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Long-term Outcomes in Children with Intestinal Failure Associated Liver Disease Treated Six-Months of Intravenous Fish Oil followed by Resumption of Intravenous Soybean Oil

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Abstract

Background: Intravenous soybean oil (SO) is a commonly used lipid emulsion for children with intestinal failure (IF), however it is associated with IF-associated liver disease (IFALD). Studies have demonstrated that intravenous fish oil (FO) is an effective treatment for IFALD. However, there is a lack of long-term data on children who stop FO and resume SO.

Objective: This study's objective was to investigate our institution's outcomes for children with IFALD treated with six months of FO who restart SO.

Methods: Inclusion criteria for FO included children with IFALD. Parenteral nutrition-dependent children resumed SO after FO and were prospectively followed for 4.5 years or until death, transplant, or PN discontinuation. The primary outcome was the cumulative incidence rate for cholestasis after FO.

Results: 48 subjects received FO, and conjugated bilirubin decreased over time (-0.22 mg/dL/week, 95% CI -0.25 , -0.19 , $p < 0.001$). The cumulative incidence rate for cholestasis resolution after 6 months of FO was 71% (95% CI 54, 82). 27 subjects resumed SO and were followed for a median of 16 months (range 3–51). While the cumulative incidence rate for enteral autonomy after three years of follow-up was 40% (95% CI 17, 26), the cumulative incidence rate for cholestasis and transplant was 26% (95% CI 8, 47) and 6% (95% CI 0.3, 25), respectively.

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Conclusion: In this study, FO effectively treated cholestasis, and SO resumption was associated with cholestasis redevelopment in nearly a quarter of subjects. Long-term FO may be warranted to prevent end-stage liver disease.

Introduction

Because of a reduction in gut mass and function, children with intestinal failure (IF) rely upon parenteral nutrition (PN). Causes of pediatric IF are short bowel syndrome, gastrointestinal dysmotility, and enterocyte disorders. With advancements in medical and surgical care, along with a multi-disciplinary approach to IF, the prognosis of children with IF has drastically improved.¹⁻³ In a study of 272 children with IF, 43% weaned from PN over 3 years.⁴ However, prolonged PN exposure causes intestinal failure associated liver disease (IFALD).²⁻⁵ The hepatobiliary consequences of PN include cholestasis, inflammation, and fibrosis, which leads to cirrhosis, portal hypertension, end stage liver disease, and death.⁵ Isolated liver or combined liver and intestinal transplants are treatments for advanced IFALD and PN-dependence. However, post-transplant, patient and graft survival is not guaranteed.¹

Historically, soy-based (SO) intravenous (IV) lipid emulsions have been prescribed as a fat source for children with IF. However, SO's high concentration of phytosterols, high omega-6:omega-3 ratio, and low antioxidant content contribute to cholestasis.⁶⁻¹⁵ In animal studies, parenteral phytosterols (cholesterol like structures in plants) and cytokines cause cholestasis, while α -tocopherol, an antioxidant, protects against cholestasis.^{14,15} In 2005, Gura *et al* reported that IFALD was reversed in two infants with short bowel syndrome when SO was replaced with low dose IV fish oil (FO).⁶ Since then, studies have demonstrated that FO is an effective treatment for IFALD.⁶⁻¹³ In contrast to SO, FO contains a negligible amount of phytosterols, a low omega-6-omega:3 fatty acid ratio, and a high α -tocopherol concentration.⁶⁻¹³

In 2008, we implemented a compassionate use protocol that provides children with IFALD with six-months of FO.^{12,13} After six months of FO, children who are cholestasis-free and remain PN-dependent, resume SO. This strategy was chosen for the following reasons. First, when this protocol was designed, two studies demonstrated that cholestasis resolved in most children within 24 months of FO.^{7,8} Second, our goal was to minimize cost; FO costs considerably more than SO and may not be covered by insurers. Third, FO is a more complicated drug to administer compared to SO. There is no drug compatibility data for FO. Last, at the time this study was designed, FO was not approved by the United States Food and Drug Administration (FDA). For these reasons, we opted to switch back to SO after FO. However, long-term data on children who receive FO for IFALD treatment followed by SO resumption is scant.¹⁶ We therefore sought to describe our institution's unique long-term experience using this approach. We believe this is a clinically relevant study since lipids play an important role in IFALD, and the optimal lipid emulsion for children with IF is controversial.

