Published in final edited form as:
Semin Pediatr Surg. 2010 February ; 19(1): 27. doi:10.1053/j.sempedsurg.2009.11.004.

Innovative Parenteral and Enteral Nutrition Therapy for Intestinal Failure

Hau D. Le, MD[1], **Erica M. Fallon, MD**[1], **Vincent E. de Meijer, MD, MSc**[1], **Alpin D. Malkan, MD**[1], **Mark Puder, MD, PhD**[1], and **Kathleen M. Gura, PharmD**[2]

[1]Department of Surgery and the Vascular Biology Program, Children's Hospital Boston, Boston, MA 02115

[2]Department of Pharmacy, Children's Hospital Boston, Boston, MA 02115

Abstract

Children with intestinal failure suffer from insufficient intestinal length or function, making them dependent on parenteral nutrition (PN) for growth and survival. PN and its components are associated with many complications ranging from simple electrolyte abnormalities to life-threatening PN-associated liver disease, which is also called intestinal failure-associated liver disease (ILALD). From a nutrition perspective, the ultimate goal is to provide adequate caloric requirements and make the transition from PN to full enteral Nutrition (EN) successful. Upon review of the literature, we have summarized the most effective and innovative PN and EN therapies for this patient population. Antibiotic-coated catheters and antibiotic or ethanol locks can be implemented, as they appear effective in reducing catheter-related infection and thus further reduce the risk of IFALD. Lipid emulsions should be given judiciously. The use of an omega-3 fatty acid-based formulation should be considered in patients who develop IFALD. Trophic feeding is important for intestinal adaptation, and EN should be initiated early to help wean patients from PN. Long term management of children with IF continues to be an emerging field. We have entered uncharted territory as more children survive complications of IF, including IFALD. Careful monitoring and individualized management to ensure maintenance of growth with avoidance of complications are the keys to successful patient outcomes.

Introduction

Intestinal failure (IF) is a condition of malabsorption that is due to reduction of functional intestinal mass necessary for adequate digestion and absorption for nutrient, fluid and growth requirements. It is often the result of dysmotility, surgical resection, a congenital defect or disease-associated loss of absorption (1). Insufficient enteral absorption combined with the metabolic demands of a growing child make most patients with IF dependent on parenteral nutrition (PN). Management of IF primarily focuses on intestinal rehabilitation using a multidisciplinary approach including nutritional, pharmacologic and surgical interventions to achieve the goal of full enteral nutrition (EN) (2). The challenge becomes providing enteral nutrition to take advantage of the remaining functional intestine, and simultaneously

*Corresponding author: Kathleen M. Gura, PharmD, 300 Longwood Avenue, Boston, MA 02115, USA, Ph: 617 -355-2336, Fax: 617-730-0601, kathleen.gura@childrens.harvard.edu.

monitoring for adequate growth and intestinal adaptation. Extensive research has been done to make PN and EN therapies more effective and safer. Advances in the understanding of micro- and macronutrients, prevention of toxicity have been made. However, complications associated with these treatments are challenging. The purpose of this review is to discuss the newest methods of optimizing pediatric parenteral and enteral nutrition in patients with IF while ensuring growth, promoting intestinal adaptation, and reducing associated complications.

Parenteral Nutrition

PN is a life-saving therapy for IF patients. Long-term use of PN, however, is associated with many complications, including central venous catheter infection and sepsis, vascular thrombosis, metabolic abnormalities, and organ dysfunction. The most serious complication, however, is PN-associated liver disease, also called intestinal associated liver disease (IFALD), with a prevalence of 25–33% in neonates (3,4).The etiology of IFALD remains to be elucidated, although is likely multi-factorial. Established risk factors of IFALD include prematurity, low birth weight, duration of PN and number of septic episodes (3,5,6). IFALD is characterized by hepatic dysfunction ranging from mild elevations of hepatic transaminases to subsequent hepatic failure (7). These abnormalities are likely to progress while the child remains on PN. The most effective treatment for IFALD is increasing enteral caloric intake while reducing PN, but this process is often impossible when intestinal function is poor (8). What follows is a review of some of the innovative and potentially effective PN and EN approaches to delay and possibly prevent complications associated with PN-administration.

1. PN Cycling

By definition, cycling of PN involves the provision of total daily PN volume in less than 24 hours. Advantages include disconnection from the intravenous line, improvement in visceral protein stores, and reduction of the incidence of hyperinsulinemia (8,9). Cycling PN is recommended for patients who are expected to be on prolonged courses of PN (i.e. >30 days) and whose cardiac, renal and endocrine function can tolerate shifts in fluid and dextrose infusion rates. Patients should be metabolically stable on their goal solutions for several days before attempting to cycle PN. In an attempt to avoid hyper- or hypoglycemia, the infusion rate is gradually increased over 1–2 hours at the beginning of the infusion and gradually decreased over the final hour of the infusion. In neonates, cycling should be limited to 6 hrs off PN due to diminished glycemic reserves (10,11). In a recent retrospective study evaluating cycling PN in infants with gastroschisis, the cycling PN group was almost 3 times less likely to develop IFALD compared to the continuous group (12). The difference, however, was not statistically significant as the sample size was small.

2. Amino Acid Consideration: Taurine

In 1984, taurine deficiency was reported in three children with severe IFALD (13). Subsequent animal studies have demonstrated that taurine, a sulfonic amino acid and end product of the transsulfuration pathway, increases tauroconjugated bile acids (14,15). and enhances bile flow (16). The development of tauroconjugated bile acids has been shown to be important in the prevention of excessive accumulation of glycine-conjugated secondary bile acids (17). Since taurine plays a role in many functions in the liver such as osmoregulation, membrane stability and anti-oxidation, its deficiency can cause liver damage. This is of concern since neonates receiving long-term PN can develop taurine deficiency (18,19). An early study showed no effect of taurine supplementation in the first 10 days of life on the development of IFALD (20). A more recent study, however, demonstrated that taurine supplementation lowered direct bilirubin level in premature infants and those with necrotizing enterocolitis (21).

