REVIEW ARTICLE

Novel Lipid-Based Approaches to Pediatric Intestinal Failure–Associated Liver Disease

Ivan R. Diamond, MD, PhD; Paul B. Pencharz, MBChB, PhD; Brian M. Feldman, MD, MSc; Simon C. Ling, MBChB; Aideen M. Moore, MD; Paul W. Wales, MD, MSc

Historically, intestinal failure–associated liver disease (IFALD) has been the greatest contributor to the morbidity experienced by children with intestinal failure. Although the cause of IFALD is multifactorial, recently much attention has been devoted to the critical role that intravenous lipid emulsions play in the development of IFALD. This attention has prompted an interest in alternate approaches to the provision of intravenous lipid in children with IFALD. The 2 approaches that have been advanced are that of lipid minimization and alternate intravenous lipid emulsions, including those containing ω-3 fatty acids. This article examines the rationale and current evidence for these approaches in children with intestinal failure. Our overall finding is that although these alternate approaches show significant promise, they have primarily been studied in uncontrolled settings, mainly in children with advanced IFALD. As such, we believe that there remains a lack of definitive evidence for their efficacy. Furthermore, important safety parameters remain to be evaluated, including the effect of these therapies on growth and development. Therefore, there is currently insufficient evidence to support the use of these novel therapies as standard of care in children with no or early IFALD with the goal of preventing the progression of liver disease.

Arch Pediatr Adolesc Med. 2012;166(5):473-478

Intestinal failure–associated liver disease (IFALD) is one of the greatest contributors to the morbidity experienced by children with intestinal failure (IF).[1,2] Although the cause of IFALD is multifactorial, including host factors such as prematurity and sepsis and components of parenteral nutrition (PN), recently the key role that intravenous lipid emulsions (ILEs) play has been recognized.[3-5] Conventional ILEs (derived from plant-based lipids, primarily soy) are thought to contribute to the development of IFALD through a number of mechanisms, including accumulation of phospholipids,[6] excess phytosterols,[7-9] predominance of ω-6 fatty acids (ω-6FAs) that are proinflammatory,[10-12] and antioxidant imbalance related to inadequate provision of alpha tocopherol.[13,14] Given this, there is substantial interest in alternate approaches to the provision of intravenous lipid in children with IF. The 2 primary approaches that have been advanced are lipid minimization and the use of ILEs containing ω-3 fatty acids (ω-3FAs), which are derived from fish oil. Furthermore, ILEs derived from other sources could be used to replace the soy-based emulsions. This review considers the rationale and current evidence for these novel lipid-based treatment approaches in children with IFALD.

Author Affiliations: Child Health Evaluative Sciences Program (Drs Diamond, Feldman, Moore, and Wales) and Group for Improvement of Intestinal Function and Treatment (Drs Diamond, Pencharz, Ling, Moore, and Wales), The Hospital for Sick Children, and Departments of Surgery (Drs Diamond and Wales), Pediatrics (Drs Pencharz, Feldman, Ling, and Moore), and Health Policy Management and Evaluation (Drs Diamond, Feldman, Moore, and Wales), The University of Toronto, Toronto, Ontario, Canada.

LIPID MINIMIZATION

Definition and Rationale

Current recommendations for PN lipids, for infants who are dependent on PN, is 2 to 3 g/kg daily.[15,16] These recommenda-

tions are revised from the historical upper limit of 4 g/kg daily. Lipid minimization refers to provision of a soy-based ILE in doses significantly lower than these recommendations. Although no consistent definition of lipid minimization exists, we have defined this to be an intravenous lipid dose, in a child receiving full (>60% of total calories) parenteral support, of less than 1 g/kg daily. However, lipid minimization has been used with intravenous lipid intakes lower than this range. Therefore, we regard our definition to be the upper range for what constitutes lipid minimization. The rationale for lipid minimization relates to the notion that lowering parenteral lipid exposure lessens the risk of IFALD.[17]

