Lipid emulsions in the treatment and prevention of parenteral nutrition–associated liver disease in infants and children

Prathima Nandivada, Gillian L Fell, Kathleen M Gura, and Mark Puder

ABSTRACT

Long-term parenteral nutrition (PN) carries the risk of progressive liver disease in infants with intestinal failure. Although PN-associated liver disease (PNALD) is multifactorial in etiology, components of soybean oil lipid emulsions have been implicated in the disease’s pathogenesis. Historically, infants with PNALD who were unable to wean from PN to full enteral feeding developed cirrhosis and end-stage liver disease, which require liver transplantation to survive. Over the past 2 decades, novel strategies for the management of parenteral lipids have improved morbidity and mortality from PNALD in infants with intestinal failure. Current strategies for the treatment of PNALD include restricting the dose of parenteral soybean oil lipid emulsion and/or replacing the soybean oil with a parenteral fish-oil lipid emulsion or emulsions of mixed-lipid sources. The purpose of this report is to review published data that evaluate these strategies in parenteral lipid management for the treatment and prevention of PNALD. Am J Clin Nutr 2016;103(Suppl):629S–34S.

Keywords: lipid emulsions, liver disease, parenteral lipids, PNALD, fish oil, soybean oil, intestinal failure

INTRODUCTION

Parenteral nutrition (PN) has revolutionized the management of infants with intestinal failure, allowing for life-saving nutritional support during intestinal growth and adaptation. However, the prolonged use of PN is associated with significant risks, including progressive liver disease. PN-associated liver disease (PNALD) presents initially with biochemical evidence of cholestasis, clinical evidence of jaundice, and failure to thrive (1). The reported incidence of PNALD varies from 25% to 60% in infants receiving long-term PN, depending on the criteria used to establish the diagnosis (2–4). The most widely used definition of PNALD requires a serum direct bilirubin (DB) concentration >2 mg/dL with no other cause of liver disease. Liver biopsies in children with PNALD showed a spectrum of cholestasis, steatosis, hepatitis, and fibrosis (1). However, biopsies are not routinely performed (4). Historically, infants with PNALD who are unable to wean from PN developed cirrhosis and end-stage liver disease, resulting in death and/or the need for transplantation in ~50% of patients (2).

The current management of PNALD relies on an understanding of its etiologies and modifiable risk factors. PNALD is a multifactorial disease associated with prolonged duration of PN, enteral nutrition intolerance, preterm birth, low birth weight, septicemia, overfeeding, and micronutrient imbalances (5, 6). The treatment of PNALD therefore requires attention to multiple patient factors and depends on the initiation of enteral feeding as early as possible. Over the past 20 y, considerable animal and human data have shown the role of soybean oil lipid emulsions (SOLEs) in the pathogenesis of PNALD. SOLE contains high amounts of phytosterols, or plant-based cholesterol-like compounds found in vegetable oils, which disrupt bile acid homeostasis and contribute to the development of cholestasis (7–9). Furthermore, the abundance of omega-6 fatty acids and relative paucity of antioxidants found in SOLEs may also potentiate inflammation and liver injury (10, 11). The mainstay of therapy for PNALD therefore relies on the elimination of PN and parenteral lipids, with advancement to full enteral nutrition. However, for infants and children who are unable to wean from PN due to insufficient bowel length or function, alternative strategies for lipid administration can be used to reduce liver damage and reverse disease progression. The purpose of this review is to provide a summary of the data that evaluate current lipid management strategies for the treatment and prevention of PNALD.

TREATMENT OF PNALD

Parenteral lipid management for the treatment of PNALD includes 2 strategies: lipid restriction and lipid replacement.
These methods were developed after the observation that increased exposure to SOLE contributes to the development and progression of PNALD (12). In children who require PN for indications other than intestinal failure, parenteral SOLE is typically provided at doses of 2−3 g·kg$^{-1}·d^{-1}$ (13). Lipid restriction decreases doses of SOLE to ≤1 g·kg$^{-1}·d^{-1}$, whereas lipid replacement eliminates SOLE all together and replaces it with an emulsion of an alternative lipid source.