3. Prevention of Catheter-Related Infection

Sepsis is a major risk factor in the development of IFALD of patients with IF (22). Patients with recurrent episodes of infection have a 30% increased chance of developing IFALD (23). The source of infection could be catheter-related, bacterial translocation from intestinal stasis, permeability, or bacterial overgrowth. Prevention of catheter-related infection is crucial in preventing and reducing the severity of IFALD. Several methods of prevention of catheter-related infection have been shown to be effective in children with IF.

Ethanol vs. Antibiotic Lock—In the PN dependent child with IF, maintaining the integrity of the central venous catheter is essential. Incidence of catheter-related infection approaches 60% over the life span of the catheter (24). The increased morbidity and mortality associated with catheter-related infection has led to the use of various antibiotic and ethanol lock techniques (25–27).

Anti-infective locks including vancomycin, ciprofloxacin, gentamicin, and amphotericin B have been studied for the prevention of catheter-related infections, with efficacy ranging between 30–100% (28). A prospective study using combination lock therapy with vancomycin and gentamicin demonstrated a significant decrease in bacteremia and clinical sepsis rate (29). Recently, attention has concentrated on ethanol locks and their effectiveness in decreasing the rate of catheter-related infections. An advantage of ethanol as compared to antibiotic locks includes an absence of resistance. Ethanol denatures proteins and is rapidly bactericidal and fungicidal (30). A prospective pilot study in 2008 documented safety and potential efficacy of ethanol locks in treating central venous catheter-associated infections (31). A randomized controlled trial is currently underway to evaluate the effect of ethanol locks on the prevention of catheter associated bacteremia and subsequent sepsis in children with IF and a history of multiple catheter-related bloodstream infections (32).

Antibiotic-Coated Catheter—Antibiotic-coated catheters have also been studied in the prevention of catheter-related infections. Minocycline-rifampin coated central venous catheters significantly delay the onset of catheter-related infection without an increased incidence of thrombosis or change in organism type (33), and reduce the incidence of both femoral and subclavian catheter-related infections (34). These impregnated catheters have not received generalized acceptance because they are more expensive, and the Centers for Disease Control and Prevention's recommendation is for short-term use only (34).

4. Impact of PN Compounding Methods and Materials

In addition to the amino acid provision, other factors have received attention regarding the prevention of PN-related complications, including protection of amino acids from light, avoidance of DEHP materials, and minimizing aluminum exposure. Premature infants and children with IF have immature or diminished antioxidant defenses which renders them more susceptible to oxidant stress. When PN is exposed to light, lipid peroxides and hydrogen peroxide are generated (35). There is an approximate 50 percent reduction in amount of hydrogen peroxide infused with PN when the entire solution and delivery system is protected from ambient light (i.e., amino acid dextrose bag, lipid syringe, and tubing) (36). However, results from a study on a large cohort of premature infants demonstrated no beneficial effect of partial light protection of PN on clinically relevant outcomes (35). This study did not provide complete protection against ambient light; therefore, further investigation is warranted.

Several avoidable excipients have been linked to IFALD. Di(2-ethylhexyl)phthalate (DEHP) is an industrial additive plasticizer found in polyvinylchloride (PVC) (37). PN infusion systems have been shown to be the most important source of DEHP load (38). Although DEHP has a rapid turnover (half-life less than 24 hours), this phthalate and its metabolites are consistently

detected in human body fluids such as plasma, urine, amniotic fluid or breast milk (39). In preterm neonates and infants who receive intensive care, DEHP has shown to increase oxidative stress and toxicity (43). PN infusion sets and containers containing DEHP have been implicated increasing this risk. A recent retrospective data from von Rettberg et al showed that changing to PVC-free infusion system decreased the overall incidence in cholestasis (43). In this retrospective study, the incidence of cholestasis dropped from 50% to 13%. The use of DEHP containing infusion sets and bags for the administration of PN increased the risk for cholestasis by a factor of 5.6. Moreover, the use of polyvinylchloride infusion sets correlated strongly with the development of IFALD.

Neonates and premature infants receiving long-term PN therapy are at high risk for developing aluminum toxicity. This metal is found in raw materials, incorporated into products during the manufacturing process, and leached from glass containers during autoclaving for sterilization (40). Accumulation of aluminum with subsequent toxicity can commonly occur in these neonates and infants due to immature kidneys and bones that have yet to mineralize (41). Specific findings of this toxicity include encephalopathy, impaired neurologic development, bone pain with development of osteopenia or osteomalacia, microcytic anemia, and cholestasis (41). In July 2004, the U.S. Food and Drug Administration (FDA) issued a mandate that required manufacturers to include the aluminum content of additives commonly used in the compounding of PN solutions (42). The amount of aluminum provided by PN should be less than 5mCg/kg/day, the threshold deemed “safe” by the FDA. Since that time, it has been difficult to easily incorporate these guidelines into clinical practice due to limitations in current product formulations. Low aluminum alternatives, such as organic phosphate salts, are not currently available in the United States, making it difficult to adhere to the FDA mandate.

