Preterm Nutrition Consensus

Parenteral Nutrition

Children's Hospital of Philadelphia®
Division of Neonatology

Title: Preterm Nutrition Consensus Part 2 Parenteral Nutrition
Brief Synopsis

Date of Initial Publication: June 2022
Revision Date:
Contact Author: Sarvin Ghavam MD
Contributing Authors Ema Urbanski, Meg Begany, Melissa Lestini, Sam Garber, Sharadha Polam, Sandeep Sadashiv, Traci Fauerback, Tom Habib

Abstract

The nutrition provided to premature neonates, specifically those most at risk, born less than 32 weeks gestation and less than 1500 grams can impact weight gain, linear growth, neurodevelopment, as well as outcomes such as chronic lung disease and sepsis. Consistent and evidenced based approach toward providing optimal nutritional support for neonates has been shown to decrease rates of necrotizing enterocolitis and feeding intolerance.

A multidisciplinary team including physicians, dietitians and lactation consultants worked together to formulate a current enteral feeding guideline and unified feeding advance approach. Topics included were enteral feeding advance guidelines, preterm diet, management of parenteral nutrition, vitamins, as well as lactation and discharge guidelines.

Consensus Goals, Parenteral Nutrition

- Evidenced based approach to Starter PN, Dextrose use, Protein and Lipid requirements
- Discussion of use of lipids and monitoring of triglycerides
- Discussion of appropriate use of PN with feeding advance initiation
- Discussion of Micronutrients
- Discussion of safety mechanisms for delivery of PN

Background

Throughout life, the greatest weight-specific protein gains occur prior to 32 weeks gestation. Several studies have shown that infants who receive only supplemental glucose lose approximately 1% of protein stores daily. Without exogenous protein intake, protein synthesis rates still remain high but break down rates increase. Extremely low birth weight infants are particularly vulnerable because of nitrogen loss with glucose administration alone. Standardization of total parenteral nutrition,
from the use of starter PN, protein and glucose requirements and management of lipid needs with triglyceride monitoring is essential in the growth and neurodevelopment of extremely premature neonates.

Previous Consensus Statement or Data from Division of Neonatology (if applicable)

None Available

Literature Summary

The literature supports the use of Stock PN within the first 6 to 8 hours of life. Initial start of 60 ml/kg using a solution with 4% amino acids gives approximately 2.4 grams of protein per kg to meet minimum goal. Beyond 1 week of life a maximum volume of 100ml/kg can be used (to avoid giving >4g/kg of amino acids). Literature supports an initial GIR of 5-8 mg/kg/min and may increase daily to maximum GIR of 14 to 18 mg/kg/min. Hyperglycemia should be avoided. Literature supports the starting of lipid infusion at 2gm/kg/day with increase to goal of 3 gm/kg/day. Hypertriglyceridemia should be avoided. Monitor triglycerides daily as lipids increased and then decrease to weekly once dose is stable and levels are acceptable, avoid stopping lipids if possible. Transition from parenteral to enteral nutrition with early fortification avoids loss of calories, and protein should be monitored to maintain a daily requirement of ≥3gm/kg/day.

Delphi Survey Round Results (if applicable)

None

Survey Results

A round of survey to the Division of Neonatology was completed in order to assess current practices in parenteral nutrition, including protein use, lipids including the use of SMOF, potassium, phosphorous and calcium usage, as well as volumes at which PN is stopped.

Consensus Statement and Clinical Recommendations

Starter PN
Goal time to start as soon as possible (within 6 – 8 hours of age)
Day 1 – Minimum of 60ml/kg

Components
- Trophamine 4%; Dextrose 10%;
- Calcium Gluconate 3.75 mEq
- Heparin 125 units; 250 ml total volume

Initial start of 60 ml/kg gives approximately 2.4 grams of protein to meet minimum goal
Beyond 1 week of life: Starter TPN max volume of 100ml/kg (to avoid giving >4g/kg of amino acids)

Glucose in PN
- Day of Life 1
  - Aim for starting GIR of 5-8 mg/kg/min
- Day 2-7
  - Aim to make small increases (1-2 mg/kg/min) daily to a goal of 10-14 mg/kg/min
  - Max 14-18 mg/kg/min
- Beyond 1st Week
  - Start at 8-10 mg/kg/min and increase to a goal of 10-14 mg/kg/min
  - Max 14-18 mg/kg/min
  - May require a central line
- Maximum D12.5 for all peripheral PN, central lines may be required in order to provide higher GIRs for neonates

Hyperglycemia

Consensus Recommendation

- Goal glucose level 60-120 mg/dL
- Avoid ≥ 150 mg/dL
- ≥180 mg/dL – Lower GIR
- ≥ 250 mg/dL–
    - Attempt decreasing GIR to min of 5 mg/kg/min
    - Lower fat emulsion dose
    - Consider DC medications causing gluconeogenesis
    - Sepsis management if septic
    - Consider treatment with low dose insulin therapy

Amino Acids

Start- upon admission to NICU

- DOL 0: goal of >2g/kg/d AA within first 24h
- DOL 1 (first custom PN day): administer 4g/kg/d
    - Evidence suggests no detriment starting on target Amino Acids on Day 1
    - Minimum-2g/kg/d; Max 4g/kg/d
- **Goal 4g/kg/d**

Lipids

- Start lipids immediately after birth when possible.
- **Start at 2g/kg/d** unless septic, fluid restricted, or bilirubin nearing exchange transfusion
- Advance by **0.5-1g/kg/d to goal 3g/kg/d**
- Monitor TG daily as lipids increased and then decrease to weekly once dose is stable and levels are acceptable.
- TG < 200mg/dL are acceptable. Reduction in lipid rate may be warranted for TG>250. Avoid stopping lipids due to EFA needs (minimum 1g/kg/d for infants <1500g). Temporarily stop if TG >400mg/dL
- SMOFlipid is FDA approved for pediatrics including neonates as of March 2022, not enough evidence to definitively recommend for use in short-term parenteral support

Carnitine

- Consider empirical supplementation with 5mg/kg/d carnitine if no enteral feeds anticipated for >7 days (based on known safety when dosing up to 20mg/kg/d)
- Maintenance dosing= 5-10mg/kg/d (10-20mg/kg/d for high TG)

Transition from Parenteral to Enteral Nutrition

- Calories are maintained during transition when early fortification strategies utilized
- During transition from PN to EN, monitor actual protein intake closely and attempt to maintain a minimum of 3 gm/kg/day
- Lipids removed when feeds reach 100 ml/kg
- PN off when feeds reach 120 ml/kg (~75% of goal)

Other Points

- For Peripheral PN <1000 mOsm/L for Peripheral PN
- A single 1.2 micron in-line filter for dextrose and AA admixtures below the Y-site where the dextrose and amino acid admixture and lipids co-infuse
- Cysteine - recommendations of 40 mg/kg/day cysteine per 1 g/kg/day of Amino Acids
  - Used when needed to enhance calcium and phosphorus solubility
- Photoprotection
  - Data from trials suggests that PN and ILE with complete photoprotection reduces indicators of oxidative stress for infants and counter effects the risk of adverse clinical outcome measures. Light protection resulted in no harm.
  - ASPEN recommends photoprotection in infants only
    - Complete photoprotection from products to compounding to patient infusion is not possible now due to limitations of materials.
    - Partial protection can be accomplished in the US and should be utilized until such materials are available for complete protection

Adjusting IV Lipids based on Triglyceride Levels

Triglyceride Level	Intervention
< 200 mg/dL	Continue to advance ILE or maintain goal dose
200-250mg/dL	Continue current ILE dose without advance, repeat TG in 24 hours
251-400 mg/dL	Decrease ILE dose by 0.5-1 g/kg/d and repeat TG in 24 hours • If TG remains 251-400, consider holding infusion for *minimum of 4 hours* and repeat TG without ILE infusing (fasting)* • Avoid decreasing below 1g/kg/d to meet essential fatty acid needs in preterm infants (soy-based lipids)
> 400 mg/dL	Hold ILE for minimum of 4 hours and repeat TG without ILE infusing* • Once TG level is <200 mg/dL, resume ILE at previously tolerated rate, then repeat TG 24 hours after ILE resumed. • Avoid decreasing below 1g/kg/d to meet essential fatty acid needs in preterm infants (soy-based lipids)

Further Goals

- Monitor for further evidence in modifying parenteral feeding recommendations
- Continue to monitor new lipid formulations for use in preterm neonates
- Monitor implementation of new PN recommendations in daily practice through the Division of Neonatology

QI Metrics

- Monitor for EUGR in neonates during the transition from parenteral to enteral nutrition

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Background

Throughout life, the greatest weight-specific protein gains occur prior to 32 weeks gestation. Several studies have shown that infants who receive only supplemental glucose lose approximately 1% of protein stores daily. Without

exogenous protein intake, protein synthesis rates still remain high but break down rates increase. Extremely low birth weight infants are particularly vulnerable because of nitrogen loss with glucose administration alone. Standardization of total parenteral nutrition, from the use of starter PN, protein and glucose requirements and management of lipid needs with triglyceride monitoring is essential in the growth and neurodevelopment of extremely premature neonates.

Previous Consensus Statement or Data from Division of Neonatology (if applicable)
None Available

Literature Search

Title	Author	Level of Evidence	Primary Outcomes and Results	Key Findings/Conclusions
Early Aggressive Nutrition in the Neonates	*Patti J Thureen 1999*	Review Article		Throughout life the greatest weight-specific protein gain occurs at prior to 32 weeks of gestation Several studies show that infants who receive only supplemental glucose lose approximately 1% of protein stores daily (or approx. 1.2 g protein loss per kg of body weight) Without exogenous protein intake, protein synthesis rates still remain high, but break down rates increase. ELBW infants are particularly vulnerable because nitrogen loss with glucose administration alone is greatest in most immature infants and lessens significantly with increasing gestational age Plasma concentrations of certain amino acids (arginine and leucine) are decreased. Secretion of insulin depends on the plasma concentrations of these amino acids and glucose limits
Nutrition Management of the Very Low-birthweight Infant. Total Parenteral Nutrition and Minimal Enteral Nutrition	David H. Adamkin NeoReviews 2006	Review Article		