Lipid restriction

Colomb et al. (12) first reported the treatment of PNALD in children with intestinal failure using lipid restriction in 2000. Over a 10-y period, they used lipid-restrictive strategies in 10 patients with 23 episodes of cholestasis. Patients were managed by discontinuing parenteral lipids in 20 episodes or switching from a purely long-chain fatty acid emulsion to a mixed medium- and long-chain fatty acid emulsion in 3 episodes. Cholestasis resolved in 19 of 23 episodes; however, 3 children developed essential fatty acid deficiency (EFAD) and all children showed growth failure, despite increasing calories in the form of dextrose. At the time of their study publication, 1 child required a liver transplant, 3 required multivisceral transplants, 5 were awaiting transplantation, and only 1 was successfully weaned from PN.

A more recent study by Cobert et al. (14) evaluated the efficacy of lipid restriction in managing patients with PNALD by comparing a cohort from 2003 to 2005 who received SOLE at 1 g·kg$^{-1}·d^{-1}$, twice weekly, with a cohort from 2003 to 2005 who received standard a SOLE dosing (2–3 g·kg$^{-1}·d^{-1}$). The groups were matched by gestational age, primary diagnosis, and birth weight. Of the 31 pairs matched, 42% of patients in the lipid-restriction group had resolution of cholestasis compared with 10% in the standard-lipid-dose group ($P = 0.013$). Within the lipid-restriction group, 13 infants remained on PN for >1 mo, and of these, 8 developed an elevated triene-to-tetren ratio (>0.05), although none of the children met criteria for EFAD, which is biochemically defined as a triene-to-tetren ratio >0.2. In addition, none of the children developed symptomatic EFAD and there were no differences in BMIs or $z$ scores for weight and head circumference between restricted and standard-lipid-dosing groups.

Although lipid restriction can be effective in some patients, the impact of significantly limiting fat intake on the growing infant brain is unknown. Studies commonly monitor for evidence of biochemical and clinical EFAD, but relative deficiencies in specific fatty acids are difficult to assess. Preterm infants are particularly susceptible to a relative deficiency in DHA due to the limited maternal to fetal transfer of DHA stores, which normally occurs late in the third trimester, and the immaturity and paucity of desaturase enzymes that convert $\alpha$-linolenic acid (18:3n−3) to DHA (15, 16). With DHA comprising 50% of neuronal plasma membranes by weight, the adequate provision of fat for the development of the neonatal brain is paramount (17). Further study is required to determine the long-term effects of lipid restriction on brain and cognitive development.

Lipid replacement: parenteral fish-oil monotherapy

An alternative strategy for the management of PNALD involves the replacement of SOLE at 1 g·kg$^{-1}·d^{-1}$ with a fish-oil lipid emulsion (FOLE) at the same dose. Clinical studies have shown that FOLE therapy leads to resolution of biochemical cholestasis, with significant decreases in morbidity and mortality. The mechanism by which FOLE contributes to the resolution of PNALD may arise from key differences in its components that render it less hepatotoxic than SOLE and other vegetable oils. FOLE (Omegaven; Fresenius Kabi) contains minimal phytosterols and is rich in $\omega$-3 fatty acids and $\alpha$-tocopherol (18). In a mouse model of PNALD, El Kasmi et al. (19) showed that FOLE prevented hepatocellular injury and cholestasis. However, the addition of stigmasterol (the most abundant phytosterol found in SOLE) to FOLE abolished this effect, causing PNALD in the mice. Ng et al. (20) investigated the role of $\alpha$-tocopherol and phytosterols in the mechanism of FOLE-mediated PNALD resolution in a piglet model of PNALD. The addition of 251 mg $\alpha$-tocopherol/L to SOLE led to the prevention of hepatic injury typically observed with the administration of SOLE alone. Interestingly, the addition of phytosterols to FOLE in the piglet model did not result in PNALD, and FOLE remained hepatoprotective. The key components of commonly used oils within clinically relevant lipid emulsions are described in Table 1.

