Parenteral Fish Oil–Containing Lipid Emulsions May Reverse Parenteral Nutrition–Associated Cholestasis in Neonates: A Systematic Review and Meta-Analysis\(^1\,2\)

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Abstract

**Background:** Growing evidence indicates that fish oil–containing lipid emulsions have a beneficial effect on parenteral nutrition–associated cholestasis (PNAC) in adults; however, data are limited in neonates regarding the effect of fish oil on PNAC.

**Objective:** We conducted a meta-analysis of studies that addressed the effect of fish oil–containing lipid emulsions on reversing and preventing PNAC.

**Methods:** We searched PubMed, the EMBASE database, and the Cochrane Library for this systematic review and meta-analysis. The methodologic assessment of studies was performed with the Jadad scale and the Newcastle-Ottawa Scale. Comprehensive Meta-Analysis version 2.0 was used for the statistical analysis. We performed a meta-analysis with the primary outcomes of reversal of PNAC and the occurrence of PNAC in newborn infants, including preterm infants, after parenteral administration of fish oil–containing lipid emulsions.

**Results:** Of the 36 studies identified, 7 fulfilled the inclusion criteria and were used in this meta-analysis, including 3 studies with 93 participants in which reversal of PNAC was an outcome and 4 studies with 1012 participants on preventing PNAC. The use of fish oil–containing lipid emulsions was more likely to reverse PNAC (OR: 6.14; 95% CI: 2.27, 16.6; \(P < 0.01\)), but the use of fish oil–containing lipid emulsions did not have a significant effect on the development of PNAC (OR: 0.56; 95% CI: 0.28, 1.10; \(P = 0.09\)) compared with soybean-based or olive oil–based lipid emulsions.

**Conclusions:** The pooled data suggest that the use of fish oil–containing lipid emulsions is effective for reversing PNAC but cannot prevent PNAC in neonates who require prolonged parenteral nutritional support. J Nutr 2015;145:277–83.

**Keywords:** fish oil; Omegaven; SMOFlipid; neonate; parenteral nutrition–associated cholestasis

Introduction

Parenteral nutrition (PN)\(^7\) is used to provide nutrients to neonates and infants who cannot tolerate enteral nutrition, such as patients with short bowel syndrome or intestinal failure and preterm infants. Among the complications associated with long-term use of PN, the incidence of PN-associated liver disease (PNALD) ranges from 40% to 85% in infants (1–4). Histologic cholestatic changes in the liver can be observed within 2 wk, and fibrosis is detected within 6 wk after commencing PN (2). PNALD may be diagnosed initially by abnormalities in laboratory findings, including increased liver enzyme and/or direct bilirubin concentrations. PN-associated cholestasis (PNAC) is defined as a concentration of direct bilirubin >2 mg/dL on 2 consecutive measurements (2). In addition to the absence of enteral feeding, preterm birth, a low-birth-weight infant, and use of plant oils are risk factors for PNAC (3, 5). Although increasing enteral feeding and reducing PN are methods to manage PNALD, increasing evidence suggests that fish oil–containing lipid emulsions have a preventive effect on and can improve PNALD (3, 6, 7). We conducted a meta-analysis on the effect of fish oil–containing lipid emulsions on reversing and preventing PNAC in neonates.

**Methods**

**Databases and search strategy** We performed this meta-analysis in accordance with the guidelines developed for systematic reviews and meta-analyses (8, 9). We searched PubMed, the EMBASE database, and the Cochrane Library by using the
search terms “neonatal intensive care unit or newborn or very low birth infant or premature infant or preterm,” “fish oil or omega-3 or Omegaven or lipid emulsion or medium chain triglycerides or soybean oil or olive oil or SMOFlipid or fat emulsion,” and “parenteral nutrition and (liver disease or cholestasis) or total parenteral nutrition (TPN) cholestasis or hyperbilirubinemia.” No restrictions were placed on the searches for language, population, or publication year. The last search was performed 15 May 2014. The titles and abstracts of the articles were screened initially, and the full-text articles were reviewed. We excluded case reports, case series, review articles, editorials, and comments. All studies were reviewed independently by 2 reviewers (HWP and NML) by using the selection criteria to determine inclusion in the meta-analysis.