Title	Author	Level of Evidence	Primary Outcomes and Results	Key Findings/Conclusions
				glucose transport and energy metabolism via a reduction in insulin and IGF. This leads to down regulation of glucose transporters at the cellular membrane level resulting in intracellular energy failure via a decrease in Na+, K+ ATPase. Causing leakage of intracellular potassium and is associated with non-oliguric hyperkalemia.
Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study	Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A. Pediatrics 2014	1	There were no differences in demographic data between SCAMP (Standardized, Concentrate with Added Macronutrients Parenteral) (n = 74) and control (n = 76) groups. Comparing cumulative 28-day intakes, the SCAMP group received 11% more protein and 7% more energy. The SCAMP group had a greater ΔHC at 28 days (P < .001). The difference between the means (95% confidence interval) for ΔHC was 5 mm (2 to 8), and ΔSDS was 0.37 (0.17 to 0.58). HC differences are still apparent at 36 weeks' corrected gestational age.	Early postnatal head growth failure in VPIs can be ameliorated by optimizing PN.
Interventions for treatment of neonatal hyperglycemia in very low birth weight infants.	M Bottino RM Cowett JC Sinclair Cochrane Review 2011	Review	Only two eligible trials were found (Collins 1991; Meetze 1998). Both were randomized but of very small size (24 and 23 neonates randomized in each trial, respectively).No trial compared reduction versus no reduction of glucose infusion.Collins 1991 compared insulin infusion with standard care. Insulin infusion had no significant effect on death or bacterial sepsis; effects on other major morbidities were not assessed. Insulin infusion resulted in significant increases in non-protein energy intake, glucose intake, and short-term weight gain.Meetze 1998 compared insulin infusion with reduction of glucose infusion. Insulin infusion had no significant effects on death, severe intraventricular hemorrhage, retinopathy of prematurity, bacterial sepsis, fungal sepsis, or necrotizing enterocolitis; effects on other major morbidities were not assessed. Insulin infusion resulted in significant increases in glucose intake and total energy intake.	Evidence from randomized trials in hyperglycemic VLBW neonates is insufficient to determine the effects of treatment on death or major morbidities. It remains uncertain whether the hyperglycemia per se is a cause of adverse clinical outcomes or how the hyperglycemia should be treated. Much larger randomized trials in hyperglycemic VLBW neonates that are powered on clinical outcomes are needed in order to determine whether, and how, the hyperglycemia should be treated

Title	Author	Level of Evidence	Primary Outcomes and Results	Key Findings/Conclusions
Safety and efficacy of early parenteral lipid and high-dose amino acid administration to VLBW infants	Vlaardingerbroek, et al, 2013	1		In VLBW infants, the administration of parenteral AA combined with lipids from birth onwards improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation. Early lipid initiation and high-dose AA were well tolerated.
Australian Neonatal parenteral nutrition consensus updated: 2017		Guideline		Commence parenteral AA within the first 24 h of birth (LOE I, GOR C), Commence parenteral AA at 2 g/kg/day (LOE II, GOR C), and Incrementally increase amino acid infusions to a maximum 4 g/kg/day by day 3–5 of life in preterm neonates (LOE I, GOR C). The safety of (1) commencement parenteral AA in excess of 3 to 3.5 g/kg/day and (2) maintenance AA intake in excess of 4.5 g/kg/day has not been proven in clinical trials.
Higher versus lower amino acid intake in parenteral nutrition for newborn infants	Cochrane Review Metanalysis Osborn et al, 2018	Systematic Review 1a RCT		Higher AA had no effect on mortality before hospital discharge Evidence insufficient to show effect on neurodevelopment Higher AA intake associated with reduction in post-natal growth failure
Total Parenteral Nutrition for the very low birthweight infant	Seminars in Fetal and Newborn Medicine Parel, Bhatia 2017	Book		Studies have shown that amino acids started at 2 g/kg/d are safe shortly after birth Current recommendations suggest 2-3.5 g/kg/d of amino acids on the first day of life, increasing to 4 g/kg/d in the first week of life.

Title	Author	Level of Evidence	Primary Outcomes and Results	Key Findings/Conclusions
A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants	Salguero Olid A et al, 2018	2		Routine supplementation in PN of preterm newborns may help to increase carnitine levels, but neither a relevant improvement in the lipid profile, or an increase in weight gain, or a decrease in morbidity, mortality or reduction of hospital stay could be demonstrated
ASPEN Pediatric Core Curriculum	ASPEN Peds Core Curriculum (2015):	Guideline		Premature infants <34 weeks GA receiving PN without carnitine can develop carnitine deficiency 6 to 10 days after birth. 2-5mg/kg/d has been shown to prevent deficiency when started in PN from Day 1 Supplementation as high as 10-20mg/kg/d used for elevated TG levels and those on PN >7days Assess carnitine status periodically when no enteral source
PLEASE SEE LITERATURE Table with regards to Lipid Usage below From parenteral to enteral nutrition: a nutrition-based approach for evaluating postnatal growth failure in preterm infants	*Miller M, et al JPEN 2014*	4		Poor growth was most associated with PN->EN phase and predictive of growth failure. Energy intakes during this phase were similar to PN phase, but protein intake decreased considerably (<3gm/kg)
Standardized Parenteral Nutrition for the Transition Phase in Preterm Infants: A Bag That Fits	*Brennan A, et al. JPEN 2018*		Database that developed to retrospectively analyze actual, hourly nutrition intake in 59 preterm infants (<34 wk,<1500 gm).	Significant energy and protein deficits during transition phase. PN solutions were not changed as feeds advanced as was d/c at 100-120 ml/kg enteral feeds. Recommends targeted nutrition during transition phase but does not offer strategy
Energy and Protein Intake During the Transition from Parenteral to	*Falciglia G, et al. JPEDS 2018*	4		5 phases of nutrition 1(0% EN), 2 (<33.3%EN), 3 (<66.7%EN), 4(<100%EN),

Title	Author	Level of Evidence	Primary Outcomes and Results	Key Findings/Conclusions
Enteral Nutrition in Infants of Very Low Birth Weight				5(100%EN). Recommend Lipids and PN through phase 3, PN through phase 4, PN through central line, order PN at intended rate, d/c central line prior to phase 5
Effect of Early Parenteral Nutrition Discontinuation on Time to Regain Birth Weight in Very Low Birth Weight Infants: A Randomized Controlled Trial	*Perrem L et al. JPEN 2019*	1b	Examine the early impact of discontinuing PN at different enteral feed volumes has on the mean difference in days to regain birth weight.	PN d/c at 100 ml/kg or 140 ml/kg. Earlier PN d/c associated with longer days to regain BW (10.9 vs. 8.1). Feeds were fortified at 140 ml/kg
Maximum tolerated osmolarity for peripheral administration of parenteral nutrition in pediatric patients	Dugan JPEN 2014 Sep;38(7):847-51	2b	Pediatric patients <18 years old (included 76 infants <2Kg only 9<1kg)	Recommend that PPN solution should be limited to osmolarity ≤1000 mOsm/L and PPN should only be used temporarily until central access is obtained
Determine the correlation between the osmolarity of PPN and the incidence of extravasation/phlebitis in the NICU	Metjian, presented at 2000 ASHP		Determine the correlation between the osmolarity of PPN and the incidence of extravasation/phlebitis in the NICU Investigators found that PPN with an osmolarity ≤1000 mOsm/L resulted in an 8% (15 of 181) incidence of extravasation/phlebitis, whereas PPN with osmolarity >1000 mOsm/L resulted in a 30% (40 of 134) incidence of extravasation/phlebitis.	The results suggested that PPN administration in neonates should be limited to 1000 mOsm/L

*Please see below for full literature review for use and advance of Intralipids for preterm neonates

**Please also note the following Guidelines published by ESPGHAN/ESPEN/ESPR/CSPEN and A.S.P.E.N.

- ESPGHAN/ESPEN/ESPR/CSPEN Guidelines on Pediatric Parenteral nutrition: Carbohydrates, Clinical Nutrition. Mesotten, D., Joosten, K., van Kempen, A., Verbruggen, S. 2018
- Appropriate Dosing for Parenteral Nutrition A.S.P.E.N. Recommendations Nov 2020
- A.S.P.E.N. Clinical Guidelines: Hyperglycemia and Hypoglycemia in the Neonate Receiving Parenteral Nutrition ASPEN Board of Directors and Puder M. JPEN 2012

Literature Summary

The literature supports the use of Stock PN within the first 6 to 8 hours of life. Initial start of 60 ml/kg using a solution with 4% amino acids gives approximately 2.4 grams of protein per kg to meet minimum goal. Beyond 1 week of life a maximum volume of 100ml/kg can be used (to avoid giving >4g/kg of amino acids). Literature supports an initial GIR of 5-8 mg/kg/min and may increase daily to maximum GIR of 14 to 18 mg/kg/min. Hyperglycemia should be avoided. Literature supports the starting of lipid infusion at 2gm/kg/day with increase to goal of 3 gm/kg/day. Hypertriglyceridemia should be avoided. Monitor triglycerides daily as lipids

increased and then decrease to weekly once dose is stable and levels are acceptable, avoid stopping lipids if possible. Transition from parenteral to enteral nutrition with early fortification avoids loss of calories, and protein should be monitored to maintain a daily requirement of ≥3gm/kg/day.

Delphi Survey Round Results (if applicable)
None

Survey Results
A round of survey to the Division of Neonatology was completed in order to assess current practices in parenteral nutrition, including protein use, lipids including the use of SMOF, potassium, phosphorous and calcium usage, as well as volumes at which PN is stopped.

Consensus Statement and Clinical Recommendations

Starter PN

Goal time to start as soon as possible (within 6 – 8 hours of age)
Day 1 – 60ml/kg

Components

- Trophamine 4%; Dextrose 10%;
- Calcium Gluconate 3.75 mEq
- Heparin 125 units; 250 ml total volume

Initial start of 60 ml/kg gives approximately 2.4 grams of protein to meet minimum goal
Beyond 1 week of life: Starter TPN max volume of 100ml/kg (to avoid giving >4g/kg of amino acids)

Glucose in PN

- Day of Life 1
  - Aim for starting GIR of 5-8 mg/kg/min
- Day 2-7
  - Aim to make small increases (1-2 mg/kg/min) daily to a goal of 10-14 mg/kg/min

    - Max 14-18 mg/kg/min
- Beyond 1st Week
    - Start at 8-10 mg/kg/min and increase to a goal of 10-14 mg/kg/min
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    - May require a central line
- Maximum D12.5 for all peripheral PN, central lines may be required in order to provide higher GIRs for neonates

Hyperglycemia

Consensus Recommendation

- Goal glucose level 60-120 mg/dL
- Avoid ≥ 150 mg/dL
- ≥180 mg/dL – Lower GIR
- ≥ 250 mg/dL–
    - Attempt decreasing GIR to min of 5 mg/kg/min
    - Lower fat emulsion dose
    - Consider DC medications causing gluconeogenesis
    - Sepsis management if septic
    - Consider treatment with low dose insulin therapy

Amino Acids

Start- upon admission to NICU

- DOL 0: goal of >2g/kg/d AA within first 24h
- DOL 1 (first custom PN day): administer 4g/kg/d
    - Evidence suggests no detriment starting on target Amino Acids on Day 1
    - Minimum-2g/kg/d; Max 4g/kg/d
- **Goal 4g/kg/d**

Lipids

- Start lipids immediately after birth when possible.
- **Start at 2g/kg/d** unless septic, fluid restricted, or bilirubin nearing exchange transfusion
- Advance by **0.5-1g/kg/d to goal 3g/kg/d**
- Monitor TG daily as lipids increased and then decrease to weekly once dose is stable and levels are acceptable.