Methods

Study Design

This is a prospective observational study. Follow-up began when a subject stopped FO and resumed SO. The study's primary outcome was the cumulative incidence rate for cholestasis during follow-up. Secondary outcomes were the cumulative incidence rate for liver transplant, death, and enteral autonomy during follow-up, and cholestasis resolution, transplant, death, and enteral autonomy during FO. Tertiary outcomes were changes in serum liver function tests during follow-up and FO, and long-term growth. Cholestasis redevelopment was defined as two serum conjugated bilirubin (CB) measurements ≥ 2 mg/dL separated by one week after FO treatment. Cholestasis resolution was defined by as two CB measurements < 2 mg/dL separated by one week during FO. Enteral autonomy was defined as the ability to maintain hydration and growth without PN.

Data included laboratory studies and data related to growth, nutrition, and common risk factors for IFALD. During FO treatment and follow-up, laboratory studies were collected on a weekly basis if available. Growth and nutritional data were collected prior to starting FO, at the end of FO, and post-FO. During follow-up, data were collected at the start of follow-up and end of each six-month follow-up period. During follow-up, the primary gastroenterology/transplant team was responsible for managing the subjects' nutrition, including lipid type and dose.

Growth was assessed by z-scores.¹⁷ Growth measurements prior to two years of age were corrected for prematurity. For subjects two years of age or older, the CDC 2–20 years standards were used.¹⁷ For subjects less than two years of age, the 0–36 months CDC standards were used.¹⁷

The study was approved by University of California Los Angeles institutional review board. The FDA approved an investigational new drug (IND) application (105,326) for FO. This study is registered at www.clinicaltrials.gov (NCT00969332).

FO Treatment

We have previously described eligibility criteria for FO.¹² Inclusion criteria includes > 2 weeks of age, < 18 years of age, a gastrointestinal disorder requiring long-term PN, and cholestasis (CB ≥ 2 mg/dL on two measurements separated by one week). Subjects with a liver disease other than IFALD, inborn error of metabolism, seafood or egg allergy, hemorrhagic disorder, hemodynamic instability, comatose state, stroke, pulmonary embolism, myocardial infarction, diabetes, or fatal chromosomal disorder, or on extracorporeal membrane oxygenation were excluded. After parental permission and child assent, if applicable, was obtained, the subject's SO (Intralipid®, Fresenius Kabi, Uppsala, Sweden) was replaced with FO (Omegaven®, Fresenius Kabi, Bad Homburg Germany). FO was dosed at 0.5 g/kg/d IV for two days, then 1 g/kg/d IV thereafter for 6 months. FO was discontinued prior to 6 months if the subject no longer required PN, underwent liver transplantation, developed a serious adverse complication attributed to FO, or was withdrawn from the study. After 6 months of FO, FO was discontinued and SO was resumed. The primary medical team was responsible for SO dosing. FO treatment could be

restarted for another six months if the subject redeveloped cholestasis. FO could be restarted as many times as inclusion criteria were satisfied.

FO Follow-up

Subjects entered into follow-up if they completed a course of FO, remained PN-dependent, resumed SO, and were available for follow-up. The study ended after 4.5 years of follow-up or if the subject expired, received a liver transplant, achieved enteral autonomy, or transitioned to a lipid emulsion composed of a mix of oils (soybean, fish, coconut, and olive oil; MO) (SMOF®, Fresenius Kabi, Bad Homburg Germany). In 2016, the FDA approved MO for adult use. During this time, it became common practice at our institution to replace SO with MO in children with IF.

Statistical Methods

To account for competing risks that may preclude the outcome of interest, non-parametric cumulative incidence functions (95% confidence interval, CI) were estimated for the primary outcome (cholestasis redevelopment during follow-up) and secondary outcomes (liver transplant, death, and enteral autonomy during follow-up and cholestasis resolution, transplant, death, and enteral autonomy during FO). For example, for the primary outcome (cholestasis redevelopment), transplant, death and enteral autonomy are considered competing risks and were accounted for in this analysis.

Wilcoxon rank tests were used to compare laboratory, growth, and nutritional data between the start and end of follow-up and FO. To account for repeated measurements, mixed effects models were fitted to examine the effect of time on these measurements during follow-up and FO separately. Gray's test was used to examine the homogeneity of the cumulative incidence rate for cholestasis resolution between subjects with CB > 5 mg/dL and those with CB ≤ 5 mg/dL at FO initiation. Hazard ratios (95% CI) were estimated using Fine and Gray's proportional sub-distribution hazards model. Logistic regression was performed to investigate the effect of birth weight and baseline CB on cholestasis resolution during FO treatment.