Eligibility criteria
Articles required to meet the following criteria for inclusion were: 1) study design included randomized controlled trial, case-control study, or prospectively or retrospectively matched cohort study; 2) patients included infants <1 y when the fish oil–containing lipid emulsions was administered to analyze the prevention of PNAC (the secondary outcome) and newborn infants, including preterm infants, for analysis of reversing PNAC (the primary outcome); 3) interventions included fish oil–containing lipid emulsions administered parenterally compared with lipid emulsions that lacked fish oil; and 4) outcomes included reversal of PNAC or the secondary outcome of PNAC occurrence after use of the fish oil–containing lipid emulsions.

Exclusion criteria were 1) case reports, case series, or single-arm cohort studies and 2) cholestasis in patients with inborn errors, such as metabolic disorders, congenital infection, or severe sepsis.

Data extraction
Two authors (HWP and NML) extracted the data independently from the full-text articles of all included studies. We extracted the following data: first author, publication year, study design, study location, study period, study population, cholestasis definition, gestational age at birth, type of lipid emulsion, sample size, reversal of cholestasis, and occurrence of cholestasis. Differences in data interpretation were resolved by discussion with a third reviewer (JHK).

Quality assessment
Two authors (HWP and NML) independently assessed the quality of the included studies by using Jadad scale for randomized control trials (10) and the Newcastle-Ottawa Scale for nonrandomized studies (11). Jadad scale assesses the quality of a randomized control trial according to randomization, double blinding, and reported dropout. If randomization and double blinding were mentioned (+1) and appropriate (+1), 2 points were given. A dropout was scored (+1) if the fate of the patients and the reason for the dropout were reported. The Jadad score ranges from 0 (bad) to 5 (good), and total scores of 4–5 correspond to good trials, whereas total scores of 0–3 correspond to poor trials.

The Newcastle-Ottawa Scale assesses study quality by evaluating 3 domains: selection (4 items), comparability (1 item), and outcome for cohort studies (exposure for case-control studies, 3 items). Each domain that meets the criteria is given a star, except for the comparability domain (which has a maximum of 2 stars). The total number of stars given determines the overall score, the maximum of which is 9 points. Any disagreements between authors were resolved by discussion and re-evaluation. Total scores of 0–3, 4–5, and 6–8 correspond to studies of low, moderate, and high quality, respectively.

Data analysis
Heterogeneity was assessed with the $I^2$ statistic (percentage of the total variation across studies), with $I^2 > 50\%$ indicating significant heterogeneity. If no heterogeneity was found, the fixed-effects model was used for the meta-analysis. A random-effects model was used for analysis when there was significant heterogeneity. A sensitivity analysis was performed to evaluate the robustness of the conclusion by removing each study sequentially and examining the effect of removing each study on the pooled OR results. The Begg-Mazumdar rank correlation test was used to detect publication bias. A funnel plot and Egger’s regression test were used to detect asymmetry on the basis of the distribution of effect sizes against the standard errors. All statistical analyses were performed with Comprehensive Meta-Analysis version 2.0 (Biostat).

Results
Study selection. A flow diagram for the study selection is shown in Figure 1. Of the 212 potentially relevant studies identified, 176 were excluded on the basis of the title or abstract. Of the remaining 36 studies, 7 fulfilled the inclusion criteria and were used for this meta-analysis (4, 12–17).

Characteristics of the included studies. The characteristics of the included studies that assessed the effect of fish oil–containing lipid emulsions on preventing and reversing PNAC are shown in Table 1. Three studies, including 93 participants (intervention: 47; control: 46), presented results on reversing PNAC as the outcome (4, 13, 15), and the other 4 studies, including 1012 participants (intervention: 471; control: 541), assessed the use of fish oil–containing lipid emulsions for preventing PNAC (12, 14, 16, 17).

The quality of the 5 nonrandomized studies (4, 12, 14, 17, 18), according to the Newcastle-Ottawa Scale, is shown in Table 2. Jadad scores for 2 randomized control trials (13, 16) were 5 in both studies.