- TG < 200mg/dL are acceptable. Reduction in lipid rate may be warranted for TG>250. Avoid stopping lipids due to EFA needs (minimum 1g/kg/d for infants <1500g). Temporarily stop if TG >400mg/dL
- SMOFlipid is FDA approved for pediatrics including neonates as of March 2022, not enough evidence to definitively recommend for use in short-term parenteral support

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- Consider empirical supplementation with 5mg/kg/d carnitine if no enteral feeds anticipated for >7 days (based on known safety when dosing up to 20mg/kg/d)
- Maintenance dosing= 5-10mg/kg/d (10-20mg/kg/d for high TG)

Transition from Parenteral to Enteral Nutrition

- Calories are maintained during transition when early fortification strategies utilized
- During transition from PN to EN, monitor actual protein intake closely and attempt to maintain a minimum of 3 gm/kg/day
- Lipids removed when feeds reach 100 ml/kg
- PN off when feeds reach 120 ml/kg (~75% of goal)

Other Points

- For Peripheral PN <1000 mOsm/L for Peripheral PN
- A single 1.2 micron in-line filter for dextrose and AA admixtures below the Y-site where the dextrose and amino acid admixture and lipids co-infuse
- Cysteine - recommendations of 40 mg/kg/day cysteine per 1 g/kg/day of Amino Acids
  - Used when needed to enhance calcium and phosphorus solubility
- Photoprotection
  - Data from trials suggests that PN and ILE with complete photoprotection reduces indicators of oxidative stress for infants and counter effects the risk of adverse clinical outcome measures. Light protection resulted in no harm.
  - ASPEN recommends photoprotection in infants only
    - Complete photoprotection from products to compounding to patient infusion is not possible now due to limitations of materials.

- Partial protection can be accomplished in the US and should be utilized until such materials are available for complete protection

Adjusting IV Lipids based on Triglyceride Levels

Triglyceride Level	Intervention
< 200 mg/dL	Continue to advance ILE or maintain goal dose
200-250mg/dL	Continue current ILE dose without advance, repeat TG in 24 hours
251-400 mg/dL	Decrease ILE dose by 0.5-1 g/kg/d and repeat TG in 24 hours • If TG remains 251-400, consider holding infusion for *minimum of 4 hours* and repeat TG without ILE infusing (fasting)* • Avoid decreasing below 1g/kg/d to meet essential fatty acid needs in preterm infants (soy-based lipids)
> 400 mg/dL	Hold ILE for minimum of 4 hours and repeat TG without ILE infusing* • Once TG level is <200 mg/dL, resume ILE at previously tolerated rate, then repeat TG 24 hours after ILE resumed. • Avoid decreasing below 1g/kg/d to meet essential fatty acid needs in preterm infants (soy-based lipids)

ILE: Intravenous Lipid Emulsion

*Per December 2021 "ASPEN Consensus Recommendation: ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations": "Infants and children who exhibit elevated TG levels (ie, >200 mg/dl) while the ILE is infusing over 24 h should have TG levels reassessed by infusing the next dose over 20 h with a repeat TG level obtained after 4 h without the ILE infusing. This ensures the initial elevated TG level was not the result of the ILE actively being infused into the patient. If the TG levels remain elevated, the infusion should continue to be held another 4 h and the TG level rechecked; the infusion should resume when the TG levels are <200 mg/dl."

- Avoid exceeding maximum doses and infusion rates of ILE.
  Maximum dose for Soy Oil ILE is 3g/kg/d
  Maximum infusion rate for Soy Oil ILE is 0.15 g/kg/h
- Monitor TG after initiation or adjustment of lipid infusion. Monitor weekly thereafter. Patients at high risk for hypertriglyceridemia (e.g. patients with sepsis, malnutrition, SGA, severe thrombocytopenia) should be monitored more frequently.
- Monitor for Essential Fatty Acid Deficiency (EFAD) in the malnourished, in patients with signs and symptoms of EFAD, or in those receiving a Soy Oil ILE dose <1 g/kg/day or when using lipid minimization dosing for any ILE.

References

1. Cober MP, Gura KM, Mirtallo JM, et al. ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations. *Nutr Clin Pract*. 2021;1–20.
2. Holtrop P, Swails T, Riggs T. Hypertriglyceridemia in extremely low birth weight infants receiving lipid emulsions. *J Neonatal Perinatal Med*. 2015;8(2):133-136.
3. Lapillone, A. et al. ESPGHAN/ESPEN/ESPN/CSPEN guidelines on pediatric parenteral nutrition: lipids. *Clin Nutr* 2018; 37(6):2324-2336
4. Salama et al. Intravenous Lipids for Preterm Infants: AReview. *Clinical Medicine Insights: Pediatrics* 2015:9 25–36
5. Sinclair, R., Schindler, T., Lui, K. et al. Hypertriglyceridaemia in extremely preterm infants receiving parenteral lipid emulsions. *BMC Pediatr* 2018: 18, 348

Further Goals

- Monitor for further evidence in modifying parenteral feeding recommendations
- Continue to monitor new lipid formulations for use in preterm neonates
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QI Metrics

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Literature Search – LIPID TOPICS

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
TRIGLYCERIDES (past 7 years) —search 12/2021					
Fat emulsions and hypertriglyceridemia (1984)	Adamkin, et al	Level 4	Plasma TG clearance	Only 10 infants. 12 hr infusion. Mean peak levels always occurred at the end of infusion(12 hr) and by 6 hr post-infusion were back to pre-infusion levels. Decreased rates of fat clearance by the less mature infants.	Continuous infusion of fat emulsion over a 20- to 24-hr period, at a level which results in plasma TG concentrations no greater than 250 mg/dl, would appear to minimize the risk of undesirable consequences.
ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations (2021)	ASPEN Parenteral Nutrition Safety Committee Cober MP, Gura KM, Mirtallo JM, et al.	Level 5? Level 7?	Consensus recommendation		-- Hypertriglyceridemia is defined as a TG level >200 mg/dl. --Infants and children who exhibit elevated TG levels (ie, >200 mg/dl) while the ILE is infusing over 24 h should have TG levels reassessed by infusing the next dose over 20 h with a repeat TG level obtained after 4 h without the ILE infusing. This ensures the initial elevated TG level was not the result of the ILE actively being infused into the

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					patient. If the TG levels remain elevated, the infusion should continue to be held another 4 h and the TG level rechecked; the infusion should resume when the TG levels are <200 mg/dl There is a risk of inadvertent rapid infusion of ILE when administered separate from PN, which may lead to hypertriglyceridemia and/or fat overload syndrome, especially when the maximum recommended rate is exceeded (>0.15 g/kg/h for SO-ILE).
Intravenous Lipid Emulsions Affect Respiratory Outcome in Preterm Newborn: A Case-Control Study (2021)	Boscarino, G.; Conti, M.G.; De Luca, F.; Di Chiara, M.; Deli, G.; Bianchi, M.; Favata, P.; Cardilli, V.; Di Nardo, G.; Parisi, P.; et al	Level 4	rate of prolonged invasive mechanical ventilation (more the 7 days)	40 cases of VLBW infants with TG >150 compared to 105 controls. Cases had an increased incidence of BPD (30.0% vs. 14.3%, $p < 0.05$) and longer duration of invasive mechanical ventilation (7 days, 95% CI 4–10 days vs. 4 days, 95% CI 1–7 days, $p < 0.01$) compared to controls. Multivariate analysis confirmed that HiTG independently influenced the duration of invasive mechanical ventilation, also in the subgroups with	Newborns with HiTG (>150) related to ILEs had a longer duration of invasive mechanical ventilation. Temporary suspension or reduction in ILEs in the case of HiTG is associated with an improvement of respiratory outcome.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Tolerance of fat emulsions in very-low birth-weight neonates. *Am J Dis Child*. 1988;142(2):145-152.	BransYW, Andrew DS, CarrilloDW, Dutton EP, Menchaca EM, Puleo-Scheppke BA.			gestational age ≤28 + 6/7 weeks or BW ≤1000 g Hypertriglyceridemia was associated with ILE infusion rates exceeding 0.16 g/kg/h	
An Evaluation to Establish the Acceptable Serum Triglyceride Levels in Neonates Receiving Intravenous Fat Emulsion Infusion in a Multicenter Retrospective Study (2020)	Chan, et al	Level 4 (6?)	Peak TG in relation to patient characteristic and clinical outcomes.	Elevated TG was associated with mortality (increased risk of severe IVH and BPD) (odds ratio [OR]: 14.4, p<0.001) in univariable analysis, but the relationship weakened (OR: 4.4, p¼0.05) after adjusting for comorbidities in multivariable logistic regression.	The frequency of TG>400 mg/dL was 5% and found only in neonates weighing<1.5 kg We would recommend starting IVFE at a higher dose (2–3 g/kg/d) and monitoring TG in neonates weighing less than 1.5 kg or with significant risk factors for hypertriglyceridemia.
Hypertriglyceridemia and Intravenous Lipid Titration During Routine Parenteral Nutrition in Small Preterm Infants (2019)	Correani A, et al	Level 4 Used large variety of ILEs	Macronutrient and energy intakes (AA, lipids, CHO, NPE, and total energy) in small preterm infants who developed or not HiTG	--196 (30%) had at least one HiTG episode during the first 10 DOL and 462 (70%) had all the TG measurements <250 mg/dL --Growth, diseases associated with prematurity, and neurodevelopment at 2Y CA in HiTG(>250mg/dL in 1st 10 days of life)	--Patients with hypertriglyceridemia had a statistically significant albeit small reduction in intravenous lipid and non-protein energy intakes due to TG monitoring and titration --A strict triglyceride monitoring and intravenous lipid titration at TG levels >250 mg/dL appear to be safe for preterm infants with BW <1250g.