Characteristics for FO responders vs. non-responders, and subjects who redeveloped cholestasis vs. subjects who remained cholestasis-free during follow-up were compared using a Chi-square test, a Fisher's exact test or a Wilcoxon rank sum test. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, 2002–2012).¹⁸

Results

FO Treatment Response

Forty-eight subjects received FO (May 2009 – July 2016) (Figure 1). FO was initiated at median of 4 months of age (range 1–249 months). Most subjects had short bowel syndrome (Table 1). CB decreased significantly over time (−0.22 mg/dL/week, 95% CI −0.25, −0.19, $p < 0.001$). Other liver function tests followed a similar trend, while albumin increased over time (Table 2). At the end of FO, 31 infants achieved cholestasis resolution, and the cumulative incidence rate for cholestasis resolution after 6 months of FO therapy was 71%

(95% CI 54, 82) (Figure 2). The median time to achieve cholestasis resolution was 13 weeks (4–24 weeks).

We compared FO non-responders to FO responders, excluding subjects who weaned from PN during FO since all of these subjects had cholestasis when PN was discontinued. FO non-responders had a higher CB at the start of FO (7.3 mg/dL (4.3–14.7) vs. 4.3 mg/dL (2.3, 10.1), $p=0.006$), were more premature (32 weeks (25–38) vs. 35 weeks (25–40), $p=0.01$) and weighed less at birth (1.3 kg (0.8–2.9) vs. 2.5 kg (0.7–4.3), $p=0.002$) compared to subjects whose cholestasis resolved. Subjects with a CB > 5 mg/dL were less likely to achieve cholestasis resolution when compared to subjects with a CB ≤ 5 mg/dL (subdistribution hazard ratio 0.35, 95% CI 0.18–0.71, $p=0.003$). After six months of FO treatment, the cumulative incidence rate for cholestasis resolution was 59% (95% CI 36, 76) for subjects with a CB > 5 mg/dL vs. 85% (95% CI 51, 96) for subjects with a CB ≤ 5 mg/dL ($p=0.001$). Logistic regression was used to examine the effect of birth weight on cholestasis resolution after adjusting for CB at the start of FO. For each 0.5 kg increase in birth weight, a child was 2 times more likely to respond to FO (odds ratio=2.03, 95% CI 1.1, 3.7, $p=0.02$). The area under the receiver operating characteristic curve ($\pm$ standard error) for this model, which included birth weight and CB, was 0.87 ± 0.07 (95% CI 0.74, 1). Age (9 months (2–249) vs. 4 months (1–99), $p=0.15$) and PN intake at FO initiation (73 kcal/kg/d (41–114) vs. 78 kcal/kg/d (49–132), $p=0.73$), and percent PN change (–17% (–49–16) vs. –13% (–59–53), $p=0.89$), Urosodiol use (45% vs. 29%, $p=0.46$) and number of septic episodes during FO (1 (0–2) vs. 1 (0–4), $p=0.64$) were similar between the two groups.

After six months of FO treatment, the cumulative incidence rate for transplant was 5% (95% CI 1, 14; $n=2$) (Figure 2). One subject received a multi-visceral transplant for advanced IFALD. The other subject received an isolated liver transplant for cirrhosis. The cumulative incidence rate for death was 7% (95% CI 2, 17; $n=3$) (Figure 2). It should be noted that one subject achieved cholestasis resolution, but then later expired (total deaths, $n=4$). Three subjects died of sepsis, and one died of respiratory failure.

Nutrition and Growth with FO

After six months of FO, the cumulative incidence rate for enteral autonomy was 13% (95% CI 5–25, $n=6$) (Figure 2). At the time PN was discontinued, all of these subjects had cholestasis. When compared to the start of FO, at the end of FO, PN intake was less (82 kcal/kg/d (40–132) vs. 61 kcal/kg/d (22–107), $p<0.001$) and weight z-scores were greater (–1.1 (–3.8–2.8) vs. –0.7 (–2.9–2.0), $p=0.02$) (Table 2).

