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SMOF SMOF Baby

(SMOF…Collaborate and Listen, Lipid's Back with a Brand New Edition)

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Newborn and Infant Critical Care Unit

Outline

- Review Lipid metabolism
  - Intravenous Lipid Emulsions
- Clinical Considerations of Intravenous Lipid Emulsion Usage
  - Intestinal Failure Associated Liver Disease
- Why SMOF?
  - Review Literature
- CHLA SMOF Usage
  - Current practices
  - Proposed guidelines and monitoring
  - Case reviews
  - ‘Troubleshooting’
- Questions

Objectives

- Understand the composition of SMOFlipid and its comparison to other traditional Intravenous Lipid Emulsion products
- Identify patient populations ideal for use of SMOFlipid
- Recognize the practice and clinical implications associated with using SMOFlipid

Lipid Review

Lipids are:

- Energy source
- Cell membrane structure
- Precursors to modulators involved of immune response

- Lipid metabolism results in lipid peroxidation and *free radical* formation
  - Can trigger chain reactions that lead to inactivation of enzymes, proteins, and other elements necessary for cell viability

Lipid Review

- Ω-3 FAs and Ω-6 FAs compete for space w/in cell membrane and are processed by the same enzymes (elongases, desaturases, etc) to generate more active downstream products
  - More prevalent FA is preferentially metabolized
- Recently, true essentiality of LA and ALA have been questioned—provision of their main downstream products (DHA, ARA) is just as effective at preventing the development of biochemical EFAD
- Emulsions w/high Ω-6 FA content have been linked w/immunosuppresive effects

IV Lipid Emulsions (ILEs)

- Oils used for preparation of ILEs:
  - Sesame
  - Olive
  - Human body fat
  - Butter
  - Corn
  - Peanut
  - Cottonseed
  - Cod liver
  - Coconut
  - Lard
  - Safflower
  - Synthetic

ILEs

- **Soybean Oil (SOFE)**
  - High PUFAs
    - Increased concentration of PUFAs in membrane increases susceptibility to oxidation and peroxidation
  - Naturally rich in phytosterols

- **Fish Oil**
  - Less pro-inflammatory than conventional SOFEs
  - Rich in α-tocopherol—added to prevent oxidation of FAs
  - FOFE has little LA and ALA but contains downstream metabolites ARA, EPA, DHA

ILEs

- **MCT Oil: Coconut or Palm Kernel**
  - Do not accumulate in liver, do not impair hepatic function
  - Devoid of EFAs
- **Olive Oil:**
  - Rich in MUFAs—more resistant to oxidative stress from free radicals
  - Lower phytosterol content, abundant in α-tocopherol

Intralipid

1961 – Arvid Wretlind in Sweden & O. Schuberth introduced Intralipid

- Oil (soybean oil) + emulsifier (egg yolk)
- First non-toxic, readily available fat emulsion

1962 became commercially available

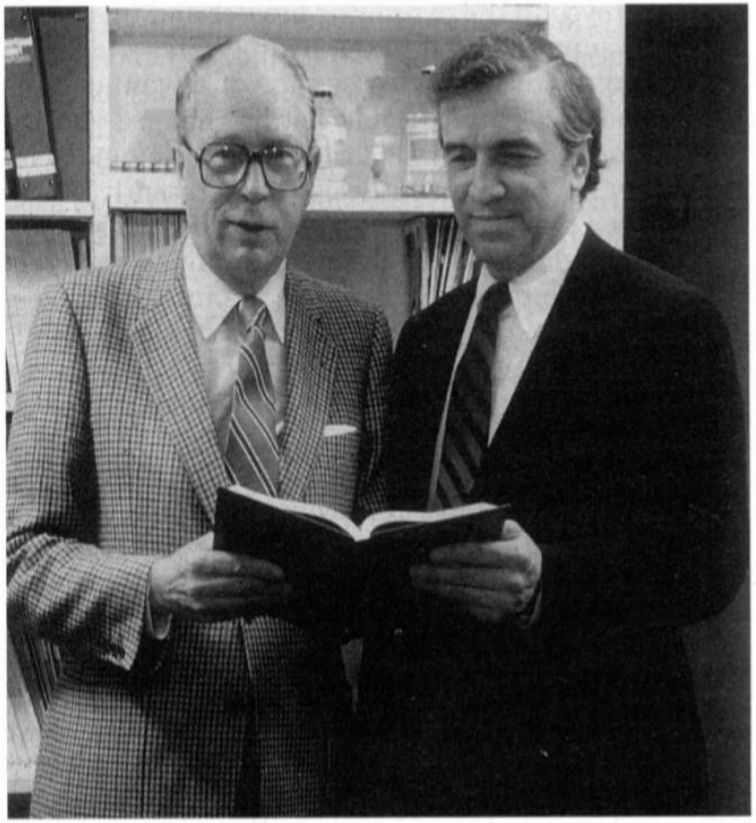


FIG. 2. Two major contributors to contemporary parenteral nutrition: Arvid Wretlind (left) and Stanley J. Dudrick (right).

Omegaven

- 10% fish oil lipid emulsion, not FDA approved, used in IRB approved protocols throughout US

Study Protocol at CHLA

- Inclusion Criteria:
  - Expecting TPN >30days
  - IFALD w/2 consecutive Conjugated Bilirubin >2 mg/dL
  - Utilized standard therapies; Age <21yrs
  - Dosing:
    - 0.5g/kg induction, increasing to 1g/kg infants/pediatrics
    - 0.2g/kg adolescents (compassionate use only)
  - Monitoring:
    - Outpatient monthly: CBC, Chem 14, Mg, Phos, TG, GGT, PT, PTT, Prealbumin, EFA, CRP

Intestinal Failure Associate Liver Disease

- Potentially life-threatening, may affect 40-60+% of pediatric patients on long-term PN
  - Historically 10-50% of children receiving prolonged PN have died from IFALD
- Pathophysiology is multifactorial
  - Directly correlated to length of time on PN
  - Higher plant sterols thought to contribute to development
    - Accumulate in liver when given IV, inhibit enzyme 7α-hydroxylase
    - Antagonizing effect on farsenoid X nuclear receptor
    - Accelerate breakdown of erythrocyte membranes, increases bili load to liver
    - Increase risk of sepsis by altering neutrophil migratory and phagocytic fxns

IFALD Management

- Lipid minimization
  - 0.5-1gm/kg/d (or MWF)
  - Increase Dextrose to improve kcals
- Omegaven
  - Omega -3 FA
    - Improve bile flow, lipid clearance, lipid uptake by extra-hepatic tissues (d/t better beta-oxidation)
- Cycling PN
  - Not effective or safe in neonates
- Reduce/eliminate copper, manganese
  - Found increased incidence of copper deficiency
- Actigall if on feeds

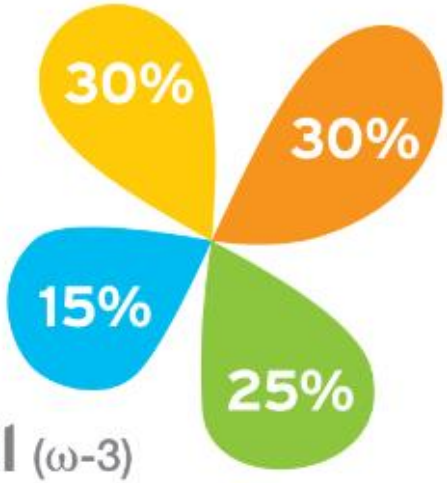
SMOFlipid

Soybean Oil (ω-6)

Provides essential fatty acids

MCT

Medium-chain triglycerides are a source of rapidly available energy[1]



Fish Oil (ω-3)

Source of EPA and DHA[2]

Olive Oil (ω-9)

Supply of monounsaturated fatty acids

SMOFlipid

- **Soybean Oil 30%**
  - Rich in n-6 polysaturated fatty acids
  - High amounts of linoleic acid and alpha linolenic acid
- **MCT 30%**
  - From coconut oil or palm kernel oil
  - Not stored in liver or adipose tissue
  - Eliminated faster from the bloodstream than LCTs
  - Undergo hydrolysis and rapid beta-oxidation independent of the carnitine enzyme system
  - Less susceptible to lipid peroxidation
- **Olive oil 25%**
  - Rich in monounsaturated fatty acid
  - Less PUFA
  - More vitamin E – important to prevent cell damage by lipid peroxidation
- **Fish oil 15%**
  - Bioactive omega2 LC PUFA EPA and DHA
  - Anti-inflammatory agents
  - Substrates for membrane phospholipids
  - Are highly unsaturated and susceptible to peroxidation

Injectable Lipid Emulsions (ILE)

Component	IntraLipid	Omegaven	SMOFlipid
Soybean Oil %	100	0	30
MCT %	0	0	30
Olive Oil %	0	0	25
Fish Oil %	0	100	15
Glycerol g/100mL	2.25	2.5	2.5
Egg Phospholipid g/100mL	1.2	1.2	1.2
Phytosterols mg/L	437 +/- 5.7	3.66	207
Vitamin E mg/100mL	3.8	15-30	16-23
LA %	50	4.4	21.4
ALA %	9	1.8	2.5
EPA %	0	19.2	3
DHA %	0	12.1	2
ARA %	0	1-4	0.15-0.6

Why SMOF?