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				infants were similar to controls	
Hypertriglyceridemia in extremely low birth weight infants receiving lipid emulsions (2015)	Holtrop et al	Level 4 prospective observational study	Serum TG >200	75 ELBW infants. TG were drawn when the dose reached 1 and 2 grams/kg/day. Found that TG levels >200 mg/dl occurred in 26.7 % of ELBW infants receiving lipid emulsions. Upon multivariate analysis, infants with TG levels >200 mg/dl had lower birth weights and earlier GA than those with TG levels <200 mg/dl.	Elevated TG levels occur commonly in ELBW infants and are associated with a lower birth weight. TG levels >200 mg/dl did not predict future mortality or morbidity.
The Use of IV Fat in Neonates (2006)	Kerner et al	Review			The administration rate of 0.15 g/kg/hour for IVFE in the neonate should not be exceeded. Serum triglyceride levels should be maintained at 150–200 mg/dL in neonates.
ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids (2018)	Lapillonne et al	See LoE in Key Findings column	Consensus recommendation		In pediatric patients with sepsis, more frequent monitoring of plasma TG concentration and dose adjustment in case of hyperlipidemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA

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					requirements (*LoE 4, GPP, conditional recommendation for*) Markers of liver integrity and function, and TG concentrations should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, ELBW infants) (*LoE 2_, RG B, strong recommendation for*) Reduction of the dosage of ILEs can be considered if TG concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children (*LoE 4, GPP, conditional recommendation for*) It is unclear at what serum level of TG adverse effects may occur Checking serum TG levels may be considered within approximately 1-2 days after initiation or adjustment of lipid infusion. Monitoring of serum TG may thereafter be performed from weekly to

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					monthly depending on the stability and history of the patient. In high risk patients (e.g. patients with high lipid or glucose dosage, sepsis, malnourishment, catabolism, ELBW infants) there is a risk of hyperlipidemia and more frequent monitoring is warranted. If plasma levels of TG are above the limits defined according to age, lowering, not stopping the dosage is recommended. In newborns including preterm infants, routine use of ILEs should be continuous over 24 h (LoE 2þþ, RG B, conditional recommendation for)
Increased risk for early hypertriglyceridemia in small for gestational age preterm infants (2020)	Rabinowicz S, et al		TG >250mg/dL in 24-34wkGA SGA study group vs AGA control group	TG >250 was reported in 22.5%of the SGA infants vs. 5.6% of the AGA infants (p = 0.007)	• SGA infants had a higher mean triglyceride level and more commonly had early hypertriglyceridemia (triglycerides > 250 mg/dL) compared with AGA infants treated with the same intravenous lipid dose. SGA was predictive of hypertriglyceridemia. • No significant association was found between TG levels and morbidities in multivariate analysis.
Is IV lipid emulsion safe in patients with hypertriglyceridemia? *Nutr Clin Pract.* 1997;12:120–123	Sacks, et al 1997	Review			When triglyceride concentrations are moderately elevated (226 to 275 mg/dL),

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					the infusion rate should be reassessed, with no further rate increases until TG levels have decreased. Once TG are >275 mg/dL, we temporarily interrupt IV lipid emulsion for 12 to 24 hours and decrease the infusion rate by 0.02 to 0.04 g/kg/h when lipid is restarted.
Intravenous Lipids for Preterm Infants: A Review (2015)	Salama, et al	Level 4		"Most if not all the dogmas that have prevented the early use of intravenous lipids have either been disproved, not based on fact, or weak. There are compelling reasons for early use of lipids, which include prevention of EFA deficiency, provision of energy, and provision of substrates for LCPUFA synthesis all of which are important for the growth and development of VLBW and ELBW infants." No treatment is without risk. Clinicians must balance the benefits versus the risks when using 2–3 g/kg/day intravenous lipid	--We believe that it does not make sense to evaluate serum triglycerides before, during, and after each change in lipid infusion. Twice a week and even weekly evaluation of serum triglycerides in otherwise stable premature infants on intravenous lipid infusion is fair enough --Studies using a higher starting dose of 2–4 g/kg/day of intravenous lipids in newborn (term, VLBW and ELBW) infants showed that these doses are well tolerated, with no significant increase in serum total triglycerides; step-wise increase in intravenous lipid infusion in VLBW and ELBW infants does not improve lipid clearance or tolerance; and more rapid infusions of intravenous lipid were found to be safe. --Heparin is another factor that enhances lipid clearance by

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				infusion from day 1 of life in VLBW and ELBW infants. We found that the benefits are much more than the risks, if any.	facilitating LPL activity. It was found that, stimulation of LPL activity with heparin in "bolus" injection is ineffectual, while slow continuous admin-istration reduces the serum TG concentration, which is useful in VLBW infants. --There is clear evidence that intravenous lipid emulsion does not have a significant effect on indirect hyper-bilirubinemia in VLBW and ELBW infants. --*we strongly recommend giving the VLBW and ELBW infants 2–3 g/kg/day intravenous lipid as a continuous infusion over 24 hours at a rate not exceeding 0.15 g/kg/h within the first 24 hours of life*
Hypertriglyceridaemia in extremely preterm infants receiving parenteral lipid emulsions (2018)	Sinclair et al	Level 4 Retrospective case review 249 infants Single center	Evaluate TG >250mg/dL(2.8mmol/L) and its association with mortality and major morbidities in extremely preterm infants on PN The clearance of LE is suggested to be saturated at concentrations above 4.5 mol/L(400mg/dL) and this was therefore taken as cut off value for severe highTG	--38/195 (19.5%) infants in whom TG measurements were performed, developed HT(>250), 10/195 (5.1%) had more than one episode of HT and 11 (5.6%) developed severe HT (>400) --23–25+ 6 weeks GA, BW <1000g, and SGA were significant risk factors for the development of TG >250 SGA was	--Given the low occurrence in infants ≥1000g and that brief periods of hypertriglyceridemia appears safe, it seems reasonable to measure TG levels when the infant reaches 3 g/kg/day and then weekly thereafter in infants ≥1000 g. --Regular monitoring is recommended especially among extreme preterm infants 23–25+ 6 weeks GA (or < 1000 g)

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				significant risk factor for TG >400 --TG>250 was associated with an increase in mortality (unadjusted OR 3.5; 95% CI 1.13–10.76; 0.033) and severe ROP (unadjusted OR 4.06; 95% CI 1.73–9.59; 0.002) on univariate analysis. However, this association was non-significant in multivariate analysis with adjustment for GA and BW.	-Emphasize decreased length of exposure to high TG with regular monitoring is beneficial --Disputes improved clearance with heparin
Toce SS, Keenan WJ. Lipid intolerance in newborns is associated with hepatic dysfunction but not infection. *Arch Pediatr Adolesc Med*. 1995;149(11):1249-1253.				TG concentrations did not differ significantly between those with an infection or without, but those with hypertriglyceridemia were more likely to have hepatic dysfunction (35% vs 12%, $P < .01$) and growth retardation (47% vs 12%, $P < .001$)	

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LIPIDS--START, ADVANCE, GOAL					
Current trends and future challenges in neonatal parenteral nutrition. J Neonatal Perinatal Med. 2014 Jan 1;7(3):157-64. doi: 10.3233/NPM-14814008. PMID: 25318631.	Adamkin DH, et al. 2014				At 18–22 months of age, the level of critical illness in the first 7 days of life was significantly associated with adverse outcomes such as Bayley MDI and PDI scores <70, moderate to severe cerebral palsy and to be identified with neurodevelopmental impairment. However, higher energy intake in the early period appeared to mediate these adverse events. The risk of necrotizing enterocolitis, late-onset sepsis, bronchopulmonary dysplasia, and neurodevelopmental impairment; ~ 2% reduction for each 1-kcal/kg/day increase of total energy received by critically ill infants in the first week of life. Overall positive growth velocity between days 7 and 28 was correlated with early (first week) nutritional practices.

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High Early Parenteral Lipid in Very Preterm Infants: A Randomized-Controlled Trial. (2021)	Alburaki W, et al	Level 2 RCT of AGA VLBW infants.	proportion of postnatal weight loss.	Lipid intake in the control group started at 0.5-1 g/kg/d and increased daily by 0.5-1 g/kg/d till reaching 3 g/kg/d. The intervention group was started on 2 g/kg/d that increased to 3 g/kg/d the following day Infants in the intervention group had a lower percentage of weight loss (10.4 vs 12.7%; P = .02). The mean triglyceride level was higher in the intervention group (1.91 _ 0.79 vs 1.49 _ 0.54 mmol/L; P = .01), however, hypertriglyceridemia was similar between the 2 groups. The incidence of EUGR was lower in the intervention group (38.6% vs 67.6%; P = .01). Head circumference z score was higher in the intervention group (_1.09 _ 0.96 vs _1.59 _ 0.98; P = .04)	In VLBW infants, provision of a high early dose(2g/kg/d) of parenteral lipid in the first week of age results in less weight loss and lower incidence of EUGR.
An Evaluation to Establish the Acceptable Serum Triglyceride Levels in Neonates Receiving Intravenous Fat Emulsion	Chan, et al 2020	6	Peak TG		We would recommend starting IVFE at a higher dose (2–3 g/kg/d) and monitoring TG in

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Infusion in a Multicenter Retrospective Study					neonates weighing less than 1.5 kg or with significant risk factors for hypertriglyceridemia.
ASPEN lipid injectable emulsion safety recommendations part 2: Neonate and pediatric considerations (2021)	ASPEN Parenteral Nutrition Safety Committee Cober MP, Gura KM, Mirtallo JM, et al.				In 30 LBWinfants receiving 10% SO-ILE at 2–3 g/kg daily infused over 24 h, serum TG concentrations were higher in those with sepsis (maximum mean TG concentration of 2.02 mmol/L [179 mg/dl] vs 1.15 mmol/L [102 mg/dl], *P* < .02).111 Daily check of serum TGs and dose reduction to 2 g/kg/day in septic LBWinfants are recommended.111 Otherwise, LBW and very LBW infants (VLBW) can tolerate high doses of ILE in the first week of life.
ASPEN Pediatric Core Curriculum, 2nd Ed, page 596 (2015)	Corkins, editor. Crill CM and Gura, KM				Initiate: 1-2g/kg/d Advance: 0.5-1g/kg/d Goal Fat (g/kg/d): Preterm 3–3.5 (Max 0.17g/kg/hr) Term 3 (Max 0.15g/kg/hr)
Committee on Nutrition of the French Society of Pediatrics (CNSFP), and French Society of Neonatology (SFN). Parenteral nutrition for preterm infants: Issues and strategy. Arch Pediatr. 2018 May;25(4):286-294. doi: 10.1016/j.arcped.2018.02.005. Epub 2018 Apr 12. PMID: 29656825.	Darmaun D, et al 2018				A minimum lipid intake of 0.5–1 g/kg/day is theoretically sufficient to cover the essential fatty acid requirement. A retrospective study on 121 preterm infants nevertheless reports an association between the amount of fat delivered during the 1st week and

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					growth at 28 days of age, and a negative correlation between growth in the 1st month and the delay in introducing lipid emulsions in preterm PN [93]. In a cohort of 48 very preterm infants, neurodevelopment assessed by the Brunet-Le´zine test at 1 year of age correlated with cumulative fat intake in the first 14 days, whereas it did not with amino acid supply.
Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. Early Hum Dev. 2012 Mar;88 Suppl 1:S25-9. doi: 10.1016/j.earlhumdev.2011.12.024. Epub 2012 Jan 20. PMID: 22264437.	dit Trolli SE, et al 2012				A significant correlation between the developmental quotient (DQ) at a corrected age of one year and the cumulative intake of energy and lipids at 14 days of life (p=0.02, p=0.01, respectively), the number of days to reach the minimum weight (p=0.02) and the weight gain from birth to D28 of life (p=0.04). There was no correlation between the DQ and early intake of proteins or carbohydrates; only the association between the DQ at one year of corrected age and the cumulative lipid intake at 14 days of life remained statistically significant (p=0.04).
Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life.	Douglas D, Connie M, Shirley G, Matt N, Kamlesh S. 2008				Infants who received 2 g/kg/d/lipid emulsion from the first day were discharged an average 6.9 days earlier than infants in the control group