Three studies that were included for primary outcome (4, 13, 18) assessed intravenous lipid emulsions with the following compositions: Omegaven (Fresenius Kabi; 100% fish oil) was used as the fish oil–containing lipid emulsion compared with Intralipid (Fresenius Kabi; 100% soybean oil) (4, 13, 18) or Liposyn II (Lake Forest; 50% soybean oil and 50% safflower oil) (19). The doses of Omegaven used were 1–1.5 g · kg$^{-1} ·$d$^{-1}$ (Table 1).

The infants were started on PN as TPN, and PN was then tapered at the beginning of enteral feeding. The median age of starting supplementation with fish oil–containing lipid emulsions was 39 wk (range: 27–68 wk) in the study by Angsten et al. (4) and 14 wk in the study by Gura et al. (18). The initiation time of the intervention with fish oil–containing lipid emulsions was not described in the study by Lam et al. (13).

The mean duration of treatment or follow-up was 6.7 mo in the study by Angsten et al. (4) and 18.4 wk (IQR: 8.7–36.4 wk) in the study by Gura et al. (18). The mean time to reverse cholestasis after initiating the use of fish oil was 2.9 mo (range: 1.4–5.9 mo) in the study by Angsten et al. (4). The median times in the fish oil and control groups were 15.7 wk (IQR: 11.7–22.6 wk) and 19.6 wk (IQR: 15.1–21.4 wk), respectively, in the study...
<table>
<thead>
<tr>
<th>Study design</th>
<th>Location, study period</th>
<th>Population</th>
<th>Definition of cholestasis</th>
<th>GA at birth, wk</th>
<th>Group</th>
<th>Lipid, maintenance dose</th>
<th>Total, n</th>
<th>Reversal of PNAC</th>
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<tr>
<td>Lam et al. (13)</td>
<td>Hong Kong, May 2009–January 2011</td>
<td>Infants with PNAC (DB &gt; 2 mg/dL)</td>
<td>DB &gt; 2 mg/dL</td>
<td>29 (26–37)²</td>
<td>Control</td>
<td>Intralipid; 1.5 g · kg⁻¹ · d⁻¹</td>
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<td>Angsten et al. (4)</td>
<td>Sweden, October 2006–October 2010 and 1985–2005</td>
<td>Infants with SBS treated with Intralipid, 1985–2005 in historical cohort</td>
<td>DB &gt; 50 μmol/L</td>
<td>26 (23–41)</td>
<td>Intervention</td>
<td>Omegaven; 1 g · kg⁻¹ · d⁻¹</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Gura et al. (18)</td>
<td>United States, September 2004–August 2006 and 1986–1996</td>
<td>Infants with PNAC (direct bilirubin &gt; 2 mg/dL) and SBS 1986–1996 in historical cohort</td>
<td>DB &gt; 2 mg/dL</td>
<td>30 ± 4</td>
<td>Control</td>
<td>Intralipid or Lyposin II; 1–4 g · kg⁻¹ · d⁻¹</td>
<td>21</td>
<td>7</td>
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Effect of fish oil–containing lipid emulsions on prevention of PNAC in neonates

<table>
<thead>
<tr>
<th>Study design</th>
<th>Location, study period</th>
<th>Population</th>
<th>Definition of cholestasis</th>
<th>GA at birth, wk</th>
<th>Group</th>
<th>Lipid, maintenance dose</th>
<th>Total, n</th>
<th>Reversal of PNAC</th>
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<tbody>
<tr>
<td>Karagiozoglou-Lampoudi et al. (12)</td>
<td>Greece, NA</td>
<td>Neonates with GA 23–36 wk and needing parenteral nutrition at least 7 d</td>
<td>DB &gt; 2 mg/dL</td>
<td>NA</td>
<td>Control</td>
<td>Soybean-based lipid emulsion; NA</td>
<td>122</td>
<td>11</td>
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<tr>
<td>Savini et al. (16)</td>
<td>Italy, January 2007–October 2011</td>
<td>Neonates with a birth weight 500–1249 g</td>
<td>DB &gt; 2 mg/dL</td>
<td>NA</td>
<td>Intervention</td>
<td>SMOFlipid, NA</td>
<td>127</td>
<td>5</td>
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</table>

Effect of fish oil–containing lipid emulsions on prevention of PNAC in neonates (Continued)
TABLE 1