Cholestasis Post-FO

Table 1 depicts data for the twenty-seven subjects who entered into follow-up. Four subjects were lost to follow-up (Figure 1). All subjects had a CB < 2 mg/dL. Median follow-up time was 16 months (3–51 months). At the three-year follow-up, the cumulative incidence rate for cholestasis was 26% (95% CI 8, 47; $n=6$) (Figure 3). For the six subjects who redeveloped cholestasis, the median time was 22 months (5–38 months).

At the three-year follow-up, the cumulative incidence rate for liver transplant was 6% (95% CI 0.3, 25; $n=1$) (Figure 3). However, it should be noted that one subject received a

transplant approximately two months after cholestasis redevelopment and the first event, cholestasis, was included in the analysis (Figure 1). Hence, the total number of transplants during follow-up was two. One subject received a multi-visceral transplant. This subject was re-referred to our institution 17 months after stopping FO for IFALD complicated by portal hypertension. The other subject received a multi-visceral transplant because he/she lacked central access. This subject remained cholestasis-free after FO, but demonstrated compensated liver disease with cirrhosis on biopsy with portal hypertension. During follow-up, there were no deaths.

CB slowly increased during follow-up (0.005 mg/dL/week, 95% CI, 0.003, 0.008, $p<0.001$) (Table 3). Of the five subjects who redeveloped cholestasis and did not receive a transplant, four subjects received a second round of FO at a median of 33 months (5–43 months) after stopping FO. Two of these four subjects redeveloped cholestasis after the second course of FO at a median of 8 weeks (3–13 weeks). These two subjects then received a third round of FO at a median of 8 months (3–14 months). One subject transitioned to MO, and the other subject remains on FO indefinitely. Each time FO was re-started, cholestasis resolved. One subject was not restarted on FO because of social and medical concerns (unable to commit to follow-up and concern for futility of care because of co-morbid medical conditions).

When follow-up subjects who did not redevelop cholestasis were compared to subjects who did redevelop cholestasis, there was no significant difference for age at the start of FO (4 months (1–99) vs. 20 months (2–82), $p=0.38$), birth weight (2.5 kg (0.7–4.3) vs. 2.5 kg (1.5–3.4), $p=0.78$), gestational age (36 weeks (27–40) vs. 34 weeks (28–40), $p=0.40$), time to resolution of cholestasis with FO (13 weeks (4–24) vs. 14 (4–24 weeks), $p=0.98$), and percent PN change during FO treatment (–20% (–59–53) vs. –8% (–13–9), $p=0.21$). Late onset sepsis was not associated with the redevelopment of cholestasis in any of the subjects.

Nutrition and Growth Post-FO

After three years of follow-up, the cumulative incidence rate for enteral autonomy was 40% (95% CI 17, 62; $n=8$) (Figure 3). PN requirement decreased over time (–2.1 kcal/kg every 6 months, 95% CI –3.70, –0.52, $p=0.01$). SO was resumed at median dose of 6.8 g/kg/week (6.1–7.3), and SO dose did not change over time (–0.11 g/kg every 6 months, 95% CI, –0.40, 0.18, $p=0.46$). Weight and height z-scores increased by 0.16 (95% CI 0.04, 0.27, $p=0.01$) and 0.18 (95% CI 0.02, 0.34, $p=0.03$) every six months, respectively (Table 3).

Discussion

This study indicates that FO treats IFALD in the majority of children; the cumulative incidence rate for cholestasis resolution in this cohort was 71%. However, when SO was resumed after six months of FO treatment, the cumulative incidence rate for cholestasis redevelopment was 26%. During this time, other children remained cholestasis-free and/or achieved enteral autonomy. Based on our findings and the results of other studies, we believe that extending FO beyond six months could help prevent cholestasis redevelopment and liver failure in some children with IF.^{6–15}

In our study, FO treatment was limited to six months, and SO was resumed in 27 subjects. While there were no deaths during follow-up, 6 children redeveloped cholestasis. One of these children received a transplant for IFALD and portal hypertension. Another received a transplant because of he/she lacked central access. This subject had non-cholestatic IFALD characterized by cirrhosis and portal hypertension. It remains unclear if transplant could have been avoided in these subjects if FO was continued. We could not decipher any significant differences between children who redeveloped cholestasis vs. those who did not redevelop cholestasis in follow-up. This is most likely a sample size issue. We speculate that children whose enteral intake does not improve, and who have repeated infections are the most susceptible to redeveloping IFALD after FO is discontinued.¹⁻⁵ In contrast to our study, in a study of 30 children with short bowel syndrome, liver function and growth improved with long-term FO (median FO course, 4.6 years (interquartile range, 4–6.2 years). None of these subjects succumbed to liver failure or required a transplant.¹¹ Based on our data and published literature, we amended our compassionate use protocol so that children who remain PN-dependent could continue FO indefinitely.⁶⁻¹⁵