FOLE monotherapy was first reported for the management of PNALD by Gura et al. (23) in 2 preterm, PN-dependent infants with plasma DB concentrations >3 mg/dL, while receiving SOLE. In these infants, SOLE was discontinued with initiation

### TABLE 1

Comparison of contents of lipid emulsions

<table>
<thead>
<tr>
<th>Product</th>
<th>Oil source</th>
<th>Linoleic acid, % by weight</th>
<th>$\alpha$-Linolenic acid, % by weight</th>
<th>EPA, % by weight</th>
<th>DHA, % by weight</th>
<th>$\alpha$-Tocopherol, mg/L</th>
<th>Phytosterols, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralipid</td>
<td>100% Soybean</td>
<td>44−62</td>
<td>4−11</td>
<td>0</td>
<td>0</td>
<td>38</td>
<td>342.89 ± 5.87$^2$</td>
</tr>
<tr>
<td>Lipofundin</td>
<td>100% Soybean</td>
<td>50</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>180 ± 40</td>
<td>621.85 ± 7.36</td>
</tr>
<tr>
<td>Clinoleic</td>
<td>20% Soybean</td>
<td>18.5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>226.83 ± 6.42</td>
</tr>
<tr>
<td>SMOFLipid</td>
<td>80% Olive</td>
<td>21.4</td>
<td>2.5</td>
<td>3.0</td>
<td>2.0</td>
<td>200</td>
<td>178.54 ± 9.56</td>
</tr>
<tr>
<td></td>
<td>30% MCT</td>
<td>25% Olive</td>
<td>15% Fish</td>
<td>4.4</td>
<td>1.8</td>
<td>19.2</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150−296</td>
<td>3.66 ± 0.59</td>
</tr>
</tbody>
</table>

$^1$Adapted from references 21 and 22 with permission. Intralipid, SMOFLipid, and Omegaven (Fresenius Kabi), Lipofundin (B. Braun), and Clinoleic (Baxter). MCT, medium chain triglyceride.

$^2$Values are means ± SD.
of FOLE monotherapy, escalating to a dose of $1 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. Both infants experienced resolution of cholestasis with FOLE administration despite an inability to wean from PN. A subsequent study by Gura et al. (24) reported that cholestasis resolved more rapidly in patients who received FOLE therapy ($9.4 \, \text{wk}$) compared with a historical cohort treated with SOLE ($44.1 \, \text{wk}$). Among the 18 patients who transitioned to FOLE, there were 2 deaths and no liver transplants compared with 7 deaths and 2 liver transplants in the SOLE cohort. Puder et al. (25) subsequently compared outcomes from FOLE monotherapy at a dose of $1 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in 42 PN-dependent children who developed PNALD while receiving SOLE with outcomes in a contemporary cohort of 49 PN-dependent children who developed PNALD and continued to receive SOLE at a dose of $1–4 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. The group who transitioned to FOLE had a significantly lower rate of mortality and/or transplantation ($9.5\%$) than did the group who continued to receive PN and SOLE ($34.7\%; P = 0.005$). Premkumar et al. (26) similarly reported their experience using FOLE monotherapy for PNALD from 2007 to 2011. In 57 PN-dependent infants who were administered FOLE monotherapy for PNALD, resolution of cholestasis was achieved in $82.5\%$ of patients. Of the $17.5\%$ of infants who died, $40\%$ died after redirection of care related to comorbid conditions (27, 28). The infants who died despite initiation of FOLE therapy were more premature at birth than were surviving infants, and $30\%$ had evidence of end-stage liver disease before FOLE initiation (26). Calkins et al. (29) more recently reported time to normalization of DB concentrations with FOLE monotherapy for PNALD. Of 10 patients who transitioned from SOLE to FOLE for treatment of PNALD, $75\%$ had normal DB concentrations by $17 \, \text{wk}$, compared with $6\%$ of a historical cohort of patients who continued to receive SOLE. Recently, a double-blind randomized controlled trial was published comparing outcomes in infants treated with SOLE ($n = 7$) or FOLE ($n = 9$) for PNALD at equivalent doses of $1.5 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (30). Although there was no difference in the median age at time of PNALD resolution, infants who received SOLE had a higher rate of increase in serum DB ($13.5 \, \mu\text{mol/ wk})$ than did infants who received FOLE ($0.6 \, \mu\text{mol/ wk}; P = 0.03$). Importantly, the study was prematurely terminated because of a trend toward increased mortality in the SOLE group (2 deaths compared with 0 deaths in the FOLE group) and parental refusal to proceed with randomization once educated about FOLE therapy. From these clinical studies, it appears that FOLE monotherapy can safely facilitate the resolution of PNALD, without the risk of EFAD, conferring a survival benefit and diminishing the need for liver transplantation. The use of parenteral FOLE is currently restricted to a compassionate use protocol through the Food and Drug Administration for those who develop PNALD in the United States, which limits its availability to patients and providers.