Parenteral Lipid Emulsion

PN is typically administered in conjunction with an intravenous lipid emulsion (ILE) to provide a caloric dense alternative to dextrose as a source of non-protein calories, and to supply essential omega-3 and omega-6 fatty acids for biologic membranes and the maintenance of immune function (43). Currently, the only FDA approved lipid emulsions in the United States are comprised of safflower oil, soybean oil (Intralipid®, Baxter Healthcare, Fresenius Kabi), or a combination of the two (Liposyn II®, Hospira), which are all rich in omega-6 fatty acids. Other ILEs that are approved for use in Europe include SMOFLipid® (Fresenius Kabi) and Omegaven® (Fresenius Kabi). These formulations utilize the potential anti-inflammatory benefit of omega-3 fatty acids. The composition of the different lipid emulsions can be seen in Table 1.

1. Types of Lipid

The first safe and effective ILE became available in Europe in 1961 with the introduction of a soybean oil-based ILE (44). Until today, soybean oil, rich in omega-6 fatty acids, continues to be the main lipid source in the various ILE on the market. Since the 1970s, however, experimental reports suggested that soybean oil-based ILE negatively influenced immunologic cell functions (45). More recently, clinical and experimental evidence suggested a role for soybean oil-based ILE in the onset of IFALD. As more evidence accumulated against soybean oil-based lipid emulsion, the development of alternative lipid emulsions, including those containing fish oil, began (46).

The difference among the ILEs is primarily the composition of the long-chain polyunsaturated fatty acids. An ILE that is made from fish oil contains high amounts of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) which have potential for an anti-inflammatory benefit. This effect is in part due to their interference with the arachidonic acid (AA) pathway and production of anti-inflammatory eicosanoids (47). These anti-inflammatory cytokines have

been shown to be hepatoprotective (48,49). On the other hand, pro-inflammatory cytokines synthesized from the omega-6 family member AA may promote liver inflammation (50). Altogether, these reports led to the creation of new parenteral ILEs that vary in their fatty acid content (omega-3/omega-6), their sources of origin (plant, vegetable, or marine) and the hydrocarbon length: long chain triglycerides (LCT) versus medium chain triglycerides (MCT).

2. Clinical experience with different ILEs

MCT/LCT-based ILEs—With the objective of reducing the high omega-6 content present in soybean oil, new ILEs based on soybean oil with MCT or olive oil have been developed. Compared to LCT, oil derived from soybean and/or safflower oils, MCT oils are more easily metabolized than the conventional soybean oil-LCT, thereby representing a rapid source of lipid energy (51). In addition, they promote better plasma clearance and do not accumulate in the liver.

The use of MCT/LCT-based ILE in pediatric surgical patients has been shown to improve immune response and better spare protein than traditional LCT-based ILE.(52). However, data on long-term PN use is still lacking.

Olive oil-based ILE—Olive oils, rich in the omega-9 monounsaturated fatty acid, oleic acid, and the antioxidant alpha-tocopherol, have also emerged as an alternative oil source. These oils contain sufficient omega-6 essential fatty acids, may preserve immune function (53)., and protect against lipid peroxidation and oxidative stress (54).

A randomized controlled trial compared the short-term effect of an olive oil-based ILE (ClinOleic®, Baxter/Clintec Parenteral S.A., Cedex, France) with the traditional soybean oil-based ILE in critically ill neonates and showed no adverse effects (55). However, long-term data on the effect of ClinOleic® on IFALD are not available.

Fish oil-based ILEs—More recently, fish oil has been introduced either as a supplement to soybean-based ILE, as an ingredient in a combination emulsion (soybean, MCT, olive, and fish oil), or as monotherapy (56). Like olive oil-based ILE, fish oil-based ILE is enriched with α-tocopherol to efficiently counteract the potential susceptibility to lipid peroxidation. Due to its high concentration of the anti-inflammatory omega-3 fatty acids EPA and DHA, fish oil may interfere with the pro-inflammatory omega-6 pathway (56). In addition, increased clearance of triglycerides and a reduction in lipogenesis may modulate hepatic injury in IFALD (56).

Fish oil-based ILE as monotherapy has been recently used patients with IF, with promising results (57). The most recent data of an open-label trial of Omegaven® (Fresenius Kabi Deutschland GmbH, Bad Homburg v.d.H., Germany) at the authors' institution showed subjects receiving fish oil-based ILE experienced mean time to reversal of cholestasis in 81 days versus 492 days ($P<0.0001$) in a historical control group who received soybean oil-based ILE (Figure 1). Patients who received the fish oil-based ILE also experienced far greater rate of reversal of cholestasis compared to the soybean controls (89% vs. 16%, respectively, $P<0.0001$). The provision of fish oil-based ILE was not associated with hypertriglyceridemia, or essential fatty acid deficiency (59). Moreover, recent evidence has shown that the frequency of hypertriglyceridemic events were more common among controls (58,60). Similar results have been reported by other centers (61–63). Despite the success, fish oil-based ILE used as monotherapy is questioned by critics for its lack of the traditionally defined essential fatty acids (i.e. α-linolenic acid and linoleic acid). However, recent evidence in a murine model suggests AA and DHA provision alone is sufficient to prevent biochemical and physiologic evidence of EFAD (64). An ongoing randomized, controlled, double-blind clinical trial comparing the

soybean-based ILE Intralipid® to the fish oil-based ILE Omegaven® will be imperative in the current debate about the efficacy and safety of parenteral fish oil-based ILEs (65).