Clinical Experience With Lipid Minimization

Evidence of the utility of lipid minimization is limited and comes only from retrospective or uncontrolled studies. Despite this, the weight of evidence suggests that cholestasis may be improved by a reduction in lipid dose. Colomb et al[18] demonstrated an association between decreases in lipid therapy and normalization of serum conjugated bilirubin (CB). Rollins et al[19] described 6 children with IFALD in whom the soy-based ILE was stopped, with subsequent resolution of cholestasis in all. However, 4 of the 6 patients received an enteral fish oil preparation, which raises the possibility of an ω-3FA effect or that resolution of cholestasis may be partly related to improved enteral tolerance.[20] Torres et al[21] described 32 patients with IFALD, of whom 31 normalized their hyperbilirubinemia with aggressive intestinal rehabilitation that included restriction of a soy-based ILE to less than 1 g/kg daily. Bianchi[22] suggested improved outcomes with a "hepato-sparing regimen" with an ILE dose less than 1.5 g/kg daily. The group from the University of Michigan described a consecutive series of 32 surgical patients receiving PN, with a CB level greater than 2.5 mg/dL or a total bilirubin level greater than 5 mg/dL (to convert bilirubin to micromoles per liter, multiply by 17.104), who were enrolled in a lipid minimization protocol.[17] Children in this series received 1 g/kg of a plant-based ILE twice a week. Fourteen patients were compared with 14 matched historical controls, with the restricted group demonstrating a mean reduction in serum CB of 0.9 mg/dL per week of therapy.

ω-3 LIPIDS

Rationale

In contrast to ω-6FAs, ω-3FAs have a number of beneficial effects that are proposed to ameliorate IFALD.[5] Fish oil–derived ILEs have been demonstrated in an animal model not to impair bile flow.[7] This finding may be related to either a reduction in phytosterols or via prostaglandin-mediated mechanisms related to the addition of ω-3FAs.[7,23,24] In addition, ω-3FAs reverse hepatic steatosis in both PN and non-PN liver disease[25,26] and decrease oxidative stress.[27] The effect on oxidative stress is augmented by the fact that many of the ILEs containing ω-3FAs also have significantly more of the antioxidant alpha tocopherol than conventional emulsions.[13,14,28] Finally, ω-3FAs have important immunomodulatory effects, resulting in fewer proinflammatory mediators.[10-12,29]

Clinical Experience With ω-3–Containing ILEs

Experience With Omegaven. Gura et al,[30] from Children's Hospital Boston, published the first report of 2 children with severe end-stage IFALD who demonstrated complete IFALD reversal after a change from soy-based Intralipid (Fresenius Kabi) to Omegaven (Fresenius Kabi), a fish oil–derived ILE. The most recent detailed publication of outcomes from this group focuses on 42 infants who received Omegaven compared with 49 individuals from a historical cohort.[31] Overall resolution of cholestasis while receiving PN in the Omegaven group was 19 compared with 2 in the control group. The risk of death or transplantation was also substantially lower in the Omegaven group (4 of 42 vs 17 of 49). However, follow-up was short, and 25% of children in the cohort received PN for fewer than 3 weeks, which limits the interpretability of these results. A recent review[32] states that more than 130 children have received Omegaven at Children's Hospital Boston with good results.

To date, 33 patients have received Omegaven at our institution, with the outcome of the first 22 analyzed in detail.[33,34] The median age at initiation of Omegaven use was 6.9 (range, 2.2-46) months. Median CB level at the start of therapy was 6.7 mg/dL (range, 3.2-13.5 mg/dL). Sixteen patients (73%) had complete and sustained resolution of hyperbilirubinemia. Four patients received a transplant before resolution of hyperbilirubinemia and 2 died (1 of IFALD and 1 of neurologic insult). In contrast to our historical liver failure mortality rate of 22% per year of infants with IF,[35] only 1 infant has died of IFALD since starting to use Omegaven in 2006.

Whereas the group in Boston only provides 1 g/kg of Omegaven as the sole parenteral lipid source, we have pursued combination therapy by mixing Omegaven (1 g/kg) with Intralipid (1 g/kg). We believe that the mixture provides for improved growth and more closely approximates normal fatty acid intake and is therefore more physiologic.

Other reports on the use of Omegaven to treat pediatric IFALD are limited to case series and single patient reports with outcomes similar to that noted in our and the Boston experience.[36-42] There has also been discussion of the possible beneficial effects of enteral fish oils.[43] Although enteral preparation use is partly related to the difficulty of obtaining Omegaven in North America, these reports are substantially confounded by the fact that children with sufficient intestinal function to tolerate enteral fish oil are likely demonstrating adequate intestinal adaptation. Therefore, IFALD resolution may be due to improved enteral tolerance.[20]

Experience With SMOFlipid. SMOFlipid (Fresenius Kabi) is a composite ILE that contains soy bean oil (30%), medium chain triglycerides (MCT) (30%), olive oil (25%), and fish oil (15%). The product has an n6:n3 ratio (ratio of ω-6FAs to ω-3FAs) of 2.5:1. The lipid composition of SMOFlipid more closely approximates the composition of breast milk than does Intralipid (**Figure**).

