JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Intravenous Lipid Emulsion Management Clinical Pathway

Last updated: August 6, 2026

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners, and other healthcare providers. It should be tailored to the care of specific patients based on their individual circumstances and the clinician's professional judgment.

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

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Summary:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) physicians, pharmacists, and registered dietitians to standardize the management of intravenous lipid emulsions (IVLE) in pediatric patients. Parenteral nutrition (PN) formulations contain carbohydrates, amino acids, electrolytes, and minerals to meet the patient's nutritional needs. Intravenous lipid emulsions became available in the United States (US) during the 1970s and currently meet the fat requirements of patients receiving PN for nutritional support. The use of IVLE as an energy source may be restricted in neonatal and pediatric patients due to elevated triglyceride levels or cholestatic liver disease. With the recent availability of multiple IVLE products, questions have arisen about their choice, use, and safe practices in neonatal and pediatric patients. This clinical pathway addresses the following questions or problems:

1. Standardize the approach and treatment of IVLE selection, monitoring, and management in neonatal and pediatric patients receiving parenteral nutrition.

2. Guide providers on the appropriate use, restriction criteria, safety considerations, and monitoring of IVLE in neonatal and pediatric patients.

Background:

Patients receiving long-term parenteral nutrition are at risk for parenteral nutrition–associated liver disease (PNALD) (Cober et al., 2021; Deshpande & Wei, 2020). The pathophysiology of PNALD remains unclear but is likely multifactorial, with documented risk factors including prematurity, prolonged PN duration, septicemia, and low birth weight (Burrin et al., 2014; Fallon et al., 2010). PNALD may be reversible, with the most effective treatment being advancement of enteral nutrition and eventual PN weaning (Calkins et al., 2013; Gura et al., 2008). If PN cannot be weaned, PNALD may progress to hepatic failure and death (Gura et al., 2006; Koletzko & Goulet, 2010).

Intralipids: Standard Dose versus Reduced Dose

Rollins et al. (2013) compared a reduced intralipid dose (1 gram per kilogram per day [g/kg/day]) with a standard dose (3 g/kg/day) and assessed effects on cholestasis markers and the risk of PNALD. The study included 28 infants of ≥26 weeks' gestation who received the majority of their nutrition via PN for at least 4 weeks. The study

demonstrated that cholestasis markers rose more slowly, and no cases of essential fatty acid deficiency (EFAD) occurred. However, there was less growth and a trend toward lower head circumference with the reduced intralipid dose. Cober et al. (2012) compared the same dosing changes in 62 surgical patients receiving chronic PN. The study showed a drop in bilirubin but no changes in liver enzymes. It also reported no differences in growth parameters, including weight gain and z-scores. In the EFAD analysis, 8 of 31 patients in the reduced-dose group had mild EFAD.

SMOFlipid® (Soybean Oil, Medium-Chain Triglycerides, Olive Oil, and Fish Oil)

Rayyan et al. (2012) compared 53 preterm neonates receiving either SMOFlipid or Intralipid® to assess safety and tolerability. The study found no difference in triglyceride levels, serious adverse effects, or growth parameters between the two groups. However, total and conjugated bilirubin levels were lower in the SMOFlipid group than in the Intralipid group. Goulet et al. (2010) compared the safety and efficacy of SMOF versus intralipids in PN-dependent patients aged 5 months to 11 years. The study found no significant differences in total adverse effects, growth parameters, lipid profile, or liver function tests. The study observed a reduction in total and conjugated bilirubin in the SMOF group compared with the Intralipid group.

Data suggest that soy-based fat emulsions are thought to promote cholestasis because they contain predominantly omega (ω)-6 long-chain polyunsaturated fatty acids and phytosterols and have a relatively low antioxidant content. The literature suggests that replacing soybean lipid preparations (SLP) with fish oil-based lipid preparations (FOLP) can reverse PNALD (Rayyan et al., 2012).

Fish Oil-Based Lipid Emulsions (Omegaven®)

Calkins et al. (2013) studied children aged 2 weeks to 18 years with PNALD who received Intralipids and compared them with patients receiving fish oil lipid preparations at standard doses. Although this study had a small sample size, it reported reversal of cholestasis, evidenced by a reduction in conjugated bilirubin to <2 milligrams per deciliter (mg/dL). The average time to reversal was 11.5 weeks (range 2.4-18 weeks) in the fish oil lipid preparations. It also noted that there were no cases of EFAD in either group. The proposed reason is the high concentrations of arachidonic acid (ARA) and docosahexaenoic acid (DHA). Le et al. (2011) treated 79 pediatric patients with cholestasis with intralipids and then switched them to fish oil-based lipid preparations for at least 4 weeks. The study reported reductions in total bilirubin, conjugated bilirubin, and triglyceride levels.

Gura et al. (2010) reported that patients who fail to receive 1 g/kg/day of fish oil-based lipid emulsions are predisposed to EFAD, as determined by an elevated triene-to-tetraene ratio (described in detail below), and may be at increased risk of treatment

failure. In rare cases of PNALD complicated by preexisting malnutrition, higher off-label doses (i.e., 1.5 g/kg/day) of fish oil-based lipid emulsions are potentially required to replete EFA stores. The use of higher doses of fish oil-based lipid emulsions may also be appropriate in patients with poor growth, limited enteral intake, and/or those whose PN provides high glucose infusion rates that make it difficult to cycle PN.

Table 1: Comparison of Intravenous Lipid Emulsion Composition and Fatty Acid Content

	Intralipid	**SMOFlipid**	**Omegaven**
Oil Source	Soybean	Soybean, MCT, Olive, and Fish	Fish
α-linolenic acid (ALA)	4-11 %	1.5-3.5 %	1.1 %
Linoleic acid (LA)	44-62 %	14-25 %	1.5 %
Eicosapentaenoic acid (EPA)	0 g	0.3 g	1.28–2.82 g
Docosahexaenoic acid (DHA)	0 g	0.05 g	1.44–3.09 g
Arachidonic acid (ARA)	0 g	0 g	0.2-2 g
dl-alpha-Tocopherol	3.8 mg	20 mg	15-29.6 mg
Phytosterols	3.48 mg	4.76 mg	0 mg

All amounts listed are per 100 milliliters (mL)

Adapted from: Gura, K., Premkumar, M. H., Calkins, K. L., & Puder, M. (2020). Intravenous fish oil monotherapy as a source of calories and fatty acids promotes age-appropriate growth in pediatric patients with intestinal failure-associated liver disease. *The Journal of Pediatrics, 219*, 98–105.e4.