<table>
<thead>
<tr>
<th>Location, study period</th>
<th>Population</th>
<th>Study design</th>
<th>Location, study period</th>
<th>Study design</th>
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<th>Study design</th>
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<tbody>
<tr>
<td>Greece, January 2010</td>
<td>prospective observational study</td>
<td>Group A: neonates with GA 23–36 wk and a birth weight &lt; 1500 g</td>
<td>December 2007 and January 2008</td>
<td>retrospective case control study</td>
<td>Group B: neonates with GA &lt; 22 wk</td>
<td>December 2009</td>
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<tr>
<td>Poland, January 2010</td>
<td>prospective observational study</td>
<td>Group A: neonates with GA 23–36 wk and a birth weight 1500–2500 g</td>
<td>December 2007 and January 2008</td>
<td>retrospective case control study</td>
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Primary outcome. Overall, 28 of the 47 neonates (59.6%) who received the fish oil–containing lipid emulsions recovered from PNAC, compared with 9 of the 46 neonates (19.6%) in the control group who showed signs of recovery. The use of fish oil–containing lipid emulsions was more likely to reverse PNAC (OR: 6.14; 95% CI: 2.27, 16.6; P < 0.01; Figure 2A) with no evidence of heterogeneity (P = 0.28, I² = 22.3%). A sensitivity analysis by sequential exclusion of individual studies showed no significant change in the results (Figure 2B). The funnel plot showed no evidence of publication bias. In addition, the Begg-Mazumdar rank correlation test (P = 1.0) and Egger’s regression test (P = 0.69) did not show evidence of publication bias.

Secondary outcome. Among the 471 patients administered fish oil–containing lipid emulsions, PNAC occurred in 14 patients (3.0%) compared with 32 of the 630 patients (5.1%) in the control group. The use of fish oil–containing lipid emulsions did not significantly affect the development of PNAC (OR: 0.56; 95% CI: 0.28, 1.10; P = 0.05), but this was not statistically significant. The results from the subgroup analyses for preventing PNAC revealed that none of the fish oil groups used Omegaven (OR: 0.13; 95% CI: 0.02, 1.03; P = 0.05) or a mixed group (OR: 0.67; 95% CI: 0.33, 1.36; P = 0.27); SMOFlipid (15% fish oil), Lipidem (10% fish oil), or the use of a combination of Omegaven with a soybean-based lipid emulsion such as ClinOleic showed a definite PNAC preventive effect (Figure 3D). The fish oil group (100% fish oil; Omegaven) tended to experience decreased development of PNAC (OR: 0.13; 95% CI: 0.02, 1.03; P = 0.05), but this was not statistically significant.
lipid emulsions on reversing PNAC may be because of the anti-inflammatory effects of the ω-3 FAs in fish oil. No significant differences (OR: 0.56; 95% CI: 0.28, 1.10; \( P = 0.093 \)) were found in comparison with the other types of lipid emulsions evaluated in this study. Among the included studies, only 1 study by Pawlik et al. (17) found a statistically significant reduction in the development of PNAC in patients who received fish oil–containing lipid emulsions. No difference in the development of PNAC (12, 16) or a trend toward a lower incidence of PNAC was observed in the ω-3 FA group (14). All studies related to the primary outcome used Omegaven, but only 1 study, by Pawlik et al. (17), used Omegaven (100% fish oil) combined with ClinOleic in a 1:1 ratio to prevent PNAC. In the subgroup analysis of secondary outcomes, the fish oil group that used Omegaven showed a decreasing tendency to develop PNAC (OR: 0.13; 95% CI: 0.02, 1.03; \( P = 0.054 \); Figure 3D). We assumed that the effect of fish oil on preventing PNAC may have been underestimated because of the low fish oil content used in the mixed group, such as SMOFlipid, Lipidem, or the use of a combination with soybean-based lipid emulsions.

Xu et al. (6) reported normalization of direct bilirubin concentrations and histologic improvement after using ω-3 FAs in an adult population after PNAC was first documented in 1971 by Peden et al. (30). A meta-analysis of these studies also demonstrated the effect of fish oil–containing lipid emulsions on reversing PNAC.