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					and at discharge, more infants in the group who started on 2 g lipids/kg/d were more or equal 10th percentile for weight for age, compared with infants who started on 0.5 g/kg/d of lipids.
Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life.	Drenckpohl et al 2008	2	Serum TG levels	In a randomized, controlled trial in 100 VLBW infants appropriate for GA, the administration of 20% SO-ILE (as a TNA) starting at either 0.5 g/kg or 2 g/kg/day resulted in higher mean serum TG concentrations initially, but only 15% of infants in the high-dose group exceeded 200 mg/dl. While receiving greater energy intake and experiencing less weight loss in that week, the high-dose ILE group also experienced statistically less NEC and ROP	Incremental increases in IVFE dosage from 0.5 to 3 g/kg/d were not better tolerated than starting at 2 g/kg/d. Premature infants starting at a higher IVFE infusion dosage had better growth, improved energy intake, less hyperglycemia, and less NEC and ROP than neonates given incremental increases in IVFE. When initiating parenteral nutrition for premature infants on the first day of life, neonatal practitioners can safely use 2 g/kg per day of IVFE, to achieve better energy intake, with minimal risks to the premature infants.
Early parenteral lipids and growth velocity in extremely-low-birth-weight infants. Clin Nutr. 2014 Jun;33(3):502-8. doi: 10.1016/j.clnu.2013.07.007. Epub 2013 Jul 18. PMID: 23958274. (2014)	Fischer CJ, et al	Level 4 retrospective cohort study	Growth velocities for weight, length and HC, from birth to DoL 28 and from birth to 36 weeks of CA and the association between the	Univariate analyses showed a significant positive association between the cumulative intakes of parenteral lipids during the first	Parenteral lipids during the first week were positively associated with weight gain in extremely-low-birth-weight infants and could improve

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			cumulative intakes of parenteral lipids or the delays in their introduction	week and i) weight gain up to day 28; ii) weight gain up to 36 weeks of corrected age; iii) head circumference growth up to day 28. There was a negative correlation between the delay in parenteral lipid introduction and weight gain up to day 28. In multivariate analyses, the association between the cumulative intakes of parenteral lipids and weight gain up to 28 days was independent of gestational age at birth, birth weight, sex, smallness for gestational age, and enteral intakes (regression coefficient: 0.19; 95% CI: 0.01-0.38) and, up to 36 weeks, independent of gestational age, birth weight, sex, smallness for gestational age and parenteral glucose and amino acids (0.16; 95% CI: 0.04-0.27).	early nutritional support of preterm neonates
ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids	Lapillonne et al 2018				In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day. (LoE 4,

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Nutrition for the Extremely Preterm Infant. Clin Perinatol. 2017 Jun;44(2):395-406. doi: 10.1016/j.clp.2017.01.012. Epub 2017 Mar 18. PMID: 28477668.	McNelis K, et al 2017				GPP, conditional recommendation for) "Current recommendation is to begin intravenous lipid emulsion at 2 g/kg/d on the day of birth," but this practice is not ubiquitous. There is evidence that early lipid emulsion delivery is associated with later neurologic development in very preterm infants.
Early Lipid Intake Improves Cerebellar Growth in Very Low-Birth-Weight Preterm Infants. JPEN J Parenter Enteral Nutr. 2020 May 8. doi: 10.1002/jpen.1868. Epub ahead of print. PMID: 32384168.	Ottolini KM, et al 2020	Level 4 Prospective observational study		study of macronutrient intake in VLBW preterm infants demonstrates a significant positive relationship between cumulative lipid intake in the first month of life and volumetric brain growth on term-equivalent MRI, specifically in the brainstem and rapidly developing cerebellum. These findings highlight the vital importance of dietary lipids for the developing preterm brain.	In VLBW infants (<1500g, </=32 weeks GA) **Total cumulative lipid intake (PN+EN) in the first month of life** is associated with significantly greater cerebellar volume by term-equivalent age. Used quantitative MRI to demonstrate significant association between cumulative lipid intake and brain growth. Long chain PUFA make up 15—30% of brain weight and are critically important to development of retina, neurogenesis, and synaptogenesis. "Studies have demonstrated that the early provision of dietary fats, including initiation of parenteral lipids at doses as high as 3 g/kg/d on the first day of life, and targeted lipid

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					fortification of enteral feeds are well-tolerated with improved neonatal growth velocities" including head circumference as a surrogate marker for brain growth. Our findings emphasize the importance of early, aggressive nutrition interventions to optimize cerebellar development in VLBW infants. Authors suggest need for future research to establish definitive goals for lipid administration to optimize neurodevelopmental outcomes specifically.
Total parenteral nutrition for the very low birth weight infant. Semin Fetal Neonatal Med. 2017 Feb;22(1):2-7. doi: 10.1016/j.siny.2016.08.002. Epub 2016 Aug 27. Erratum in: Semin Fetal Neonatal Med. 2018 Feb;23 (1):75. PMID: 27576106.	Patel P, Bhatia J. 2017				In VLBW infants, the initial dose of lipid emulsion could be 2 g/kg/day and step-wise increments of lipid emulsion by 0.5-1 g/kg/ d to a maximum of 3 g/kg/d should be followed. However, a lower initial dose and a maximum of 3 g/kg/d is also practiced widely.
Paust H, Schroder H, Park W, Jakobs C, Frauendienst G. Fat elimination in parenterally fed low birth weight infants during the first two weeks of life. *JPEN J Parenter Enteral Nutr*. 1983;7(6):557-559.	Paust H et al 1983			In 18 LBW infants receiving 10% SO-ILE at 2 g/kg/day infused at 0.084 g/kg/h, serum TG concentrations did not exceed a mean value of 1 mmol/L (85 mg/dl) in the	

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				first week of PN therapy	
Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants. JPEN J Parenter Enteral Nutr. 2018 Jan;42(1):122-131. doi: 10.1177/0148607116678196. Epub 2017 Dec 11. PMID: 27875287.	Roelants JA et al 2018				All VLBW infants with randomization to 5 different PN regimes including mixed and soy fat emulsions; no beneficial effect of early high dose AA and mixed fat emulsions on survival and/or neurodevelopmental outcomes although velocity of growth was improved early and maintained at 2 years corrected age.
Intravenous Lipids for Preterm Infants: A Review	Salama et al 2015	Review		Increased energy intake by adding lipid to parenteral nutrition improves nitrogen retention and utilization significantly, resulting in positive nitrogen balance,[3,41,42] decreases energy expenditure and glucose utilization by reducing lipogenesis,[2,3] reduces both carbon dioxide production and oxygen consumption,[2,3,43] provides higher	There is no evidence to support the common practice of gradually increasing the daily lipid intake to induce further lipid clearance. Studies using a higher starting dose of 2–4 g/kg/day of intravenous lipids in newborn (term, VLBW and ELBW) infants showed that these doses are well tolerated, with no significant increase in serum total triglycerides; stepwise increase IVLE in VLBW and ELBW infants does not improve lipid clearance or tolerance; and more rapid infusions of IVLE were found to be safe.

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				energy storage, increases the net fat storage, and most importantly, prevents essential fatty acid deficiency.	
Randomized clinical trial of early aggressive versus late and slow intravenous lipid infusion in preterm infants and bilirubin and lipid profiles (2013)	Salama G, et al	Level 3	Lipid profiles and total serum bilirubin of early aggressive vs late and slow IVLE infusion in VLBW preterm infants over the first 7 days of life. Group A: D10% only for 48 hrs before slow advance of AA and lipid, Group B: D10% with slow advance of AA and lipids; Group C: D10% with 3.5g/kg AA and 2g/kg/ lipids at birth, advanced to 3g/kg/ lipid next day	Levels of bilirubin, total cholesterol and TG increased linearly and significantly over the 1st 7 days in all groups, but did not rise to a serious level that needed intervention. The changes in parameters were not different between the 3 groups	Levels of bilirubin, total cholesterol and TG increased linearly and significantly over the 1st 7 days in all groups, but did not rise to a serious level that needed intervention. The changes in parameters were not different between the 3 groups
Albumin synthesis in very low birth weight infants is enhanced by early parenteral lipid and high-dose amino acid administration.	Vlaardingerbroek H, et al 2016	RCT			To date there is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance. VLBW randomized to 2.4 g AA+ 2 g/kg/day lipids showed higher rate of albumin synthesis than other two groups; higher incidence of hyperlipidemia in those starting lipids at 2-3g/k/day (early lipid group)

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					○ Inborn VLBW infants were randomized to receive from birth onwards either 2.4 g amino acids/(kg(·)d) (control group), 2.4 g amino acids/(kg(·)d) plus 2 g lipids/(kg(·)d) (AA + lipid group), or 3.6 g amino acids/(kg(·)d) plus 2 g lipids/(kg(·)d) (high AA + lipid group). On postnatal day 2, infants received a primed continuous infusion of [U-(13)C6,(15)N]leucine. Mass spectrometry was used to determine the fractional and absolute albumin synthesis rates (FSR and ASR, respectively). ○ The median FSR was 6.5%/d in the control group, 10.6%/d in the AA group, and 12.3%/d in the high AA + lipid group, while the median was 84 mg/(kg(·)d) in the control group, 138 mg/(kg(·)d) in the AA group, and 160 mg/(kg(·)d) in the high AA + lipid group

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
USE OF CARNITINE IN PN					
Carnitine in parenteral nutrition. *Gastroenterology*. 2009;137(5)(suppl):S129-S134 (2009)	Borum PR.	Level 7?			Nutritional supplementation of carnitine should be 2–5 mg/kg/day
Carnitine supplementation of parenterally fed neonates. *Cochrane Database Syst Rev*. 2000;(4):CD000950. (2000)	Cairns PA and Stalker PJ	1 Systematic Review		14 studies were identified, 6 met the selection criteria. The results of the review are limited by the fact that the studies were generally short term and studied different outcomes.	The review of trials found not enough evidence to show any benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis, or weight gain in neonates requiring PN. More research is needed. Authors' conclusions: We found no evidence to support the routine supplementation of parenterally fed neonates with carnitine
ASPEN Pediatric Core Curriculum, 2nd Ed, (2015)	Corkins, editor. (pages 226-227) (pages 601-602)	Reference book		Preterm infants→Immature biosynthesis and lack of placental transfer in the 3rd trimester Potential to improve fatty acid oxidation,	Carnitine can be supplemented in the PN solution at a dose of 2-5mg/kg/d Supplementation as high as 10-20mg/kg/d has been used in patients with elevated TG levels and those on PN >7days