Essential Fatty Acid Deficiency (EFAD)

The concept of essential fatty acids was first proposed by the Burrs in the 1920s (Spector, 2015). At that time, fatty acids were discovered to be essential nutrients with Linoleic (LA) and Alpha-Linolenic (ALA) fatty acids preventing and reversing essential EFAD (Spector, 2015). Physical manifestations of EFAD typically occur after 2-4 weeks of prolonged deficiency and may include dry, scaly skin; rashes; alopecia; growth restriction; increased infections; and poor wound healing (Anez-Bustillos, 2018; Le, 2009; Mogensen, 2017).

EFAD is commonly diagnosed clinically by assessing the triene-to-tetraene ratio, also known as the T:T ratio (Fell, 2015). The concept of the T:T ratio, also referred to as the Holman ratio, was developed in 1960 through fatty acid isomerization analysis by Ralph Holman (Yamanaka, 1981). The T:T ratio is specifically calculated by dividing the triene Mead Acid (MA; C20:3ω9) by the tetraene Arachidonic Acid (ARA; C20:4ω6)

(Yamanaka, 1981). According to the Mayo Clinic, essential fatty acid reference ranges, a T:T ratio >0.083 for infants <1 month of age, >0.05 for ages 1-17 years, and >0.038 for ages >17 years may indicate EFAD. It is important to note that this ratio can be a false indicator of EFAD, as it only evaluates the omega-9-to-omega-6 fatty acid ratio and does not assess omega-3 fatty acid status (Anez-Bustillos, 2018; Bernstein, 2022). Thus, a complete fatty acid profile must be considered for accurate interpretation. This is particularly important with patients receiving long-term parenteral nutrition with alternative fish-oil or olive-oil-based IVLE, individuals with fat-malabsorptive disorders, or conditions that require a low-fat diet as medical nutrition therapy, such as chylothorax and various types of metabolic disorders, including Wolman Disease and FAODs (Bernstein, 2022; Estes-Doetsch, 2022; Mogensen, 2017).

Soybean-based intralipid emulsions contain sufficient EFAs to prevent EFAD, but they also have an elevated omega-6:omega-3 ratio, which can contribute to a heightened inflammatory response (Fell, 2015; Gramlich, 2019). Alternative intralipid emulsions, including SMOFlipid and Omegaven, on the other hand, offer more potent anti-inflammatory properties but may increase the risk of EFAD with inadequate dosing and prolonged use (Fell, 2015; Gramlich, 2019).

Alpha-Linolenic Acid (ALA; C18:3ω3) and Linoleic Acid (LA; C18:2ω6) are essential fatty acids that the body cannot synthesize and must be obtained through dietary intake (Fell, 2015; Estes-Doetsch, 2022). These essential fatty acids are further metabolized into the omega-3 fatty acids Eicosapentaenoic Acid (EPA; C20:5ω3), Docosapentaenoic Acid (DPA; C22:5ω3), and Docosahexaenoic Acid (DHA; C22:6ω3) as well as the omega-6 fatty acid Arachidonic Acid (ARA; C20:4ω6) required as important mediators in healthy inflammatory responses, gene expression, neurological development, and cardiovascular health (Anez-Bustillos, 2018; Lagerstedt, 2001).

In the setting of low ALA or LA, the desaturase enzymes produce less EPA and ARA and instead metabolize the non-essential omega-9 fatty acid Oleic Acid (OA; C18:1ω9) to MA. Elevated MA and low ARA concentrations lead to an elevated T:T ratio (Gramlich, 2019). With severely fat-restricted diets, omega-6 fatty acid intake decreases, leading to lower ARA and higher MA production, resulting in either an elevated or a normal T:T ratio. Similarly, prolonged use of alternative intralipid emulsions containing higher amounts of omega-3 fatty acids may lead to elevated ALA, EPA, and DHA levels but low ARA levels, thereby preventing increased MA production and resulting in a normal T:T ratio. If the T:T ratio is elevated but the EFAs are within normal limits, this indicates a false positive for EFAD. This scenario does not require any dietary changes. If the T:T ratio is within normal limits but the EFAs are low, this indicates a false negative for EFAD. In this situation, omega-3 and/or omega-6 supplementation should be provided to correct the deficiency (Bernstein, 2022; Metametrix, 2007). Studies have also

demonstrated that EFAD can be prevented with supplementation with DHA and ARA alone (Le, 2014).

In conclusion, the best indicators for accurately assessing EFAD are the omega-3 and omega-6 essential fatty acids ALA (C18:3ω3) and LA (C18:2ω6) as well as their downstream metabolites EPA (C20:5ω3), DPA (C22:5ω3), DHA (C22:6ω3), and ARA (C20:4ω6) regardless of an elevated or normal T:T ratio (Anez-Bustillos, 2018; Bernstein, 2022; Fell, 2015; Le, 2009). Additionally, it is important to consider the ARA:DHA ratio, as a balanced omega-6:omega-3 ratio positively influences neurological development and inflammatory processes and decreases the risk of obesity (Bernstein, 2022; Carlson, 2016; Simopoulos, 2016).

Table 2: Essential Fatty Acid Recommendations and Estimated Intrauterine Accretion Rates in Preterm Infants

	Minimum recommendations for preterm infants	**Estimated needs based on third-trimester intrauterine accretion rates**
α-linolenic acid (ALA)	385–1540 mg/kg/day	106 mg/kg/day
Linoleic acid (LA)	≥55 mg/kg/day	4 mg/kg/day
Arachidonic acid (ARA)	18–45 mg/kg/day	212 mg/kg/day
Docosahexaenoic acid (DHA)	12–60 mg/kg/day	43–60 mg/kg/day
Eicosapentaenoic acid (EPA)	≤20 mg/kg/day	Fetal accretion rate unknown

Note: these recommendations are for preterm infants only.

Table adapted from multiple sources, including Carlson & Colombo, 2016; Lapillonne & Moltu, 2016; Robinson & Martin, 2017.