### Discussion

The incidence of PNALD is 40–85% in infants who receive long-term PN support (1–4). Among neonates receiving PN for >2 wk, 20% shows signs of developing PNAC (5). In a study by Skouroliakou (14), 10.9% of very-low-birth-weight infants and 1.96% of low-birth-weight infants developed cholestasis regardless of the type of intravenous lipid emulsion used. Growing evidence indicates that fish oil–containing lipid emulsions have beneficial effects on PNAC (3, 6, 7, 12–14, 19); however, the study sample sizes were insufficient to ensure the effect of fish oil on PNAC. We attempted to evaluate the effect of fish oil–containing lipid emulsions in neonates, including preterm infants, which is a major population that requires nutritional support parenterally for survival early in life.

The PNAC mechanism is unknown, but possible causes after PN could be amino acid composition, lack of stimuli for bile formation in the gastrointestinal tract, or a line-associated infection or sepsis (20–22). Moreover, a high amount of phytosterol was observed in the soybean-based lipid emulsion in patients with PNAC, and phytosterol accumulation is caused by a decrease in bile flow in an animal model (23) and in neonates (24). Increased amounts of hepatotoxic phytosterol and a proinflammatory mediator were also observed because of high amounts of ω-6 PUFAs in a soybean-based lipid emulsion (25). The accumulation of phytosterol can reduce bile secretion in the liver by reducing synthesis of bile acids, altering membrane functions, and forming sludge and/or stones (25).

In addition to the phytosterols in the soybean-based lipid emulsion, the anti-inflammatory actions of fish oil are proposed as a possible mechanism for the observed hepatoprotective effects (26, 27). The effect of fish oil–containing lipid emulsions on reversing and preventing PNAC could be explained by the high amounts of ω-3 FAs, including EPA (20:5n–3) and DHA (22:6n–3), and the low amounts of ω-6 FAs in fish oil compared with soybean-based lipid emulsions (28).

In contrast to soybean-based lipid emulsions and medium-chain TG derived from coconut oil, fish oil can prevent the inflammatory response and reduce ongoing inflammation and oxidative stress through EPA and DHA, while blocking the generation of proinflammatory cytokines (14, 26, 27). Skouroliakou et al. (24) demonstrated the antioxidant mechanism of ω-3 FAs, compared with a soybean-based lipid emulsion, by measuring vitamin A and vitamin E concentrations and total antioxidant potential in preterm infants. Miloudi et al. (29) reported reduced PN-related oxidative stress by using Omegaven compared with Intralipid. The effect of fish oil–containing lipid emulsions on reversing PNAC may be because of the anti-inflammatory effects of the ω-3 FAs in fish oil. No significant differences (OR: 0.56; 95% CI: 0.28, 1.10; \( P = 0.093 \)) were found in comparison with the other types of lipid emulsions evaluated in this study. Among the included studies, only 1 study by Pawlik et al. (17) found a statistically significant reduction in the development of PNAC in patients who received fish oil–containing lipid emulsions. No difference in the development of PNAC (12, 16) or a trend toward a lower incidence of PNAC was observed in the ω-3 FA group (14). All studies related to the primary outcome used Omegaven, but only 1 study, by Pawlik et al. (17), used Omegaven (100% fish oil) combined with ClinOleic in a 1:1 ratio to prevent PNAC. In the subgroup analysis of secondary outcomes, the fish oil group that used Omegaven showed a decreasing tendency to develop PNAC (OR: 0.13; 95% CI: 0.02, 1.03; \( P = 0.054 \); Figure 3D). We assumed that the effect of fish oil on preventing PNAC may have been underestimated because of the low fish oil content used in the mixed group, such as SMOFlipid, Lipidem, or the use of a combination with soybean-based lipid emulsions.

Xu et al. (6) reported normalization of direct bilirubin concentrations and histologic improvement after using ω-3 FAs in an adult population after PNAC was first documented in 1971 by Peden et al. (30). A meta-analysis of these studies also demonstrated the effect of fish oil–containing lipid emulsions on reversing PNAC.

