ESPGHAN Committee on Nutrition Position Paper. Intravenous Lipid Emulsions and Risk of Hepatotoxicity in Infants and Children: a Systematic Review and Meta-analysis

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ABSTRACT

The aim of the present article was to perform a systematic review with meta-analysis of available scientific evidence regarding the role of different intravenous lipid emulsions (ILE) in the pathogenesis of cholestasis and parenteral nutrition–associated liver disease. A systematic review of the literature (up to March 2015) identified 23 randomized controlled trials (RCTs). Of these, 17 were performed in preterm infants or critically ill neonates with a short duration of intervention, 2 in older children with short-term use (following surgery or bone marrow transplantation), 1 in neonates with long-term use, and 3 in infants and children receiving long-term parenteral nutrition (PN). Meta-analysis showed no differences in the rate of cholestasis or bilirubin levels associated with short-term use of different ILEs. Because of high heterogeneity of the long-term studies no meta-analysis could be performed. Available studies found that the use of multicomponent fish oil (FO)-containing ILE compared with pure soya bean oil (SO), ILE-reduced liver enzymes, and bilirubin levels in noncholestatic children on long-term PN and one other RCT found that FO-based ILE-reversed cholestasis in a proportion of patients. The ESPGHAN Committee on Nutrition concludes that there is no evidence of a difference in rates of cholestasis or bilirubin levels between different ILE for short-term use in neonates. The use of multicomponent FO-containing ILE may contribute to a decrease in total bilirubin levels in children with IF on

What Is Known

- There is evidence that intravenous lipid emulsions (ILE) play a role in the pathogenesis of cholestasis and parenteral nutrition–associated liver disease.
- A number of trials have suggested that novel fish oil–containing ILE could have a beneficial effect on cholestasis and parenteral nutrition–associated liver disease.

What Is New

- The present systematic review identified 23 randomized controlled trials, which evaluated the effect of different ILEs on cholestasis.
- Meta-analysis showed no differences in the rate of cholestasis or bilirubin levels associated with short-term use of different ILE formulations in preterm infants, neonates, and children.
- Although quality data are lacking there is some evidence that the use of multicomponent fish oil–containing ILE may contribute to a decrease in total bilirubin levels in children with intestinal failure on prolonged parenteral nutrition.

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prolonged PN. Well-designed RCTs are, however, lacking and long-term effects have not been determined.

Key Words: children, fish oil, infants, lipids, medium-chain triglycerides, neonates, olive oil, soya bean oil

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During the last 3 decades, parenteral nutrition (PN) has been increasingly used to improve nutritional status in paediatric patients ranging from premature infants not fully tolerating enteral nutrition to children with intestinal failure (IF). IF is defined as the inability of the gut to absorb the minimal fluids and energy requirements necessary to sustain life and growth (1). Normal or catch-up growth and long-term survival have become possible in children with chronic IF who depend on total or (more often) complementary PN (2–5). Along with technological advances and improvements in clinical understanding, and the widespread adoption of guidelines provided by expert teams (6), the quality of paediatric PN has dramatically improved. PN-associated liver disease (PNALD), however, has long been considered as one of the most frequent and life-threatening complications of PN, especially in children with chronic IF (7,8). PNALD is defined as cholestasis occurring in the setting of PN, if other specific causes of liver injury have been excluded. Cholestasis is usually defined as an elevated conjugated serum bilirubin ($\geq$2 mg/dL [34.2 μmol/L]) (9). Overall cholestasis affects a large number of patients receiving PN; it may develop in 40% to 60% of infants (10) and up to 85% of neonates (11) who require long-term PN. Moreover, evidence of liver dysfunction may occur as early as 14 days after initiating PN in neonates (12).

The term IF-associated liver disease (IFALD) (13,14), often used interchangeably with PNALD, is a broader term including causes other than PN such as underlying disease, massive intestinal resection (15), sepsis (16,17), and absence of enteral feeding (10). Because the focus of the present article is on the role of intravenous lipid emulsions (ILE) we will use the term PNALD.

Risk factors for PNALD are related to many factors, but are particularly associated with individual PN constituents, whether as deficiencies, excesses, or toxicity (10). The possible toxicity of ILE, in particular, is a focus of concern. Lipids are recognized as an indispensable component of non-protein energy intake in patients receiving PN. In addition to their high caloric value and low osmolality, the use of ILE also prevents the complications of using glucose as the sole non-protein energy source, including essential fatty acid deficiency, hyperglycaemia, and hepatic steatosis (18,19). A possible role of ILE in the pathogenesis of cholestasis was suggested by several studies (20,21).

Because of the recent availability of a new generation of ILE and promising results in the prevention and treatment of PNALD, the aim of the present article is to summarize the scientific evidence regarding the role of different ILE in the pathogenesis of cholestasis and PNALD and to perform a systematic review with, where appropriate, a meta-analysis on the effect of different types of ILE on cholestasis and PNALD.