Another lipid emulsion, SMOFLipid®, which contains 30% soybean oil, 30% MCT oil, 25% olive oil and 15% fish oil, was created to take advantage of the anti-inflammatory effect of fish-oil and reap benefits of olive oil and MCT as described above, while still providing a sufficient amount of linoleic acid. To date, SMOFLipid® has shown to be well tolerated in surgical patients in short-term treatment (66,67). Long-term data of SMOFLipid® are not available. However, a randomized controlled trial is underway comparing SMOFLipid® to the soybean-based ILE Intralipid® to investigate the prevention of progression of IFALD in infants with IF and early liver dysfunction (68).

3. Vitamin E

Oxidative stress has been proposed as the second “hit” leading to the cell injury and death pathway of hepatocytes with abnormal accumulation of fat (69). Therefore, antioxidant therapy has been suggested as a therapeutic option in treating IFALD. Results in animal models demonstrated vitamin E was able to protect hepatic injury (70). Although no benefit has been demonstrated in humans, high concentration of vitamin E in Omegaven® (Table 1) is probably one of the factors that contributed to the success of Omegaven® in preventing and reversing IFALD (71,72).

4. Lipid dose

Feeding beyond the liver’s ability to utilize carbohydrate and fat can cause accumulation of by-products in the liver and thereby result in IFALD. Although standard guidelines recommend administering the ILE at a dose <2.5 $g.kg^{-1}.day^{-1}$, a dose >1 $g.kg^{-1}.day^{-1}$ has been associated with the development of IFALD (73,74). Judicious use of ILEs, at a dose ≤1 $g.kg^{-1}.day^{-1}$, has been shown effective in preventing IFALD (74,75). In neonates, however, decreasing or withholding lipids for extended periods may be detrimental due to lack of fat reserves and the high risk of growth retardation. Unlike older infants, the enzymatic pathways of the premature infant are not adequately developed and cannot efficiently convert ALA and LA to their active moieties DHA and AA, thus making supplementation with these downstream active fatty acids even more crucial (76,77).

Enteral Nutrition

Although many patients with IF depend on PN for survival and growth, enteral nutrition (EN) should be started as soon as the gut is functional. Enteral feeding is preferred because it is more economical, easier, and safer than PN. Enteral feeding is also more physiological and can protect against stress-induced gastropathy and gastrointestinal hemorrhage. In patients with IF, successful implementation of EN and PN can greatly enhance the intestinal rehabilitation process and the patient’s quality of life.

1. Trophic feeds

Enteral feeding exposes the gastrointestinal tract to nutrient and hormonal stimuli, which are not present when the patient is not fed enterally (78). Luminal substrates and intraluminal nutrients are essential for development of intestinal adaptation (79). Even with minimal enteral nutrition (e.g. trophic feeds), human intestinal epithelial cell growth, brush-border enzyme activity and motility are enhanced (80). Initiation of feeding is therefore recommended early in the postoperative period. In patients where even trophic feedings may not be tolerated, non-nutritive sucking may be encouraged as it facilitates the development of sucking behavior and may improve tolerance to enteral feedings and assist in the transition from tube to bottle feedings (81).

2. Aggressive vs. gradual transition to enteral feedings

Feedings are typically begun at a low rate and gradually advanced as tolerated. Feedings are usually slowly advanced until goal volumes are tolerated, and held if stool output exceeds 30–40 cc $.kg^{-1}.day^{-1}$. Retrospective reviews have demonstrated the percentage of calories fed within 6 weeks postoperative and 3 months adjusted age in neonates following intestinal resection correlated with decreased duration of PN, and subsequently decreased risk of bacteremia and liver dysfunction (3,82). Another review demonstrated that initiation of EN and discontinuation of PN resulted in normalization of marked hyperbilirubinemia and improvement in liver function (83).

3. Pancreatic enzymes

In IF, digestion of fat is not well tolerated as a result of bile salt malabsorption, thereby resulting in decreased micelle formation and fat digestion. Gastric hypersecretion can additionally occur after small bowel resection and may reduce nutrient absorption by inactivating pancreatic enzymes (78). To decrease fat malabsorption, pancreatic enzymes such as Creon® (Solvay, Marietta, Georgia) or Pancrease® (McNeil Pharmaceutical, Spring House, PA) can be initiated. Goals of replacement therapy include reduction of abdominal distension and pain, improved quality and decreased frequency of stool, and objective assessment of weight gain and growth. Standard dosing does not exist although the proposed doses are lower than what it is typically used for the treatment of pancreatic insufficiency (84).

4. Role of prokinetic agents

Nausea, vomiting, and abdominal distension are commonly observed signs and symptoms which can indicate intolerance to EN. Prokinetic agents such as metoclopramide, erythromycin, and cisapride have been shown to promote gastric motility(85),although their side effect profiles mandate judicious use. Metoclopramide, a central and peripheral dopamine type II receptor antagonist, may cause dystonic reactions and extrapyramidal symptoms (2). Erythromycin, a motilin receptor agonist, is associated with drug interactions, delayed gastric emptying at high doses, and cardiac complications when administered intravenously (2). Cisapride, a $5\text{-}HT_3$ agonist, is associated with cardiac arrhythmias and sudden death. Despite the potential adverse effects, these medications are commonly and effectively used in pediatric IF patients.

Conclusion

Pediatric IF is a complex and unique problem. A child with IF has distinctive metabolic needs that must be met by balancing both parenteral and enteral routes, while maintaining adequate growth and avoiding complications associated with PN. Given the uniqueness of IF, special attention is required during each phase of growth and adaptation for each patient. Efforts must be made to deliver a balanced PN solution, avoid catheter related infections, lower the dose of ILE, possibly the use omega-3-based ILE rather than mainly omega-6 based ILE, and advance to EN as soon as the patient can tolerate. Additional research is needed to refine the enteral formulas and parenteral macro- and micronutrients for this emerging patient population.