### Table 2: The Newcastle-Ottawa scale for the risk of bias and quality assessment of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
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<tbody>
<tr>
<td>Gura et al. (18)</td>
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<td>Angsten et al. [4]</td>
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<td>Skouroliakou et al. (14)</td>
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<td>Karagiozoglou-Lampoudi et al. (12)</td>
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1 Each domain that meets the criteria is given a star. The total number of stars determines the overall score (quality): 0–3 (low), 4–5 (moderate), and 6–8 (high).

2 When there was no significant difference in the response rate between the two groups based on the chi-square test (**P** = 0.054; Figure 3D).
compared with other lipid emulsions. In the included studies, the mean time to reverse cholestasis was 4.7- to 5-fold faster in the fish oil–containing lipid emulsions group than in the soybean-based lipid emulsion group (4, 18) but was similar in both groups in the study by Lam et al. (13).

Low-birth-weight infants and prematurity are risk factors for PNAC (22, 23). A high incidence of PNAC occurs in preterm and growth-restricted infants, which may be a specific population to use to further evaluate the protective role of fish oil–containing lipid emulsions.

Moreover, fish oil–containing lipid emulsions were safely used as early as 23–27 wk of gestation (4, 14) and in neonates with birth weights of 500–1249 g from the first day of life (16, 17). We assumed that the anti-inflammatory effect of fish oil could have a major role for preventing and reversing PNAC, particularly in preterm infants < 32 wk of gestation who have decreased antioxidant capacity (31). However, the use of fish oil–containing lipid emulsions did not affect the development of PNAC.

Initially, manufacturers did not recommend monotherapy with fish oil, which was not started until 2005 (32). Among the studies included, fish oil was used as a monotherapy in 1 study (4), and fish oil was used in combination with other forms of oils, such as SMOFlipid or ClinOleic, in the other studies (12–14, 16–18).

The risk of an essential FA deficiency because of the use of fish oil as monotherapy was proposed because of the low concentration of ω-6 FAs, but it was not observed in a study in which Omegaven was used at 1 g · kg⁻¹ · d⁻¹ (13, 14). The effect of fish oil–containing lipid emulsions on measurements of growth acceleration are inconsistent (24), including body weight and head circumference (13), compared with soybean-based lipid emulsions. Ursodeoxycholic acid, cyclic TPN, light protection for PN, tapering the soybean-based lipid emulsion, and antibiotics to decontaminate bacterial overgrowth are used to treat PNAC (22, 29, 33). Enteral feeding is the best strategy to reverse and prevent PNAC, with as little as 10% of caloric intake showing beneficial effects (22, 34–36). In this meta-analysis, we demonstrated that fish oil–containing lipid emulsions could be useful in infants to reverse PNAC for whom enteral feeding is intolerable.

No definitive publication bias was found as assessed by the Begg-Mazumdar rank correlation test and funnel plot (Figure 4), but we must interpret the results cautiously, because this meta-analysis was performed with small trials and included only 3 (for reversal of PNAC) and 4 (for prevention of PNAC) studies. The use of enteral fish oil is tolerable for other adult diseases (26) and for premature infants with short bowel syndrome. In all of the included studies, fish oil–containing lipid emulsions were administered intravenously; thus, there is no information on enteral use of fish oil.

In this meta-analysis, fish oil–containing lipid emulsions were more likely to reverse PNAC in neonates who required long-term parenteral nutritional support compared with other types of lipid emulsions. However, no evidence supports the use of fish oil–containing lipid emulsions to prevent PNAC in neonates, including preterm infants. Well-designed randomized controlled trials that use lipid emulsions that contain 100% fish oil, such as Omegaven, to evaluate the preventive effects of fish oil on PNAC are warranted, and further studies are needed to evaluate the effect of fish oil–containing lipid emulsions on growth, safety, and
and efficacy of enteral fish oil–containing lipid emulsions for reversing and preventing PNAC in preterm infants.

Acknowledgments
We thank Eun-Mi Kim of the Library of the Konkuk University School of Medicine for providing help in the literature search. HWP, NML, and JHK jointly reviewed the studies for eligibility and summarized the data; HWP drafted the manuscript; KSK and S-NK provided critical revisions of the manuscript for important intellectual content; S-NK analyzed the data. All authors read and approved the final manuscript.

References