While FO treats cholestasis, it remains unclear if FO has anti- or pro-fibrotic properties.^{20,21} A study by Nandivada, *et al* described 51 children with cirrhosis. 76% (n=39) of these children achieved cholestasis resolution during FO. The remaining 24% of children received a transplant (n=5) or expired (n=11). However, liver biopsy data on this cohort was not available.²⁰ In a smaller study of children with biopsy proven fibrosis who were treated with FO, fibrosis remained stable or improved in three children while fibrosis progressed in the other three children.²¹ In adults with IFALD, FO reduced concentrations of two fibrosis biomarkers, matrix metalloproteinase (MMP-9) and transforming growth factor beta 1 (TGFβ1) when compared to lipid emulsions containing some soybean oil.²² An *in vitro* study showed that FO inhibited the transformation of liver epithelial cells to myofibroblasts.²² In contrast, in a rabbit model, animals who received a combination SO and FO (dosed at only 0.2 g/kg/d) had increased fibrosis on liver biopsy compared to animals who only received SO.²³ Hence, FO's effect on liver fibrosis is controversial and requires further study. In our study, one the subjects who received a transplant during follow-up was cholestasis-free, but demonstrated cirrhosis on biopsy. It is unknown what would have happened to this subject's liver histology if he/she remained on FO.

Because FO is dosed at 1 g/kg/d, there are concerns that long-term FO could contribute to poor growth or an essential fatty acid deficiency. However, studies have demonstrated that growth improves with FO, and FO is not associated with an essential fatty acid deficiency.^{12,19} In this study, weight z-scores improved during FO. The lack of growth faltering with FO is most likely secondary to increased enteral intake that occurs with intestinal adaptation, and increased provisions of parenteral glucose.

The risk of cholestasis redevelopment with SO resumption may outweigh any theoretical or potential risks with FO. Cholestasis redevelopment after successful FO treatment could increase the risk for malnutrition, sepsis, hospitalizations, liver failure, the need for transplant, and death. If FO is not continued after IFALD resolution, IV lipid options for children with IF are low dose SO or MO. Low dose SO is associated with growth deceleration and essential fatty acid deficiencies, especially with doses < 1 g/kg/d.^{24,25} In a

study of seven children whose cholestasis resolved with FO (median treatment time, interquartile range, 9–27 months), SO was restarted after FO treatment, and one subject (17%) re-started FO for cholestasis.¹⁶ In contrast to our study, the aforementioned study had a smaller sample size (7 vs. 27), slightly shorter duration of follow-up (median 14 months vs. 16 months), and longer duration of FO treatment (median 21 months vs. 6 months).¹⁶

In the current study, 30% of subjects were transitioned from SO to MO during follow-up. MO is now a common IV lipid option for children with IF. However, the long-term effect of MO on cholestasis- and transplant-free survival is unknown. It is also unclear if substituting MO for FO after cholestasis resolution vs. long-term FO is of any benefit. Potential advantages to MO include a greater provision of fat calories since it can be dosed at > 1 g/kg/d compared to low dose SO and FO; MO contains less phytosterols than SO at an equivalent dose; and MO's omega-6:omega-3 fatty acid ratio appears to be more physiologically appropriate.^{26–27} Despite these potential advantages, data comparing MO to SO for IFALD prevention or treatment is debatable.^{26–27} In a randomized controlled pilot study comparing SO to MO for the treatment of IFALD, the difference of CB concentrations at the beginning and end of the study were larger in the MO group vs. the SO group ($p=0.001$).²⁷ However, when a subject who was considered an outlier was included, this result was no longer statistically significant.²⁷ As of today, there is no data comparing MO to FO for IFALD treatment, and it remains unclear if MO will modify the incidence of cholestasis in children with IF. Unfortunately, in this study we cannot comment on the incidence of cholestasis re-development with MO.

