# Comparison of composite lipid emulsion containing fish oil to soy-based lipid reduction for cholestasis prevention in neonates requiring abdominal surgery

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## Background

Intestinal failure associated liver disease (IFALD) (also called Parenteral Nutrition associated liver disease) is a form of cholestatic liver disease in patients receiving prolonged parenteral nutrition [1]. IFALD is estimated to occur in 40-60% of children and up to 85% of neonates receiving prolonged parenteral nutrition [2]. The clinical spectrum of IFALD includes hepatic steatosis, cholestasis, fibrosis, and can progress to hepatic cirrhosis, portal hypertension, and end stage liver disease [2]. The most common cause of intestinal failure and need for prolonged parenteral nutrition in the neonate is short bowel syndrome [3]. There are varying definitions of short bowel syndrome, but a recent panel of experts defined it as, "surgical resection, congenital defect, or disease associated loss of absorption characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted normal diet [4]." Common causes of neonatal short bowel syndrome include necrotizing enterocolitis, gastroschisis, atresia, and volvulus [3, 5]. Because of the wide range of clinical symptoms and causes, many research protocols use laboratory signs of cholestasis with increased direct or conjugated bilirubin as a marker for development of IFALD. Due to the potential complications associated with the development of IFALD, research looking into the prevention of this disease is important.

There have been many studies looking at the causes of IFALD in pediatric patients. While the ultimate cause is likely multifactorial, one of the largest culprits contributing to IFALD is the lipid component of parenteral nutrition [6]. Current practice in most of the United States includes use of a soybean oil based product (Intralipid®) for supplementation of neonates. It is believed this soy-based product contributes to IFALD due to its high phytosterol content, high amount of omega-6 polyunsaturated fatty acids (PUFA) compared to omega-3-PUFA, and low amount of antioxidants [1]. Two current strategies to combat this problem include use of alternative lipids and lowered dosing of soy-based lipid. One alternative composite lipid, Smoflipid®, a mixture of soybean, MCT, olive, and fish oils is promising as it provides necessary essential fatty acids while also providing an increased amount of omega-3-PUFA, and decreased phytosterols. Studies have shown a reduced risk of IFALD progression in neonates transitioned from a soy-based lipid to Smoflipid, with decreased bilirubin (direct, conjugated, or total). These studies have also shown a shift in fatty acid profile toward anti-inflammatory fatty acids such as DHA and EPA in patients receiving Smoflipid [7-11]. With Smoflipid having a potential role in reducing the risk of IFALD progression, it could be inferred that these patients may then have a reduced risk of IFALD development with treatment from parenteral nutrition initiation. However, studies on long-term Smoflipid and risk of IFALD development in at-risk patient populations are lacking.

The role of soy-based lipid reduction as a preventative strategy for IFALD has also been investigated at dosing of ≤ 1g/kg/d compared to standard dosing of 2-3 g/kg/d. These studies have shown mixed reviews, with some showing a decrease in bilirubin (direct, conjugated, or total) and risk of IFALD development, while others have shown no difference in cholestasis development with lipid reduction [12-14]. Even studies showing no difference in cholestasis development, have shown other differences when soy-based lipids are reduced, including a smaller degree of change in direct bilirubin in the soy-based lipid reduction group [15].

Lipid intake in the neonatal period is crucial for retinal and brain development along and an important source of calories for growth [16]. Due to this essential nature of lipid intake during the neonatal period, concern has been raised regarding lipid restriction and its effects on neonatal growth and neurodevelopmental outcomes. Studies investigating neurodevelopmental outcomes of infants treated with lipid restriction have shown development within normal ranges for the patient's age and similar to those of patients treated with standard soy-based lipid dosing [17, 18]. Studies have shown mixed results with regards to growth and neonates treated with lipid restriction. Rollins et al showed a greater increase in weight z-score for patients on standard soy-based dosing compared to reduced dosing, but found no difference in length or head circumference [13]. Other studies have found similar growth when comparing patients both in the neonatal period and into early childhood [18, 19]. The role of the various lipid strategies in the prevention of IFALD is still unclear at this time. Further studies are needed to better understand this disease, its prevention, and its outcomes. During this study we hope to compare two possible preventative strategies and determine a future direction for studying Smoflipid and soy-based lipid reduction.

**Specific Aim**

This study is designed to be a single center, pilot study to evaluate the prevention of cholestasis in neonates requiring abdominal surgery with intestinal failure, divided into two treatment groups, one receiving composite lipid emulsion (Smoflipid® 20%) at standard dosing and the other receiving soy-based lipid (Intralipid® 20%) at reduced dosing. The rate of cholestasis development in the two treatment groups will be compared to a historical control cohort which received soy-based lipid (Intralipid® 20%) at standard dosing of 2 to 3 g/kg/d.