There are currently a limited number of long-term outcome studies in children managed with FOLE monotherapy for PNALD. Premkumar et al. (31) recently provided an updated study in PN-dependent infants managed with FOLE monotherapy for PNALD at a single institution from 2007 to 2013, extending the observation and accrual period from their previous study by $2 \, \text{y}$. This study included 97 patients and reported an $86\%$ survival rate. As in their previous study, the severity of cholestasis at FOLE initiation and degree of prematurity at birth directly correlated with mortality risk. In addition, Nandivada et al. (32) reported that children with cirrhosis due to PNALD who expe-

Lipid replacement: mixed-lipid emulsions

The use of mixed-lipid emulsions, containing various combinations of fish oil, plant-based oils, and medium-chain triglycerides (MCTs), has also been of interest in the management of PNALD, although there are few studies reporting clinical
outcomes. These mixed-lipid emulsions include SMOFLipid (30% soybean oil, 30% MCTs, 25% olive oil, 15% fish oil) (Fresenius Kabi), ClinOleic (80% olive oil, 20% soybean oil) (Baxter), and Lipofundin (50% soybean oil, 50% MCTs) (B.Braun). In a mouse model of PN-induced steatosis, the effect of the mixed lipids SMOFLipid and ClinOleic were compared with the pure SOLE Intralipid and the pure FOLE Omegaven. All mice except those fed Omegaven showed steatosis after 19 d of being fed a PN-equivalent diet, and mice administered ClinOleic and SMOFLipid developed EFAD as quantified by an elevated triene to tetraene ratio. Few clinical studies exist that evaluated mixed-lipid emulsions for the treatment of PNALD. One study in 8 PN-dependent children administered SMOFLipid (dose range from 0.64 to 3.5 g \cdot kg^{-1} \cdot d^{-1}) for PN-associated jaundice and hyperbilirubinemia reported that 5 of the 8 children experienced normalization of bilirubin concentrations over 6 mo of SMOFLipid therapy, with the median total bilirubin for the group decreasing from 8.4 mg/dL (range: 4.2–15.7 mg/dL) before SMOFLipid initiation to 1.1 mg/dL (range: 0.4–12.5 mg/dL) at the end of 6 mo (42). In this study, no comment was made about EFAD evaluation, and there was no report of transaminase concentrations or liver biopsy results to assess for primary liver injury. Further investigation of the mixed-lipid emulsions is required to ascertain safety and clinical benefit in the treatment of PNALD.

**PREVENTION OF PNALD**

The prevention of PNALD in infants expected to have long-term PN dependence is a primary goal in managing pediatric intestinal failure. Strategies are multifaceted and should include the prevention of catheter-related bloodstream infections and bacterial overgrowth in the gut, avoidance of overfeeding, and, when possible, initiation of early enteral feeding (6). In addition, the growing understanding of the harm of SOLE in infants with intestinal failure has resulted in lipid-management strategies to prevent cholestasis that mirror the treatment strategies previously discussed.