- **Omega-6: Omega-3 < 4:1 is thought to reduce inflammation**
  - Ratio < 2.5:1 has shown improvement in bile flow in animal models
- Intralipid has a ratio of 8:1
  - Does not have any DHA which is important for neurodevelopment
  - Alpha-linolenic acid in Intralipids can not be converted into DHA
- Omegaven has a ratio of 1:7
  - Used mainly as a rescue therapy for infants with advanced IFALD
- SMOFlipid has a ratio of 2.5:1
  - Omega 6: Omega 3 ratio was lower in those receiving SMOFlipid compared to those receiving intralipid (Tomsits 2010)

Why SMOF?

- Omega -3 LC PUFA are more bioavailable with SMOFlipid
  - Crucial in premature infants for growth and development
- Omega-3 LC PUFA from fish oil has shown in animal models to be improve outcomes in endotoxaemia and sepsis
  - Has potent immunomodulatory and anti-inflammatory properties
    - Inhibiting cyclooxygenase pathway
  - In post-op patients fish oil infusions
    - Lower the production of eicosanoids from AA
    - Increase the production of EPA derived leukotrienes
- In utero the 3rd trimester is when most of DHA is accumulated
  - Premature infants are born with a DHA deficit as well as inefficient ALA to DHA conversion
- As noted previously in Tomsits et al – the benefit of increased vitamin E is seen with SMOFlipid

Inflammation

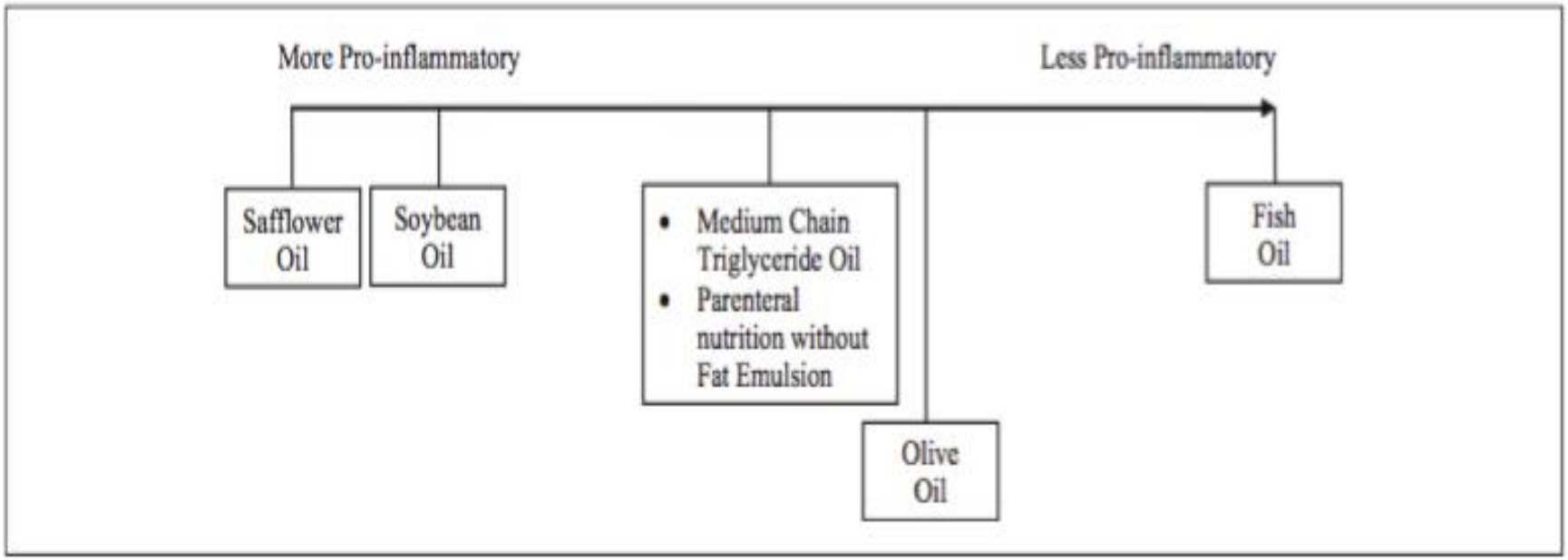


Figure 4. Categorization of oil sources used for commercially available intravenous fat emulsions based on relative systemic inflammatory activity.
Note: this is a relative (not absolute) figurative scale to demonstrate relative inflammatory activity.

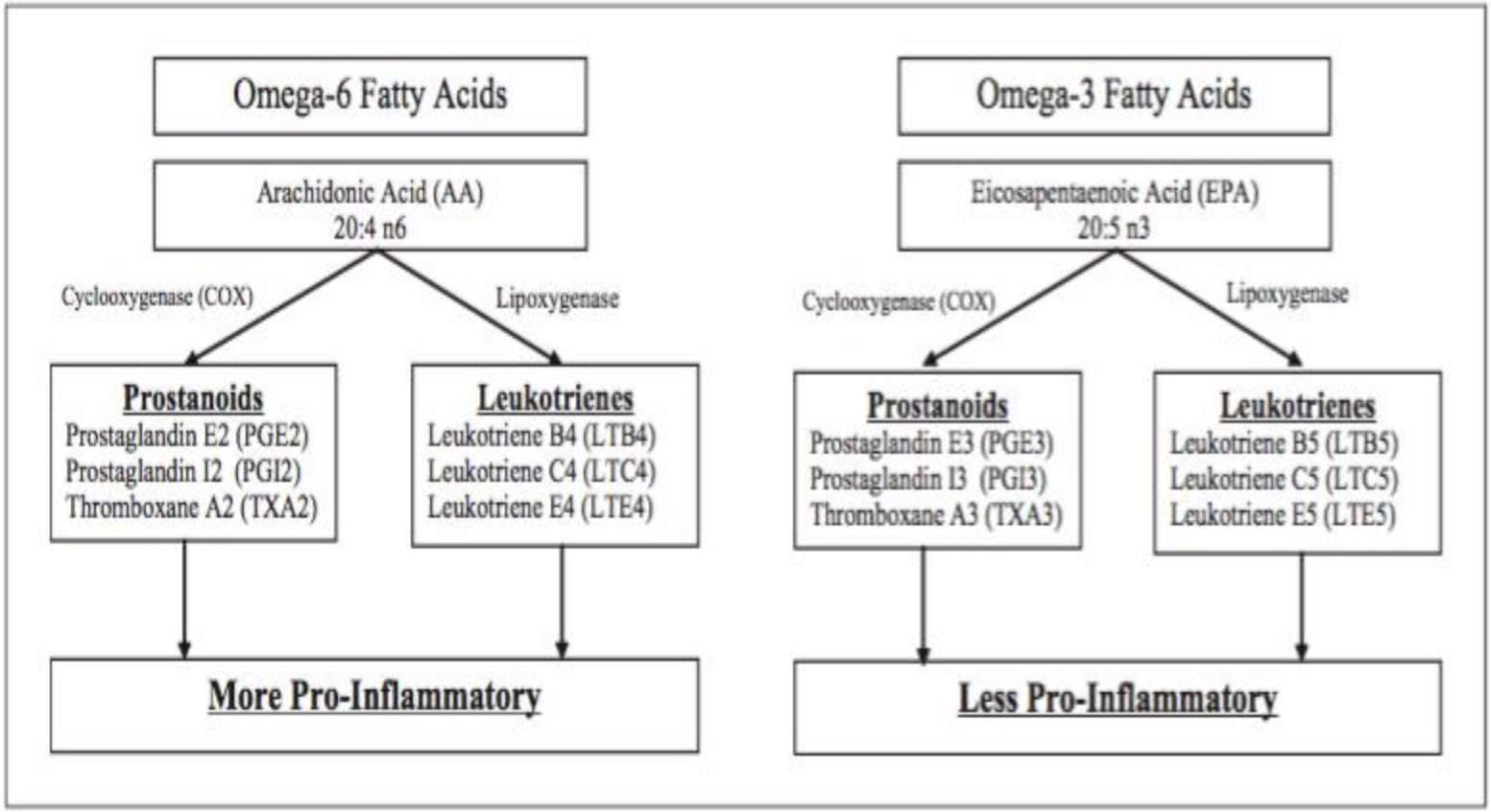


Figure 2. Relative proinflammatory eicosanoids from metabolites of ω-6 and ω-3 fatty acids.
Adapted from Lee S, Gura KM, Kim S, Arsenault DA, Bistrian BR, Puder M. Current clinical applications of omega-6 and omega-3 fatty acids. *Nutr Clin Pract*. 2006;21:323-341.[7]