A number of studies have examined SMOFlipid relative to standard soy-based lipids in pediatric populations, including preterm infants, at doses of lipid up to 3.5 g/kg daily.[44-47] The results of these studies have confirmed the safety of SMOFlipid and it being a suitable replacement for a soy-based lipid. Some of the outcomes from these trials are of direct relevance to children with IFALD. Skouroliakou et al[47] demonstrated reduced oxidative stress with SMOFlipid relative to Intralipid in a randomized controlled trial of 38 preterm infants. However, serum bilirubin levels did not differ at day 14 of treatment. Tomsits et al[45] compared SMOFlipid to Intralipid in 60 premature neonates and demonstrated improvements in serum γ-glutamyl transferase with SMOFlipid. Goulet et al[44] studied 28 children receiving home PN randomized to receive SMOFlipid vs Intralipid for a month. At the end of this period, whereas the total bilirubin levels had decreased in the SMOFlipid group during the trial, total bilirubin levels had increased in the Intralipid group. Finally, there are 3 case series from Europe of SMOFlipid being used for the management of advanced IFALD, much in the same way that Omegaven has been used in North America.[48-50] Of the 23 patients treated across these 3 series, 18 demonstrated complete resolution of their conjugated hyperbilirubinemia despite receiving conventional doses of lipid.

OTHER ALTERNATE ILEs

Outside North America, there are other emulsions, including mixtures of soy and coconut (Lipofundin MCT; B. Braun) and olive and soy (Clinoleic; Baxter).[51] By reducing ω-6FA exposure, these emulsions may play a role in the management of IFALD.

There is one randomized study of Lipofundin MCT in pediatric surgical patients that is not of particular relevance to those with IF.[52] There was also a 3-day trial of Lipofundin MCT vs a soy-based emulsion that did not demonstrate differences in total bilirubin; however, the duration of the study was too short for a difference to be expected. On the basis of fatty acid profiles, the authors concluded that the conventional emulsion may be preferred from a nutritional perspective.[53] A recent 7-day randomized study of Lipofundin MCT vs Lipoplus (B. Braun), an emulsion with similar composition to SMOFlipid, although with less fish oil (10% vs 15%), demonstrated increased levels of fatty acids associated with reduced inflammation with the fish oil ILE but no difference in total bilirubin.[54]

Five pediatric randomized studies[55-59] assessed the safety of Clinoleic in preterm infants for a short period. Given the duration, these studies did not address changes in liver function in a meaningful way. However, Clinoleic was associated with improved antioxidant measures, with one study showing decreases in proinflammatory cytokines. One medium-term study (60 days) of children with stable liver function at trial enrollment did not demonstrate any adverse hepatic consequences with Clinoleic.[60] Trials comparing Clinoleic and SMOFlipid are ongoing.[51] The hepatic outcomes from these studies will be of particular interest.

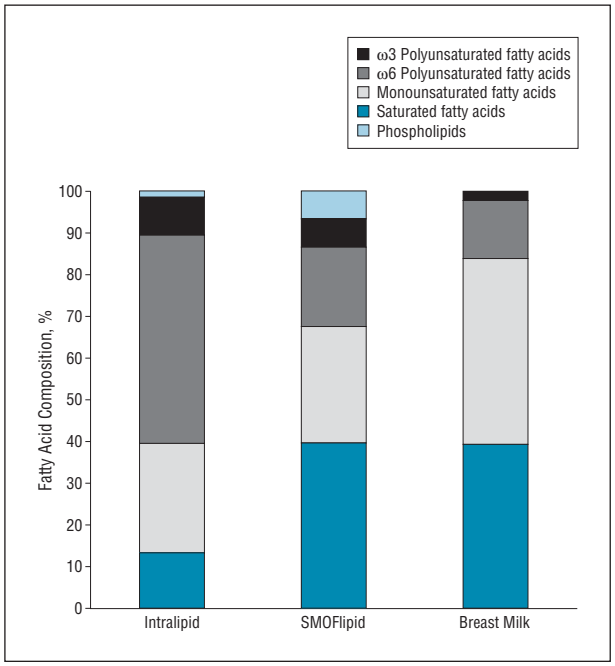

Figure. Fatty acid composition of Intralipid, SMOFlipid, and breast milk. Although Intralipid contains ω-3 fatty acids, it is all in the form of alpha-linoleic acid, which is not available for use by the infant because of immaturity of metabolic pathways. See the "Experience with SMOFlipid" subsection of the "Clinical Experience With ω-3–Containing ILEs" section for an explanation of SMOFlipid.