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				lipid tolerance, and positive nitrogen balance and weight gain	
Impact of l-carnitine supplementation on metabolic profiles in premature infants. J Perinatol. 2017 May;37(5):566-571. doi: 10.1038/jp.2016.253. Epub 2017 Jan 12. PMID: 28079870. (2017)	Clark RH, Chace DH, Spitzer AR.	Level 4 (?6)	Hospital outcomes (mortality rates, spontaneous intestinal perforation and/or necrotizing enterocolitis, grades 3 and 4 IVH, and PVL)	When adjusted for GA and BW, there were no significant differences between supplemented and nonsupplemented infants in any of these morbidities (hospital outcomes). Carnitine-supplemented infants had a higher rate of ROP, but when adjusted for GA and BW, this finding was not statistically significant. Growth velocity from birth to 28 days was not different between the two groups.	l-Carnitine supplementation is common in prematurely born neonates and is associated with higher carnitine levels, but is not associated with improved short-term hospital outcomes. In infants at highest risk of developing low levels of FC, monitoring carnitine levels to adjust nutritional supplementation may permit more appropriate therapy.
Diagnosis of Carnitine Deficiency in Extremely Preterm Neonates Related to Parenteral Nutrition: Two Step Newborn Screening Approach. *Int J Neonatal Screen*. 2019;5(3):29. (2019)	Ramaswamy M, Anthony Skrinska V, Fayez Mitri R, Abdoh G.	Level 4 (?6)	Carnitine deficiency on initial NBS or 32wk PMA dried blood spot (DBS) testing	Two tiered approach to NBS—at birth and at 32wks PMA. The first cohort (GA 23-29wks and BW 590-1090g, median 24wks and 790g) included neonates who were diagnosed with	Since percentage of neonates who develop deficiency is relatively small, prophylactic L-carnitine supplementation in TPN in all extremely preterm infants is not clinically justified. The majority (>80%) of the extremely preterm neonates

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				carnitine deficiency on initial DBS. The second cohort (23-31wks GA and BE 610-1890g, median 28wks and 920g) included infants whose carnitine levels were normal on initial DBS but diagnosed later with carnitine deficiency on S32 GA equivalent DBS, which was related to TPN. Only 8.56% of the extremely preterm neonates developed carnitine deficiency	who develop carnitine deficiency do so after being on TPN for a while, and will benefit from the two-step newborn screening approach for a timely diagnosis of carnitine deficiency and treatment with l-carnitine supplements in TPN
A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants. (2018)	Salguero Olid A, et al	1 Systematic review			Routine supplementation in PN of preterm newborns may help to increase carnitine levels, but neither a relevant improvement in the lipid profile, or an increase in weight gain, or a decrease in morbidity, mortality or reduction of hospital stay could be demonstrated
Novel Nutrient Task Force, Parenteral Multi-Vitamin and Multi-Trace Element Working Group; American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors, ASPEN position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. (2012)	Vanek VW, et al	Level 7?	ASPEN position paper		Recommended routine carnitine supplementation of 2-5mg/kg/d to neonatal PN if no enteral source is provided.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
USE OF SMOFlipid—search 9/2021					
Neonatal parenteral nutrition—NICE Guideline	National Institute for Healthcare Excellence 2020				For preterm and term babies with parenteral nutrition-associated liver disease, consider giving a composite lipid emulsion rather than a pure soy lipid emulsion. ***
Comparison of Soybean-based Oil and MCT-olive-fish-soy Oil Intravenous Lipid Emulsions on Soluble Adhesion Markers in Preterm Neonates with Sepsis: A Randomized Controlled Trial.	Abdelkareem M 2019	2 RCT			
Daily Enteral DHA Supplementation Alleviates Deficiency in Premature Infants.	Baack ML, et al 2016				
What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels?	Baack ML, et al 2015	CT			
Effects of parenteral nutrition formulas on plasma lipid profile in children with bone marrow transplantation.	Baena-Gómez MA, et al 2013	CT			

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Changes in Antioxidant Defense System Using Different Lipid Emulsions in Parenteral Nutrition in Children after Hematopoietic Stem Cell Transplantation.	Baena-Gómez MA, et al 2015	CT			
The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: a randomized controlled trial.	Beken S, et al 2014	CT			***
Is intravenous fish oil associated with the neurodevelopment of extremely low birth weight preterm infants on parenteral nutrition?	Biagetti C et al 2021				
Does intravenous fish oil affect the growth of extremely low birth weight preterm infants on parenteral nutrition?	Biagetti C et al 2019				
Double blind exploratory study on de novo lipogenesis in preterm infants on parenteral nutrition with a lipid emulsion containing 10% fish oil.	Biagetti C, et al. 2016	CT			***
Head Circumference Growth Is Enhanced by SMOFlipid in Preterm Neonates.	Bin-Nun A et al. 2020				
Body Composition following Necrotising Enterocolitis in Preterm Infants.	Binder C, et al. 2018	CT			
A Mixed Lipid Emulsion Containing Fish Oil and Its Effect on Electrophysiological Brain Maturation	Binder C, et al 2019	2 RCT			***

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
in Infants of Extremely Low Birth Weight: A Secondary Analysis of a Randomized Clinical Trial.					
Standardised neonatal parenteral nutrition formulations - Australasian neonatal parenteral nutrition consensus update 2017.	Bolisetty S, et al. 2020				
The evolving use of intravenous lipid emulsions in the neonatal intensive care unit.	Calkins KL, et al. 2019				
Low-Dose Parenteral Soybean Oil for the Prevention of Parenteral Nutrition-Associated Liver Disease in Neonates With Gastrointestinal Disorders.	Calkins KL, et al. 2017	CT			***
Inpatient outcomes of preterm infants receiving ω-3 enriched lipid emulsion (SMOFlipid): an observational study	Choudhary, et al 2018	Comparative study	preterm infants (mean gestational age 26.7 weeks) requiring PN for >14 days evaluated as primary outcome mortality and rates of severe neonatal morbidities	.	The authors reported lower incidence of late onset sepsis and greater weight at 36 weeks before conception with Smoflipid® versus Intralipid, in addition to less retinopathy of prematurity (ROP) and greater rates of intraventricular hemorrhage (any grade) with Intralipid.
A dose response randomised controlled trial of docosahexaenoic acid (DHA) in preterm infants.	Collins CT, et al 2015	CT			
The N3RO trial: a randomised controlled trial of docosahexaenoic acid to reduce bronchopulmonary dysplasia in preterm infants < 29 weeks' gestation.	Collins CT, et al. 2016	CT			**

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Docosahexaenoic Acid and Bronchopulmonary Dysplasia in Preterm Infants.	Collins CT, et al. 2017	CT			**
Oxygen saturation to fraction of inspired oxygen ratio in preterm infants on routine parenteral nutrition with conventional or fish oil containing lipid emulsions. Pediatr Pulmonol 2020;55:2377–82.	Correani A, Dell'Orto V, Nobile S, et al. 2020				
Growth of Head Circumference and Body Length in Preterm Infants Receiving a Multicomponent vs a Soybean-Based Lipid Emulsion: A Randomized Controlled Trial.	Costa S, et al 2021	2 RCT			MLE is associated with improved HC growth in comparison with a pure SLE. Also associated with improved linear growth.
Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids.	D'Ascenzo R, et al 2011	CT			***
Higher docosahexaenoic acid, lower arachidonic acid and reduced lipid tolerance with high doses of a lipid emulsion containing 15% fish oil: a randomized clinical trial.	D'Ascenzo R, et al 2014	2 RCT			***
Impact of human milk pasteurization on gastric digestion in preterm infants: a randomized controlled trial.	de Oliveira SC, et al 2017	2 RCT			
The metabolic effects of two different lipid emulsions used in parenterally fed premature infants--a randomized comparative study.	Demirel G, et al 2012	CT			***

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Use of Lipids in Neonates Requiring Parenteral Nutrition JPEN 2020	Deshpande GC and Cai W 2020	1 Meta-analysis			Compared with either pure soybean or soybean/olive-oil based emulsions, composite fish-oil containing lipid emulsions such as SMOF reduce oxidative stress/lipid peroxidation and also increase DHA and EPA levels. May be associated with improved infant development and the prevention of morbidity.
Fish Oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates.	Deshpande G, et al 2014	2 RCT			Significant reduction in F2-isoprostane, significant increases in (RBC) EPA levels, and significantly greater increase in α-tocopherol level for SMOF vs OO/SO. There were no significant differences in clinical outcomes or growth parameters between groups.
Preventing the Progression of Intestinal Failure-Associated Liver Disease in Infants Using a Composite Lipid Emulsion: A Pilot Randomized Controlled Trial of SMOFlipid.	Diamond IR, et al 2017	2 RCT			***
Influence of different intravenous lipid emulsions on growth, development and laboratory and clinical outcomes in hospitalised	Edward RR, et al 2018	1 SR			***

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
paediatric patients: A systematic review.					
Leaching of plasticizers from polyvinylchloride perfusion lines by different lipid emulsions for premature infants under clinical conditions.	Faessler D, et al. 2017				
Oral Cholecystagogue Cholescintigraphy: A Systematic Review of Fatty Meal Options.	Fotos JS, Tulchinsky M 2015				
Incidence of Complications Associated with Parenteral Nutrition in Preterm Infants < 32 Weeks with a Mixed Oil Lipid Emulsion vs a Soybean Oil Lipid Emulsion in a Level IV Neonatal Intensive Care Unit.	Franco S 2020				
Parenteral lipid emulsions in the preterm infant: current issues and controversies	Frazer and Martin. 2021	Review			Studies on the benefit of fish oil-containing lipid emulsions in reducing neonatal morbidities are mixed, and meta-analyses of these studies do not support their routine use for the reduction of preterm morbidities Fish oil-containing lipid emulsions may not be without risks in the preterm population "…the use of fish oil-containing lipid

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					emulsions compromises ARA status." Recommend use of Intralipid
Compatibility of intravenous ibuprofen with lipids and parenteral nutrition, for use as a continuous infusion.	Garcia J, et al 2018				
Parenteral Fish-Oil Lipid Emulsions in Retinopathy of Prematurity: A Retrospective Comparative Study.	Gharehbaghi G 2020				No differences among the two groups in their need for treatment (P = 0.51), ROP zones (P = 0.62), and plus disease (P = 0.38). Although no difference was seen in ROP stages between the groups (P = 0.41), in subgroup analysis, Stage 3 (severe ROP) occurred significantly lower in the SMOFlipid group (P = 0.04) and Stage 0 occurred significantly higher in the SMOFlipid-treated infants (P = 0.05)
Assessing whether early attention of very preterm infants can be improved by an omega-3 long-chain polyunsaturated fatty acid intervention: a follow-up of a randomised controlled trial.	Gould JF, et al 2018	2 RCT			

