PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

IV Fat Emulsion Clinical Practice Guideline

Clinical Guideline Name	IV Fat Emulsion Clinical Guideline
Effective Date	December 2019; Revised June 2020
Approved By	Department of Pediatric Newborn Medicine Clinical Practice Council_____ CWN PPG _____ BWH SPP Steering _____ Nurse Executive Board/CNO_____

This is a clinical practice guideline. While the guideline is useful in approaching IV Fat Emulsion use and management, clinical judgment and/or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.

I. Purpose of guideline

- To educate staff about IV Fat Emulsion (IVFE) options in the NICU
- To provide guidance around decision-making about IVFE therapy, particularly for neonatal patients on prolonged parenteral nutrition who are at risk for or who have established intestinal failure associated liver disease (IFALD)

II. Primary goals of IV Fat Emulsion therapy

- Source of non-glucose energy to support metabolism and growth
- Prevention of essential fatty acid deficiency

III. Context

For 45 years, IntraLipid has been the predominant IVFE used for preterm infants in the U.S. In 2016, the FDA approved SMOFlipid, a new-generation IVFE that has been used in Europe for ~10 years and may offer some advantages over IntraLipid for neonatal patients. Another alternative IVFE is Omegaven, which was approved by the FDA in 2018, but has historically been used on a compassionate-use basis for patients with established IFALD.

IV. Key facts about IntraLipid, SMOFlipid, and Omegaven

- **IntraLipid**
  - Soybean oil-based emulsion
  - Approved by FDA for adults and children
  - Relatively high in essential n-6 (linoleic) and n-3 (alpha-linolenic) polyunsaturated fatty acids
  - Implicated in IFALD pathogenesis
  - Non-nutritive phytosterols, pro-inflammatory properties may contribute to liver injury
  - No DHA or EPA, potential adverse effects on brain and retinal development in preterm infants who have limited ability to synthesize these fatty acids
  - Black box warning for preterm infants; nutritional benefits usually outweigh potential harms
  - Contains ≤ 25 mcg/L aluminum
- **SMOFlipid**
  - Blend of **S**oybean, **M**edium chain triglyceride, **O**live, and **F**ish oil emulsions
  - Approved by FDA in 2016 for adults, not yet approved for children
  - Higher n-3 polyunsaturated fatty acids including DHA and EPA, lower phytosterols than IntraLipid
  - Potential advantages over IntraLipid for preterm infants:
    - DHA and EPA from fish oil may be better for brain and lung development, hepatoprotective
    - Higher Vitamin E and lower phytosterols may also be hepatoprotective
  - At SMOFlipid dose of 3 g/kg/day, dose of soybean oil emulsion is approximately 1 g/kg/day, with phytosterol exposure equivalent to IntraLipid 1 g/kg/day
  - Also carries black box warning for preterm infants
  - Also contains ≤ 25 mcg/L aluminum
- **Omegaven**
  - Fish oil emulsion
  - Approved by FDA for use in pediatric patients in 2018
  - Lower in essential fatty acids than IntraLipid and SMOFlipid; adequate to prevent essential fatty acid deficiency despite these lower levels
  - Higher DHA, EPA than IntraLipid and SMOFlipid
  - Effective in reversing established IFALD
  - Also carries black box warning for preterm infants

- Also contains ≤ 25 mcg/L aluminum

Table 1. Comparison of 3 IV Fat Emulsions (IVFE)*

	IntraLipid	SMOFlipid	Omegaven
	Percent		
Soybean oil	100	30	0
Medium chain triglyceride	0	30	0
Olive oil	0	25	0
Fish oil	0	15	100
	Percent		
Linoleic acid (n-6)	50	21.4	4.4
Alpha-linolenic acid (n-3)	9	2.5	1.8
DHA (n-3)	0	2	12.1
EPA (n-3)	0	3	19.2
	mg/L†		
Phytosterols	348 ±33	47.6	0
Alpha-tocopherol (Vitamin E)	38	200	150-296

DHA is docosahexaenoic acid and EPA is eicosapentaenoic acid.
*Adapted from Anez-Bustillos et al. 2017[1]
†Raman et al. 2017[2]

V. Summary of evidence regarding IVFE emulsions for neonatal patients

IntraLipid vs. SMOFlipid for neonatal patients at risk for or with established IFALD

Potential benefits of SMOFlipid include the provision of DHA and EPA from fish oil and the ability to provide energy from sources other than carbohydrate, while also limiting exposure to pro-inflammatory and hepatotoxic effects of IntraLipid. One small (n=24) study[3] of PN-dependent infants <24 months old with direct bilirubin 1-3 mg/dL at baseline found that participants randomized to SMOFlipid had direct bilirubin 2.75 mg/dL lower at study endpoint vs. IntraLipid (p=0.001). A dose of 3 g/kg/day was used in both groups. That study provides some data to support the effectiveness of SMOF in reducing the progression of IFALD in infants. However, a case report[4] of 2 patients unable to feed enterally for a prolonged period suggests that IFALD can progress despite SMOFlipid therapy and Omegaven may be required to reverse the progression of IFALD in some situations.