Like other studies, our data show that FO reverses cholestasis as indicated by a drastic decrease in liver function tests.^{6–15} With improved survival rates for children with IF, research is needed to determine the optimal lipid emulsion for children with IF that will promote appropriate growth without compromising nutrition and liver function. This is particularly relevant since intestinal adaptation may take years.^{1–3} It is important to note that not all children with IFALD will respond to FO. In our study, four children received liver transplants (2 during FO and 2 during follow-up). While FO may not eliminate transplant entirely, timing of FO initiation is critical. Similar to our study, another study showed that children with greater CB concentrations and lower birth weights were more likely to fail FO therapy compared to children with lower CB concentrations and greater birth weights.²⁸ This indicates that early FO initiation is important, particularly in low birth weight and premature infants who have immature livers and are at high risk for infections.^{2–4, 28}

We recognize that our study has limitations. The quantity and accuracy of our data are limited by sample size, drop-outs, and variable follow-up times. This study was conducted at a single site, and lacks a control group. Like other studies that have examined the efficacy of FO, we are unable to account for confounding factors, particularly lipid dose, enteral intake, infections, and various components of parenteral nutrition.^{7–9, 11, 12} Data for enteral intake were not available since many subjects take *ad libitum* feeds which is not accurately recorded by caregivers.

Conclusion

In this study, the cumulative incidence rate for children with IF who restarted SO after a six-month FO treatment and redeveloped cholestasis was 26%. The cumulative incidence rate for enteral autonomy was 40%. Considering the risk-benefit ratio of FO, long-term FO may be warranted in some children to prevent end-stage liver disease.

Acknowledgments

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Abbreviations:

SO	soybean oil
IF	intestinal failure
IFALD	intestinal failure associated liver disease
FO	fish oil
PN	parenteral nutrition
IV	intravenous
CB	conjugated bilirubin
MO	mixed oil lipid emulsion
AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	gamma-glutamyl transferase
AP	alkaline phosphatase

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Clinical Relevancy Statement

Intravenous fish oil (FO) has been shown to treat pediatric intestinal failure associated liver disease (IFALD). The optimal duration of FO remains unknown. In this study, cholestasis redeveloped in some children who resumed a conventional soybean-based lipid emulsion after successful treatment with FO. Long-term FO may be warranted in some children with intestinal failure to prevent liver disease recurrence.

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Figure 1.

Flow Chart. Each follow-up period was 6 months. PN, parenteral nutrition. ^aOne of the subjects redeveloped cholestasis received a transplant, so the patient is counted twice in this figure.

Outcome	Cumulative Incidence Rates
Death	0.07 (0.02 – 0.17)
Transplant	0.05 (0.01 – 0.14)
Enteral Autonomy	0.13 (0.05 – 0.25)
Cholestasis Resolution	0.71 (0.54 – 0.82)

Figure 2. Cumulative incidence rates (95% confidence interval) for death, transplant, enteral autonomy and cholestasis resolution after 6 months of fish oil.

Figure 3.

Cumulative incidence rates (95% confidence interval) for cholestasis, transplant and enteral autonomy during follow-up. Each follow-up period was 6 months.

Table 1.**Subject Characteristics**

	Fish Oil Treatment n=48	Follow-Up n=27
Age, months	4 (1–249) ^a	10 (6–104)
Sex – Male	60 (29)	63 (17)
Race – White	75 (36)	78 (21)
Ethnicity – Hispanic	67 (32)	70 (19)
Gestational age, week	34 (23–40)	35 (27–40)
Gastrointestinal diagnosis		
Necrotizing enterocolitis	25 (12)	19 (5)
Gastroschisis	21 (10)	30 (8)
Atresia	19 (9)	22 (6)
Volvulus	17 (8)	11 (3)
Other ^b	19 (9)	19 (5)
Small bowel length, cm ^c	20 (0–170)	20 (0–170)
No. of gastrointestinal surgeries	0 (0–3)	0 (0–3)
No. of sepsis episodes ^d	1 (0–4)	1 (0–10)
Ursodiol	44 (21)	37 (10)

Data are represented as medians (ranges) or % (n).

^aOne subject was 20 years of age at the start of fish oil. A single subject exception was granted.

^bOther includes pseudo-obstruction, tufting enteropathy, microvillus inclusion disease, spontaneous intestinal perforation, megacystis microcolon intestinal hypoperistalsis syndrome, total agangliosis, and meconium plug syndrome.

^cSmall bowel length was measured during an operation in 29 and 19 subjects in the fish oil and follow-up cohort, respectively.

^dSepsis was defined as a positive blood culture requiring > 5 days of intravenous antibiotics.

Table 2.

Liver function, nutrition, and growth during fish oil.