CURRENT STATUS OF NOVEL LIPID-BASED APPROACHES

Much of the data regarding the novel lipid-based approaches are in children with advanced IFALD. However, optimal clinical outcomes will likely be achieved by preventing the development of IFALD. Although on the basis of the available data it seems like the novel lipid-based approaches may be beneficial for the prevention of IFALD, it is important to recognize that they have not been formally evaluated in this setting, although clinical trials with this aim are ongoing.[61,62] Therefore, we believe that although the novel approaches may be appropriate for those with advanced IFALD, given the dearth of alternative therapies in those with early or no liver disease, these approaches should only be used in the context of randomized controlled trials.[63] Our caution relates primarily to the lack of high-quality evidence for the efficacy of these approaches and the limited safety data, including an understanding of the effect on growth and development. This concern is further highlighted by a recent publication from our group showing that only 10% of infants receiving PN with a CB level of 2 mg/dL progressed to more advanced IFALD, defined as a serum CB level greater than 6.7 mg/dL.[64] Therefore, should the threshold for initiation of a novel lipid-based approach be set at 2 mg/dL, as is already occurring at some centers, only 10% of surgical infants treated with a novel approach would be expected to benefit relative to conventional management.

Quality of Evidence

It is essential to recognize that all published data on lipid minimization,[17-19,21,22] Omegaven,[30-34,36-42] and SMOFlipid[48-50]

in established IFALD are from retrospective or uncontrolled studies. Furthermore, although SMOFlipid and other alternate ILEs have been suggested on the basis of the randomized trials to be associated with improved hepatic outcomes, the patient populations in these studies were either normal preterm infants or children receiving home PN with stable liver function rather than patients with IF at high risk of progressive IFALD.

Uncontrolled studies are subject to both known and unknown confounders. As such, inferences about the potential efficacy of these therapies must be tempered by this fact. The most prevalent confounder in the setting of patients with IF is the degree of enteral support with weaning of the PN concomitant with the novel lipid-based therapy. However, in our experience, there was only a median 10% increase in enteral tolerance in our patients who responded to Omegaven. Resolution of advanced cholestasis in this setting based on our historical experience is highly unusual.[34,35]

Uncontrolled studies also do not allow one to assign causality, which is a particular issue when one considers the effect of Omegaven. Omegaven, as it has been used in those with advanced IFALD, represents both an alternate lipid source and a form of lipid minimization. The lipid dose used by the group in Boston and most of the other publications was 1 g/kg daily, and the mean lipid dose in our cohort was 1.4 g/kg daily. These doses are substantially lower those that typically used for parenteral lipids in infants and within the range of lipid intake that we regard as lipid minimization. Therefore, the beneficial effect of Omegaven may be related to a reduced lipid dose rather than a qualitative change in lipid source. The experience with SMOFlipid in advanced IFALD and the experience from the use of ω3 lipids in animal models of IFALD argue against the effect of Omegaven as being only one of dose restriction. However, until data are available from clinical trials that control for both dose and source, this question remains unanswered. However, both Omegaven and SMOFlipid contain more alpha tocopherol than Intralipid, with this antioxidant being another potential confounder.

Safety Concerns

Concerns Related to Lipid Restriction. The long-term implications of reduced lipid dose on growth and development are unknown. Therefore, although dose restriction may be appropriate for the treatment of advanced liver disease, it may not be acceptable in the preventive setting. We believe that there needs to be a higher level of evidence in terms of long-term safety and efficacy before substantially altering recommended parenteral fat and energy intake in infants given, the critical role that lipids, including both ω-6FAs and ω-3FAs, play in neurodevelopment.[65]

Reducing lipid intake also has the potential to result in essential fatty acid deficiency (EFAD). In the series by Cober and Teitelbaum[17] of 32 patients treated with lipid minimization, biochemical evidence of EFAD was noted in 8. Although the group in Boston has reported on patients with biochemical evidence of EFAD as assessed by the triene-tetraene ratio, they have stated that clinically significant EFAD has not occurred in their patients taking Omegaven.[32] Other groups have, however, noted this complication.[41] Although de Meijer et al[66] may be correct asserting that the 0.1% to 0.7% linoleic acid content of Omegaven is sufficient to prevent EFAD, we maintain that further evidence is needed regarding the use of any ILE at a lipid dose of less than 1 g/kg daily during a prolonged period in developing infants, especially in those with minimal or no liver disease. This assertion is further highlighted by a recent study by Malone et al,[67] demonstrating marked abnormalities of essential fatty acid profiles in 10 children who received only Omegaven (1 g/kg daily) for greater than 3 months. The fact that these children had normal triene-tetraene ratios, which are typically regarded as diagnostic for EFAD, may challenge the validity of this marker in children with IF. However, the clinical significance of these findings requires further evaluation.