Acknowledgments

HDL was the recipient of the Joshua Ryan Rappaport Fellowship and supported by the Children's Hospital Surgical Foundation (Boston, MA). EMF, VEM and ADM were supported by the Children's Hospital Surgical Foundation (Boston, MA). MP was supported by the National Institutes of Health (grant DK069621-05) and the Children's Hospital Surgical Foundation (Boston, MA).

The authors would like to thank Dr. Christopher Duggan for his input on enteral nutrition for IF patients and review of the manuscript.

References

1. O'Keefe S, Buchman AL, Fishbein TM, et al. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol 2006;4:6–10. [PubMed: 16431298]
2. Ching YA, Gura K, Modi B, et al. Pediatric intestinal failure: nutrition, pharmacologic, and surgical approaches. ASPEN 2007;22:653–663.
3. Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001;139:27–33. [PubMed: 11445790]
4. Kubota A, Yonekura T, Hoki M, et al. Total parenteral nutrition-associated intrahepatic cholestasis in infants: 25 years' experience. J Pediatr Surg 2000;35:1049–1051. [PubMed: 10917294]
5. Kelly DA. Liver complications of pediatric parenteral nutrition--epidemiology. Nutrition 1998;14:153–157. [PubMed: 9437702]
6. Christensen RD, Henry E, Wiedmeier SE, et al. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. J Perinatol 2007;27:284–290. [PubMed: 17344923]
7. Freund HR. Abnormalities of liver function and hepatic damage associated with total parenteral nutrition. Nutrition 1991;7:1–5. discussion 5–6. [PubMed: 1802177]
8. Chwals WJ. The metabolic response to surgery in neonates. Curr Opin Pediatr 1994;6:330–340.
9. Schiller WR. Burn management in children. Pediatr Ann 1996;25:434–438.
10. Collier S, Crouch J, Hendricks K, et al. Use of cyclic parenteral nutrition in infants less than 6 months of age. Nutr Clin Pract 1994;9:65–68. [PubMed: 8078440]
11. Takehara H, Hino M, Kameoka K, et al. A new method of total parenteral nutrition for surgical neonates: it is possible that cyclic TPN prevents intrahepatic cholestasis. Tokushima J Exp Med 1990;37:97–102. [PubMed: 2128784]
12. Jensen AR, Goldin AB, Koopmeiners JS, et al. The association of cyclic nutrition and decreased incidence of cholestatic liver disease in patients with gastroschisis. J Ped Surg 2009;44:183–189.
13. Cooper A, Betts JM, Pereira GR, et al. Taurine deficiency in the severe hepatic dysfunction complicating total parenteral nutrition. J Ped Surg 1984;19:462–466.
14. Sweeny DJ, Barnes S, Diasio RB. Bile acid conjugation pattern in the isolated perfused rat liver during infusion of an amino acid formulation. JPEN J Parenter Enteral Nutr 1991;15:303–306. [PubMed: 1907679]
15. Yousef IM, Tuchweber B, Vonk RJ, et al. Lithocholate cholestasis-sulfated glycolithocholate-induced intrahepatic cholestasis in rats. Gastroenterol 1981;80:233–241.
16. Guertin F, Roy CC, Lepage G, et al. Effect of taurine on total parenteral nutrition-associated cholestasis. JPEN J Parenter Enteral Nutr 1991;15:247–251. [PubMed: 1907674]
17. Zaman N, Tam YK, Jewell LD, et al. Effects of taurine supplementation in parenteral nutrition-associated hepatosteatosis and lidocaine metabolism. Drug Metabol Disp 1996;24:534–541.
18. Vinton NE, Laidlaw SA, Ament ME, et al. Taurine concentrations in plasma, blood cells, and urine of children under-going long-term parenteral nutrition. Pediatrics 1987;21:399–403.
19. Dahlstrom KA, Ament ME, Laidlaw SA, et al. Plasma amino acid concentrations in children receiving long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 1988;7:748–754. [PubMed: 3141604]
20. Cooke RJ, Whitington PF, Kelts D. Effect of taurine supplementation on hepatic function during short-term parenteral nutrition in the premature infant. J Pediatr Gastroenterol Nutr 1984;3:234–238. [PubMed: 6423796]
21. Spencer AU, Yu S, Tracy TF, et al. Parenteral nutrition-associated cholestasis in neonates: multivariate analysis of the potential protective effect of taurine. JPEN J Parenter Enteral Nutr 2005;29:337–343. discussion 343-334. [PubMed: 16107596]
22. Sondheimer JM, Asturias E, Cadnapaphornchai M. Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 1998;27:131–137. [PubMed: 9702641]
23. Beath SV, Davies P, Papadopoulou A, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg 1996;31:604–606. [PubMed: 8801324]