INTRAVENOUS LIPID EMULSIONS

The first ILE was introduced in the early 1960s and was considered a major breakthrough in PN care. The first commercially available product consisted of the long-chain triglyceride (LCT) soya bean oil (SO) (22). These ILE contained small amounts of n-3 fatty acids and high amounts of n-6 essential fatty acids, mostly linoleic acid, whereas the remaining profile mostly included saturated fatty acids such as palmitic and stearic, in descending concentrations (22). In the late 1980s, mixed preparations containing 50% medium-chain triglycerides (MCT) and 50% soya-based LCT became available (MCT/SO). MCT were long advocated as a superior substrate for PN use, because they are hydrolysed more quickly than LCT and possess many unique physiochemical and metabolic properties making them theoretically advantageous more than their LCT counterparts. These advantages include preferential lipoprotein lipase hydrolysis, non–carnitine-dependent metabolism, and rapid oxidation (23). In the late 1990s, a new olive oil (OO)/SO lipid (OO/SO) emulsion (OO:SO = 4:1) with lower (20% vs 60%) amounts of polyunsaturated fatty acid (PUFA), a high amount of monounsaturated oleic acid, and higher vitamin E content started to be used in patients on long-term PN (24–26). The potential advantages of OO/SO ILE are to decrease the risks related to an excessive intake of PUFAs such as increased peroxidation and also to decrease the phytosterol load (27,28).

More recently fish oil (FO) has become available, either alone or in combination with other oils. FO has several theoretical advantages, including a high concentration of added α-tocopherol (4- to 8-fold the amount in SO), and no phytosterols. Moreover, FO is a rich source of docosahexaenoic acid (DHA), which is important for neurodevelopment and visual function, and also a source of eicosapentaenoic acid (EPA). EPA has been shown to favourably modulate inflammatory pathways, both directly by decreasing the production of pro-inflammatory cytokines and indirectly by an increase in secretion of interleukin-10, an anti-inflammatory cytokine, by hepatic macrophages (29). Furthermore, both DHA and EPA serve as precursors of inflammation-resolving mediators (ie, resolvins and protectins) (30). Theoretically high levels of EPA may, however, prolong bleeding time and increase LDL cholesterol levels, but clinical importance of these effects is unclear (31). In animal models, FO delivered intravenously improves biliary flow and decreases cholestasis (32), whereas it upregulates bile acid transport mechanisms (33). It also reduces de novo lipogenesis, stimulates β-oxidation, and decreases hepatic steatosis (34,35).

The characteristics of widely used commercially available ILE are presented in Table 1.

MECHANISMS OF PNALD PATHOGENESIS

Various mechanisms have been proposed for the possible role of ILE in PNALD, including modulation of oxidative stress and inflammation (by peroxidation of PUFAs and differences in α-tocopherol content), competition of transport (by differences in phytosterol content), and by differences in lipid clearance (13,40).

Oxidative Stress

Excessive intake of linoleic acid, which is converted to arachidonic acid, a precursor of proinflammatory agents (such as tumour necrosis factor-α, interleukin-6, platelet activating factor, and adhesion molecules), may have adverse effects on the liver causing chronic inflammation, which could consequently lead to liver cholestasis and fibrosis (29,36,41,42). PUFAs such as linoleic acid can undergo peroxidation causing the production of lipid peroxides, unstable molecules that can trigger chain reactions resulting in inactivation of enzymes, proteins, and other elements necessary for the viability of cells (22,43–45). This oxidative stress is considered to be one of the possible causes of liver toxicity resulting from lipids. In animal models, reactive oxygen species increased during oxidative stress leading to decreased bile production and contributing to cholestasis (46). In addition, low levels of the antioxidant α-tocopherol in SO ILE (47) can modulate the risk of oxidative stress (45,48); therefore, some lipid emulsions contain added α-tocopherol (24). Accordingly, new generations of ILE aim to provide n-3 and to reduce n-6 fatty acids load while

TABLE 1. Characteristics of commercially available intravenous lipid emulsions used in reported randomized controlled trials (27,36–39)