ω3-Specific Concerns. The major theoretical concerns regarding an imbalance between ω-3FA and ω-6FA intake relate to the ability of ω-3FAs to downregulate arachidonic acid, which may result in growth suppression, immunosuppression, increased lipid peroxidation, and delayed hemostasis.[68,69] Neonatal animal models have, however, not demonstrated impairment in bone composition or growth.[70] No significant complications associated with Omegaven use in children have been reported in either the Boston or Toronto experience. There is a case report of a burr cell hemolytic anemia in a child with IF treated with Omegaven that resolved after discontinuation of the treatment.[71] Given that ω-3FAs are known to alter red blood cell membrane dynamics, it is likely that this adverse effect was related to Omegaven.[72]

Another theoretical concern is increased hepatic fibrosis demonstrated in a rabbit model of IFALD.[73] One of the limitations in assessing this issue clinically is that liver biopsies are rarely performed in patients with IFALD, especially when the child is demonstrating biochemical evidence of resolution. However, in a report of 2 cases, Soden et al[74] demonstrated progressive fibrosis with Omegaven use despite biochemical normalization. In addition, although Omegaven may result in normalization of hyperbilirubinemia, a biochemical improvement in serum CB does not rule out ongoing liver injury contributing to progressive fibrosis.[75] It is therefore unclear whether the progressive fibrosis was related to the fact that the child continued to receive PN with ongoing liver injury, the progressive fibrosis was the result of healing of the injury inflicted before the start of Omegaven therapy, or fibrosis is a specific adverse consequence of treatment with Omegaven.

Despite the apparent safety of Omegaven, we maintain that further experience with this and other related emulsions, such as SMOFlipid, are needed to ensure that the preparations are not associated with rare but serious adverse events. This additional experience is especially important when one considers the use of emulsions in patients with no or early IFALD, in whom the risk-benefit ratio is different from those with advanced IFALD.

CONCLUSIONS

Novel lipid-based approaches seem to be promising for the management of IFALD. However, high-quality evidence

on which to base treatment recommendations is lacking, especially for the prevention of IFALD. Therefore, more research, including data from high-quality clinical trials, is needed to better evaluate the efficacy of these approaches before their adoption in children with early IFALD. Furthermore, additional safety parameters, including the effect on nutrition, essential fatty acid profiles, and long-term growth and development, must be addressed.

Accepted for Publication: December 20, 2011.
Correspondence: Paul W. Wales, MD, MSc, Division of General Surgery, The Hospital for Sick Children, 555 University Ave, Room 1526, Toronto, Ontario, Canada M5G 1X8 (paul.wales@sickkids.ca).
Author Contributions: *Study concept and design:* Diamond. *Analysis and interpretation of data:* Diamond, Pencharz, Feldman, Ling, Moore, and Wales. *Drafting of the manuscript:* Diamond. *Critical revision of the manuscript for important intellectual content:* Diamond, Pencharz, Feldman, Ling, Moore, and Wales. *Study supervision:* Pencharz, Feldman, Ling, Moore, and Wales.
Financial Disclosure: The authors have received investigator-initiated trial funding from Fresenius Kabi, the manufacturer of both Omegaven and Intralipid, to evaluate SMOFlipid for the prevention of IFALD. Dr Diamond is the recipient of a Graduate Studentship Award from the Canadian Liver Foundation and the Chisholm Memorial Fellowship, Post Graduate Medical Education Office, University of Toronto. Dr Diamond was also supported by a fellowship award from the Canadian Institutes of Health Research, with additional support from the Surgeon Scientist Training Program, Department of Surgery, University of Toronto. Dr Feldman is supported by a Canada Research Chair in Childhood Arthritis.
Additional Contributions: The following members of the Group for Improvement of Intestinal Function and Treatment team, our multidisciplinary intestinal rehabilitation program, provided contributions to our experience with and understanding of IFALD: J. Darch, J. Brennan-Donnan, J. Bowers, M. Carricato, K. Cormier, G. Courtney-Martin, L. Coxson, N. D'Amato, M. De Angelis, N. de Silva, A. Fecteau, D. Fierheller, D. Grant, A. Gold, D. Harrison, J. Hawes, L. Ives-Baine, P. Kean, C. Kosar, C. Koziolek, K. Lang, J. Maxwell, K. Murch, C. Newman, V. Ng, C. Patterson, A. Rogers, M. Rugg, and S. So.