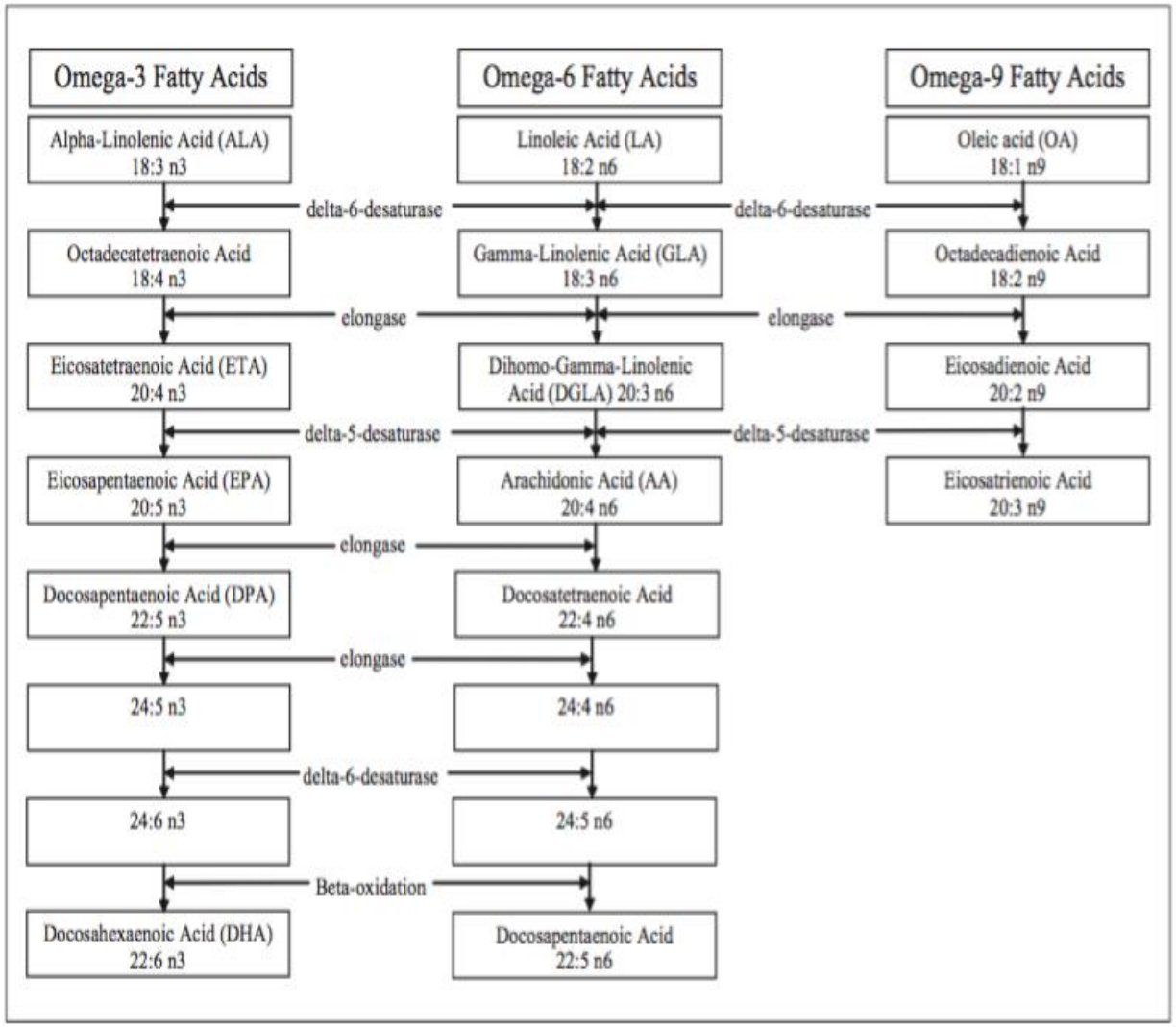


Figure 1. Metabolic pathways of ω-6 and ω-3 fatty acids.
Adapted from Le HD, Meisel JA, de Meijer VE, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81:165-170,[2] with permission from Elsevier.

Why SMOF?

- Jacintho, T Manzoni. et al
  - Studied fish oil lipid emulsion on human activated mononuclear leukocytes
  - Decrease in lymphocytes proliferation, decreased IL2 and IL 6 production and increased IL-10 production
    - Effect enhanced when fish oil was mixed with MCT oil and soybean oil
    - Opposite effects seen in soybean oil only emulsions
- Omega 3 FA
  - Decreased cytokine production, NK cell cytotoxicity, antibody production
  - Suppression of neutophil chemotatic responsiveness to leukotriene B4
- DHA helps to restore the oxygen dependent bactericidal mechanisms of monocytes

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Omega-3 in Surgical Patients

- Meta-analyses
- Increased omega-3 may improve outcomes
  - Liver function
  - Improvement in immune and inflammatory response
  - Decreased LOS
  - Reduced risk of complications
- Benefits noted when given pre-op, post-op or entire perioperative period
- *none of the studies are in the pediatric population

Table 1. Latest studies/meta-analyses evaluating the benefits of *n*-3 PUFA (polyunsaturated fatty acids) in parenteral nutrition in surgical populations *.

Author	Year	Population	Intervention	Duration	Result
Jiang [117]	2010	Colectomy and rectotomy (n = 206)	LCT vs LCT+fish oil	7 days post-surgery	Significant reduction in LOS and SIRS
Wang [115]	2012	Gastrointestinal surgery (n = 64)	MCT/LCT *vs.* LCT+fish oil	5 days post-surgery	Amelioration of liver function and immune status
Han [116]	2012	Major surgery (n = 38)	MCT/LCT *vs.* LCT+fish oil	7 days post-surgery	Reduced postoperative liver dysfunction and infection rate
Zhu [119]	2012	Colectomy and rectotomy (n = 57)	LCT *vs.* fish oil	7 days post-surgery	Reduced LOS
Zhu [120]	2012	Liver transplantation (n = 98)	Oral diet *vs.* standard PN vs fish oil PN	7 days post-surgery	Reduced incidence of liver injury, decreased LOS and infectious complications
Berger [121]	2013	Cardiopulmonary bypass surgery (n = 28)	Fish oils vs saline	12 and 2 h before surgery and after surgery	Decreased biological and clinical signs of inflammation
De Miranda Torrinhas [118]	2013	Surgery for gastrointestinal cancer (n = 63)	MCT/LCT *vs.* fish oil	3 days post-surgery	Significant increase in IL-10 levels (day 3), decrease in IL-6 and IL-10 levels (day 6), less decline in leukocyte oxidative burst
Chen [123]	2010	Major abdominal surgery, meta-analysis (n = 892)	Fish oil *vs.* various control emulsions	Various	Decreased LOS in the hospital and ICU, reduced postoperative infection rate, improved liver function
Li [124]	2013	Major surgery, meta-analysis (n = 1487)	Fish oil	Various	Decreased infection rate, LOS, and liver dysfunction; no effect on mortality
Pradelli [125]	2012	Subgroup analysis in patients undergoing major abdominal surgery and not admitted to ICU (n = 740)	*n*-3 PUFA-enriched *vs.* standard lipid emulsions	Various	Significant reduction in the infection rate and LOS
Tian [126]	2013	Surgical patients, meta-analysis (n = 306)	Fish oil/LCT/MCT *vs.* LCT/olive oil	Various	No significant difference, fish oil less toxic to liver when compared to LCT or olive oil

* Adapted from Klek *et al.* 2015 [122]. Abbreviations: ICU = intensive care unit; LCT = long-chain triglycerides; LOS = length of stay; MCT = medium-chain triglycerides; PN = parenteral nutrition; RCT = randomized clinical trial; SIRS = systemic inflammatory response syndrome.

Preventing Progression of IFALD Using SMOF

- Multicenter blinded, randomized
- Comparing Intralipid and SMOFlipid, up to 12 weeks
  - 24 infants, both groups receiving 90+% of kcals from PN

- Infants receiving SMOFlipid had lower conjugated bili, more likely to have decrease in D.Bili to 0
- Time to full enteral tolerance did not differ statistically between groups

- Compared to Intralipid, SMOF reduces risk of progressive IFALD in infants with intestinal failure

Current Practice: NICCU

- Increasingly and more regularly dosing SMOF 1-3gm/kg/d for:
  - transitioning infants w/increasing Dbili or LFT trends from IL to SMOF
  - lymphatic malformation, chylothorax, bowel resection patients
  - Used in 1 preemie with severe necrotizing fasciitis

- Excellent success and tolerance: downtrending dbilis/LFTs
- Better growth w/more balanced PN kcal distribution
- Anecdotally: short gut pt's at high risk for enteral intolerance have exceeded expectations—improved GI health, absorption, tolerance?