**Study Objectives**

1. Primary: The primary objective of this study is to determine the number of infants receiving Smoflipid at typical dosing (2-3 g/kg/d) and the number of infants receiving Intralipid reduction (1g/kg/day) that develop cholestasis compared to historical controls receiving Intralipid at standard dosing (2-3g/kg/day). Cholestasis will be defined as direct bilirubin greater than 2mg/dL for at least two measurements, 5-7 days apart.

2. Secondary (comparison of each listed parameter between the prospective treatment groups in addition to comparison of each treatment group with historic controls):
    a. Growth (rate of change)

i. Weight, length, and head circumference at enrollment, on a weekly basis while receiving study lipid, and 2-3 weeks post-study lipid completion.
ii. Weight, length, and head circumference at 36 weeks corrected gestational age and time of discharge.

b. Essential fatty acid profile differences and development of deficiency
c. Average total caloric intake for all patients on weekly basis
    i. Average lipid dose delivered on weekly basis
d. Feeding tolerance/ percentage of total calories from enteral feeds
    i. Time to achievement of enteral autonomy (full enteral feedings)
    ii. Percentage of enteral calories at end of study
    iii. Percentage of patients in each group with enteral autonomy
e. Transaminase, alkaline phosphatase, GGT levels at enrollment, every 4 week time point, and end of study
f. Triglyceride concentration at baseline, weekly, and end of study
g. Rates of other diagnoses in each study group
    i. Retinopathy of prematurity as diagnosed by Ophthalmologic examination
    ii. Chronic lung disease as defined by need for oxygen at time of discharge or 36 weeks corrected gestational age (if at least 28 days of age), whichever comes first.
h. Rates of adverse and serious adverse events in each group
i. Length of stay
j. Two year neurodevelopmental differences using ASQ-3 screening

**Study Population**

**Inclusion criteria**

Infants admitted to the Riley Hospital Neonatal Intensive Care Unit (NICU), regardless of postmenstrual or corrected gestational age, with anticipated need for parenteral nutrition for four or more weeks PLUS one or more of the additional inclusion criteria listed below will be eligible for inclusion within the study and for randomization. Inclusion criteria include:

- Anatomic intestinal defect: Neonate with intestinal atresia, omphalocele, gastroschisis or volvulus with or without intestinal resection and need for parenteral nutrition pre or post-operatively.
- Ischemic/perforation intestinal injury: Neonates with spontaneous intestinal perforation or necrotizing enterocolitis requiring surgical intervention with need for parenteral nutrition post-operatively.

**Exclusion criteria at time of study enrollment**

- Infant with current weight less than 750 grams
- AST or ALT greater than 5 times the upper limit of normal within 2 weeks of enrollment

- Direct bilirubin  greater than 2 mg/dL on any consecutive measurement 5-7 days apart within 2 weeks of enrollment
- Severe coagulopathy with elevated INR greater than 2.0 or clinically significant bleeding as determined by the primary and research teams
- Culture confirmed sepsis with positive blood, urine, or CSF culture within 2 weeks (14 days) of enrollment
- Renal failure requiring dialysis
- Cyanotic heart disease requiring prostaglandin therapy
- Hypertriglyceridemia (greater than 250mg/dL) at time of enrollment

**Enrollment/Randomization**

A maximum total of 50 prospective patients, 25 per arm, will be enrolled in the study. Patients will be eligible for enrollment if they meet the above listed enrollment criteria. Once patients are determined to meet enrollment criteria, the parents of the patient will be approached and informed consent will be obtained. Please see separate informed consent document for full consent details.

Stratified randomization will be used to divide patients into each treatment group. Patients will be initially stratified based on the diagnosis of necrotizing enterocolitis or spontaneous intestinal perforation (ischemic/perforation group) or anatomic intestinal abnormality. Once stratified based on diagnosis, patients in each stratum will then be randomized to receive either Smoflipid or Intralipid reduction as described below. Group randomization will be based on premade concealed envelopes.

This study will not be blinded as the caloric dose of the lipid strategies will vary and potentially influence other TPN dosing. Both IV lipids will be given as a solution separate from the remaining TPN. This separate IV lipid will be given as two 12 hour infusions over a 24 hour period.

In the event of slower than anticipated patient enrollment, a minimum of 24 patients (12 per treatment group) will be enrolled in order to obtain needed feasibility data.