REFERENCES

1. Vanderhoof JA, Langnas AN. Short-bowel syndrome in children and adults. *Gastroenterology*. 1997;113(5):1767-1778.
2. 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(1):27-33.
3. Kaufman SS. Prevention of parenteral nutrition-associated liver disease in children. *Pediatr Transplant*. 2002;6(1):37-42.
4. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. *Curr Opin Organ Transplant*. 2009;14(3):256-261.
5. Diamond IR, Sterescu A, Pencharz PB, Wales PW. The rationale for the use of parenteral omega-3 lipids in children with short bowel syndrome and liver disease. *Pediatr Surg Int*. 2008;24(7):773-778.
6. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med*. 2000;132(7):525-532.
7. Van Aerde JE, Duerksen DR, Gramlich L, et al. Intravenous fish oil emulsion attenuates total parenteral nutrition-induced cholestasis in newborn piglets. *Pediatr Res*. 1999;45(2):202-208.
8. Llop JM, Virgili N, Moreno-Villares JM, et al. Phytosterolemia in parenteral nutrition patients: implications for liver disease development. *Nutrition*. 2008; 24(11-12):1145-1152.
9. Clayton PT, Bowron A, Mills KA, Massoud A, Casteels M, Milla PJ. Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology*. 1993;105(6):1806-1813.
10. Heller A, Koch T, Schmeck J, van Ackern K. Lipid mediators in inflammatory disorders. *Drugs*. 1998;55(4):487-496.
11. Broughton KS, Wade JW. Total fat and (n-3):(n-6) fat ratios influence eicosanoid production in mice. *J Nutr*. 2002;132(1):88-94.
12. Grimm H, Tibell A, Norrlind B, Blecher C, Wilker S, Schwemmle K. Immunoregulation by parenteral lipids: impact of the n-3 to n-6 fatty acid ratio. *JPEN J Parenter Enteral Nutr*. 1994;18(5):417-421.
13. Antébi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr*. 2004;28(3):142-148.
14. 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(1):55-60.
15. Zlotkin SH, Stallings VA, Pencharz PB. Total parenteral nutrition in children. *Pediatr Clin North Am*. 1985;32(2):381-400.
16. Canada T, Crill C, Guenter P. *ASPEN Parenteral Nutrition Handbook*. Silver Spring, MD: American Society of Enteral and Parenteral Nutrition; 2009.
17. Cober MP, Teitelbaum DH. Prevention of parenteral nutrition-associated liver disease: lipid minimization. *Curr Opin Organ Transplant*. 2010;15(3):330-333.
18. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *JPEN J Parenter Enteral Nutr*. 2000;24(6):345-350.
19. Rollins MD, Scaife ER, Jackson WD, Meyers RL, Mulroy CW, Book LS. Elimination of soybean lipid emulsion in parenteral nutrition and supplementation with enteral fish oil improve cholestasis in infants with short bowel syndrome. *Nutr Clin Pract*. 2010;25(2):199-204.
20. 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(6):1015-1018.
21. Torres C, Sandler A, Artis K, Higginbothan K, Arciniegas S, Mohan P. IFALD: resolution of cholestasis using traditional soybean intravenous lipid emulsion (ILE). Paper presented at: Sixth International Pediatric Intestinal Failure and Rehabilitation Symposium; September 9-11, 2010; Chicago, IL.
22. Bianchi A. From the cradle to enteral autonomy: the role of autologous gastrointestinal reconstruction. *Gastroenterology*. 2006;130(2 suppl 1):S138-S146.
23. Beckh K, Kneip S, Arnold R. Direct regulation of bile secretion by prostaglandins in perfused rat liver. *Hepatology*. 1994;19(5):1208-1213.
24. Iyer KR, Spitz L, Clayton P; British Association of Paediatric Surgeons. BAPS prize lecture: new insight into mechanisms of parenteral nutrition-associated cholestasis: role of plant sterols. *J Pediatr Surg*. 1998;33(1):1-6.
25. Alwayn IP, Andersson C, Zauscher B, Gura K, Nosé V, Puder M. Omega-3 fatty acids improve hepatic steatosis in a murine model: potential implications for the marginal steatotic liver donor. *Transplantation*. 2005;79(5):606-608.
26. Alwayn IP, Gura K, Nosé V, et al. Omega-3 fatty acid supplementation prevents hepatic steatosis in a murine model of nonalcoholic fatty liver disease. *Pediatr Res*. 2005;57(3):445-452.
27. Yeh SL, Chang KY, Huang PC, Chen WJ. 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(1):32-36.
28. Wanten G, Beunk J, Naber A, Swinkels D. Tocopherol isoforms in parenteral lipid emulsions and neutrophil activation. *Clin Nutr*. 2002;21(5):417-422.
29. Hao W, Wong OY, Liu X, Lee P, Chen Y, Wong KK. ω-3 fatty acids suppress inflammatory cytokine production by macrophages and hepatocytes. *J Pediatr Surg*. 2010;45(12):2412-2418.
30. Gura KM, Duggan CP, Collier SB, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics*. 2006;118(1): e197-e201. doi:10.1542/peds.2005-2662.
31. 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.
32. Fallon EM, Le HD, Puder M. Prevention of parenteral nutrition-associated liver disease: role of omega-3 fish oil. *Curr Opin Organ Transplant*. 2010;15(3):334-340.
33. Diamond IR, Grant RC, De Silva N, Pencharz PB, Wales PW. Combination therapy with Omegaven® and Intralipid® in children with intestinal failure and advanced parenteral nutrition associated liver disease (PNALD). Paper presented at: XI International Small Bowel Transplant Symposium; September 9-12, 2009; Bologna, Italy.