Current Practice: IR/HPN

- Pediatrics- transitioning those kiddos on minimal PO/EN to SMOF, pending vendor availability and insurance authorization
  - Based on upcoming CHLA guidelines, likely to transition all IR/HPN pts to SMOF
- Teens/adults- >18 all transitioned to SMOF
  - Teens previously on Omegaven study protocol transitioned to SMOFlipid successfully
- As of now- we have zero patients on the Omegaven study protocol and suspect future uses will be primarily for salvage therapy only

Proposed CHLA Guidelines for the Use of SMOFlipid

- Indications:
  - Preterm neonates <34 weeks should receive SMOFlipid as their standard ILE
  - Term neonates, surgical neonates, pediatric patients should switch from Intralipid to SMOFlipid if PN is required beyond 2 weeks
  - Infants and children with established or anticipated intestinal failure on PN should receive SMOFlipid as their standard ILE

- Contraindications
  - Soy, olive, fish, egg allergy
  - TG >1000mg/dL

Proposed CHLA Guidelines for the Use of SMOFlipid

- Dosage:
  - Starting dose 0.5gm/kg/d over 24hrs
  - Can advance by 0.5gm/kg/d as tolerated
  - Maximum dose 2.5gm/kg/d (3gm/kg/d in preterm infants OK)
- Cautions
  - Lipid clearance is slowest in the most premature infants
  - SMOFlipid may be cleared more slowly than Intralipid at high doses
  - EFA present in SMOFlipid may interfere with platelet function
    - Pt's requiring therapy for coagulopathy, discontinuation of SMOF should be considered
    - Pt's scheduled for elective surgery, can consider withholding SMOF x48hrs prior to surgery

Proposed CHLA Guidelines for the Use of SMOFlipid

- Monitoring:
  - TG should be monitored pre-lipid administration and daily as lipid concentrations are advanced and twice weekly per routine PN monitoring. TG should also be checked at times of severe infection
    - Same levels of TG can be used to stop or modify lipid dose as would be done with Intralipid
  - **Vitamin E** levels should be checked **after 2 weeks of therapy**, again 4 weeks later, and at **3-6mo intervals** thereafter. If levels are elevated, more frequent monitoring and adjustment of PN composition may be indicated
  - EFA levels are not routinely recommended and not until after minimum of 4 weeks of SMOF at usual dose. In pt's receiving very low doses of lipid or w/clinical findings suggestive of EFAD, earlier assessment may be warranted

CHLA PN Lab Monitoring

- TPN Panel: daily while initiating/advancing PN, twice weekly once stable or as otherwise clinically indicated
  - CMP/Chem 14 (fractionated bili not included)
  - Mg/PO4
  - **TG: <200-250mg/dL**
- Fractionate bilirubin: at least weekly once total bili >2-3 outside of newborn period
  - **Direct/Conjugated Bili <2-3**

CHLA PN Lab Monitoring

- "Chronic Nutrition Labs": check after 4-6 weeks on PN and Q1-3 months thereafter; or as otherwise clinically indicated
  - Vitamin A
  - Vitamin D
  - **Vitamin E:**
    - Parenteral recommendations for parenteral vitamin E in premature infants suggest a dose that does not increase plasma concentration **>80micromol/L (35mg/L)**
    - AAP Committee on Nutrition suggested safe and effective blood levels between **23-46mmol/L (10-20mg/L)**
  - Copper
  - Zinc
  - **EFAs**
    - **Triene:Tetraene ratio >0.2** indicative of EFAD

BG YMT

- Ex 27 5/7 week female transferred at DOL 19 for concern of L chest/abdomen cellulitis vs. necrotizing fasciitis
- OSH:
  - DOL 16: hypotensive, 3rd spacing with oliguria/anuria, required dopamine, abdominal distention with no pneumatosis noted on KUB
    - Exploratory laparotomy reportedly normal
    - Started on Vancomycin and cefotaxime
  - After ex-lap noted to have skin discoloration that worsened rapidly with sloughin skin, erythema and dusky areas with decreased perfusion
    - Ampicillin added
    - Tissue culture: enterococcus faecalis
  - DOL 19: Left flank abscess aspirated prior to transfer

BG YMT

- CHLA course:
  - DOL 19: On admission taken to OR for surgical debridement
    - 12x10cm area down to the fascia and muscle of the left abdomen, back, flank and chest
  - Debridement on DOL 21 and DOL 24
  - Completed 4 week course of Zosyn
  - Irrigation, debridement and cadaveric allograft on DOL 110

- Nutrition:
  - Protein increased in TPN
  - Increased copper, selenium, and zinc
  - Changed lipid emulsion from Intralipids to SMOFlipid for Omega 3 and Vitamin E

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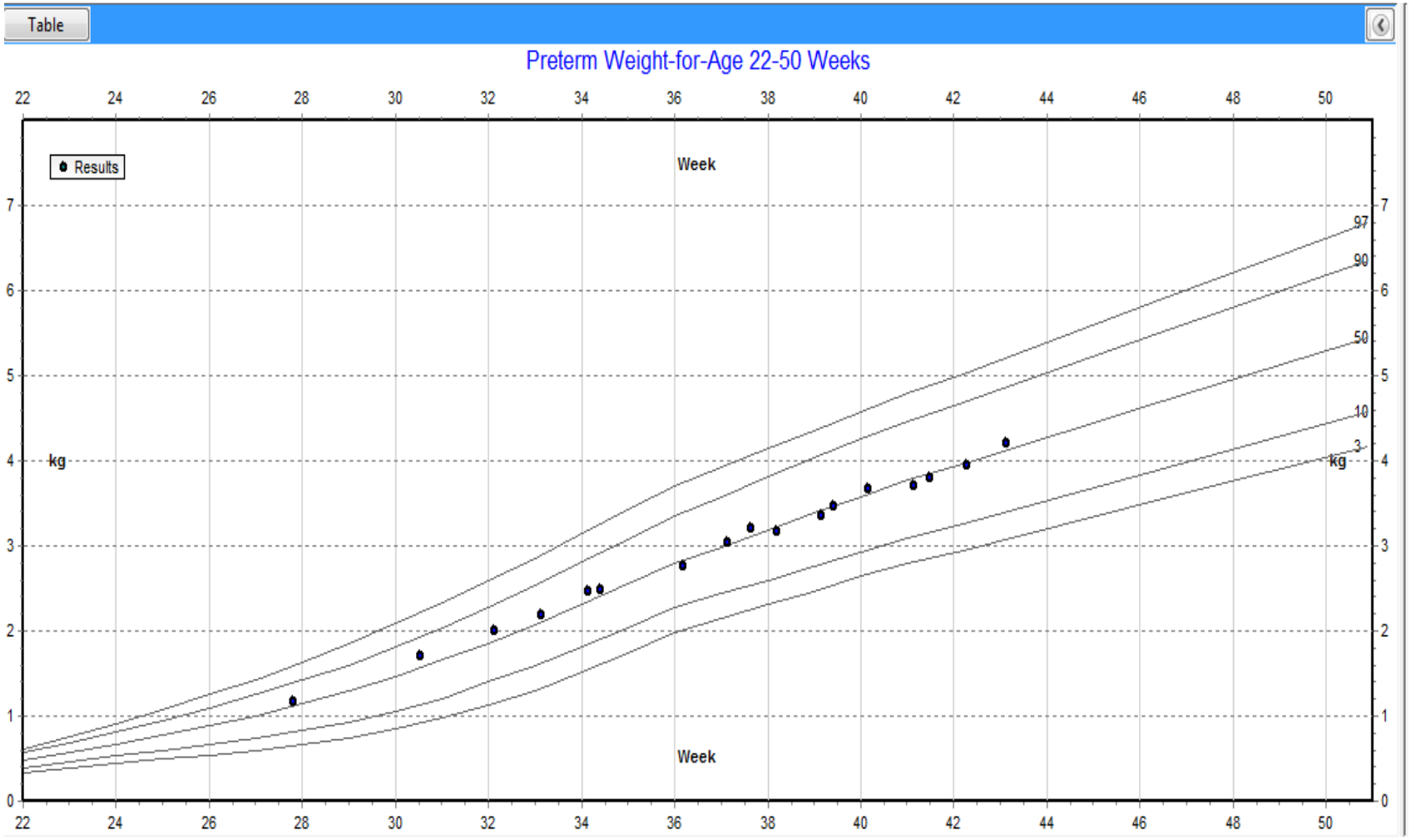