**Historic Controls**

A group of 24 patients previously treated in the Riley NICU from the years 2016 – 2017 will be used as a historic control cohort. Historic patients will be eligible for enrollment in the study if they have one of the above listed diagnoses, received post-operative parenteral nutrition, and were treated with soy-based lipid at standard dosing (2-3 g/kg/day). Historic patients will be ineligible to participate if any of the above listed exclusion criteria are true at the time of their abdominal surgery. Historic patients will be matched to prospective patients when able. This matching will first utilize in order: 1. days of parenteral lipid therapy, 2. diagnosis, 3. birth gestational age, and 4. birth weight when selecting for inclusion.

**Study Procedures**

1. Smoflipid® (20% lipid emulsion) treatment group
    a. Advancement:
        i. Smoflipid will be started at 1 g/kg/d on day 1 of parenteral nutrition after enrollment and advanced by 1 g/kg/d each subsequent day to a goal maximum of 3 g/kg/d
    b. Maintenance and weaning [8]:
        i. The Table below will be used as a guide for weaning Smoflipid as enteral nutrition is initiated and advanced.
        ii. Patients will continue to be monitored by a clinical dietician and pharmacist as per standard of care. Pending their recommendations, along with the clinical state of the child, the actual dose of Smoflipid needed may vary by individual patient.
    c. Other parenteral nutrition components
        i. Amino acid will be provided to meet estimated protein requirements only and will not be increased as a form of caloric intake.
            1. Term infant approximate goal of 3 g/kg/day and preterm infant approximate goal of 3.5 – 4 g/kg/day.
        ii. Glucose infusion will be utilized and advanced per standard protocol to provide remainder of estimated non-protein caloric need of each individual patient.
            1. Maximum glucose infusion rate (GIR) while enrolled in study of 16 mg/kg/min. If further caloric intake is required, Smoflipid will be increased to a maximum of 3 g/kg/d.

**Table 1: Smoflipid dosage recommendations for weaning as enteral feeds advanced**

| % calories from PN | Volume enteral feeds (ml/kg/d) | Enteral calories (kcal/kg/d) | Lipid (g/kg/d) |
|---|---|---|---|
| 80-100% | ≤20-40 | ≤30 | 3 |
| 60-80% | 40-60 | 30-40 | 3 |
| 50-60% | 60-80 | 40-50 | 2.5 |
| 40-50% | 80-100 | 50-60 | 2 |
| 30-40% | 100-110 | 60-70 | 1.5 |
| 20-30% | 120 | 70-90 | 1 |
| <20% | >120 | >90 | 0 |

2. Intralipid® (20% lipid emulsion) reduction treatment group
    a. Advancement:
        i. Intralipid:
            1. Intralipid will be started on day 1 of parenteral nutrition at 1g/kg/d

2. Intralipid dose will be maintained at 1g/kg/d while enrolled in the study and receiving parenteral nutrition, unless other clinical concerns arise as documented by primary team.
    a. If further caloric intake is required, Intralipid may be increased at the discretion of the treating faculty based on the needs of the individual patient.

ii. Other parenteral nutrition components:
1. Amino acid will be provided to meet estimated protein requirements only and will not be increased as a form of caloric intake.
    a. Term infant approximate goal of 3 g/kg/day and preterm infant approximate goal of 3.5 – 4 g/kg/day.
2. Glucose infusion will be utilized and advanced per standard protocol to provide remainder of estimated non-protein caloric need of each individual patient.
    a. Maximum glucose infusion rate (GIR) while enrolled in study of 16 mg/kg/min. If further caloric intake is required, Intralipid will be increased at the discretion of the treating faculty based on needs of the individual patient.

3. All Study Patients:
    a. Enteral feedings:
        i. Enteral breast milk or formula choice will be at the discretion of the primary faculty physician and advanced per physician practice.

    b. Anthropometric Measurements:
        i. Each group will have growth monitored per standard protocol with daily weights and weekly head circumference (OFC) and length.
        ii. Weekly measurements used for research purposes will include weekly weight, length, and OFC as documented directly by the research team (primary investigators or same registered dietician).
        iii. Corrected measurements will also be documented with weight, length, and OFC documented at 36 weeks (+/- 3 days) corrected gestational age.
        iv. Follow-up measurements at 2 – 3 weeks after stopping study lipid or time of discharge, whichever comes first.
        v. At each time point, anthropometric measurements will be replicated in triplicate and the average value for that measurement will be reported within the study.
        vi. In the event of safety concerns to the patient or research team, as raised by the research team, patient care team, or regulatory entities, the study measurements will be conducted by the bedside patient nurse. These measurements will include length board use.