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Is SMOF lipid emulsion better than soy-based lipid emulsion for low birth weight preterm neonates?	Gupta, K 2020				
Impact of Parenteral Lipid Emulsion Components on Cholestatic Liver Disease in Neonates.	Guthrie G et al 2021	Review			
Depletion and enrichment of phytosterols in soybean oil lipid emulsions directly associate with serum markers of cholestasis in preterm parenteral nutrition-fed pigs.	Guthrie G et al 2021				
Growth and Clinical Outcome in Very Low-Birth-Weight Infants After the Introduction of a Multicomponent Intravenous Lipid Emulsion.	Hill NS, et al 2020			207 infants (Soy LE, 105 vs Mixed LE, 102) were included in the study.	Significantly fewer infants in the Mixed LE cohort developed any stage ROP (Soy LE 59% vs Mixed LE 39%, P = .005) or IVH (Soy LE 27% vs Mixed LE 15%, P = .03) during their admission. Mixed LE was also associated with significantly lower mean (P = .01), minimum (P = .03), and maximum (P = .04) total bilirubin concentrations across the first 4 weeks after birth. There was no difference in growth velocity or weight, length, and head circumference z-score change.
ESPGHAN Committee on Nutrition Position Paper.	Hojsak I, et al. 2016	Review			**

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Intravenous Lipid Emulsions and Risk of Hepatotoxicity in Infants and Children: a Systematic Review and Meta-analysis.					
Intravenous fish oil containing lipid emulsion attenuates inflammatory cytokines and the development of bronchopulmonary dysplasia in very premature infants: A double-blind, randomized controlled trial.	Hsiao CC, et al 2019	2 RCT			***
Pediatric Smoflipid Therapy: Patient Response and Safety Concerns	Huff et al 2020	6 Retrospective chart review single institution		We identified multiple safety concerns, including EFAD (54%), rapid infusion (17%), and missed doses (51%). No patient characteristics were found to correlate with Smofllpid therapy and diagnosis of EFAD.	In our patient population, Smoflipid therapy led to cholestasis resolution in patients with lower direct bilirubin or less-severe IFALD. Use of Smoflipid is also associated with significant safety concerns, and its use should be coupled with close monitoring in pediatric patients, particularly in neonates.
Intravenous fish oil containing lipid emulsion attenuates inflammatory cytokines and the development of bronchopulmonary dysplasia in very premature infants: A double-blind, randomized controlled trial.	Jackson, et al 2020	RCT		A total of 136 neonates were included. Nine of 55 patients (16.4%) in the Intralipid group and 2 of 81 patients (2.5%) in the SMOFlipid group developed cholestasis, defined as direct bilirubin > 2 mg/dL or direct bilirubin	Use of SMOFlipid as the lipid emulsion component of PN may be beneficial in prevention of PNAC in NICU patients that are receiving PN for ≥2 weeks.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
				> 20% of total bilirubin, when total bilirubin is >5 mg/dL, on or before 30 days post initiation of PN (P = .007).	
The effects of two mixed intravenous lipid emulsions on clinical outcomes in infants after gastrointestinal surgery: a prospective, randomized study.	Jiang W, et al 2019	CT			**
Alternative lipid emulsions versus pure soy oil based lipid emulsions for parenterally fed preterm infants.	Kapoor V, Glover R, Malviya MN 2015	Review			***
Lipid emulsions for parenterally fed preterm infants.	Kapoor V, et al 2019	1 Cochrane review			**Authors' conclusions** In the current review, we did not find any particular LE with or without fish oil to be better than another LE in preterm infants for prevention of PNALD/cholestasis, growth, mortality, ROP, BPD and other neonatal outcomes. In preterm infants with surgical conditions or cholestasis, there is currently insufficient evidence from randomised studies to determine with any certainty if fish oil LEs

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					offer advantage in prevention or resolution of cholestasis or in any other clinical outcome. Further research, with larger well-designed trials, is warranted to evaluate the ideal composition of LE in preterm infants and the role of fish oil-containing and other LEs in the prevention and resolution of PNALD, ROP and other clinical outcomes.
Lipid emulsions for parenterally fed term and late preterm infants.	Kapoor V, et al 2019				**Authors' conclusions** Based on the current review, there is insuKicient data from randomised studies to determine with any certainty, the potential benefit of any LE including fish oil-containing LEs over another LE, for prevention or resolution of PNALD/cholestasis or any other outcomes in term and late preterm infants with underlying surgical conditions or cholestasis. There were no studies in infants without surgical conditions or cholestasis.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					Further research is required to establish role of fish oil or lipids from other sources in LEs to improve PNALD/cholestasis, and other clinical outcomes in parenterally fed term and late preterm infants.
Comparison of lipid emulsions on antioxidant capacity in preterm infants receiving parenteral nutrition.	Köksal N, et al 2011	CT			**
SMOFlipid Protects Preterm Neonates against Perinatal Nutrition-Associated Cholestasis.	Kasirer Y, et al 2019	6?? Retrospective review		Infants in the SMOFlipid period had a lower incidence of PNAC (6 vs. 13%; p = 0.022), lower peak direct bilirubin levels (3.2 vs. 7.1 mg/dL; p = 0.018), and a shorter length of stay (51 vs. 60 days; p = 0.019)	SMOFlipid was hepatoprotective in our population of preterm neonates <1,500 g receiving long-term TPN as compared with those receiving Lipofundin(Soy), despite similar levels of exposure to both intravenous lipid load and duration in the two groups.
Fish oil- and soy oil-based lipid emulsions in neonatal parenteral nutrition: a systematic review and meta-analysis.	Kotiya P, et al 2016	1 Systematic review/Meta-analysis			***
A double-blind randomised controlled trial of fish oil-based versus soy-based lipid preparations in the	Lam HS, et al 2014	2 RCT			***

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
treatment of infants with parenteral nutrition-associated cholestasis.					
Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial.	Larsen BM, et al 2012	2 RCT			
Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants.	Larsen BM, et al 2015	CT			
Impact of SMOFLipid on Pulmonary Alveolar Development in Newborn Guinea Pigs.	Lavoie JC, et al 2018				
Current Evidence for the Use of Smoflipid® Emulsion in Critical Care Patients for Parenteral Nutrition	Leguina-Ruzzi Aa and Ortiz R 2020	Review Adult and peds			Although controversial data are available indicating the contraindications or effectiveness of its use, most of studies presented indicate favorable benefits associated with improved clinical outcomes. (e reported roles of this supplementation include positive immunomodulatory and anti-inflammatory effects, positive impact in liver

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					function, reduction of hospital stay, and nosocomial infections as additional contributions to its energetic role, which in many cases results in reduced total costs per patient
Low-Dose Intravenous Soybean Oil Emulsion for Prevention of Cholestasis in Preterm Neonates.	Levit OL, et al 2016	CT			**
Short-term exposure to exogenous lipids in premature infants and long-term changes in aortic and cardiac function.	Lewandowski AJ, et al. 2011	CT			
Parenteral fish-oil-based lipid emulsion improves fatty acid profiles and lipids in parenteral nutrition-dependent children.	Le HD, et al 2011	CT			***
Association of Retinopathy of Prematurity With Low Levels of Arachidonic Acid: A Secondary Analysis of a Randomized Clinical Trial.	Löfqvist CA, et al 2018	2 RCT			
Resolvin D1 and lipoxin A4 improve alveolarization and normalize septal wall thickness in a neonatal murine model of hyperoxia-induced lung injury. PLoS One 2014;9:2147483647.	Martin CR, Zaman MM, Gilkey C. 2014				
New generation lipid emulsions increase brain DHA and improve body composition, but not short-term	Molina TL et al, 2020			After 3 weeks of treatment, brain DHA	Concluded that a soybean oil emulsion

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
neurodevelopment in parenterally-fed preterm piglets.				content in SMOF, EXP and ENT pigs was higher ($P < 0.01$) in FC but not HC vs. IL pigs. There were no differences in brain weight or neuron density among treatment groups. Inflammatory cytokine TNFα and IL-1β expression in brain regions were increased in IL pigs ($P < 0.05$) compared to other groups. Overall growth velocity was similar among groups, but IL pigs had higher percent body fat and increased insulin resistance compared to other treatments ($P < 0.05$).	increased select brain inflammatory cytokines and multicomponent lipid emulsions enriched with DHA and AA in parenteral lipids results in increased cortical DHA and improved body composition without affecting short term neurodevelopmental outcomes.
Reversal of Intestinal Failure-Associated Liver Disease in an Infant Treated With Mixed Lipid Emulsion and Multidisciplinary Intestinal Rehabilitation Program.	Molinos, et al. 2020	6			Single patient case presentation—cholestasis resolved with reduced SMOF and aggressive enteral feeding
Early versus late parenteral nutrition for critically ill term and late preterm infants.	Moon K, et al 2020	1 Cochrane	defined early PN as commencing within 72 hours of admission, and late PN as commencing after 72 hours of admission		**Authors' conclusions** Whilst late commencement of PN in term and late preterm infants may have some benefits, the quality of the evidence was low and hence

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					our confidence in the results is limited. Adequately powered RCTs, which evaluate short-term as well as long-term neurodevelopmental outcomes, are needed.
Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial.	Najm S, et al 2017	2 RCT			The SMOF group had significantly higher EPA and DHA levels at postnatal days 7, 14, and 28 and PMA 32 wk compared with the OO/SO group. The SMOF group had a decreased ARA:DHA ratio from 1 wk after birth up to PMA 32 wk compared with the OO/SO group. There were no significant differences between groups in growth or morbidity
A comparison of 2 intravenous lipid emulsions: interim analysis of a randomized controlled trial.	Nehra D, et al 2013	2 RCT			***
Influence of Human Milk and Parenteral Lipid Emulsions on Serum Fatty Acid Profiles in Extremely Preterm Infants.	Nilsson AK, et al 2018	CT			
Effect of a small priming dose on myoclonic movements after intravenous anaesthesia induction with Etomidate-Lipuro in children.	Nyman Y, et al 2011	CT			

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
New-generation fish oil and olive oil lipid for prevention of oxidative damage in preterm infants: Single center clinical trial at university hospital in Turkey	Ozkan H, et al 2019	RCT		<32 wk, n = 89	Total antioxidant capacity was significantly higher in the SMOF group (day 7). BPD was significantly lower in the SMOF group (14.1%) than the OO/SO group (31.2%), and the rate of severe BPD was also significantly lower in the SMOF group (7.1% vs 19.1%, respectively). The duration of mechanical ventilation was also significantly lower in the SMOF group (10.3 vs 18.5 d, respectively).
A randomized comparative trial on the therapeutic efficacy of topical aloe vera and Calendula officinalis on diaper dermatitis in children.	Panahi Y, et al 2012	2 RCT			
Administration of an Intravenous Fat Emulsion Enriched with Medium-Chain Triglyceride/ω-3 Fatty Acids is Beneficial Towards Anti-Inflammatory Related Fatty Acid Profile in Preterm Neonates: A Randomized, Double-Blind Clinical Trial.	Papandreou P, et al 2020	2 RCT			Administration of MCT/ω-3 PUFA-enriched IVFE in preterm neonates is beneficial in changing the FA profile consistent with attenuated inflammatory response.
Early Postnatal Changes of Bone Turnover Biomarkers in Very Low-	Papandreou P, et al	2 RCT			***