34. Diamond IR, Sterescu A, Pencharz PB, Kim JH, Wales PW. Changing the paradigm: Omegaven for the treatment of liver failure in pediatric short bowel syndrome. *J Pediatr Gastroenterol Nutr*. 2009;48(2):209-215.
35. Diamond IR, de Silva N, Pencharz PB, Kim JH, Wales PW; Group for the Improvement of Intestinal Function and Treatment. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. *J Pediatr Surg*. 2007; 42(5):806-811.
36. Jain SK, Pahwa M. Management of short gut syndrome by omega 3 fatty acid infusion. *Clin Nutr*. 2007;26(6):810. doi:10.1016/j.clnu.2007.08.008.
37. Calhoun AW, Sullivan JE. Omegaven for the treatment of parenteral nutrition associated liver disease: a case study. *J Ky Med Assoc*. 2009;107(2):55-57.
38. Cheung HM, Lam HS, Tam YH, Lee KH, Ng PC. Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. *Clin Nutr*. 2009;28(2):209-212.
39. Chung PH, Wong KK, Wong RM, Tsoi NS, Chan KL, Tam PK. Clinical experience in managing pediatric patients with ultra-short bowel syndrome using omega-3 fatty acid. *Eur J Pediatr Surg*. 2010;20(2):139-142.
40. Pawlik D, Lauterbach R, Turyk E. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. *Pediatrics*. 2011;127(2): 223-228.
41. Sigalet D, Boctor D, Brindle M, Lam V, Robertson M. Elements of successful intestinal rehabilitation. *J Pediatr Surg*. 2011;46(1):150-156.
42. Ekema G, Falchetti D, Boroni G, et al. Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (omega-3 fatty acids). *J Pediatr Surg*. 2008;43(6):1191-1195.
43. Tillman E, Crill C, Black DD, et al. Enteral fish oil for treatment of parenteral nutrition-associated liver disease in six infants with short-bowel syndrome. *Pharmacotherapy*. 2011;31(5):503-509.
44. Goulet O, Antébi H, Wolf C, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2010;34(5):485-495.
45. Tomsits E, Pataki M, Tölgyesi A, Fekete G, Rischak K, Szollár L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 2010; 51(4):514-521.
46. Rayyan M, Devlieger H, Jochum F, Allegaert K. 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. *JPEN J Parenter Enteral Nutr*. 2012;36(1 suppl):81S-94S.
47. Skouroliakou M, Konstantinou D, Koutri K, et al. A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr*. 2010;64(9):940-947.
48. Muhammed R, Bremner R, Protheroe S, Johnson T, Holden C, Murphy MS. Resolution of parenteral nutrition associated jaundice on changing from a soya-oil emulsion to a complex mixed-lipid emulsion [published online ahead of print]. *J Pediatri Gastroenterol Nutr*. 2011. doi:10.1038/ejcn.2010.98.
49. Ferreira N, Falconer J, Harley C, et al. Improved serum bilirubin with SMOF lipid in children with intestinal failure on long term parenteral nutrition. Paper presented at: British Society of Paediatric Gastroenterology, Hepatology and Nutrition Winter Meeting; January 28-30, 2009; Sheffield, England.
50. Anish A, Lawson A, Cram H, et al. SMOF lipid in intestinal failure associated liver disease: experience in a regional centre. Paper presented at: British Society of Paediatric Gastroenterology, Hepatology and Nutrition Winter Meeting; January 27-29, 2010; Liverpool, England.
51. Deshpande G, Simmer K. Lipids for parenteral nutrition in neonates. *Curr Opin Clin Nutr Metab Care*. 2011;14(2):145-150.
52. Lai H, Chen W. Effects of medium-chain and long-chain triacylglycerols in pediatric surgical patients. *Nutrition*. 2000;16(6):401-406.
53. Socha P, Koletzko B, Demmelmair H, et al. Short-term effects of parenteral nutrition of cholestatic infants with lipid emulsions based on medium-chain and long-chain triacylglycerols. *Nutrition*. 2007;23(2):121-126.
54. D'Ascenzo R, D'Egidio S, Angelini L, et al. Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids. *J Pediatr*. 2011;159(1):33-38, e1.