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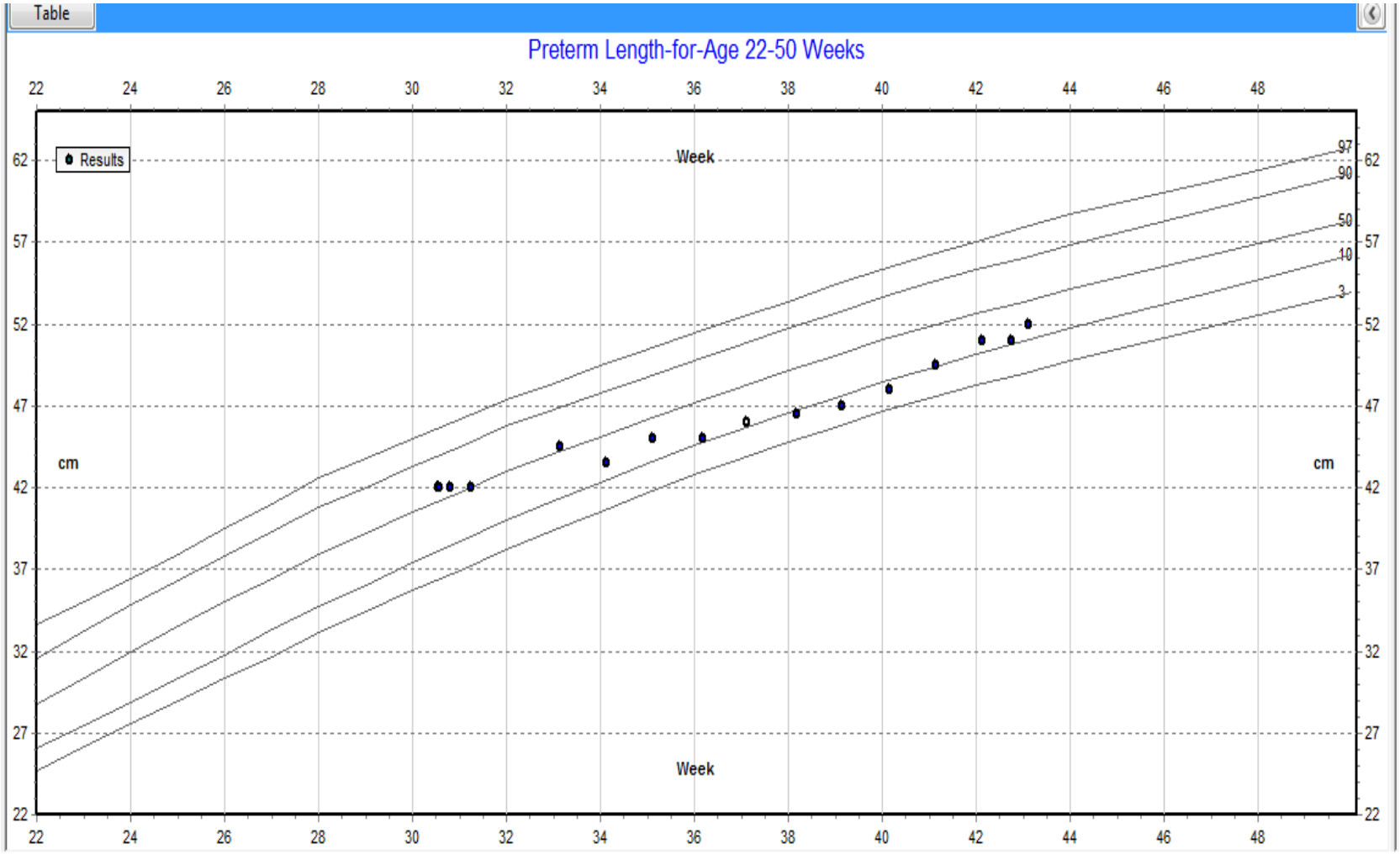

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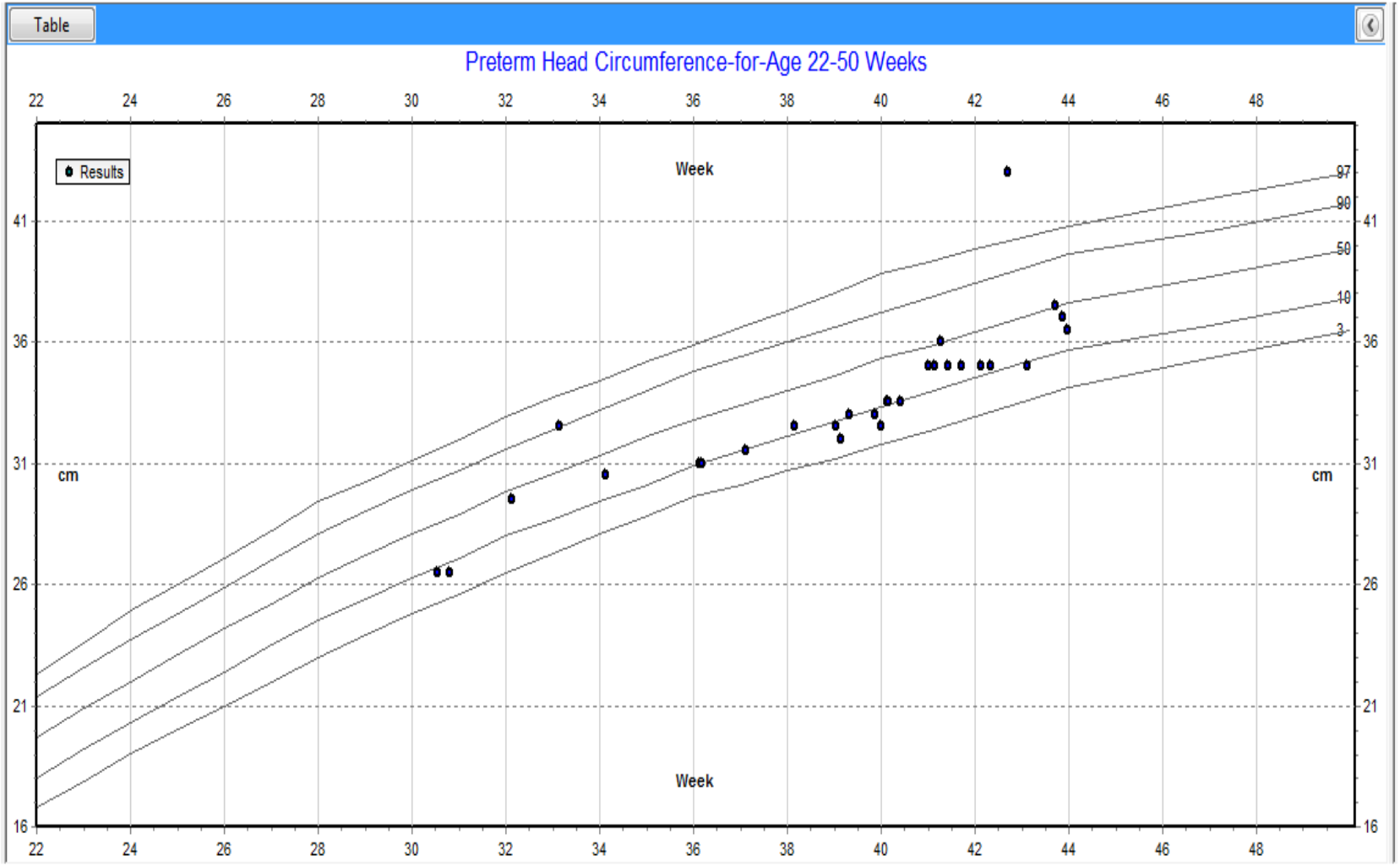