Table 3: Essential Fatty Acid Adequate Intakes (AI)

Age Range	Linoleic Acid (LA; C18:2ω6)	α-Linolenic Acid (ALA; C18:3ω3)
Infants and Children		
0-6 months	4.4 grams/day	0.5 grams/day
7-12 months	4.6 grams/day	0.5 grams/day
1-3 years	7 grams/day	0.7 grams/day
4-8 years	10 grams/day	0.9 grams/day
Males		
9-13 years	12 grams/day	1.2 grams/day
14-18 years	16 grams/day	1.6 grams/day
>18 years	17 grams/day	1.6 grams/day
Females		
9-13 years	10 grams/day	1 gram/day
14-18 years	11 grams/day	1.1 grams/day
>18 years	12 grams/day	1.1 grams/day

Reprinted from: Trumbo, P., Schlicker, S., Yates, A. A., & Poos, M. (2002). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. *Journal of the American Dietetic Association, 102*(11), 1621–1630. https://doi.org/10.1016/S0002-8223(02)90346-9.

Cohorts of Special Circumstances:

Allergies/Hypersensitivity Reactions

Franz et al. (2021) reviewed the risk of type I immunoglobulin E ([IgE]-mediated) hypersensitivity reactions associated with IVLE used in parenteral nutrition and other clinical settings. They found that true IgE-mediated reactions are rare, and most reported adverse events represent non–IgE-mediated infusion reactions rather than true anaphylaxis. Potential allergenic components include egg phospholipids (used as emulsifiers), soybean oil, and fish oil, though clinically significant cross-reactivity in patients with reported food allergies appears uncommon. The authors emphasize that a documented food allergy does not automatically contraindicate lipid emulsion therapy.

The authors recommend an individualized risk–benefit assessment, particularly for patients with a history of severe IgE-mediated reactions. Careful allergy history-taking, close monitoring during initial infusions in higher-risk patients, and prompt discontinuation with standard anaphylaxis management if symptoms occur are advised. Overall, the review supports cautious but appropriate use of lipid emulsions when

clinically indicated, rather than routine avoidance in patients with reported egg, soy, or fish allergies.

Table 4: Package Insert Labeling for Potential Allergens Contained In, and Hypersensitivity Contraindications To, Lipid Emulsion Products

Product	Package Insert-Specified Allergen (Mass/volume %)	Package Insert-Specified Hypersensitivity Contraindication
Intralipid (Fresenius Kabi)	Egg yolk phospholipids (1.2%) Soybean oil (20%)	None listed
SMOFlipid (Fresenius Kabi)	Egg yolk phospholipids (1.2%) Soybean oil (6%) Olive oil (5%) Fish oil (16%)	Fish, egg, soybean, or peanut protein
Omegaven (Fresenius Kabi)	Egg yolk phospholipids (1.2%) Fish oil (10%)	Fish or egg protein
Clinolipid® (Baxter)	Egg yolk phospholipids (1.2%) Soybean oil (4%) Olive Oil (16%)	Egg and soybean proteins

Reprinted from: Cober, M. P., Gura, K. M., Mirtallo, J. M., et al. (2021). *ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations*. *Nutrition in Clinical Practice, 36*(6), 1106–1125.

Intestinal Rehabilitation

Intestinal failure (IF) in pediatric patients often requires prolonged parenteral nutrition, placing infants at high risk for intestinal failure–associated liver disease (IFALD). Traditional soybean oil–based lipid emulsions are rich in omega-6 fatty acids and phytosterols, both of which are implicated in proinflammatory effects and impaired bile flow. Mixed lipid emulsions such as SMOFlipid (soybean oil, medium-chain triglycerides, olive oil, and fish oil) were developed to provide a more balanced fatty acid profile, reduce exposure to phytosterols, and incorporate omega-3 fatty acids with anti-inflammatory and hepatoprotective properties. Survey data from pediatric intestinal rehabilitation and transplant centers demonstrate widespread adoption of mixed lipid emulsions for both prevention and treatment of IFALD. However, variability in practice remains regarding dosing and timing of initiation (Raghu et al., 2022).

Comparative studies evaluating SMOFlipid versus soybean oil emulsions suggest that mixed lipid formulations improve liver outcomes. Daniel et al. (2021) found improved liver function parameters in pediatric patients receiving SMOFlipid compared with Intralipid. Similarly, Belza et al. (2020) observed a more favorable trajectory of IFALD evolution in infants treated with SMOFlipid than in those treated with soybean oil

emulsions. In the early management of infants with IF, Casson et al. (2020) demonstrated reduced incidence and severity of cholestasis in patients receiving SMOFlipid compared with Intralipid, supporting early implementation of mixed lipid emulsions as a preventive strategy.

SMOFlipid has also been used therapeutically in established IFALD as part of comprehensive intestinal rehabilitation programs. Molinos et al. (2021) reported reversal of cholestasis in an infant treated with a mixed lipid emulsion in combination with multidisciplinary intestinal rehabilitation strategies, including enteral feeding optimization and PN cycling. These findings reinforce that lipid modification is most effective when integrated into a structured, multidisciplinary approach to IF management.

Fish oil–based lipid emulsions used as monotherapy have demonstrated efficacy in reversing severe IFALD, particularly in progressive cases. Gura et al. (2020) described the use of fish oil IVLE beyond labeled indications, highlighting successful reversal of cholestasis in pediatric IF patients. However, considerations of essential fatty acid sufficiency and long-term nutritional adequacy have led many centers to preferentially use mixed lipid emulsions, such as SMOFlipid, for ongoing management and to reserve fish oil monotherapy for refractory cases.

Overall, the current literature supports SMOFlipid as a safe and effective alternative to traditional soybean oil emulsions in pediatric patients with intestinal failure. Evidence suggests improved liver biochemistries, reduced incidence or progression of cholestasis, and a growing consensus among intestinal rehabilitation centers supporting its use for both prevention and treatment of IFALD (Belza et al., 2020; Casson et al., 2020; Daniel et al., 2021; Raghu et al., 2022). When incorporated into a multidisciplinary intestinal rehabilitation program, SMOFlipid plays a central role in optimizing hepatic outcomes while maintaining adequate nutritional support (Molinos et al., 2021).

Congenital Diaphragmatic Hernia

No studies describe the optimal lipid emulsion for patients with congenital diaphragmatic hernia (CDH). Therefore, the potential risks and benefits of different lipid emulsions should be considered when choosing a lipid emulsion for patients with CDH.