24. Fratino G, Molinari AC, Mazzola C, et al. Prospective study of indwelling central venous catheter-related complications in children with Broviac or clampless valved catheters. Hematol Oncol 2002;24:657–661.
25. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249–1272. [PubMed: 11303260]
26. Messing B, Peitra-Cohen S, Debure A, et al. Antibiotic-lock technique:a new approach to optimal therapy for catheter related sepsis in home-parenteral nutrition patients. JPEN 1988;12:185–189.
27. Dannenberg C, Bierbach U, Rothe A, et al. Ethanol-lock technique in the treatment of blood stream infections in pediatric patients oncology patients with Broviac catheter. J Pediatr Hem Onc 2003;25:616–621.
28. Segarra-Newnham M, Martin-Cooper EM. Antibiotic lock technique: a review of the literature. Ann Pharmacother 2005;39:311–318. [PubMed: 15623848]
29. Al-Hwiesh AK. Tunneled catheter-antibiotic lock therapy for prevention of dialysis catheter-related infections: a single center experience. Saudi J Kidney Dis Transplant 2008;19:593–602.
30. Metcalf SCL, Chambers ST, Pithie AD. Use of ethanol locks to prevent recurrent central line sepsis. J Infect 2004;49:20–22. [PubMed: 15194244]
31. Broom J, Woods M, Allworth A, et al. Ethanol lock therapy to treat tunneled central venous catheter-associated blood stream infections: results from a prospective trial. Scand J Infect Dis 2008;40:399–406. [PubMed: 18418801]
32. NIH. In. p. National Institute of Health; University of Pittsburgh. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2009 [cited 2009 Sept 2010]. Pediatric Ethanol Lock Therapy. Available from: http://www.clinicaltrials.gov/ct2002/show/NCT00948441 NLM Identifier: NCT00948441
33. Chelliah A, Heydon KH, Zaoutis TE, et al. Observational trial of antibiotic-coated central venous catheters in critically ill pediatric patients. Pediatr Infect Dis J 2007;26:816–820. [PubMed: 17721377]
34. Lorente L, Lecuona M, Ramos MJ, et al. The use of rifampicin-miconazole-impregnated catheters reduces the incidence of femoral and jugular catheter-related bacteremia. Clin Infect Dis 2009;47:1171–1175. [PubMed: 18808356]
35. Sherlock R, Chessex P. Shielding parenteral nutrition from light: does the available evidence support a randomized, controlled trial? Pediatrics 2009;123:1529–1533. [PubMed: 19482764]
36. Lavoie JC, Belanger S, Spalinger M, et al. Admixture of a multivitamin preparation to parenteral nutrition: the major contributor to in vitro generation of peroxides. Pediatrics 1997;99
37. Sjoberg P, Bondesson U, Sedin G, et al. Dispositions of di- and mono-(2-ethylhexyl) phthalate in newborn infants subjected to exchange transfusions. Eur J Clin Invest 1985;15:430–436. [PubMed: 3938415]
38. Von Rettberg H, Hannman T, Subotic U, et al. Use of Di(2-Ethylhexyl)Phthalate containing infusion systems increases the risk for cholestasis. Pediatrics 2009;124:710–716. [PubMed: 19651587]
39. Silva MJ, Barr DB, Reidy JA, et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Health Perspect 2004;112:331–333. [PubMed: 14998749]
40. Bohrer D, Cicero do Nascimento P, Binotto R, et al. Contribution of the raw material to the aluminum contamination in parenterals. JPEN 2002;26:382–388.
41. Poole RL, Hintz SR, Mackenzie NI, et al. Aluminum exposure from pediatric parenteral nutrition: meeting the new FDA regulation. JPEN 2008;32:242.
42. Aluminum in large and small volume parenterals used in total parenteral nutrition--FDA. Proposed rule. Fed Regist 1998;63:176–185. [PubMed: 10176836]
43. Wretlind A. Development of fat emulsions. JPEN J Parenter Enteral Nutr 1981;5:230–235. [PubMed: 6788972]
44. Schuberth O, Wretlind A. Intravenous infusion of fat emulsions, phosphatides and emulsifying agents. Acta Chir Scand 1961;13:S278–S284.
45. Nordenstrom J, Jarstrand C, Wiernik A. Decreased chemotactic and random migration of leukocytes during Intralipid infusion. Am J Clin Nutr 1979;32:2416–2422. [PubMed: 116537]

46. Alwayn IP, Gura K, Nose V, et al. Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. Pediatr Res 2005;57:445–452. [PubMed: 15659701]
47. Chen MF, Lee YT, Hsu HC, et al. Effects of dietary supplementation with fish oil on prostanoid metabolism during acute coronary occlusion with or without reperfusion in diet-induced hypercholesterolemic rabbits. Int J Cardiol 1992;36:297–304. [PubMed: 1428263]
48. Yeh SL, Chang KY, Huang PC, et al. Effects of n-3 and n-6 fatty acids on plasma eicosanoids and liver antioxidant enzymes in rats receiving total parenteral nutrition. Nutrition 1997;13:32–36. [PubMed: 9058445]
49. Chen WJ, Yeh SL. Effects of fish oil in parenteral nutrition. Nutrition 2003;19:275–279. [PubMed: 12620534]
50. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest 2001;108:15–23. [PubMed: 11435451]
51. Ulrich H, Pastores SM, Katz DP, et al. Parenteral use of medium-chain triglycerides: a reappraisal. Nutrition 1996;12:231–238. [PubMed: 8862527]
52. Lai H, Chen W. Effects of medium-chain and long-chain triacylglycerols in pediatric surgical patients. Nutrition 2000;16:401–406. [PubMed: 10869893]
53. Yaqoob P, Knapper JA, Webb DH, et al. Effect of olive oil on immune function in middle-aged men. Am J Clin Nutr 1998;67:129–135. [PubMed: 9440387]
54. Sala-Vila A, Barbosa VM, Calder PC. Olive oil in parenteral nutrition. Curr Opin Clin Nutr Metab Care 2007;10:165–174. [PubMed: 17285004]
55. Webb AN, Hardy P, Peterkin M, et al. Tolerability and safety of olive oil-based lipid emulsion in critically ill neonates: a blinded randomized trial. Nutrition 2008;24:1057–1064. [PubMed: 18619813]
56. de Meijer VE, Gura KM, Le HD, et al. Fish Oil-Based Lipid Emulsions Prevent and Reverse Parenteral Nutrition-Associated Liver Disease: The Boston Experience. JPEN J Parenter Enteral Nutr 2009;33 (5):541–547. [PubMed: 19571170]
57. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678–e686. [PubMed: 18310188]
58. Puder M, Valim C, Meisel JA, et al. Parenteral Fish Oil Improves Outcomes in Patients With Parenteral Nutrition-Associated Liver Injury. Ann Surg 2009;250(3):395–402. [PubMed: 19661785]
59. de Meijer VEL HD, Meisel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition dependent patient. J Pediatr Gastroenterol Nutr. (In Press).
60. Lee SI, Valim C, Johnston P, et al. The Impact of Fish Oil-Based Lipid Emulsion on Serum Triglyceride, Bilirubin, and Albumin Levels in Children with Parenteral Nutrition-Associated Liver Disease. Pediatr Res. 2009 Aug 14; [Epub ahead of print].
61. Calhoun AW, Sullivan JE. Omegaven for the treatment of parenteral nutrition associated liver disease: a case study. J Ky Med Assoc 2009;107:55–57. [PubMed: 19263944]
62. Diamond IR, Sterescu A, Pencharz PB, et al. Changing the paradigm: Omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2009;48:209–215. [PubMed: 19179884]
63. Cheung HM, Lam HS, Tam YH, et al. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. Clin Nutr 2009;28:209–212. [PubMed: 19261360]
64. Le HD, Meisel JA, de Meijer VE, et al. The essentiality of arachidonic acid and docosahexaenoic acid. Prostaglandins Leukot Essent Fatty Acids 2009;81(2–3):165–170. [PubMed: 19540099]
65. Morgado N, Rigotti A, Valenzuela A. Comparative effect of fish oil feeding and other dietary fatty acids on plasma lipoproteins, biliary lipids, and hepatic expression of proteins involved in reverse cholesterol transport in the rat. Ann Nutr Metab 2005;49:397–406. [PubMed: 16227687]
66. Grimm H, Mertes N, Goeters C, et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. Eur J Nutr 2006;45:55–60. [PubMed: 16041475]