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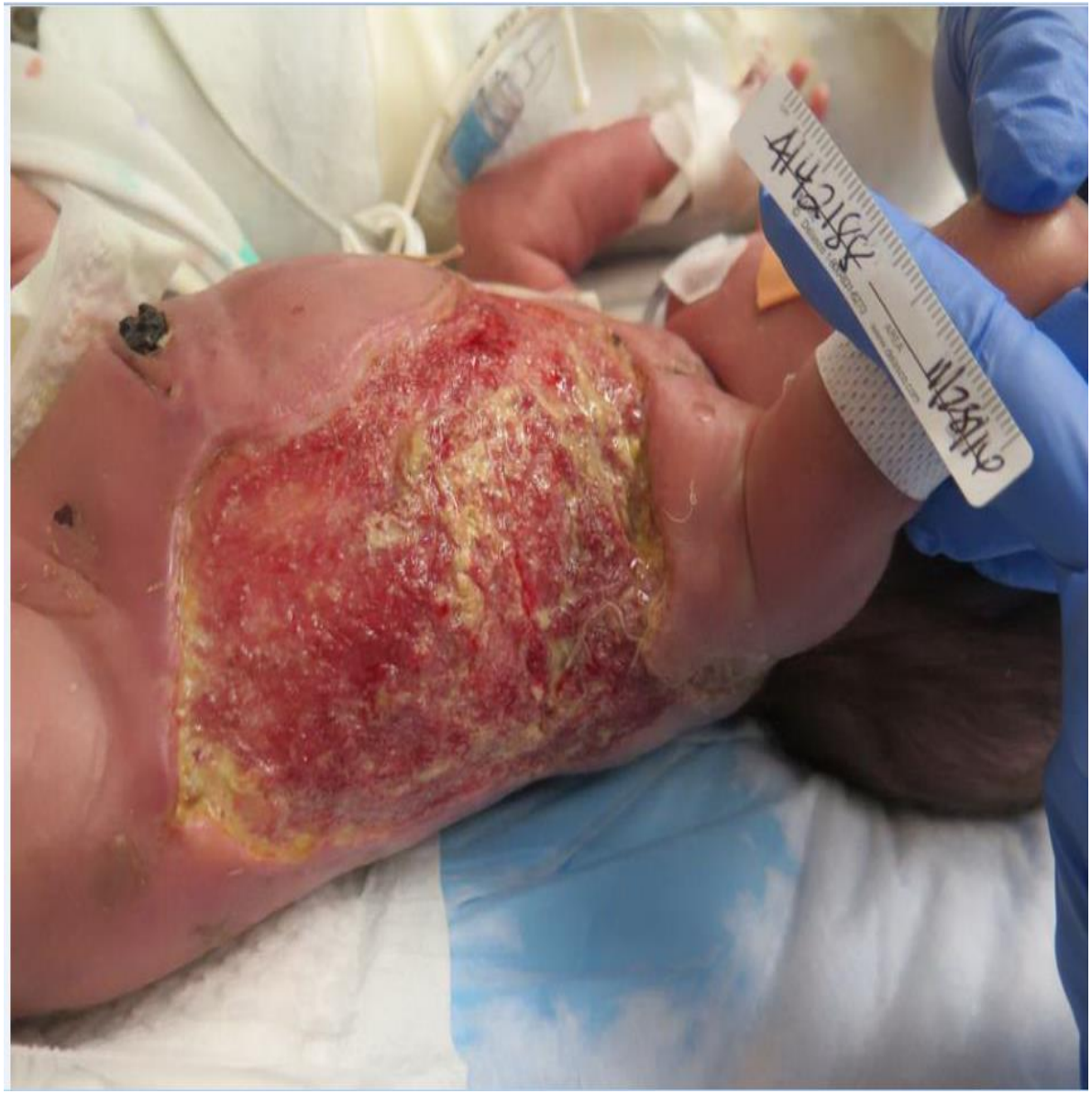

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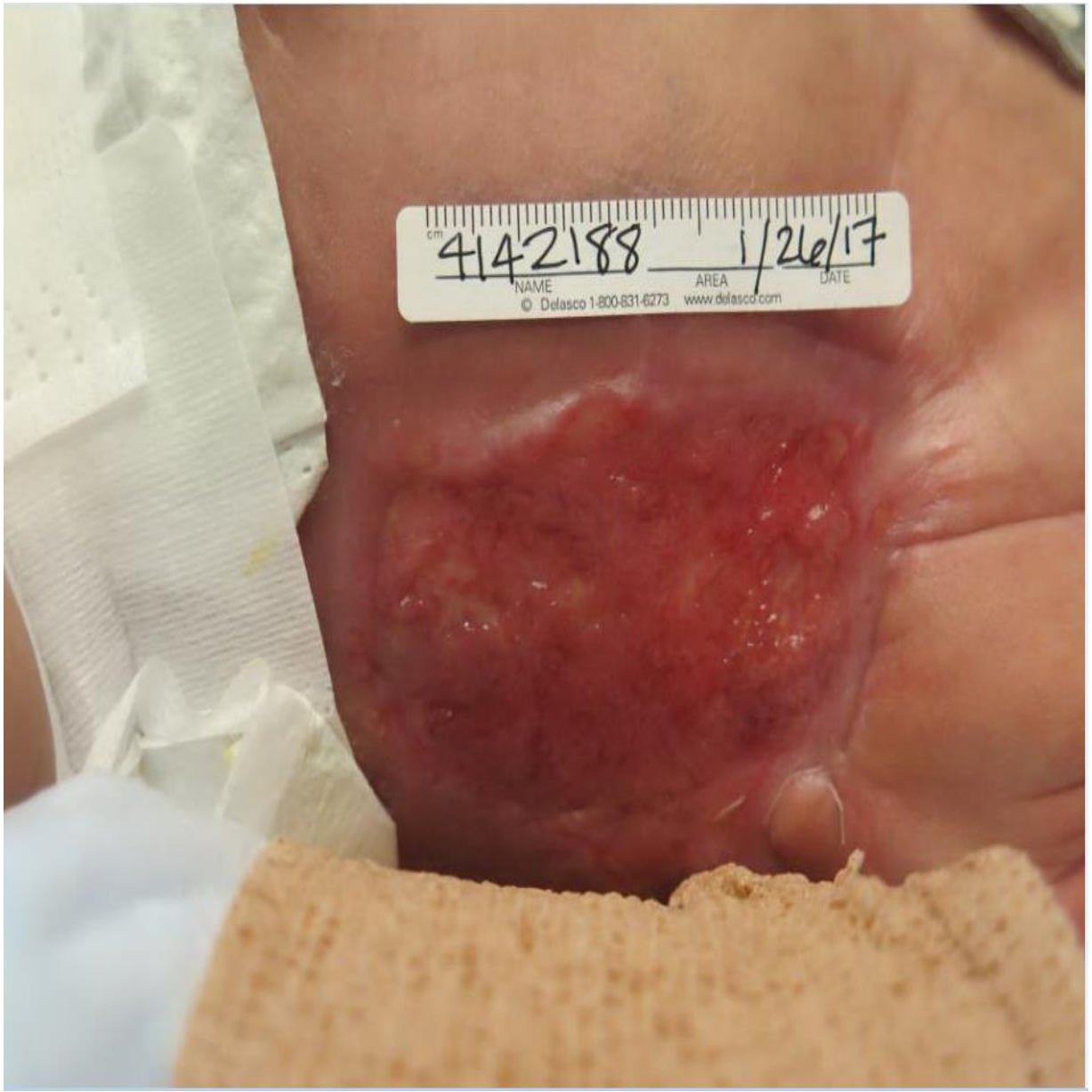

BG MG

- Twin B, ex 28 5/7 female infant
- Transferred from OSH for feeding intolerance
  - h/o medically treated NEC, transabdominal penrose drain placed given persistent intra-abdominal air pocket
- CHLA NICCU course (abbreviated)
  - s/p extensive LOA and ileostomy
  - Cholestasis, transaminitis, elevated AFP (presumed to be secondary to a liver hematoma)
  - s/p ostomy takedown and stoma repair, and s/p subsequent bedside exploration of wound with no evidence of infections or incarcerated bowel

BG MG – Nutritional Assessment

- Poor growth in terms of weight, length and head circumference
- Malnourished
  - Growth charts
  - Protein deficiency
    - Alopecia
  - Likely mineral deficiency and metabolic bone disease
- Given her cholestasis changed from Intralipid to SMOFlipid
  - Also optimized her TPN with increase in Calcium, Phosphorus, Zinc
  - Increased protein in TPN

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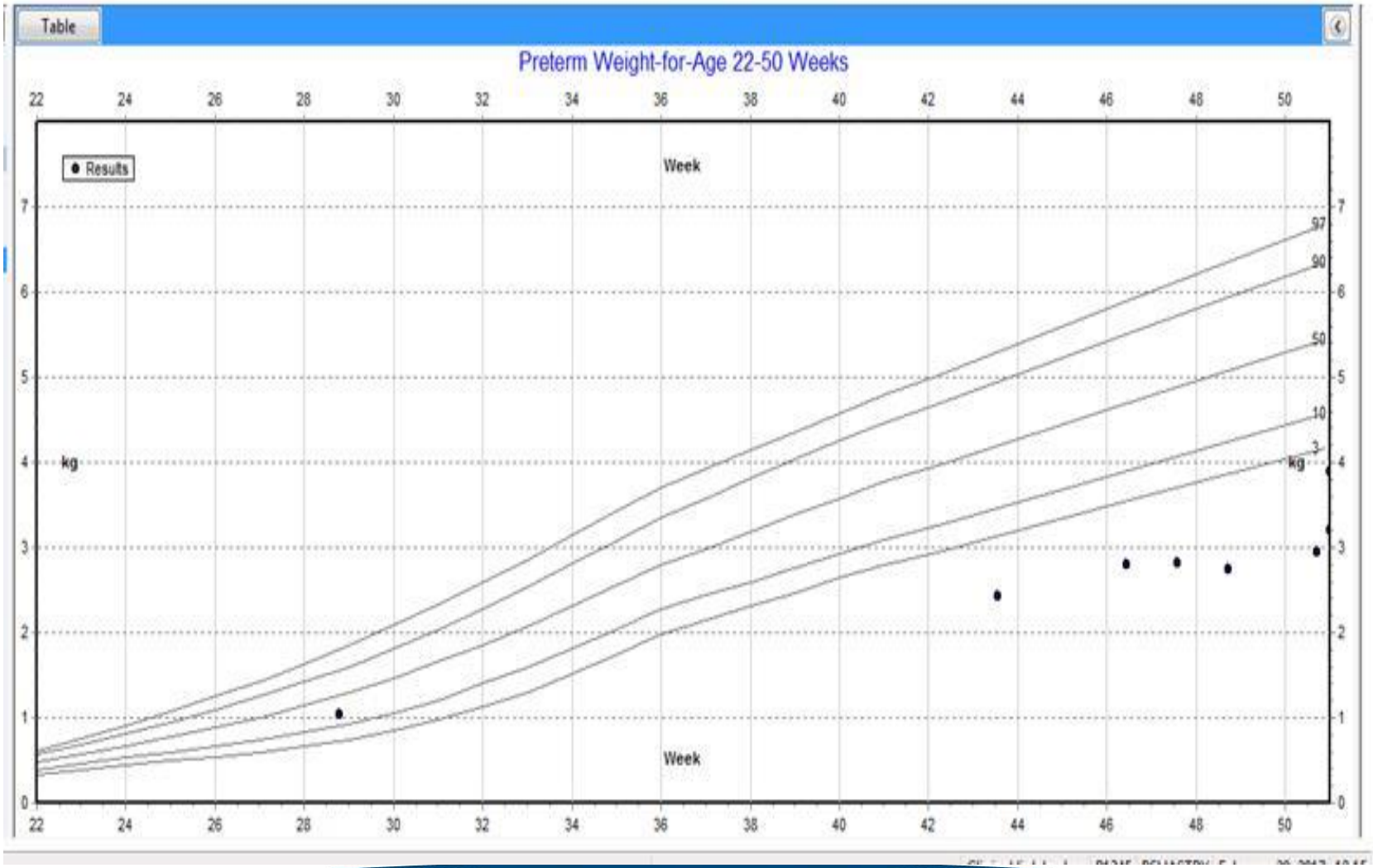