**Lipid restriction**

Limited data suggest that the restriction of parenteral SOLE from 2–3 g \cdot kg^{-1} \cdot d^{-1} to 1 g \cdot kg^{-1} \cdot d^{-1} in infants with intestinal failure may prevent the development of PNALD (12, 43, 44). Sanchez et al. (43) reported their experience using lipid restriction in a cohort of surgical infants expected to receive long-term PN with the use of SOLE at 1 g \cdot kg^{-1} \cdot d^{-1} throughout the patient’s PN course. These infants were compared with a control cohort of infants who received standard SOLE dosing (2–3 g \cdot kg^{-1} \cdot d^{-1}). The authors found a significant reduction in the incidence of PNALD in the lipid-restricted group compared with the standard-dose group (22% compared with 43%; \( P = 0.002 \)). On multivariable relative risk regression, infants treated with standard lipid provisions were 1.77 times more likely to develop PNALD than those who were lipid restricted (95% CI: 1.2, 2.7; \( P = 0.007 \)). In 6 cases (4 infants in standard-dose group, 2 infants in low-dose group), discontinuation of SOLE and initiation of FOLE monotherapy were required to reverse PNALD. The authors concluded that early lipid restriction should be considered in all surgical infants who require PN as a preventative measure against PNALD.

Similar findings were reported by Rollins et al. (44) in a prospective randomized controlled trial in surgical patients born at ≥26 wk of gestation who were anticipated to require ≥50% of daily caloric intake from PN for at least 4 wk. Participants were randomly assigned to receive SOLE at a restricted dose of 1 g \cdot kg^{-1} \cdot d^{-1} or a standard dose of 3 g \cdot kg^{-1} \cdot d^{-1}. Both groups received similar amounts of calories and protein from PN. With an average duration of therapy of 5.4 wk, the total increase in DB concentrations from baseline was smaller in the lipid-restricted group than in the standard group (\( P = 0.04 \)). Weight \( z \) score increased more in the standard group, but none of the patients developed EFAD.

Several recent studies, however, suggest that lipid restriction has no impact on the incidence of PNALD. In a prospective, multicenter, randomized controlled trial, 136 neonates with a gestational age of ≥29 wk were randomly assigned to receive SOLE at a dose of 1 g \cdot kg^{-1} \cdot d^{-1} or a standard dose of 3 g \cdot kg^{-1} \cdot d^{-1} within 48 h of life. Levit et al. (45) reported that there was no difference in the incidence of cholestasis between patients in either dosing group, defined as a DB ≥15% of total bilirubin at 28 d of life (69% compared with 63%; 95% CI: −0.1%, 0.22%; \( P = 0.45 \)). Whereas the lipid-restricted group received less SOLE and fewer total calories over time compared with the standard-dose group (\( P < 0.001 \) and \( P = 0.03 \), respectively), weight, length, and head circumference at 28 d of life, discharge, and over the follow-up period were not different (\( P > 0.2 \) for all). Similarly, Nehra et al. (46) compared the impact of SOLE at dose of 1 g \cdot kg^{-1} \cdot d^{-1} or 2–3 g \cdot kg^{-1} \cdot d^{-1} on the incidence of cholestasis in infants with intestinal failure and also found no difference in time to development of cholestasis or in the incidence of PNALD. The authors concluded that SOLE restriction was inadequate to prevent or delay the onset of PNALD. However, many institutions that manage infants with intestinal failure have shifted to dosing SOLE at 1 g/kg per day, given the potential benefit.

**Lipid replacement**

As in the treatment of PNALD, practitioners have also investigated the use of alternative lipid emulsions in the prevention of PNALD. The majority of studies evaluated novel mixed-lipid emulsions, containing combinations of vegetable oils and, in some cases, fish oil. These emulsions are not currently approved for use in children in the United States, and the data evaluating their efficacy are conflicting.