c. Diagnoses associated with Prematurity:
    i. Each patient's chart will be reviewed for documentation of retinopathy of prematurity or bronchopulmonary dysplasia (chronic lung disease). The absence or presence of these diseases at the time of discharge will be noted for each study patient, particularly those patients born prematurely at less than 37 weeks gestation.

d. Length of Stay:
    i. An ICU length of stay will be calculated for each patient based on their admit date and discharge date from the Riley NICU.
    ii. For patients transferred to another unit prior to discharge the transfer date will also be documented. For these patients a NICU length of stay and total hospital length of stay will be calculated.

e. Laboratory monitoring (see Table 2 below for reference schedule):
    i. Effort will be made to draw all study lab tests along with other standard of care, routinely scheduled labs.
    ii. The schedule outlined here is a schedule of minimum laboratory work to be obtained. These studies may be obtained more often by the patient's primary clinical team. Any lab test obtained by the primary team within 3 days for weekly labs or within one week for less frequent labs will be used in place of the research lab test.
    iii. Of note all lab tests listed could be considered standard of care, with the exception of INR.
    iv. Essential fatty acid profiles will be obtained every 4 weeks (28 days) while receiving study lipid regimen.
        1. Blood volume needed 0.3-1mL
        2. Considered standard of care in any patient on alternative lipid dosing, such as patients enrolled in this study.
        3. If diagnosed with essential fatty acid disorder, defined as triene:tetraene ratio >0.05:
            a. If Smoflipid dose is less than 3 g/kg/d, SMOF will be increased by 0.5 g/kg/d or to 3 g/kg/d maximum
            b. Those receiving Smoflipid at 3 g/kg/d will be changed to Intralipid at current Smoflipid dose
            c. Those receiving Intralipid will have their dose increased by 0.5 g/kg/d to maximum of 3 g/kg/d
    v. Total and fractioned bilirubin levels will be monitored at least once weekly (7 days)
    vi. Liver function panel and gamma-glutamyl transferase (GGT) will be monitored at least every 2 weeks (14 days).
    vii. Triglyceride levels will be monitored within the first 48 hours of lipid initiation and then once weekly (7 days).

1. If triglyceride level >250 mg/dL will decrease dose of study lipid by 1g/kg/d to minimum of 2 g/kg/d of Smoflipid or 1 g/kg/d three days per week for Intralipid
2. Lipid infusion will be held if triglyceride level > 400 mg/dL
    a. Once triglyceride level <400 mg/dL lipid infusion can be restarted. A lower dose can be used if deemed necessary by the primary care team and dietician.

viii. Bleeding studies
1. Platelets will be monitored once weekly until stable (minimum 2 consistent values, 5-7 days apart) and then once every 4 weeks.
2. INR will be measured once weekly until stable (at least 2 consistent values, 5-7 days apart) and then once every 4 weeks.
    a. Blood volume 1.7 mL
    b. Because this lab is not standard of care, the cost will be covered by research funds, not by the individual patient.

ix. Glucose will be monitored at initiation of parenteral nutrition until stable and then with significant changes in glucose infusion rate. This can be performed via basic metabolic profile (BMP), point of care (POC) glucose, or any other lab source that provides a blood glucose measurement.
1. If the blood glucose is >200 mg/dL on more than one measurement separated by at least 3 hours, the primary team will consider decreasing the patient's GIR.
2. If blood glucose is <50 mg/dL the primary team will consider increasing the GIR.

x. Blood volume:
1. Minimum blood volume per each phlebotomy event are listed in Table 2.
2. Total minimum blood volume 24.4 mL per patient over the 14 blood draws during the study.

xi. Post-study monitoring:
1. As indicated in Table 2, triglyceride, hepatic function panel, GGT, essential fatty acid panel, platelet count, and INR will be measured 2-3 weeks post-study completion or at time of discharge, whichever comes first.
    a. This time frame will be for all patients enrolled in the study, regardless of their length of time within the study.
    b. If the patient is to be discharged from the hospital prior to this 2-3 week time period, labs will be drawn within 3 days of discharge, prior to leaving the hospital.