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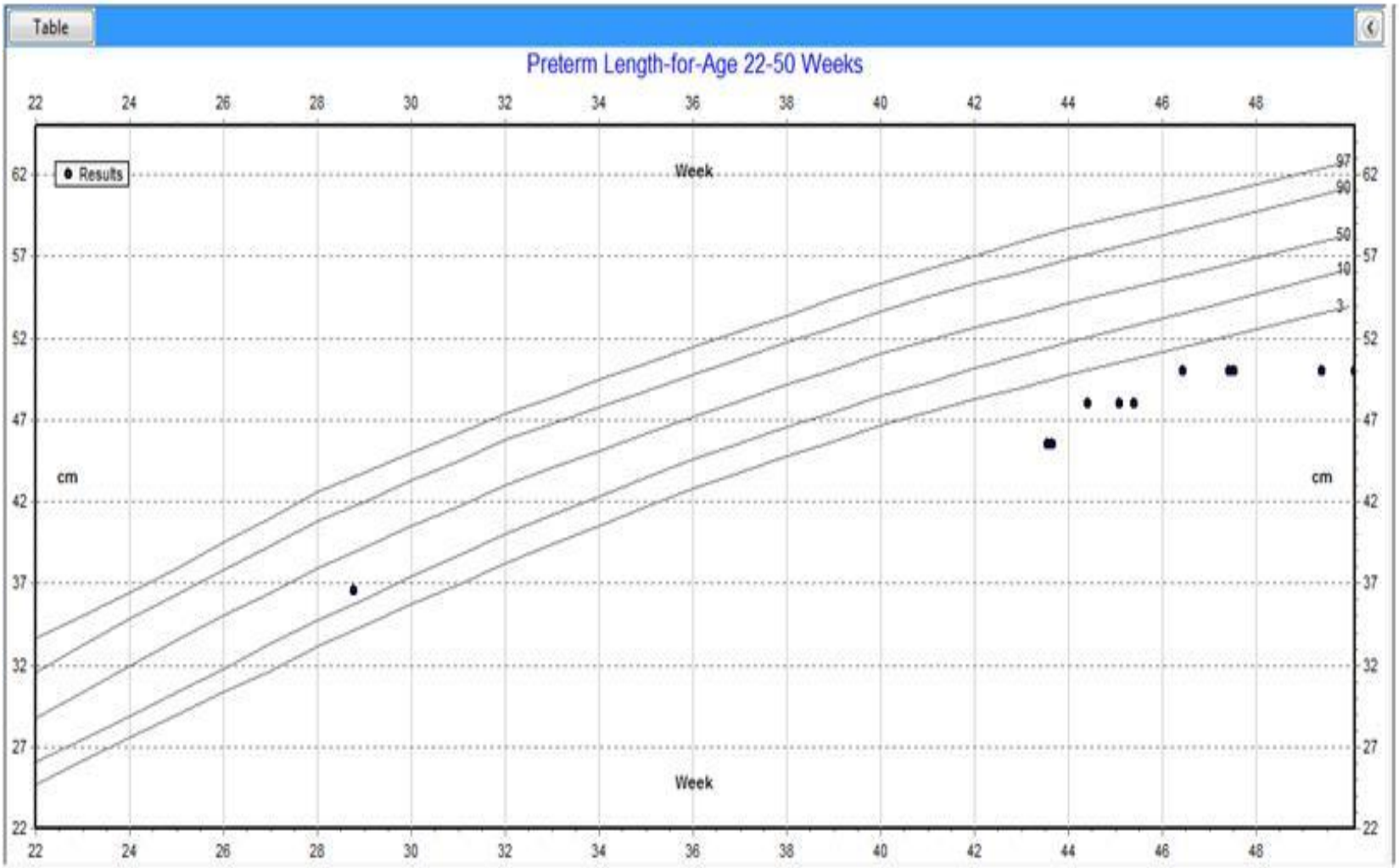

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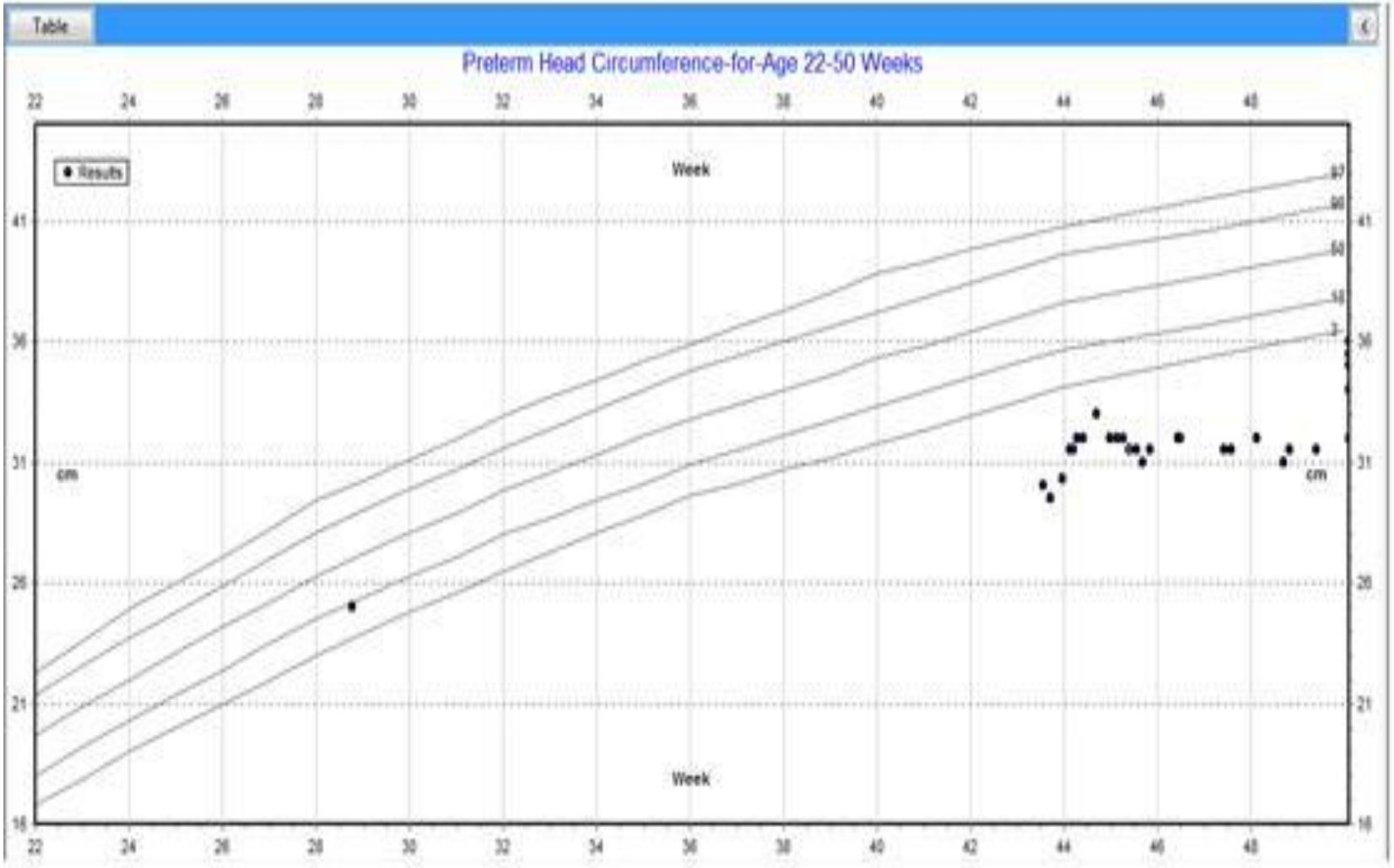