Suboptimal growth is common in patients with CDH (Gien, 2017; Leeuwen, 2017). All infants with CDH, even those with less severe CDH, are “at risk for poor nutritional outcomes” (Vu, 2017). Providing sufficient calories during initial hospitalization is paramount (Bathgate, 2021). Recommended dietary reference intakes and predictive equations underestimate the increased calorie and protein requirements of infants with CDH (Haliburton, 2016).

Clinical status can delay feeds, but prolonged PN (defined as 12 additional PN days in a study by Gien et al. (2017) may improve growth and survival. Of note, increased direct bilirubin levels have been reported in infants with CDH on PN, but this is thought to be temporary (Yoshida, 2020).

Oftentimes, reasons unrelated to PN account for elevated direct bilirubin levels in neonates with CDH. For example, this is frequently seen in patients on extracorporeal membrane oxygenation (ECMO), and PN is not associated with the development of direct hyperbilirubinemia in children on ECMO (Alexander, 2022). In addition, elevated levels can be related to obstructive jaundice, which has been described in patients with right CDH (García-Muñoz, 2001; Schiffler,1988).

Because no studies have investigated SMOFlipid in the CDH population, we cannot recommend when to switch from Intralipid to SMOFlipid. However, SMOFlipid is approved for use in infants and may be beneficial for those who have been on PN for >2 weeks and are expected to continue on PN (Jackson, 2021). Despite limited data on the benefits of SMOFlipid, significant adverse effects appear unlikely, and prolonged Intralipid use is associated with PNALD.

When Gura et al. (2008) concluded that children with intestinal failure receiving Omegaven and Intralipid had similar growth, it is important to note that the two groups received the same total calories from PN. Intralipid and SMOFlipid provide 2 kilocalories (kcal)/mL and are dosed at 3 g/kg/day for infants. Omegaven, by comparison, provides 1.12 kcal/mL and is dosed at 1 g/kg/day. Similar energy intake from PN may not be achievable in cases of increased energy needs and limited PN volume (when PN is switched from Intralipid to Omegaven). Omegaven should be reserved for those with true PNALD.

Cardiac Patients

Neonates and infants admitted to the cardiovascular intensive care unit (CVICU) with congenital heart disease have unique nutrient requirements given their underlying pathophysiology. In these patients, impaired gut perfusion and high necrotizing enterocolitis (NEC) risk often result in prolonged feed intolerance and reliance on PN support before, during, and after surgical intervention. Additionally, cardiopulmonary bypass and mechanical circulatory support increase inflammatory processes and predispose patients to organ dysfunction, heightening the relevance of liver disease. Thus, providing IVLE that minimizes inflammation and risk of parenteral nutrition-associated liver disease (PNALD) is warranted in this population. SMOFlipid, a mixed lipid containing fish oil (with EPA/DHA omega-3 fatty acids) limits omega-6 fatty acids and phytosterols, and a growing body of evidence suggests hepatoprotective, anti-inflammatory, immune-modulatory, and antioxidant properties compared to 100% soybean oil IVLE such as Intralipid (Burrin, 2014; Calder, 2010; Diamond, 2017; Haines,

2022; Lam, 2018; Lapillone, 2018; Larsen, 2012; Larsen, 2015; Martindale, 2020; Notz, 2022). Therefore, SMOFlipid is now regarded as the preferred IVLE in cardiac and surgical patients at many institutions, with broad clinical consensus supporting its use in infants with congenital heart disease (Chan, 2025).

In addition to some cardiac-specific data, evidence from neonatal and pediatric surgical, ICU, and intestinal failure populations remains highly applicable due to similar degrees of illness severity, inflammation, and perioperative feeding intolerance with prolonged PN dependence. Two studies evaluating infants requiring open-heart surgery demonstrated improved fatty acid status and a lower inflammatory response with a mixed lipid IVLE containing fish oil compared with a 100% soybean oil IVLE. Another study in infants who underwent cardiopulmonary bypass and gastrointestinal surgery found a similar anti-inflammatory response (Hanindita, 2020; Larsen, 2012). In a recent multicenter randomized controlled trial of infants requiring major gastrointestinal surgery and parenteral nutrition, SMOFlipid was associated with lower conjugated bilirubin at 28 days, reduced cholestasis at 84 days, and shorter hospital stays compared with Intralipid (Abrams, 2024). Additional recent studies show that, compared with Intralipid, SMOFlipid is associated with smaller increases in liver function tests, more rapid resolution of PNALD (30 vs. 67 days), and a higher rate of resolution by the end of parenteral nutrition (50–80% vs. minimal improvement). Among these studies, three included infants and children with congenital heart disease, heart failure, or ECMO. While hepatic benefits were most commonly observed with prolonged parenteral nutrition, some were evident even with median durations of 9-10 days (Casson, 2020; Haines, 2023; Hudson, 2023; Kulpins, 2023; Naik, 2024).

Additional clinical benefits of SMOFlipid include reduced sepsis and UTI risk (Haines, 2023; Pradelli, 2020), improved growth (Hudson, 2023; Naik, 2024), decreased incidence of NEC (Casson, 2020), lower serum triglycerides/plasma lipid clearance (Calder, 2010; Diamond, 2017; Lam, 2018; Lapillonne, 2018; Larsen, 2012; Martindale, 2020; Notz, 2022; Pereira-da-Silva, 2017), reduced oxidative stress (Skouroliakou, 2010), and decreased inflammatory markers (Hanindita, 2020). Moreover, these IVLEs enhance the availability of long-chain fatty acids, which are vital for neurologic and immune development, particularly in preterm infants (Vlaardingerbroek, 2015).

In contrast, 100% soybean oil IVLE has been associated with an increased mortality rate, morbidity rate, postoperative recovery time, length of stay, pulmonary vascular resistance, and impaired pulmonary gas exchange (Furukawa, 2002; Haines, 2022; Hanindita, 2020; Lapillonne, 2018; Larsen, 2012; Mayer, 2003; Tilley, 2001; Wanten, 2007). Furthermore, in adult ICU populations, mixed lipid emulsions have been shown to decrease markers of liver dysfunction (Calder, 2018; Piper, 2009), reduce infection rates, hospital length of stay, and decrease inflammatory markers, including in surgical patients (Antebi, 2004; Bae, 2017; Barbosa, 2010; Grau-Carmona, 2015; Grimm, 1994;

Haines, 2022; Mertes, 2006; Notz, 2022; Pradelli, 2020; Wanten, 2007; Wei, 2010; Weiss, 2002).