**Table 2: Minimum laboratory requirements while enrolled in study** (TG= triglyceride, HFP = Hepatic Function Panel, FB = fractionated bilirubin, GGT= gamma glutamyl transferase, EFA = essential fatty acids, PLT= platelet count) (Blood volume is minimum required to perform all tests listed)

| | Week | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | +2-3 |
| | TG | TG | TG | TG | TG | TG | TG | TG | TG | TG | TG | TG | TG | TG |
| | HFP | FB | HFP | FB | HFP | FB | HFP | FB | HFP | FB | HFP | FB | HFP | HFP |
| | GGT | | GGT | | GGT | | GGT | | GGT | | GGT | | GGT | GGT |
| | | | | | EFA | | | | EFA | | | | EFA | EFA |
| | PLT | PLT | | | PLT | | | | PLT | | | | PLT | PLT |
| | INR | INR | | INR | | | | INR | | | | INR | | INR |
| Blood Volume (mL) | 3.1 | 2.8 | 0.8 | 2.2 | 1.7 | 0.5 | 0.8 | 2.2 | 1.7 | 0.5 | 0.8 | 2.2 | 1.7 | 3.4 |

f. Neurologic Follow-up:
    i. ASQ-3 at 2 years of age:
        1. All prospective patients will have an ASQ-3 obtained during the 2nd year of life (age 2 year 0 day to 2 year 364 days).
        2. ASQ-3 will be obtained in one of three manners:
            a. In person: if patient has previously scheduled appointment at Riley
            b. Via phone: if able to confirm identity of parent or guardian
            c. Via mail (electronic or standard): if able to confirm proper mailing address of patient and parent/guardian
        3. ASQ-3 will be completed by the subject's parent or guardian with the aid of one of the primary investigators.
        4. If the subject receives a score within the "monitoring zone" or below threshold of "normal" in any developmental area:
            a. Parent/guardian will be notified of this score
            b. If known developmental delays exist will document if patient is receiving services for delay.
            c. If no previously known developmental delay will refer patient to their primary care physician for further developmental screening and referral for proper services and follow-up.

g. Stopping study Lipid:
    i. Once a study subject reaches one of the following parameters they will stop receiving study lipid, whichever parameter occurs first:
        1. Maximum time of 12 weeks (84 days).
        2. Cholestasis with direct bilirubin of ≥3 mg/dL on two consecutive lab draws at least 5-7 days apart.
        3. Lipid or parenteral nutrition discontinuation for more than one week (7 days).
        4. Subject is discharged home or transferred from Riley Hospital for Children.

ii. Once a subject reaches one of these time points, their lipid treatment, including lipid choice and dose, will be at the discretion of their primary treating physician.
iii. Subjects will continue to be followed by the research team in order to have the following information documented:
    1. Anthropometric measurements at 36 weeks corrected gestational age.
    2. Follow-up anthropometric measurements at 2 – 3 weeks after stopping study lipid or at the time of discharge.
    3. Follow-up laboratory testing at 2 – 3 weeks after stopping study lipid if still admitted to Riley Hospital for Children.
    4. Documentation of prematurity complications.
    5. Discharge and/or transfer date to determine length of stay.
    6. ASQ-3 screen during the second year of life.
iv. Subjects leaving the study secondary to parental request may not have further follow-up performed if at the request of the parent.

**Historic Controls**

Historic controls will have their charts reviewed to document the same information as for prospective patients. For historic controls, this information will be limited to their time admitted to Riley Hospital only. Information recorded will include:

1. Diagnosis and procedures:
    a. Documentation of diagnosis making eligible for study participation
    b. Documentation of surgery performed
2. Parenteral nutrition:
    a. Length of parenteral nutrition: Documentation of total days of parenteral nutrition including start date, stop date, and dates not receiving parenteral nutrition.
    b. Lipid dosing: maximum lipid dose, average lipid dose on weekly basis
    c. Glucose dosing: documentation of glucose infusion rate (GIR) including maximum dose and weekly average GIR dose
    d. Protein dosing: documentation of maximum amino acid dose received and weekly average amino acid dose
    e. Discontinuation of parenteral nutrition: including reason for discontinuing and for what length of time.
3. Enteral Feeding:
    a. Autonomy: the time from start of enteral feeding until complete enteral autonomy (enteral feeding only) will be documented for each patient.
    b. Weekly enteral feeding: On a weekly basis an average of enteral feeding intake will be determined both in volume and calories. Based on these calculations a percentage of overall intake related to parenteral nutrition will be determined.

