limitations. This is a retrospective cohort, single-center study with a small sample size. Participants received SO ILE if

born prior to 2017 and MO ILE thereafter. Therefore, potential confounding variables, such as changes in medical practice cannot be accounted for and may have influenced outcomes. Some participants in the MO ILE group received SO ILE because of drug compatibility issues. Although this is a limitation, this may reflect actual clinical practice since clinicians now have access to multiple lipid emulsions. The red blood cell membrane fatty acid content was only available for a subset of infants. Blood samples were also not available immediately after birth. Last, we were unable to account for the fatty acid content of enteral nutrition. Most infants in the study received maternal or donor breast milk, and the fatty acid composition of an individual's breast milk varies.[37]

In conclusion, in comparison with infants with GI disorders who received SO ILE, infants with GI disorders who received a four-oil ILE, MO ILE, still exhibited a decline in DHA and ARA status. There was no difference in cholestasis. However, in infants who received parenteral nutrition for >28 days, MO ILE was associated with a slower rise in conjugated bilirubin compared with SO ILE. Regardless of lipid type, promoting enteral nutrition, decreasing parenteral nutrition days, and preventing infections remains the cornerstone for the management of parenteral nutrition–associated cholestasis and IF-associated liver disease.

AUTHOR CONTRIBUTIONS

Lauren J. Lee: Data curation; formal analysis; writing—original draft; writing—review and editing; methodology. **Esther S. Kim:** Data curation; formal analysis; methodology; writing—review and editing. **Tahmineh Romero:** Formal analysis; writing—review and editing. **Kara L. Calkins:** Conceptualization; data curation; formal analysis; visualization; Writing—review and editing; investigation; supervision; funding acquisition; methodology.

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CONFLICT OF INTEREST STATEMENT

Kara L. Calkins has served as an advisor for Fresenius Kabi and has received research support from Fresenius Kabi. Kara L. Calkins has served as an advisor for Mead Johnson Nutrition and Baxter. Kara L. Calkins serve as an institutional principal investigator, with no salary funding, for a consortium database sponsored by Mead Johnson Nutrition.

ORCID

Kara L. Calkins https://orcid.org/0000-0001-6658-7981

REFERENCES

1. Modi BP, Galloway DP, Gura K, et al. ASPEN definitions in pediatric intestinal failure. *JPEN J Parenter Enteral Nutr*. 2022;46(1):42-59. doi:10.1002/jpen.2232
2. Carter B, Karpen S. Intestinal failure-associated liver disease: management and treatment strategies past, present, and future. *Semin Liver Dis*. 2007;27(3):251-258. doi:10.1055/s-2007-985070
3. Fullerton BS, Sparks EA, Hall AM, Duggan C, Jaksic T, Modi BP. Enteral autonomy, cirrhosis, and long term transplant-free survival in pediatric intestinal failure patients. *J Pediatr Surg*. 2016;51(1):96-100. doi:10.1016/j.jpedsurg.2015.10.027
4. Kabi Fresenius. *Intralipid 20% Prescribing Information*. Kabi Fresenius; 2015.
5. El Kasmi KC, Anderson AL, Devereaux MW, et al. Phytosterols promote liver injury and Kupffer cell activation in parenteral nutrition-associated liver disease. *Sci Transl Med*. 2013;5(206):206ra137. doi:10.1126/scitranslmed.3006898
6. Hsieh AT, Anthony JC, Diersen-Schade DA, et al. The Influence of Moderate and High Dietary Long Chain Polyunsaturated Fatty Acids (LCPUFA) on baboon neonate tissue fatty acids. *Pediatr Res*. 2007;61(5):537-545. doi:10.1203/pdr.0b013e318045bec9
7. Shin BC, Ghosh S, Dai Y, Byun SY, Calkins KL, Devaskar SU. Early life high-fat diet exposure maintains glucose tolerance and insulin sensitivity with a fatty liver and small brain size in the adult offspring. *Nutr Res*. 2019;69:67-81. doi:10.1016/J.NUTRES.2019.08.004
8. Colombo J, Carlson SE, Cheatham CL, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. *Am J Clin Nutr*. 2013;98(2):403-412. doi:10.3945/AJCN.112.040766
9. Kabi Fresenius. *SMOFlipid Prescribing Information*. Kabi Fresenius; 2018.
10. Ng K, Stoll B, Chacko S, et al. Vitamin E in new-generation lipid emulsions protects against parenteral nutrition-associated liver disease in parenteral nutrition-fed preterm pigs. *JPEN J Parenter Enteral Nutr*. 2016;40(5):656-671. doi:10.1177/0148607114567900
11. Harvey K, Xu Z, Walker C, et al. Parenteral lipid emulsions in guinea pigs differentially influence plasma and tissue levels of fatty acids, squalene, cholesterol, and phytosterols. *Lipids*. 2014;49(8):777-793. doi:10.1007/s11745-014-3927-2
12. Le HD, Meisel JA, de Meijer VE, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81(2):165-170. doi:10.1016/j.plefa.2009.05.020
13. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. position paper. *Nutr Clin Pract*. 2012;27(2):150-192. doi:10.1177/0884533612439896
14. Baker MA, Cho BS, Anez-Bustillos L, et al. Fish oil-based injectable lipid emulsions containing medium-chain triglycerides or added α-tocopherol offer anti-inflammatory benefits in a murine model of parenteral nutrition–induced liver injury. *Am J Clin Nutr*. 2019;109(4):1038-1050. doi:10.1093/ajcn/nqy370
15. Kim ES, Lee LJ, Romero T, Calkins KL. Outcomes in preterm infants who received a lipid emulsion with fish oil: an observational study. *JPEN J Parenter Enteral Nutr*. 2023;47(3):354-363. doi:10.1002/jpen.2464
16. Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: initial report from the pediatric intestinal failure consortium. *J Pediatr*. 2012;161(4):723-728.e2. doi:10.1016/j.jpeds.2012.03.062
17. Wang N, Yan W, Hong L, et al. Risk factors of parenteral nutrition-associated cholestasis in very-low-birthweight infants. *J Paediatr Child Health*. 2020;56(11):1785-1790. doi:10.1111/jpc.14826
18. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010;125(2):e214-e224. doi:10.1542/peds.2009-0913
19. Centers for Disease Control and Prevention, National Center for Health Statistics. *Growth Charts—Data Table of Infant Length-for-Age Charts*. Centers for Disease Control and Prevention, National Center for Health Statistics; 2024.
20. Centers for Disease Control and Prevention, National Center for Health Statistics. *Growth Charts—Data Table of Infant Head Circumference-for-Age Charts*. Centers for Disease Control and Prevention, National Center for Health Statistics; 2024.