Bone Marrow Transplant

Patients undergoing a hematopoietic stem cell transplant (HSCT) are at risk of developing treatment-associated complications. One of the most concerning complications, sinusoidal obstructive syndrome (SOS), now known as veno-occlusive disease (VOD), impacts the liver and has a suggested incidence of 10-20% with a daunting 80% mortality rate once a patient develops multi-organ failure (Cairo, 2020). Cholestasis is a significant component of SOS, and 70% of SOS diagnoses occur in the presence of hyperbilirubinemia. Another major complication in HSCT patients is mucositis, which often necessitates parenteral nutrition (PN) to provide adequate nutritional support and, in doing so, improves survival outcomes and mitigates non-relapse mortality (Harman, 2009).

Intralipid, a pure soybean oil injectable lipid emulsion product, contains the essential fatty acids linoleic acid (LA) and α-linolenic acid (ALA). In addition to these two essential fatty acids, SMOFlipid, a mixed-oil injectable lipid emulsion, contains two additional essential fatty acids, Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids (along with arachidonic acid) are necessary for the formation of leukotrienes, thromboxane, and prostaglandins, all of which help regulate the immune response (Gramlich, 2019). Additionally, SMOFlipid contains vitamin E (tocopherol) and has lower phytosterol content than Intralipid. These unique aspects of SMOFlipid, along with an improved LA:ALA ratio, have been repeatedly reported to contribute to enhanced anti-inflammatory signaling and reduced hepatotoxicity, both of which are desired therapeutic outcomes in the HSCT patient population (Gramlich, 2009; Llop Talaveron, 2018; Rayyan, 2012). Compared with Intralipid, SMOFlipid is associated with a lower incidence of parenteral nutrition-associated cholestasis (PNAC) (2.4% vs 11.5%) in pediatric patients treated for at least 28 days (Abrams, 2024). Patients treated with SMOFlipid showed a greater decrease in bilirubin levels, especially direct bilirubin, compared with those receiving Intralipids (Abrams, 2024; Rayyan, 2012).

Knowing the role of cholestasis and hyperbilirubinemia in the setting of SOS, along with the potential of SMOFlipid to improve immune system regulation, improve the anti-inflammatory cascade, and minimize the detrimental effect PN can have on cholestasis and bilirubin levels, it is reasonable to favor the incorporation of SMOFlipid as the preferred lipid source in patients undergoing HSCT.

Premature Infants

Current nutrition goals for preterm infants emphasize achieving postnatal growth similar to that of the fetus (Koletzko, 2021). Adequate energy intake from PN can significantly

improve postnatal growth in preterm infants (Joosten, 2018). Preterm infants have increased energy needs, with a recommended PN intake of 90-120 kcal/kg/day (Joosten, 2018). These energy needs cannot be met with Omegaven at the recommended dose of 1 g/kg/day when all other PN components are optimized (glucose infusion rate [GIR] of 12 mg/kg/minute [min], 4 g/kg/day protein). Therefore, the routine use of Omegaven is not indicated in patients <1500 grams.

Inborn Error of Metabolism (IEM)

Patients with inherited metabolic disorders (IMDs) have unique nutritional requirements that vary according to their underlying metabolic diagnosis (Bernstein et al., 2022; Parikh et al., 2015). These disorders may be associated with an increased risk of life-threatening acute metabolic decompensation, chronic malnutrition, or both (Bernstein et al., 2022; Wajner et al., 2020). As a result, management often requires specialized nutrition support, including higher lipid doses and prolonged parenteral nutrition administration, compared with the general pediatric population, even in the presence of complications (Bernstein et al., 2022).

Certain metabolic disorders impair the utilization of long-chain fatty acids, necessitating alternative lipid strategies, while others may develop temporary impairments during periods of metabolic stress or severe intercurrent illness (Baker & Burton, 2021; Parikh et al., 2015). Additionally, some patients are at increased risk for hepatic steatosis, cholestatic liver disease, or dysregulated inflammatory responses, which may influence lipid emulsion selection (Pericleous et al., 2017; Wajner et al., 2020). Patients with IMDs may also belong to other high-risk populations, including premature infants, patients with intestinal failure, recipients of hematopoietic stem cell transplantation, and those requiring ketogenic diet therapy (Cairo et al., 2020; Chomtho et al., 2022; Dressler et al., 2017; Lowe et al., 2019). Patients with IMDs requiring specialized nutritional management should be closely followed by a biochemical geneticist and/or metabolic dietitian to ensure that the selected lipid emulsion, including SMOFlipid, is appropriate for their individual metabolic condition (Bernstein et al., 2022; Parikh et al., 2015).

Long-chain fatty acid oxidation disorders (LC-FAODs) are characterized by an inability to oxidize long-chain fatty acids efficiently (Baker, 2021; Bernstein, 2022). Patients with severe LC-FAODs may require restriction of long-chain fatty acids to 10% of total energy intake. However, preventing and/or reversing a life-threatening acute metabolic crisis also requires adequate calorie intake to meet increased energy demands during intercurrent illnesses. This may require PN, including IVLE. Under these circumstances, a patient is more likely to benefit from and less likely to be harmed by SMOFlipid than by Intralipid, since the former has a more even profile of fatty-acid chain lengths, including medium chains, which bypass the enzymatic and transporter defects of the LC-FAODs.

Impaired utilization of long-chain fatty acids (LC-FAs) may manifest in IEMs other than LC-FAODs, particularly during more severe intercurrent illnesses. Since beta-oxidation occurs intramitochondrially, LC-FAOD physiology can be part of global mitochondrial dysfunction, whether primary or secondary to another IEM. Patients with primary mitochondrial diseases may require treatment with IVLE despite defective fatty acid oxidation, including long-chain fatty acids (Parikh, 2015). It has been demonstrated that the specific elevation of hydroxylated long-chain acylcarnitine species may distinguish patients with mitochondrial myopathies (Vissing, 2019). There is a growing number of IEM characterized by secondary mitochondrial dysfunction, including several organic acidemias such as Propionic Acidemia and Methylmalonic Acidemia (Wajner, 2020). Under these circumstances, there is a greater risk of inadequate nutritional support from the 16- and 18-carbon fatty acids that constitute nearly all of Intralipid, compared with the wide variety of chain lengths provided by SMOFlipid.