    c. Milk intake: The particular milk prescribed to each patient will be documented along with the particular form of additives and fortification used.
4. Measurements:
    a. Weight, length, and head circumference will be recorded on a weekly basis for each patient.
    b. Corrected measurements will also be obtained for each patient at 36 weeks corrected gestational age and the time of discharge from the Riley NICU. Given these are historic patients, the values obtains closest to these dates will be used for the purposes of this study.
5. Laboratory values:
    a. Laboratory values listed above for prospective patients will be documented for historic patients if available within the electronic medical record.
    b. If cholestasis is diagnosed the interventions and treatments received by the patients will be documented.
6. Diagnoses of prematurity
    a. Patients born less than 37 weeks will also have their chart reviewed for documentation of retinopathy of prematurity and bronchopulmonary dysplasia or chronic lung disease. Presence or absence of these diagnoses will be documented.
7. Length of stay:
    a. The admit date and discharge date from the Riley NICU will be documented and a length of calculated for each patient.
    b. For patients transferred from the Riley NICU to the floor the transfer date and discharge date from the hospital will also be documented and a NICU length of stay and overall hospital length of stay will be documented.
8. Neurologic Follow-up:
    a. Any patient that has an ASQ-3 performed during year 2 of life will have this information documented.
        **i.** This is not required to be included in the study and will only be documented if information is available.

**Study Duration**

Patients will continue to receive study lipid until one of the following points, whichever should come first:

1. The maximum time for receiving study lipid per the study team will be 12 weeks (84 days).
2. Cholestasis with direct bilirubin of ≥3 mg/dL on two consecutive lab draws at least 5-7 days apart.
3. Lipid or parenteral nutrition discontinuation for more than one week (7 days).
4. Discharge home or transfer to another facility outside of Riley Hospital for Children.

Once one of these parameters are met, as noted previously, the lipid dosing would be at the discretion of the patient's primary physician. The patient will remain in the study to have follow-up laboratory, growth, and neurodevelopmental information collected.

**Adverse Events and Serious Adverse Events**

All patients will be monitored on a daily basis for the development of any adverse events (AE) from the start of the study lipid until one week (7 days) after leaving the study. An adverse event is defined as any untoward medical occurrence in a research subject temporally associated with the use of the study drug, whether or not it is related to the drug. Any worsening of a pre-existing condition or illness is considered an adverse event. This includes pre-existing and or new clinical conditions or morbidities associated with prematurity or the patient's underlying diagnoses. Laboratory abnormalities or vital sign changes are considered adverse events only if they meet the specific criteria listed in the table below. A serious adverse event (SAE) is an AE that leads to death of a subject, life-threatening event, persistent or significant disability, or an important medical event requiring medical or surgical intervention to prevent a serious outcome.

Many possible AE and SAE are listed in Table 3 below. Patients will be monitored continuously by one of the principal investigators, Dr. Huff or Dr. Vanderpool, for possible AEs and SAEs. Clinical significance and relation to the study will be determined by Dr. Huff and/or Dr. Vanderpool based on best medical judgement. Unanticipated events that are determined to be an AE related or possibly related to the research drug will be promptly reported to the IRB by Dr. Huff or Dr. Vanderpool within 5 business days. Major protocol issues, including drug administration issues or errors, will also be reported to the IRB within 48 hours. Events that are determined to be an SAE or lead to death of a patient will be promptly reported to the IRB within 24 hours.

A separate Data and Safety Monitoring Committee (DSMC) will be used to monitor patient outcomes and AE along with SAE events. The DSMC members will not include the primary investigation team and will be made up of other experts from Neonatology (Dr. Ed Liechty), Pediatric General Surgery (Dr. Matthew Landman), Pediatric Gastroenterology (Dr. Emily Hon), and Statistics. The DSMC will meet within 2 weeks following enrollment of the first 10 patients. Further enrollment will be put on hold pending initial DSMC review. If no safety concerns are found by independent DSMC review, patient enrollment will proceed. DSMC will meet subsequently every 6 months for the duration of the study.

Adverse events are defined using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Modifications to these definitions may be made if inappropriate for the neonatal patient population. Some specific events and definitions are listed in Table 3 below. This table does not include the CTCAE v4.0 grade 5, as this is defined as death in a patient. Therefore, any death of a patient will be defined as grade 5, irrelevant of the specific diagnostic category within CTCAE v4.0 or listed below.