	Start of Fish Oil	End of Fish Oil	p-value ^a n=48	Mean Change per week (95% CI) ^b	p-value n=48
CB, mg/dL	5.1 (2.3, 14.7)	0.4 (0.1, 23.4)	p<0.001	-0.22 (-0.25, -0.19)	<0.001
AST, IU/L	132 (33, 509)	82 (22, 454)	p<0.001	-6.40 (-7.36, -5.44)	<0.001
ALT, IU/L	101 (19, 552)	67 (14, 336)	0.02	-3.99 (-4.81, -3.16)	<0.001
GGT, IU/L	135 (27, 636)	98 (25, 776)	0.21 ^c	-1.91 (-3.73, 0.10)	0.04 ^c
Platelets, K	189 (41, 599)	185 (25, 570)	0.60	0.61 (-0.29, 1.50)	0.18
AP, IU/L	350 (146, 2407)	341 (108, 860)	0.49 ^c	-2.03 (-3.46, -0.59)	0.006 ^c
Albumin, mg/dL	3.4 (2.0, 5.0)	3.7 (2.0, 4.6)	0.26 ^c	0.01 (0.01, 0.02)	<0.001 ^c
PN, kcal/kg/d	82 (40, 132)	61 (22, 107)	p<0.001 ^c	--	--
Fat, g/kg/wk	7.1 (2.0, 24.5)	6.9 (0, 7.7)	0.002 ^c	--	--
Weight Z-score	-1.1 (-3.8, 2.8)	-0.7 (-2.9, 2.0)	0.02 ^c	--	--
Height Z-score	-1.5(-4.7, 1.7)	-1.6 (-4.9, 0.8)	0.14 ^c	--	--

Data are represented as medians (ranges). CB, conjugated bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; AP, alkaline phosphatase; PN, parenteral nutrition.

^aWilcoxon signed rank were used to compare the start of fish oil vs. end of fish oil.

^bMixed models were fitted to investigate the effect of time.

^cGGT, n=30; AP, n=46; albumin, n=42; PN, n=46; fat, n=46; weight z-score, n=44; height z-score, n=43.

Table 3.

Liver function, nutrition, and growth during follow-up.

	Start of Follow-Up	End of Follow-Up	p- value ^a n=27	Mean Change ^b (95% CI) n=27	p- value n=27
CB, mg/dL	0.2 (0.1, 1.5)	0.2 (0.1, 8.8)	0.06 ^e	0.005 (0.003, 0.008) ^c	<0.001 ^e
AST, IU/L	47 (23, 155)	55 (16, 553)	0.67	0.16 (0.03, 0.28) ^c	0.01
ALT, IU/L	55 (17, 197)	47 (14, 231)	0.98	0.06 (−0.06, 0.18) ^c	0.4
GGT, IU/L	69 (12, 445)	79 (18, 536)	0.19 ^e	0.63 (0.36, 0.90) ^c	<0.001 ^e
Platelets, Kx1000	289 (93, 705)	200 (27, 446)	0.003	−0.21 (−0.38, −0.05) ^c	0.01
AP, IU/L	338 (218, 1012)	266 (90, 672)	0.002	−0.73 (−1.04, −0.41) ^c	<0.001
Albumin, mg/dL	3.9 (2.8, 4.9)	3.6 (1.7, 4.6)	0.11	−0.0004 (−0.0015, 0.0007) ^c	0.5
PN, kcal/kg/d	66 (41, 103)	64 (12, 81)	0.005	−2.1 (−3.70, −0.52) ^d	0.01
Fat, g/kg/wk	6.8 (6.1, 7.3)	6.6 (0, 15.0)	0.87	−0.11 (−0.40, 0.18) ^d	0.5
Weight Z-score	−0.4 (−2.4, 1.2)	−0.60 (−2.4, 1.4)	0.81	0.16 (0.04, 0.27) ^d	0.01
Height Z-score	−1.2 (−4.7, 0.8)	−1.1 (−3.9, 2.9)	0.10	0.18 (0.02, 0.34) ^d	0.03

CB, conjugated bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; AP, alkaline phosphatase. Values in median (min, max).

^a Paired tests were used to compare the start of follow-up vs. end of follow-up.

^b Mixed models were fitted to investigate the effect of time.

^c Mean change per week.

^d Mean change per follow-up period.

^e CB, n=25; GGT, n=21. Each follow-up period was 6 months.