Certain IEMs can be secondarily complicated by hemophagocytic lymphohistiocytosis or other abnormal inflammatory responses, which may either be caused or characterized by defective lipid metabolism. A prototypical example of this phenomenon is Wolman's Disease, a severe form of Lysosomal Acid Lipase Deficiency (Pericleous, 2017; Selvanathan, 2023). Accumulating cholesteryl esters and triglycerides can cause a wide variety of complications beyond systemic inflammation, including but not limited to hepatic steatosis, liver disease, cirrhosis, and intestinal failure. Additionally, patients with Wolman Disease require near-complete elimination of dietary fat (particularly long-chain fatty acids) and are therefore at high risk of essential fatty acid deficiency. Under the extreme circumstances arising from the nature of the condition itself and its treatment, the more balanced provision of medium-chain and long-chain fatty acids, as well as omega-3 and omega-6 essential fatty acids, by SMOFlipid is superior to the predominantly long-chain omega-6 essential fatty acids provided by Intralipid. Another IEM characterized by an increased risk of systemic inflammation is Lysinuric Protein Intolerance (Duval, 1999).

Some patients with metabolic genetic conditions may require treatment with the ketogenic diet, either for seizure disorder or for the underlying pathophysiology. A prototypical example of this is Pyruvate Dehydrogenase Deficiency, which is characterized by carbohydrate-induced lactic acidosis and impaired extraction of energy from carbohydrates since the transition from glycolysis to the Krebs cycle is defective (Sofou, 2017). Patients with this inborn error of energy metabolism may require much higher amounts of fat in order to maintain the higher ketogenic ratios required for seizure and/or metabolic control.

Ketogenic Diet (KD)

It was first recognized that the physiologic state of ketosis has an antiseizure effect during the early 1920s. Since this discovery was made, the KD has been increasingly

applied to the treatment of epilepsy, including super-refractory cases. Its implementation requires maintaining a specific ratio between grams of ketogenic fat and grams of anti-ketogenic carbohydrate and protein. The classic KD provides fats and non-fats according to either a 4:1 or 3:1 ratio. Ongoing experience with the KD has demonstrated that medium-chain triglycerides (MCTs) are more ketogenic than long-chain triglycerides (LCTs). Proposed mechanistic explanations for this observed difference between MCTs and LCTs include the rapid clearance of MCTs from the bloodstream; the fact that MCTs do not require the carnitine shuttle to enter the mitochondrial matrix for beta-oxidation, unlike LCTs; and the rapid metabolism of MCTs relative to LCTs. The first reported use of parenteral MCTs was in a 5-year-old female with Lennox-Gastaut Syndrome and intractable diarrhea who failed treatment with Intralipid and continued to have breakthrough seizure activity. She was changed to an IVLE containing both MCTs and LCTs in a 70:30 ratio. Her treatment response included seizure control and robust ketosis (Rosenthal, 1990).

Over the subsequent decades, there have been multiple reports of successful treatment with parenteral MCTs for intractable epilepsy. In 2018, Dressler et al. reported the specific use of SMOFlipid, specifically in 5 out of 17 patients requiring ketogenic parenteral nutrition for surgery, status epilepticus, vomiting, food refusal, and gradual introduction of enteral feeds in neonates diagnosed with Ohtahara Syndrome. The median duration of ketogenic parenteral nutrition was 3 days, with a maximum of 41 days (Dressler, 2018). In 2019, Lowe et al. reported the specific use of SMOFlipid at >4 g/kg/day for 10 consecutive days, with a maximum fat prescription of 4.78 g/kg/day. A more recent case series published in 2022 detailed outcomes of parenteral versus enteral initiation of KD for super-refractory status epilepticus attributable to a wide range of immune, infectious, and neurometabolic etiologies. Ketosis was achieved more quickly with parenteral initiation of the KD, using SMOFlipid or Lipidem infusions. Both of these IVLEs have higher MCT content than Intralipid. The initiation of the KD using this method was safe and effective (Chomtho, 2022).

Clinical Management:

- **Intralipid**
    - Dosing: infused over 24 hours

Table 5: Dosing recommendations for Intralipid

	Neonate	Infant	Child	Adolescent
Initiation	1-2 g/kg	2 g/kg	1-2 g/kg	1 g/kg
Advancement	0.5-1 g/kg	1 g/kg	0.5-1 g/kg	1 g/kg
Goal	3 g/kg	2.5-3 g/kg	2-2.5g/kg	1-2 g/kg

- Safety:
  - Adverse Effects:
    - Hyperlipidemia (10%), hyperglycemia (10%), nausea (10%), vomiting (10%), hypoproteinemia (10%), abnormal hepatic function tests (10%)
  - Contraindications:
    - Disturbances in normal fat metabolism, such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis, if accompanied by hyperlipidemia
  - Warnings and Precautions:
    - Hypersensitivity, risk of infections, fat overload syndrome, refeeding syndrome, aluminum toxicity, and hypertriglyceridemia
  - Administration Risks:
    - Maximum rate of infusion for neonates is 0.15 g/kg/hr, and for infants and children, 0.15 g/kg/hr
- Cost:
  - $37.98 per 100 mL
    - Cost estimates are based on average wholesale pricing from Merative Micromedex® RED BOOK®, accessed June 2026

- **SMOFlipid**
  - Criteria for Use:
    - Restricted to patients meeting one of the following criteria:
      - Receiving SMOFlipid prior to hospitalization
      - Patients receiving a ketogenic diet or diagnosed with an inborn error of metabolism
      - Pediatric patients with congenital heart disease AND undergoing cardiac surgery within 28 days
      - Patients who have been evaluated by the intestinal failure teams:
        - The Hopkins Resource for Intestinal Vitality and Enhancement (THRIVE) is the intestinal rehab team at Johns Hopkins Hospital (JHH)
        - Care Under Intestinal Rehabilitation Excellence (CUIRE) is the intestinal rehab team at JHACH
      - Pediatric patients who have undergone a bone marrow transplant and are at risk for veno-occlusive disease (VOD)
      - Utilization for prevention of parenteral nutrition-associated cholestasis in patients who are anticipated to be on PN for >28 days