55. Deshpande GC, Simmer K, Mori T, Croft K. Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' gestation) neonates: a randomised controlled trial. *J Pediatr Gastroenterol Nutr*. 2009;49 (5):619-625.
56. Göbel Y, Koletzko B, Böhles HJ, et al. Parenteral fat emulsions based on olive and soybean oils: a randomized clinical trial in preterm infants. *J Pediatr Gastroenterol Nutr*. 2003;37(2):161-167.
57. 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(11-12):1057-1064.
58. Gawecka A, Michalkiewicz J, Kornacka MK, Luckiewicz B, Kubiszewska I. Immunologic properties differ in preterm infants fed olive oil vs soy-based lipid emulsions during parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2008;32(4): 448-453.
59. Roggero P, Mosca F, Giannì ML, et al. F2-isoprostanes and total radical-trapping antioxidant potential in preterm infants receiving parenteral lipid emulsions. *Nutrition*. 2010;26(5):551-555.
60. Goulet O, de Potter S, Antébi H, et al. Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *Am J Clin Nutr*. 1999;70(3):338-345.
61. US National Institutes of Health. Can SMOFlipid®, a composite parenteral nutrition lipid emulsion, prevent progression of parenteral nutrition associated liver disease in infants? http://www.clinicaltrials.gov/ct2/show/NCT00793195. Accessed September 13, 2011.
62. US National Institutes of Health. Efficacy of an omega-3 enriched intravenous fat emulsion in the prevention of parenteral nutrition induced injury in infants. http://www.clinicaltrials.gov/ct2/show/NCT00512629. Accessed September 13, 2011.
63. Diamond IR, Pencharz PB, Wales PW. What is the current role for parenteral lipid emulsions containing omega-3 fatty acids in infants with short bowel syndrome? *Minerva Pediatr*. 2009;61(3):263-272.
64. Nasr A, Diamond IR, De Silva NT, Wales PW. Is the use of parenteral omega-3 lipid emulsions justified in surgical neonates with mild parenteral nutrition-associated liver dysfunction? *J Pediatr Surg*. 2010;45:980-986.
65. Clandinin MT, Van Aerde JE, Merkel KL, et al. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. *J Pediatr*. 2005;146(4):461-468.
66. de Meijer VE, Le HD, Mosel JA, Gura KM, Puder M. Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr*. 2010;50(2):212-218.
67. Malone FR, Javid P, Davis C, et al. Long-term parenteral fish oil-based lipid monotherapy in children is associated with biochemical alterations in essential fatty acids. Paper presented at: XI International Small Bowel Transplant Symposium; September 15-18, 2011; Washington, DC.
68. Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci U S A*. 1993;90(3):1073-1077.
69. Heird WC. The role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. *Pediatr Clin North Am*. 2001;48(1):173-188.
70. Weiler HA, Fitzpatrick-Wong SC. Modulation of essential (n-6):(n-3) fatty acid ratios alters fatty acid status but not bone mass in piglets. *J Nutr*. 2002;132 (9):2667-2672.
71. Mallah HS, Brown MR, Rossi TM, Block RC. Parenteral fish oil-associated burr cell anemia. *J Pediatr*. 2010;156(2):324-326, e1.
72. Fischler L, Meredith DO, Reinhart WH. Influence of a parenteral fish-oil preparation (Omegaven) on erythrocyte morphology and blood viscosity in vitro. *Clin Hemorheol Microcirc*. 2003;28(2):79-88.
73. Kohl M, Wedel T, Entenmann A, et al. Influence of different intravenous lipid emulsions on hepatobiliary dysfunction in a rabbit model. *J Pediatr Gastroenterol Nutr*. 2007;44(2):237-244.
74. Soden JS, Lovell MA, Brown K, Partrick DA, Sokol RJ. Failure of resolution of portal fibrosis during omega-3 fatty acid lipid emulsion therapy in two patients with irreversible intestinal failure. *J Pediatr*. 2010;156(2):327-331.
75. Fitzgibbons SC, Jones BA, Hull MA, et al. Relationship between biopsy-proven parenteral nutrition-associated liver fibrosis and biochemical cholestasis in children with short bowel syndrome. *J Pediatr Surg*. 2010;45(1):95-99.