**Table 3: Definition of Specific Adverse and Serious Adverse Events**

| **Event** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Definition of adverse event | Mild transient symptoms only | Moderate illness or condition with | Severe illness or condition | Life threatening illness or |

| | | | | |
|---|---|---|---|---|
| | monitored or symptomatic treatment. Aware of symptom but tolerated and no functional interference | new or significant altered treatment, causes some interference with normal activity or care. | unresponsive to medical treatment, incapacitating with inability to perform usual activity and interference with normal functions. | condition, required major surgery or respiratory support. |
| Hyperthermia (axillary temperature) | 38.0-38.5 ºC on single measurement | 38.5-39.0 ºC on single measurement | ≥38.5 ºC on two or more consecutive measurements | ≥39.0 ºC for two or more measurements despite environmental intervention or need for increased IV fluid volume |
| Pulmonary deterioration | Not applicable | FiO2 increase by 0.20-0.30 or new non-invasive ventilation or increase in MAP >3 during study drug infusion | FiO2 increase by 0.31-0.50 or new invasive ventilation or increase in MAP >5-7 during study drug infusion | FiO2 increase >0.50 or need for escalation in type of invasive ventilation or increase in MAP >7 during study drug infusion |
| Hypertension (defined as systolic blood pressure greater than the 95%ile for postmenstrual age) | Hypertension for less than a 24 hour period and no treatment needed | Hypertension 24-48 hours and no treatment needed | Hypertension for >48 hours or requiring treatment | Hypertension requiring multiple treatment types |
| Hyperglycemia | Transient glucose >180mg/dL for single determination with no further action taken | Glucose 180-250mg/dL for at least 2 determinations 6 hours apart | Glucose 251-350mg/dL for at least 2 determinations 6 hours apart or need for insulin or change in IV fluid | Glucose >350mg/dL, change in mental status, diuresis or dehydration |
| Hypoglycemia | Transient glucose <50mg/dL on single measure | Glucose <50mg/dL on repeated measures, responds to treatment with | Glucose <40mg/dL on repeated measures or need for multiple dextrose boluses or need | Glucose <40mg/dL with change in mental status, seizures, glucose |

| | | | | |
|---|---|---|---|---|
| | | single intervention | for change in IV glucose infusion to >10mg/kg/min | unresponsive to glucose infusions, or need for glucagon or steroids |
| Elevated liver enzymes (AST and/or ALT) | 1.5-2.0x normal (90-125 U/L) | 2.1-4.0x normal (126-245 U/L) | 4.1-10.0x normal (246-600 U/L) | >10.0x normal (>600 U/L) |
| Hypertriglyceridemia | 150-250 mg/dL | 250-500 mg/dL | 500-1000 mg/dL | >1,000 mg/dL |
| Elevated creatinine (at >72 hours of age or older) | 1.3-1.8 mg/dL | 1.9-2.3 mg/dL | 2.4-3.4 mg/dL | ≥ 3.5mg/dL |
| Oliguria (urine output (UO) over 24 hour period) | UO <1.0 mL/kg/h | UO 0.5-1.0 mL/kg/h | UO <0.5 mL/kg/h | UO <0.3 mL/kg/h |
| Anemia (based on laboratory value) | Hct <34% | Hct <28% | Hct <24% | Hct <20% and/or cardiovascular instability from the anemia |
| Thrombocytopenia (platelet counts in 1000/cumm) | 75-100 | 50-75 | 25-50 with no bleeding | <10 and/or bleeding |
| Coagulation study abnormalities | INR 1.5-2.0 | INR 2.0-2.5 | INR >2.5 with no clinically significant bleeding | INR >3.0 and/or >2.5 with clinically significant bleeding |
| Thrombosis (thrombus confirmed with imaging and radiographic report) | Non-inclusive thrombus with no associated symptoms. | Non-inclusive thrombus but with symptoms such as edema. | Thrombus leading to need for anticoagulation therapy but with no organ compromise. | Need for anti-coagulation therapy with compromise of extremity or organ related to thrombus. |
| Neutropenia (Absolute neutrophil count) | 1600-2000 | 1000-1599 | 500-999 | <500 |
| Mental status | Mild irritability, possibly within normal range | Persistently irritable and/or intermittent lethargy | Lethargy, stupor, still arousable, single seizure | Non-responsive, need for respiratory intervention due to change |

| | | | | |
|---|---|---|---|---|
| Systemic infection (including sepsis and/or bacteremia with positive blood culture) | Positive blood culture but not treated (felt to be contaminant) | Treated ≥5 days of consecutive antibiotics, antivirals or antifungals with no cardiovascular instability. | Treated for systemic symptoms, including cardiovascular instability and ≥5 days of anti-microbial with response to treatment. | Treated for systemic symptoms, including cardiovascular instability and ≥5 days of anti-microbial no or slow response to treatment. |