- If PN is anticipated to continue for >28 days and direct bilirubin begins to rise (direct bilirubin >1 mg/dL), consider switching to SMOF earlier in the course, to reduce the risk of PNALD
- Please contact the Pharmacy and Therapeutics (P&T) Committee Chair if seeking approval outside of the inclusion criteria

- Dosing: infused over 24 hours

Table 6: Dosing recommendations for SMOFlipid

	Neonate	**Infant**	**Child**	**Adolescent**
Initiation	1-2 g/kg	2 g/kg	1-2 g/kg	1 g/kg
Advancement	0.5-1 g/kg	1 g/kg	0.5-1 g/kg	1 g/kg
Goal	3 g/kg	2.5-3 g/kg	2-2.5g/kg	1-2 g/kg

- Safety:
  - Adverse Effects:
    - Hypertension (10%), nausea (9%), vomiting (7%), hyperglycemia (5%), abdominal pain (4%), flatulence (4%), increased serum triglycerides (3%), dyspepsia (2%), urinary tract infection (2%), anemia (2%), catheter infection (2%), sepsis (2%)
  - Contraindications:
    - Hypersensitivity to fish, egg, soybean, or peanut protein or any other component of the formulation; severe hyperlipidemia or hypertriglyceridemia (triglycerides > 1,000 mg/dL)
  - Drug Interactions:
    - May decrease levels/effects of vitamin K antagonists
  - Administration Risks:
    - Maximum rate of infusion for neonates is 0.15 g/kg/hr, for infants and children it is 0.15 g/kg/hr
    - For adults, dose may increase to a maximum rate of 0.5 g/kg/hr
- Cost:
  - $29.01 per 100 mL
    - Cost estimates are based on average wholesale pricing from Merative Micromedex RED BOOK, accessed June 2026

- **Omegaven**
  - Criteria for Use:
    - Restricted to treatment of parenteral nutrition-associated cholestasis (direct bilirubin ≥ 2 mg/dL) in patients less than 18 years of age
    - Patients who are anticipated to be on PN for >14 additional days
    - Please contact the Pharmacy and Therapeutics (P&T) Committee Chair if seeking approval outside of the inclusion criteria
  - Dosing
    - 1 g/kg/day, infused over 12 hours
  - Safety:
    - Adverse Effects:
      - Vomiting (46%), agitation (35%), bradycardia (35%), apnea (20%), viral infection (16%), erythema (12%), rash (8%), abscess (7%), neutropenia (7%), hypertonia (6%), incision site erythema (6%)
    - Contraindications:
      - Hypersensitivity to fish or egg or to any component of the formulation; severe hemorrhage disorders, severe hyperlipidemia, or severe disorders of lipid metabolism (triglycerides > 1,000 mg/dL)
    - Warnings and Precautions:
      - Risk of death, hypersensitivity, risk of infections, fat overload syndrome, refeeding syndrome, hypertriglyceridemia, aluminum toxicity, anemia
    - Drug Interactions:
      - May enhance the adverse/toxic effects of medications with antiplatelet properties and enhance the anticoagulant effect of anticoagulants. Requires monitoring of therapy.
    - Administration Risks:
      - The maximum rate of infusion for neonates is 0.15 g/kg/hr, for infants and children, it is 0.15 g/kg/hr
      - Infusion should be completed within 12 hours
  - Cost:
    - $125.59 per 100 mL
      - Cost estimates are based on average wholesale pricing from Merative Micromedex RED BOOK, accessed June 2026

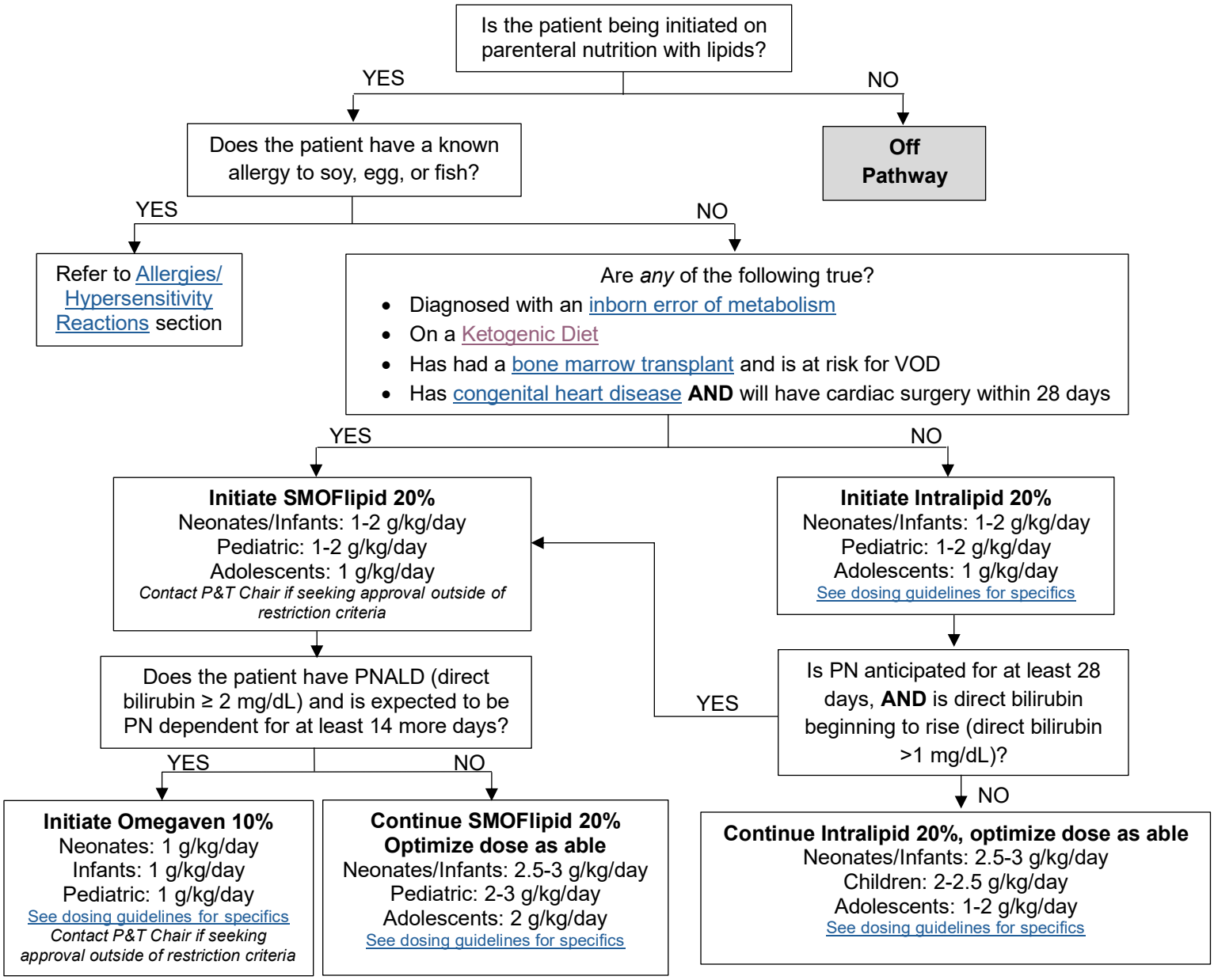
- **Monitoring**
  - Essential Fatty Acid Panel
    - Patients with adequate prehospital oral or enteral nutrition (including fat intake) who receive the recommended intravenous lipid emulsion dose during PN are considered at low risk for EFAD