In a study investigating the impact of the addition of fish oil to a soybean/olive oil emulsion on the incidence of retinopathy, Pawlik et al. (47) randomly assigned 130 infants weighing <1250 g at birth to either an experimental regimen of soybean, olive, and fish-oil emulsion (n = 60) or a control group of parenteral soybean and olive oil emulsion (n = 70). The maximum daily dose of lipids was similar in both groups (3.5 g \cdot kg^{-1} \cdot d^{-1}), with the experimental group receiving 1.2 g \cdot kg^{-1} \cdot d^{-1} as fish oil and 2.3 g \cdot kg^{-1} \cdot d^{-1} as the soybean/olive oil blend and the control group receiving 3.5 g \cdot kg^{-1} \cdot d^{-1} as soybean/olive oil. Although not the primary outcome of the study, the authors reported that those infants who received a parenteral lipid emulsion containing fish oil had less cholestasis than those who received a lipid emulsion lacking fish oil. PNALD was diagnosed 6 times more frequently in the soybean/olive oil group.
compared with the group with fish oil included in the lipid emulsion ($n = 20$ compared with 3, respectively; RR: 0.18; 95% CI: 0.055, 0.56) (48).

Other investigators also studied the effectiveness of various blends of parenteral lipid emulsions and found that the incidence of PNALD and liver dysfunction was similar regardless of oil type. In a single-center randomized controlled trial, 144 “uncomplicated” preterm infants were randomly assigned to receive lipid emulsions composed of soybean oil alone, MCT/soybean oil, soybean/MCT/olive/fish oil, soybean/olive oil, or soybean/MCT/fish oil (49). Therapy started within 1 h of birth and continued for 21 d, with doses ranging from 1 to $3 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. Only 3 patients (2.1%) developed PNALD: 1 in the MCT/soybean oil group, 1 in the MCT/soybean/fish-oil group, and 1 in the soybean/MCT/olive/fish-oil group. At 6 wk, no differences in liver function were observed. Likewise, a recent meta-analysis reported that there was inadequate evidence to support the use of mixed-lipid emulsions in the prevention of PNALD (50).

Recently, a double-blind randomized controlled study comparing the incidence of PNALD in 10 infants who received SOLE and 9 infants who received FOLE at the same dose ($1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) was performed. However, the incidence of cholestasis in both groups was significantly lower than expected, resulting in an inability to assess for differences in the incidence of PNALD. Median maximum DB was also not significantly different between the groups. The use of FOLE was not associated with increased risk of growth impairment, coagulopathy, infectious complications, hypertriglyceridemia, or adverse neurodevelopmental outcomes; however, the cohort size was too small to generalize these results. No patient in either group developed EFAD (51).

CONCLUSIONS

PNALD remains a significant cause of morbidity and mortality in infants with intestinal failure. A multifaceted approach is required to appropriately prevent and treat PNALD, taking the associated risk factors into account. Reducing exposure to SOLE may be important in the management of PNALD. However, the optimal management strategy for each patient is based on the risks and benefits associated with lipid restriction and lipid replacement. Lipid restriction can be effective in treating PNALD, but it carries the risk of EFAD and unknown consequences on long-term neurodevelopment. Lipid replacement with FOLE monotherapy is also effective and does not lead to EFAD. However, it is available in the United States only through a compassionate-use protocol through the Food and Drug Administration. The use of lipid restriction and lipid replacement in the prevention of PNALD remains controversial and requires further study.

The authors’ responsibilities were as follows—PN: drafted the majority of the text, and critically revised and provided final approval for the manuscript; GLF: drafted portions of the text, and critically revised and provided final approval for the manuscript; KMG and MP: determined the topic of the review, designed the review, and critically revised and provided final approval for the manuscript. A license agreement for the use of Omegaven was signed by Boston Children’s Hospital and Fresenius Kabi, and a patent has been submitted by Boston Children’s Hospital on behalf of MP and KMG. No funding for this research was provided by Fresenius Kabi. PN and GLF had no conflicts of interest to report.

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