67. Mertes N, Grimm H, Furst P, et al. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Ann Nutr Metab 2006;50:253–259. [PubMed: 16508253]
68. Simons LA, Hickie JB, Balasubramaniam S. On the effects of dietary n-3 fatty acids (Maxepa) on plasma lipids and lipoproteins in patients with hyperlipidaemia. Atherosclerosis 1985;54:75–88. [PubMed: 3888229]
69. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998;114:842–845. [PubMed: 9547102]
70. Becvarova I, Saker KE, Swecker WS Jr, et al. Peroxidative protection of parenteral admixture by D-alpha-tocopherol. Vet Ther 2005;6:280–290. [PubMed: 16550490]
71. Soden JS, Devereaux MW, Haas JE, et al. Subcutaneous vitamin E ameliorates liver injury in an in vivo model of steatocholestasis. Hepatology 2007;46:485–495. [PubMed: 17659596]
72. Goulet O, Joly F, Corriol O, et al. Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant 2009;14:256–261. [PubMed: 19444108]
73. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39–S70. [PubMed: 15568296]
74. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525–532. [PubMed: 10744588]
75. Colomb V, Jobert-Giraud A, Lacaille F, et al. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. JPEN J Parenter Enteral Nutr 2000;24:345–350. [PubMed: 11071594]
76. Crawford MA, Costeloe K, Ghebremeskel K, et al. The inadequacy of the essential fatty acid content of present preterm feeds. Eur J Pediatr 1998;157:S23–S27. [PubMed: 9462903]
77. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? J Pediatr Gastroenterol Nutr 2009;48:S16–S24. [PubMed: 19214053]
78. Jeejeebhoy KN. Management of short bowel syndrome: avoidance of total parenteral nutrition. Gastroenterology 2006;130:S60–S66. [PubMed: 16473074]
79. Goulet O. Short bowel syndrome in pediatric patients. Nutrition 1998;14:784–787. [PubMed: 9785362]
80. Perdikis DA, Basson MD. Basal nutrition promotes human intestinal epithelial (Caco-2) proliferation, brush border enzyme activity, and motility. Crit Care Med 1997;25:159–165. [PubMed: 8989193]
81. Pimenta HP, Moreira ME, Rocha AD, et al. Effects of non-nutritive sucking and oral stimulation on breastfeeding rates for preterm, low birth weight infants: a randomized clinical trial. J Pediatr (Rio J) 2008;84:423–427. [PubMed: 18923786]
82. Sondheimer JM, Cadnapaphornchai M, Sontag M, et al. Predicting the duration of dependence on parenteral nutrition after neonatal intestinal resection. J Pediatr 1998;132:80–84. [PubMed: 9470005]
83. Javid PJ, Collier S, Richardson D, et al. The role of enteral nutrition in the reversal of parenteral nutrition-associated liver dysfunction in infants. J Pediatr Surg 2005;40:1015–1018. [PubMed: 15991188]
84. Stevens, T.; Conwell, D. Pancreatic Enzyme Replacement and Bile Acid Therapy. In: Matarese, LE.; Steiger, E.; Seidner, DL., editors. Intestinal Failure and Rehabilitation: A Clinical Guide Boca Raton. CRC Press; 2005. p. 161-172.
85. Karamanolis G, Tack J. Promotility medications--now and in the future. Dig Dis 2006;24:297–307. [PubMed: 16849857]