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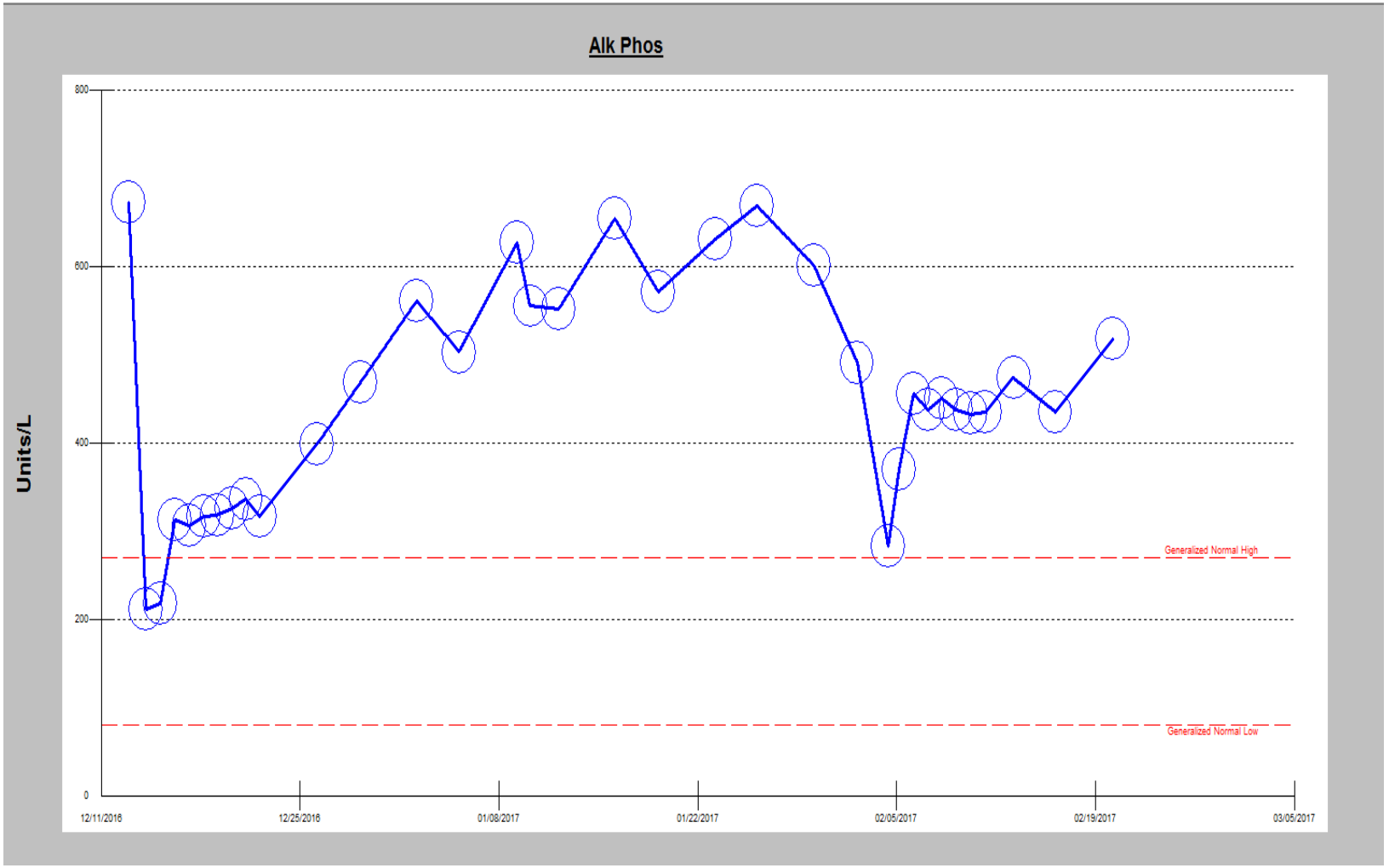

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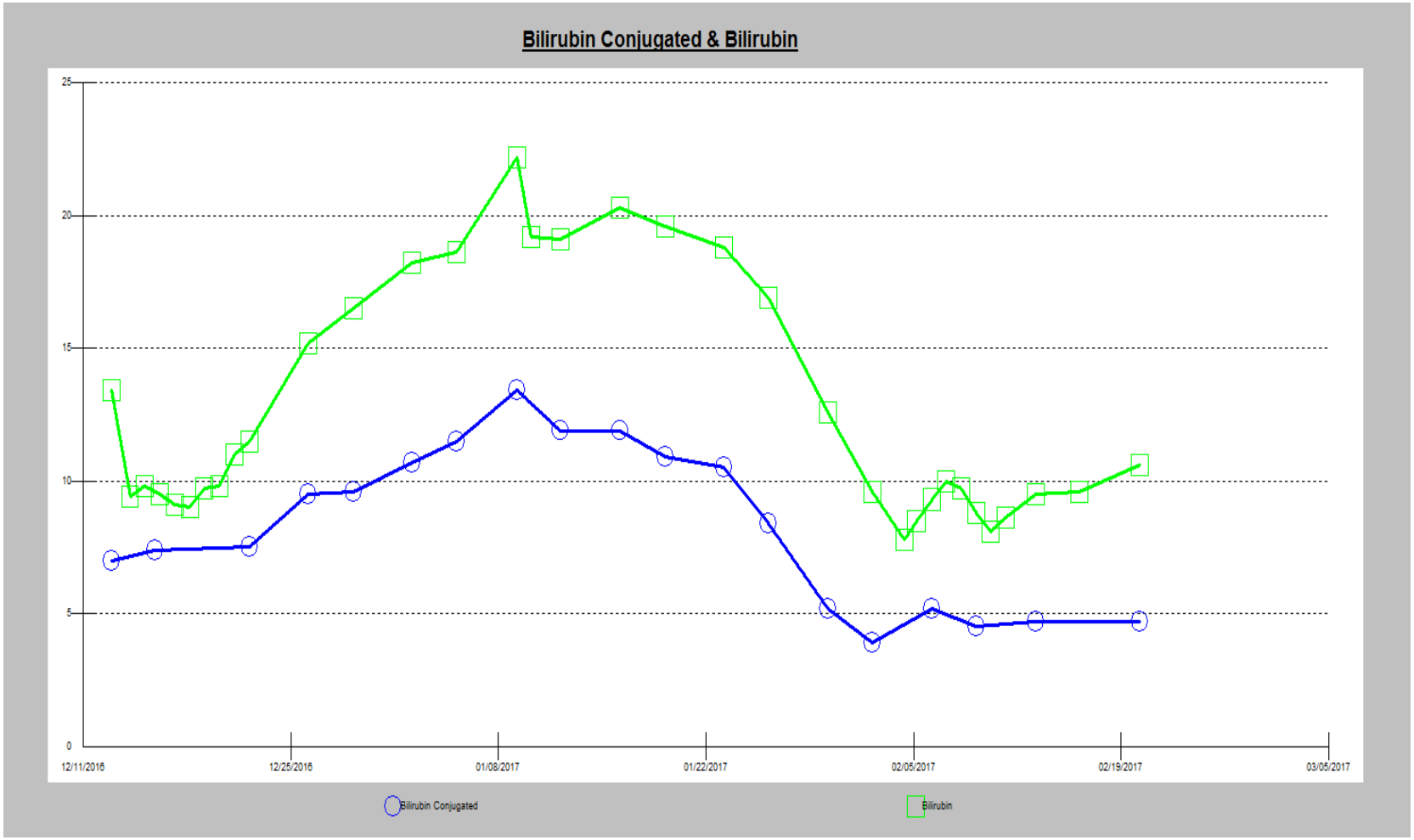

Troubleshooting SMOF & Discussion

- If Vit E levels elevated, look to decrease MVI dosing vs SMOF
  - Can alternate IL and SMOF use
- Drug compatibilities thought to be similar to IL or Omegaven but awaiting pharmacy input
- Current FDA approval in adults only
  - FDA approval for pediatrics anticipated by the end of the year (or w/in next 2years?)
- Reimbursement/Cost:

  SMOF vs IL
  - 250mL = $180 vs $250
  - 100mL = $170 vs $120

References

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Questions?