- Overall, there is biologic plausibility and limited clinical evidence (1 study) that SMOFlipid may limit the progress of IFALD as compared with IntraLipid at 3 g/kg/day.
- Plausible benefits of SMOFlipid 3 g/kg/day vs. IntraLipid 1 g/kg/day (higher energy delivery and more Vitamin E, no greater exposure to phytosterols) but no clinical studies.
- In cases of severe and progressive IFALD, transition from SMOFlipid to Omegaven may be required to reverse IFALD.

IntraLipid vs. SMOFlipid as routine lipid emulsion

Provision of DHA and EPA via SMOFlipid has the potential to benefit brain and retina development and reduce inflammation, which contributes to chronic lung disease. A comprehensive Cochrane review[5] identified 11 clinical trials (n=1048 participants) comparing soybean emulsion (e.g. IntraLipid) vs. SMOFlipid as the primary IVFE for preterm infant populations. The quality of evidence was rated as low or very low, suggesting that further research is needed to improve confidence in these conclusions. A more recent pre-post comparison study[6] of 1297 very low birth weight infants found lower odds of any retinopathy, cholestasis and osteopenia, as well as improved lipid tolerance. These overall results support the safety of SMOFlipid but do not demonstrate substantial clinical advantages of either lipid emulsion, consistent with the non-inferiority designation for SMOFlipid in adult patients. However, further research, including larger well-designed trials, is needed to evaluate the ideal composition of lipid emulsions for preterm infants in the prevention and/or resolution of relevant clinical outcomes.

- Despite plausible advantages, current literature does not support routine use of SMOFlipid over IntraLipid as the primary IVFE therapy for preterm infants.[5]

Potential risk of prolonged IVFE therapy: essential fatty acid deficiency (EFAD)

Essential fatty acid deficiency (EFAD) is a potential risk of prolonged IVFE therapy. Omegaven use is not associated with this complication,[7-9] whereas a recent, small study reported essential fatty acid deficiency in over half of infants receiving IntraLipid at a low dose (<1.5 g/kg/day) [9] Some publications describe "favorable" effects of SMOFlipid on fatty acid profiles e.g. lower ratio of n-6 to n-3 fatty acids, higher DHA.[3,10-12] However, anecdotal data suggests that some neonates may develop EFAD in association with SMOFlipid therapy, particularly if the dose is restricted.

VI. IntraLipid 20%

Indications: IntraLipid is the IVFE of choice in neonates without qualifications for SMOFlipid or Omegaven. It is also considered for use in the case of persistent essential fatty acid deficiency (EFAD), that is unresponsive to increased Omegaven dose, with the intent of optimizing Linoleic Acid (n-6 essential fatty acid).

Contraindications: Hypersensitivity to egg, soybean, or to any active ingredient or excipient. Severe hyperlipidemia.

Administration:

- Use a 1.2 micron in-line filter. Do not administer through DEHP sets or lines.
- Syringe hang time: 24 hours.
- Tubing change time: 24 hours.

Dose:

- Initiate at 1 g/kg/day.
- Advance by 0.5-1 g/kg/day to target dose of 3 g/kg/day.
    - 1, 2 and 3 g/kg/day provides 5, 10 and 15 mL/kg/day, respectively.

Monitoring:

- See NICU Parenteral Nutrition Guideline and/or IV Fat Emulsion Clinical Practice Guideline Summary for standard laboratory monitoring guidelines including triglyceride and direct bilirubin levels, as well as management of hypertriglyceridemia associated with IVFE therapy.

Compatibility: TPN. For compatibility with medications, see NICU Drug Administration Guidelines.

Adverse Effects: Aluminum toxicity (increased risk with renal impairment), hypertriglyceridemia.

VII. SMOFlipid 20%

Consultation with NICU dietitian and clinical pharmacist is required.

Indications:

(1) *Prevention of IFALD in infants at high risk.*

a. SMOFlipid is the preferred IVFE for full term and preterm infants expected to require parenteral nutrition for ≥21 days (e.g. complicated NEC, severe IUGR with poor motility, congenital GI anomaly, chylothorax).
b. The degree of risk for an individual infant is based on clinical judgement regarding the underlying disease(s) and anticipated duration of dependence on parenteral nutrition.
c. SMOFlipid 3 g/kg/day is preferable to IntraLipid at a restricted dose (<1.5 g/kg/day) in this situation due to the ability to provide more energy as fat.

(2) *Prevention of IFALD progression.*

a. SMOFlipid is the preferred IVFE for infants with mild IFALD (direct bilirubin 1-1.9 mg/dL) who are expected to remain dependent on parenteral nutrition for ≥ 14 days.
b. See next section regarding consideration of Omegaven therapy if the direct bilirubin level continues to rise while on SMOFlipid therapy.

Contraindications: Hypersensitivity to fish, egg, soybean, or peanut protein, or to any active ingredient or excipient; prior allergy to SMOFlipid. Severe hyperlipidemia.