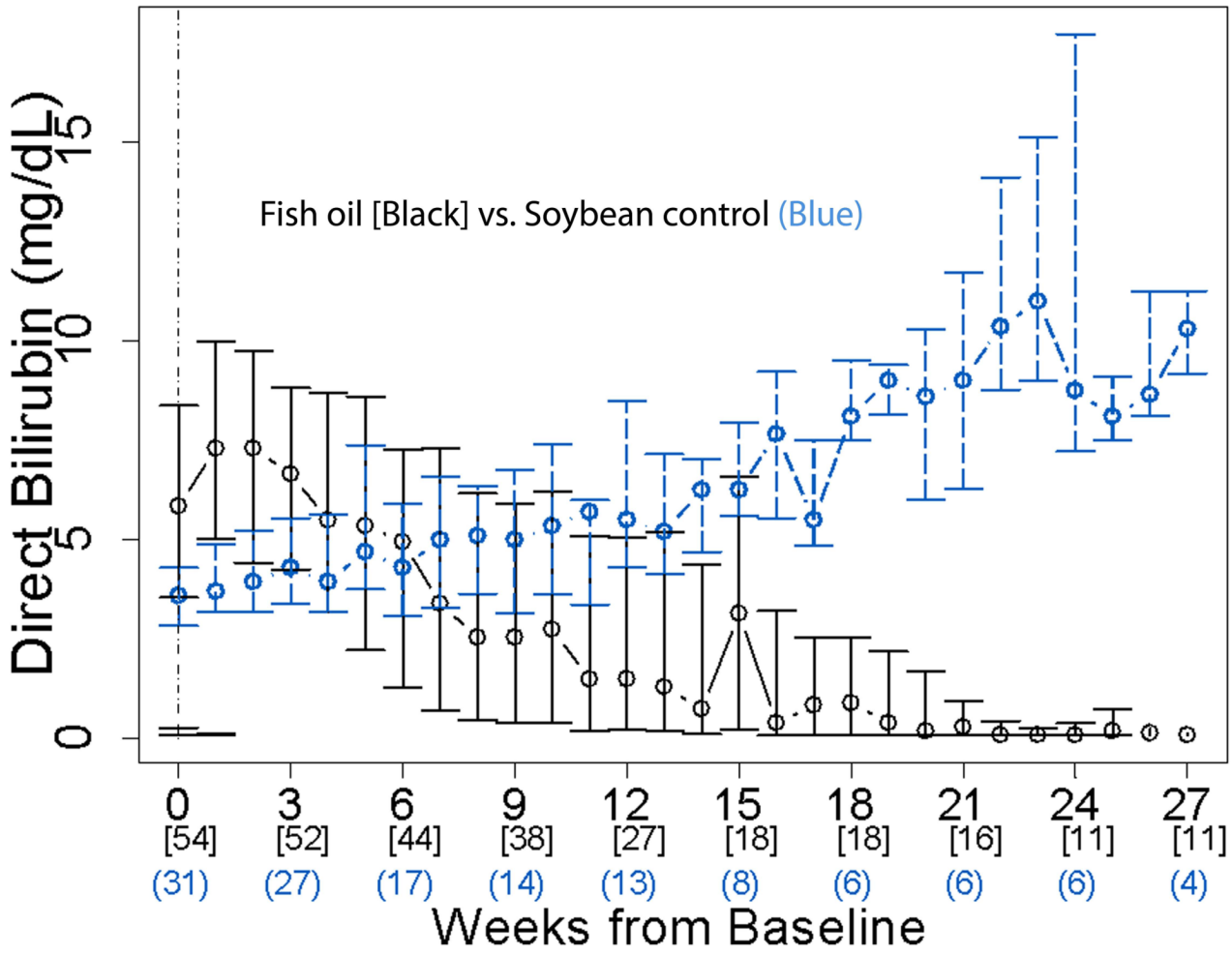

Figure 1.

Weekly median trends direct bilirubin levels from baseline until cessation of PN. Mean time to reversal of cholestasis while receiving PN in the fish oil group (N=56) was 81 days compared to 492 days (P<0.0001) in the historical control soybean group (N=31). The rate of reversal while on PN of the fish oil group was 89% compared to 16% of the soybean controls (P<0.0001). [Black] and (Blue) represent number of subjects in the fish oil group and the soybean control group, respectively, at specific time points.

Table 1

Comparison and characteristics of parenteral lipid emulsions

Product Manufacturer	**Intralipid® Baxter Healthcare/ Fresenius Kabi**	**Liposyn II® Hospira**	**ClinOleic® Baxter Healthcare/ Parenteral S.A.**	**SMOFLipid® Fresenius Kabi**	**Omegaven® Fresenius Kabi**
Oil source (g)					
Soy bean	10	5	2	3	0
Safflower	0	5	0	0	0
MCT	0	0	0	3	0
Olive oil	0	0	8	2.5	0
Fish oil	0	0	0	1.5	10
α-tocopherol (mg/L)	38	NP	32	200	150–296
Phytosterols (mg/L)	348 ± 33	383	327 ± 8	47.6	0
Fat composition (g)*					
Linoleic	5.0	6.5	0.9	2.9	0.1–0.7
α-Linolenic	0.9	0.4	0.1	0.3	< 0.2
EPA	0	0	0	0.3	1.28 –2.82
DHA	0	0	0	0.05	1.44 –3.09
Oleic	2.6	1.8	2.8	2.8	0.6 – 1.3
Palmitic	1.0	0.9	0.7	0.9	0.25 – 1
Stearic	0.35	0.34	0.2	0.3	0.05 – 0.2
Arachidonic	0	0	0.03	0.05	0.1 – 0.4

MCT: medium chain triglyceride; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid

Semin Pediatr Surg. Author manuscript; available in PMC 2011 February 1.