21. Centers for Disease Control and Prevention, National Center for Health Statistics. *Growth Charts—Data Table of Infant Weight-for-Age Charts*. Centers for Disease Control and Prevention, National Center for Health Statistics; 2024.
22. Fenton TR, Kim JH. A Systematic Review and Meta-Analysis to Revise the Fenton Growth Chart for Preterm Infants. *BMC*. 2013; 13:59. http://www.biomedcentral.com/1471-2431/13/59
23. Neu J. Necrotizing enterocolitis. *Pediatr Clin North Am*. 1996;43(2): 409-432. doi:10.1016/S0031-3955(05)70413-2
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf*. 2009;42(2):377-381. doi:10.1016/J.JBI.2008.08.010
25. Christensen RD, Henry E, Wiedmeier SE, Burnett J, Lambert DK. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. *J Perinatol*. 2007;27(5): 284-290. doi:10.1038/sj.jp.7211686
26. Hojsak I, Colomb V, Braegger C, et al. ESPGHAN Committee on Nutrition Position Paper. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children. *J Pediatr Gastroenterol Nutr*. 2016;62(5):776-792. doi:10.1097/MPG.0000000000001121
27. Lacaille F, Gupte G, Colomb V, et al. Intestinal failure-associated liver disease. *J Pediatr Gastroenterol Nutr*. 2015;60(2):272-283. doi:10.1097/MPG.0000000000000586
28. Huff KA, Cruse W, Vanderpool C. Lipid strategies to prevent intestinal failure-associated liver disease in neonates: a pilot trial. *JPEN J Parenter Enteral Nutr*. 2023;47(4):482-493. doi:10.1002/jpen.2483
29. Duggan CP, Jaksic T. Pediatric intestinal failure. *N Engl J Med*. 2017; 377(7):666-675. doi:10.1056/nejmra1602650
30. Diamond IR, Grant RC, Pencharz PB, et al. Preventing the progression of intestinal failure–associated liver disease in infants using a composite lipid emulsion: a pilot randomized controlled trial of SMOFlipid. *JPEN J Parenter Enteral Nutr*. 2017;41(5):866-877. doi:10.1177/0148607115626921
31. Belza C, Wales JC, Courtney-Martin G, de Silva N, Avitzur Y, Wales PW. An observational study of SMOFlipid vs intralipid on the evolution of intestinal failure-associated liver disease in infants with intestinal failure. *JPEN J Parenter Enteral Nutr*. 2020;44(4):688-696. doi:10.1002/jpen.1692
32. Hudson AS, Tyminski N, Turner JM, Silverman JA. Intestinal failure-associated liver disease and growth pre- and post-transition to a composite lipid emulsion. *J Pediatr Gastroenterol Nutr*. 2023;76(6): 830-836. doi:10.1097/MPG.0000000000003763
33. Abrams SA, Ernst KD, Weitkamp JH, et al. Safety and efficacy of a composite lipid emulsion with fish oil in hospitalized neonates and infants requiring prolonged parenteral nutrition—a randomized, double-blind, multicenter, controlled trial. *J Nutr*. 2024;154(12):3615-3625. doi:10.1016/j.tjnut.2024.10.005
34. Kurvinen A, Nissinen MJ, Gylling H, et al. Effects of long-term parenteral nutrition on serum lipids, plant sterols, cholesterol metabolism, and liver histology in pediatric intestinal failure. *J Pediatr Gastroenterol Nutr*. 2011;53(4):440-446.
35. Goulet O, Lamazière A, Abi Nader E, Talbotec C, Wolf C, Lambe C. Erythrocyte fatty acid membrane composition in children on long-term parenteral nutrition enriched with ω-3 fatty acids. *Am J Clin Nutr*. 2022;115(2):422-431. doi:10.1093/AJCN/NQAB263
36. Ho BE, Chan SC, Faino AV, et al. Evaluation of SMOFlipid in pediatric intestinal-failure patients and its effects on essential fatty acid levels. *JPEN J Parenter Enteral Nutr*. 2021;45(3):546-552. doi:10.1002/jpen.1850
37. Castillo F, Castillo-Ferrer FJ, Cordobilla B, Domingo JC. Inadequate content of docosahexaenoic acid (DHA) of donor human milk for feeding preterm infants: a comparison with mother's own milk at different stages of lactation. *Nutrients*. 2021;13(4):1300. doi:10.3390/nu13041300

SUPPORTING INFORMATION

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

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