        - Check EFA panel once on PN for 3 months
    - Patients with inadequate prehospital nutrition are considered at high risk for preexisting EFAD
        - Consider checking EFA panel once on PN for >28 days, sooner at the discretion of the medical team
    - If receiving less than the recommended dose of lipid emulsions per age for ≥2 weeks, check an EFA panel
    - Holman or Triene: Tetraene (T:T) ratio = Mead Acid (MA) divided by (÷) Arachidonic Acid (ARA)
        - Assesses omega-9: omega-6 only and not omega-3 status. Omega-3 status can be an unreliable indicator of EFAD, especially with long-term use of alternative lipid emulsions, fat-malabsorptive conditions, fat-restrictive diets, chylothorax, and various metabolic disorders
    - Omega-3 and six fatty acids to monitor for accurate assessment of EFAD (regardless of a normal or elevated T:T ratio):
        - Alpha-Linolenic Acid (ALA; C18:3ω3), Linoleic Acid (LA; C18:2ω6), Eicosapentaenoic Acid (EPA; C20:5ω3), Docosapentaenoic Acid (DPA; C22:5ω3), Docosahexaenoic Acid (DHA; C22:6ω3), and Arachidonic Acid (ARA; C20:4ω6)
        - If any of these fatty acids are deficient, correct with omega-3 and/or omega-6 supplementation
    - ARA:DHA ratio = Arachidonic Acid (ARA) ÷ Docosahexaenoic Acid (DHA)
        - Ratio reference range goal is 2.1-4.6
    - If normal EFA panel, recheck in 3-4 months
        - If continuing to receive less than the recommended dose of Intralipid per age for ≥2 weeks or the patient is at higher risk of EFAD, recheck the EFA panel in 1 month
        - If abnormal EFA panel, recheck in 1 month
    - If the patient is experiencing signs or symptoms of EFAD (dry skin, alopecia, and dermatitis), then recheck the EFA panel
        - Normal EFA panel: recheck in 3-4 months
        - Abnormal EFA panel: recheck in 1 month
- Laboratory ordering
    - Comprehensive Metabolic Panel (CMP), Magnesium (Mg), and Phosphorus (Phos)
        - Recommend obtaining prior to initiating PN
        - Obtain daily until tolerating goal PN regimen
    - Triglyceride (TG)
        - Recommend obtaining prior to initiating PN
        - Recheck 2-3 times per week while fat emulsion is advanced

        - Obtain weekly once tolerating goal PN regimen
    - Individual lab checking recommendations may apply depending on the patient's clinical condition

Johns Hopkins All Children's Hospital

Inpatient Intravenous Lipid Emulsion Management Clinical Pathway



Monitoring Guidelines

Essential Fatty Acid Panel

- Patients with adequate prehospital oral/enteral nutrition (including fat intake) receiving the recommended IVLE dose during PN are considered at low risk for EFAD
  - Check EFA panel once on PN for 3 months
- Patients with inadequate prehospital nutrition are considered at high risk for preexisting EFAD
  - Consider checking EFA panel once on PN for >28 days, sooner at the discretion of the medical team
- If receiving less than the recommended dose of intralipids per age for ≥2 weeks, check EFA panel
  - Normal EFA panel: recheck in 3-4 months
  - If patient continues to receive less than recommended dose of intralipids per age for ≥2 weeks, recheck EFA panel in 1 month
    - Abnormal EFA panel: recheck in 1 month
- If signs or symptoms of EFA (dry scaly skin rashes, alopecia, poor growth, poor wound healing), recheck the EFA panel
  - Normal EFA panel: recheck in 3-4 months
  - Abnormal EFA panel: recheck in 1 month
- Labs:
  - CMP, Mg, and Phos (recommend obtaining prior to initiating PN and daily until tolerating goal PN regimen)
- Triglycerides:
  - Recommended prior to initiating PN
  - Recheck 2-3 times per week while fat emulsion is advancing
  - Weekly once tolerating goal PN regimen
- Individual lab checking recommendations may apply depending on the patient's clinical condition

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Outcome Measures:

- Reduction in IFALD incidence:
    - Decrease the incidence and severity of intestinal failure–associated liver disease (IFALD), as measured by peak direct bilirubin levels and progression to cholestasis during lipid therapy
- Appropriate lipid utilization:
    - Achieve ≥90% adherence to pathway-recommended lipid selection, dosing (g/kg/day), and monitoring parameters within 6 months of implementation
- Metabolic safety optimization:
    - Reduce lipid-related adverse events (e.g., hypertriglyceridemia >250 mg/dL, essential fatty acid deficiency, infusion-related reactions) by 25% within 12 months of pathway implementation

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Formulary Management and Medication Use Policy Committee (FMMPC): August 6, 2026

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Date Content Last Revised: August 6, 2026

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Disclaimer:

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners, and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for diagnosing, managing, or preventing specific diseases or conditions. The physician must make the ultimate judgment regarding the care of a particular patient in light of the patient's individual circumstances.

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