Administration:

- Use a 1.2 micron in-line filter. Do not administer through DEHP sets or lines.
- Syringe hang time: 24 hours.
- Tubing change time: 24 hours.

Dose:

- Initiate at 1 g/kg/day.
- Advance by 0.5-1 g/kg/day to target dose of 3 g/kg/day.
  - 1, 2 and 3 g/kg/day provides 5, 10 and 15 mL/kg/day, respectively.
- If switching from IntraLipid at dose higher than 1 g/kg/day, change from IntraLipid to SMOFlipid at the same dose as the IntraLipid and advance to 3 g/kg/day.
- Avoid doses <2.5-3 g/kg/day for greater than 2-3 days in attempt to avoid potential risk of EFAD

Monitoring:

- See NICU Parenteral Nutrition Guideline for standard laboratory monitoring guidelines including triglyceride and direct bilirubin levels, as well as and management of hypertriglyceridemia associated with IVFE therapy.
- In addition to standard laboratory monitoring, monitoring for patients on SMOFlipid for ≥2-4 weeks should include a fatty acid profile 2-4weeks after initiation of SMOFlipid and every 2-4 weeks thereafter. A Triene:Tetraene ratio >0.2 indicates biochemical essential fatty acid deficiency. If the Triene:Tetraene ratio is elevated or rising over time on the maximum dose of SMOFlipid, consider switching to IntraLipid at the standard dose or Omegaven if other criteria are met.
- Routine monitoring of Vitamin E status is not recommended, but because SMOFlipid contains more Vitamin E than IntraLipid, consider measuring serum Vitamin E if symptoms of toxicity are present.

Compatibility: TPN, acetaminophen, ciprofloxacin, fluconazole, heparin, metronidazole, morphine, penicillin, vancomycin.

Likely compatibility*: Ampicillin, cefotaxime, cefoxitin, ceftazidime, clindamycin, dobutamine, furosemide, gentamicin, hydrocortisone, meropenem, piperacillin-tazobactam, tobramycin.

***Compatible with SMOFlipid at a lower concentration and compatible with IntraLipid. Please evaluate risks versus benefits on a case-by-case basis of extrapolating this data as compatible depending on other access options, etc.**

- Compatibility data limited; team should discuss risks versus benefits of medication administration options depending on available access.
- To avoid concerns for medication incompatibilities, and if clinically appropriate/feasible, consider consultation with PICC team to discuss options for double lumen central access versus alternative access site (example: Extended Dwell PIV).

Adverse Effects: Aluminum toxicity (increased risk with renal impairment), hypertriglyceridemia.

VIII. Omegaven 10%

Consultation with NICU dietitian and clinical pharmacist is required.

Indications:

(1) *Management of infants with severe and/or progressive IFALD.*

a. Infants with IFALD that is progressing despite SMOFlipid therapy may require Omegaven for reversal of liver disease, particularly if initiation of enteral nutrition is not expected for a prolonged period.
b. Eligibility for Omegaven therapy includes direct hyperbilirubinemia ≥2 mg/dL and expected to be on PN for at least 2 weeks.
c. Given the complex decision-making required, consider consultation with a Boston Children's Hospital service experienced with Omegaven therapy and appropriate for the patient's underlying disease (e.g. surgery, GI / CAIR team).
d. Omegaven should be continued until direct bilirubin levels are < 2 mg/dL or until the patient no longer requires PN.

Contraindications: Hypersensitivity to fish, egg protein, or any components of the product. Severe hyperlipidemia. Severe hemorrhagic disorders.

Administration:

- Use a 1.2 micron in-line filter. Do not administer through DEHP sets or lines.
- Syringe hang time: 24 hours.
- Tubing change time: 24 hours.

Dose:

- 1 g/kg/day
  - Provides 10 mL/kg/day

Monitoring:

- See NICU Parenteral Nutrition Guideline and IV Fat Emulsion Clinical Guideline Summary for standard laboratory monitoring guidelines including triglyceride and direct bilirubin levels, as well as and management of hypertriglyceridemia associated with intravenous lipid therapy.
- In addition to standard laboratory monitoring, Baseline Fatty Acid Panel should be checked prior to initiation of Omegaven therapy and q2-4 weeks thereafter.
- A Triene:Tetraene ratio >0.2 indicates biochemical essential fatty acid deficiency. If the Triene:Tetraene ratio is elevated or rising over time on the maximum dose of Omegaven, consider switching to IntraLipid to optimize Linoleic Acid delivery.

Compatibility: TPN.

- Compatibility data limited; team should discuss risks versus benefits of medication administration options depending on available access.
- To avoid concerns for medication incompatibilities, and if clinically appropriate/feasible, consider consultation with PICC team to discuss options for double lumen central access versus alternative access site (example: Extended Dwell PIV).

Adverse Effects: Aluminum toxicity (increased risk with renal impairment), hypertriglyceridemia.

IX. References

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