**Criteria for Stopping Study**

1) Individual Patient Stopping Criteria:
   a) Development of progressive cholestasis as defined by direct bilirubin of 3 mg/dL or greater on two separate lab draws 5 to 7 days apart.
   b) Clinically significant laboratory abnormalities that change the clinical course of the patient, or the patient's care and are deemed related to the study drug by the primary investigators (Dr. Huff or Dr. Vanderpool). The laboratory abnormalities include, but are limited to:
      i) Change in liver function with AST or ALT greater than 5 times the upper limit of normal or GGT greater than 3 times the upper limit of normal for patient age.
      ii) Creatinine greater than 2 times upper limit of normal for patient age.
      iii) Clinically significant coagulopathy with INR greater than 2.5 or INR greater than 1.5 and clinically significant bleeding.
      iv) Clinically significant thrombocytopenia with platelet count less than 30 or less than 50 with bleeding.
      v) Persistent hyperglycemia with glucose greater than 200 mg/dL despite changes in parenteral nutrition glucose infusion rate.
         (1) Inability to tolerate appropriate calorie intake due to elevated glucose infusion rate that may be required with lipid reduction.
      vi) Persistent hypertriglyceridemia (on 3 or more lab draws each at least 24 hours apart) greater than 250 mg/dL despite decreasing or holding lipid dose.
   c) At the request of the parent or legal guardian.
   d) At the request or recommendation of the patient's primary physician and care team.

If the patient is withdrawn from the study, treatment including parenteral nutrition administration and macronutrient content will be provided at the discretion of the primary faculty physician providing patient care.

2) Study Stopping Criteria:
   a) DSMC or primary investigator initiated study cessation:
      i) As noted a Data Safety and Monitoring Committee (DSMC) of experts from Neonatology, Gastroenterology, Surgery and Statistics will meet within 2 weeks of the first 10 subjects and following at least every six months during the remainder of the study period. They will review patient recruit, patient outcomes, and adverse events in both prospective patient populations. Significant patient safety concerns will

be determined by the DSMC. These patient concerns include, but are limited to, finding a significant amount of AE or SAE within one study group or a large difference in outcomes between study treatment arms.

ii) In adequate patient recruitment. We anticipate recruiting an average of 4 patients per study month. If there is a significant lag and will be unable to obtain our full number of patients within a reasonable time, this will be reason to terminate the study early.

b) Principle investigators will consider study cessation if SAEs occur within a specific treatment arm out of proportion to what would be expected from typical disease course.

**Statistical Considerations**

Our goal is to recruit 25 patients into each group. Given this is a pilot study, the minimum number needed per arm would be 12 patients as per published statistician recommendations [21]. The reasoning for using a pilot study include determining the feasibility of performing a larger scale study. Performing a pilot study prior to the large-scale study will give us information on patient recruitment and retention, along with design flaws that may be remedied prior to future studies.

All data will be summarized by group at each time point; summaries will include frequencies and proportions for categorical variables and mean, standard deviation, and range for continuous variables. Distributions of continuous variables will be examined. Parenteral nutrition characteristics will be recorded and tabulated. Tabulated categorical outcomes will include: proportions of subjects with cholestasis or IFALD, essential fatty acid deficiency, enteral autonomy at end of study, retinopathy of prematurity, chronic lung disease, and adverse events. Tabulated continuous measurements will include: growth rates, essential fatty acid profile, total caloric intake, percentage of calories from enteral intake, time to enteral autonomy, lipid dose delivered, bilirubin level, liver enzymes, gamma-glutamyl transferase (GGT), triglycerides, and length of stay. Fisher's Exact Tests will be used to compare between groups for categorical variables. Time to enteral autonomy will be evaluated using Kaplan-Meier survival curves and a log-rank test. Mixed models will be used to compare between groups and compare within groups over time for continuous variables measured throughout the study. Length of stay will be compared using a Wilcoxon Rank Sum test. A 5% significance level will be used for all tests mentioned.

**Privacy/Confidentiality Issues**

Patient information will be kept only in de-identified and encrypted manners in print or electronically. A single REDCap database with encrypted patient information will be used and shared only between the investigators. A single encrypted key with limited patient information to identify patients will be maintained by the study investigator to identify patients in the event of adverse events related to the study.

**Follow-up and record retention**

The time period of study lipid dosing and monitoring is anticipated to be 12 – 15 months. As noted, patient follow-up will take place 2 years after study completion with a neurodevelopmental screen. The information obtained from this study will be retained by the primary investigators for a period of 7 years after study completion in compliance with all regulations that apply. During this time, all information will be maintained in a secure fashion with no further access granted outside of the primary investigation team.

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