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Birth-Weight Neonates-The Effect of Two Parenteral Lipid Emulsions with Different Polyunsaturated Fatty Acid Content: A Randomized Double-Blind Study.	2020				
Parenteral fish oil-containing lipid emulsions may reverse parenteral nutrition-associated cholestasis in neonates: a systematic review and meta-analysis.	Park HW, et al 2015	1 Systematic review and meta analysis			***
Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: a prospective, randomized study.	Pawlik D, et al 2014	CT			***
Parenteral nutrition-associated cholestasis and triglyceridemia in surgical term and near-term neonates: A pilot randomized controlled trial of two mixed intravenous lipid emulsions.	Pereira-da-Silva L, et al 2017	2 RCT			***
Comparison of liver function with two new/mixed intravenous lipid emulsions in children with intestinal failure.	Pichler J, et al 2014				
Very low birth weight preterm infant complications where parenteral nutrition is soy or fish oil-based: A retrospective study in Shanghai.	Qian T et al 2020				Both fish oil-containing and soybean oil-based parenteral lipid emulsions are safe and well-tolerated by preterm infants. However, the use of the SMOF lipid emulsion did not significantly reduce the incidence of cholestasis,

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					ROP and BPD in VLBW infants
Growth in Infants and Children With Intestinal Failure-associated Liver Disease Treated With Intravenous Fish Oil.	Raphael BP et al, 2020				Infants with IFALD treated with FOLE showed comparable somatic growth to those treated with SOLE in early infancy, and improved somatic growth up to 24 months of age, supporting its wider use in this patient population.
Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized double-blind study in preterm infants.	Rayyan M, et al 2012	2 RCT		<34 wk, n = 53	Significantly higher EPA and α-tocopherol but not DHA concentrations for SMOF vs SO. The ω-3:ω-6 ratio also increased significantly for SMOF vs SO. Both groups had similar lipid peroxidation as measured by plasma MDA levels and similar increases in body weight
A Mixed Lipid Emulsion for Prevention of Parenteral Nutrition Associated Cholestasis in Extremely Low Birth Weight Infants: A Randomized Clinical Trial.	Repa A, et al 2018	2 RCT			***
Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants.	Roelants JA, et al 2018	2 RCT			
Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for	Rollins MD, et al 2013	CT			

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
parenteral nutrition-associated liver disease: a pilot study.					
The effect of 5 intravenous lipid emulsions on plasma phytosterols in preterm infants receiving parenteral nutrition: a randomized clinical trial.	Savini S, et al 2013	2 RCT			
Parenteral omega-3 fatty acid lipid emulsions for children with intestinal failure and other conditions: a systematic review.	Seida JC, et al 2013	1 Systematic review			
Dose of intravenous lipids and rate of bacterial clearance in preterm infants with blood stream infections.	Shouman B, et al 2012	CT			
Parenteral MCT/omega-3 Polyunsaturated Fatty Acid-Enriched Intravenous Fat Emulsion Is Associated With Cytokine and Fatty Acid Profiles Consistent With Attenuated Inflammatory Response in Preterm Neonates: A Randomized, Double-Blind Clinical Trial.	Skouroliakou M, et al 2016	2 RCT			The SMOF group had significantly higher α-tocopherol, DHA, and EPA levels, lower linolenic acid level, and a lower ω-6:ω-3 ratio compared with the SO group. There were no significant differences between groups in growth or morbidity.
A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among children.	Stassijns J, et al 2016	1 Systematic Review			
A Randomized Trial of Parenteral Nutrition Using a Mixed Lipid Emulsion Containing Fish Oil in Infants of Extremely Low Birth Weight:	Thanhaeuser M, et al 2020	2 RCT			Parenteral nutrition using a mixed lipid emulsion containing fish oil did not improve neurodevelopment of extremely low birth

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Neurodevelopmental Outcome at 12 and 24 Months Corrected Age, A Secondary Outcome Analysis.					weight infants at 12 and 24 months corrected age (Soy vs SMOF)
Fish oil-containing multicomponent lipid emulsion vs soy-based lipid emulsion and neurodevelopmental outcomes of children born < 29 weeks' gestation.	Torgalkar R, et al 2020				
Response to Letter to the Editor from Kunal Gupta MBBS, MD: Is SMOF lipid emulsion better than soy-based lipid emulsion for low birth weight preterm neonates?	Torgalkar R, Shah PS. 2020				
Multi-component lipid emulsion vs soy-based lipid emulsion for very low birth weight preterm neonates: A pre-post comparative study.	Torgalkar R et al 2019				Compared with Intralipid, SMOF-LE was not associated with differences in mortality and major morbidities but was associated with lower odds of any retinopathy, cholestasis, and osteopenia; and improved lipid tolerance.
Lipid Formulations for Patients Requiring Parenteral Nutrition: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines – An Update [Internet]	Tran K, Butcher R 2019	Review			
Effects of fish oil-containing lipid emulsions on retinopathy of prematurity in very low birth weight infants.	Tu CF, et al 2020				Compared with soybean-based lipid solutions, the use of fish

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					oil-containing lipid solutions may be associated with a lower incidence of ROP and decreased need for bevacizumab treatment in preterm infants.
Morbidity outcomes of very low birth weight neonates receiving parenteral nutrition with fish oil enriched lipid emulsion or lipid emulsion with soybean oil: an observational study. Am J Perinatol 2020. doi:10.1055/s-0039-1701026. [Epub ahead of print: 27 Jan 2020].	Uberos J, et al. 2020	6 Observational study		P1=Intralipid P2=SMOF	During P2, there were fewer cases of moderate to severe ronchopulmonary dysplasia (BPD) and of cholestasis, but more cases of late sepsis, mainly *Staphylococcus epidermidis*. No changes in the prevalence of other neonatal comorbidities were observed. We believe that the SMOFlipid used in PN could discreetly improve the prevalence of cholestasis or BPD
Optimal timing for intravascular administration set replacement.	Ullman AJ, et al 2013	Review			
Effects of two different lipid emulsions on morbidities and oxidant stress statuses in preterm infants: an observational study. *J Matern Fetal Neonatal Med*. 2018;31(7):850-856.	Unal et al, 2018	6 Observational study.			Total antioxidant capacity was significantly higher in the SMOF group (day 7) than the OO/SO group. There were no significant differences in morbidity rates between the groups. However, there were

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					(statistically insignificant) lower rates of ROP (9.4% vs 11.7%) and chronic lung disease (4.7% vs 6.7%) for the SMOF vs OO/SO groups.
Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition.	Uthaya S, et al 2016	2 RCT			**
Parenteral Fish-Oil Lipid Emulsions in the Prevention of Severe Retinopathy of Prematurity: A Systematic Review and Meta-Analysis.	Vayalthrikkovil S, et al 2017	1 Systematic review and meta-analysis			***
Parenteral lipid administration to very-low-birth-weight infants--early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis.	Vlaardingerbroek H, et al 2012	1 Systematic review and meta-analysis			**
Adaptive regulation of amino acid metabolism on early parenteral lipid and high-dose amino acid administration in VLBW infants - a randomized, controlled trial.	Vlaardingerbroek H, et al 2014	2 RCT			
Growth and fatty acid profiles of VLBW infants receiving a multicomponent lipid emulsion from birth.	Vlaardingerbroek H, et al 2014	2 RCT			Significantly higher EPA and DHA concentrations for SMOF vs SO. By discharge, the SMOF group had significantly greater weight gain,

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					increase in weight *z*-score, and increase in head circumference *z*-score, than those given SO. Clinical outcomes and mortality rates did not differ significantly between groups.
Parenteral nutrition with fish oil-based lipid emulsion reduces the risk of cholestasis in preterm infants.	Wang YL, et al 2021				In premature infants, PN with fish oil-based lipid emulsions is associated with a lower incidence of PN-associated cholestasis compared with soybean oil-based lipid emulsions.
Effect of an Olive Oil-Based Lipid Emulsion Compared With a Soybean Oil-Based Lipid Emulsion on Liver Chemistry and Bile Acid Composition in Preterm Infants Receiving Parenteral Nutrition: A Double-Blind, Randomized Trial.	Wang Y, et al 2016	2 RCT			
The effects of different lipid emulsions on the lipid profile, fatty acid composition, and antioxidant capacity of preterm infants: A double-blind, randomized clinical trial.	Wang, Y 2016	2 RCT			**
Parenteral Fish-Oil Containing Lipid Emulsions Limit Initial Lipopolysaccharide-Induced Host Immune Responses in Preterm Pigs.	Yakah W et al 2021				Host priming with soybean oil in the early postnatal period preserves a higher AA:DHA ratio and the ability to acutely respond to

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					an external stimulus. In contrast, fish-oil containing lipid emulsions increase DHA, exacerbate a deficit in AA, and limit the initial LPS-induced inflammatory responses in preterm pigs.
Parenteral lipid emulsions induce unique ileal fatty acid and metabolomic profiles but do not increase the risk of necrotizing enterocolitis in preterm pigs.	Yakah W et al 2021		NEC development		Exposure to parenteral lipid emulsions induces unique intestinal fatty acid and metabolomic profiles; however, these profiles are not linked to a difference in NEC risk in preterm pigs.
Early enteral fat supplement and fish oil increases fat absorption in the premature infant with an enterostomy.	Yang Q, et al 2013	CT			
Randomized controlled trial of early enteral fat supplement and fish oil to promote intestinal adaptation in premature infants with an enterostomy.	Yang Q, et al 2014	2 RCT			
Effects of two different lipid emulsions on antioxidant status, lipid peroxidation and parenteral nutrition- related cholestasis in premature babies, a randomized-controlled study.	Yildizdas HY, et al 2019	2 RCT			Thiobarbituric acid reactive substances levels were significantly lower (day 7) in the SMOF group than in the OO/SO group, but not after 28 d. However, superoxidase dismutase levels decreased over time in the SMOF group and were

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
					significantly lower than the OO/SO group by day 28. Cholestasis was significantly lower in SMOF group (0% vs 18.2%), and neonates regained birth weight earlier than in the OO/SO group. There was no significant difference in other morbidities.
Safety and efficacy of parenteral fish oil-containing lipid emulsions in premature neonates.	Zhao Y, et al 2015				