Abbreviation	Intralipid 20% SO	ClinOleic 20% OO/SO	Lipofundin 20% MCT/SO	SMOFlipid 20% multicomponent FO-containing	Omegaven 10% FO
Year of introduction	1960s	1990s	1980s	2000s	1990s
	Oil source, %				
Soya bean	100	20	50	30	0
MCT	0	0	50	30	0
Olive	0	80	0	25	0
Fish	0	0	0	15	100
	Fatty acids (% of total fatty acid)				
Linoleic acid	53	18.7	29.1	37.2	4.4
Arachidonic acid	0.1	0.5	0.2	1.0	2.1
α-Linolenic acid	8	2.3	4.5	4.7	1.8
Eicosapentaenoic acid	0	0	0	4.7	19.2
Docosahexaenoic acid	0	0	0	4.4	12.1
n-6:n-3 ratio	7:1	9:1	7:1	2.5:1	1:8
Phytosterols (mg/L) based on Angsten et al (39)*	348±33	237 ± 8	NA	47.6	0
Phytosterols (mg/L) based on Xu et al (27)†	439.07 ± 5.72	274.38 ± 2.60	278.14 ± 5.09	207	No phytosterols, squalene 26.7 mg/L
α-Tocopherol (mg/L)	38	32	85 ± 20	200	150–296

FO, fish oil; MCT, medium-chain triglycerides; OO, olive oil; SO, soya bean oil.
* Data in the table are the mean value when an interval is given from the manufacturer (39).
† Independently evaluated concentration of 9 different phytosterols and sqalene (27).

enhancing α-tocopherol intake (40). Levels of α-tocopherol in different ILE are presented in Table 1.

Phytosterols

Another major concern is related to plant sterols (PS), also called phytosterols. PS are steroid alcohols which belong to plant cell membranes, similar to cholesterol in mammals. PS have a striking structural similarity to bile acids. Conventional SO ILEs contain significant quantities of PS and their long-term use leads to a progressive increase in PS content in human cell membranes and plasma lipoproteins (27). Enterally, PS are poorly absorbed by the human intestine, but their blood concentrations are closely associated with cholestasis in children and adults (49–53). PS have been shown to reduce bile acid secretion in rats and to inhibit secretory function in isolated rat hepatocytes (54). The mechanism leading to cholestasis is thought to be the antagonism of nuclear farnesoid X receptor (FXR) which regulates bile excretion via the multidrug resistance transporter 2, responsible for the transport of bile components out of the hepatocyte (55). Multidrug resistance transporter 2–deficient mice develop cholestasis (56) and mice lacking the FXR are exposed to bile acid liver injury (57), whereas treatment with an FXR agonist has shown a hepatoprotective effect in a rat model of intrahepatic and extrahepatic cholestasis (58). Furthermore, there is evidence presented from animal models that total PN suppresses both bile acid production and hepatocyte export (bile acid–induced bile salt export pump) leading to intrahepatic bile acid accumulation, and PS can cause inhibition of bile acid–induced bile salt export pump expression (59). Information available in the literature related to PS concentrations in ILE is scarce; a study which compared PS concentrations in 8 commonly used parenteral ILE demonstrated that concentrations of the various steroidal compounds varied greatly between the ILE, with the highest levels found in SO ILE (Table 1) (27). This was confirmed in a recent study in premature infants comparing an SO ILE and multicomponent FO-containing ILE (SMOFlipid; Fresenius Kabi, Germany—SO, MCT, olive, and fish oil) (37). It has, however, recently been shown in piglet model that the difference in cholestasis and liver injury among novel ILE, especially for the group receiving multicomponent FO-containing ILE, were only weakly correlated with plasma and hepatic PS content suggesting that other components could influence liver injury (59). Savini et al measured PS in preterm infants receiving different types of ILE and found that PS serum levels were positively correlated with PS intake (60). Cholestasis was, however, rare and there was no difference in the liver function tests between groups (60).

Activation of the Reticuloendothelial System

Although the metabolism of the oxidized fraction of the ILE is relatively well known, far less understood is the destiny of the nonoxidized fraction, which is sequestered by the reticuloendothelial cells (RECs) in the liver (ie, Kupffer cells) and also by the spleen, bone marrow, and lungs. In children, chronic administration of ILE may overload REC and induce their acute or chronic activation leading to hematologic disorders, accompanied by liver dysfunction and cholestasis (61,62). In a rat model, ILE infusion resulted in downregulated hepatic lipase activity and fat vacuoles in Kupffer cells and hepatocytes, with morphological signs of increased Kupffer cell activity, suggesting that ILE may activate macrophages (63). In a mouse model, total PN was shown to reduce the number of hepatic REC and to impair their function, resulting in poor survival after intraportal bacterial challenge (64). CD14 and toll-like receptor 4/MD-2 expression both showed significant reductions (64). Some authors have hypothesized that intestinal injury with increased intestinal permeability combined with administration of PN promote lipopolysaccharide-toll-like receptor 4 signalling-dependent Kupffer cell activation as an early event in the pathogenesis of IFALD/PNALD (65). No relation between IFALD, liver REC, and ILE has, however, yet been established in humans.

ROLE OF DIFFERENT ILE IN THE PATHOGENESIS OF PNALD

ILE (10% vs 20%)

There are clinically significant differences in commercially available 10% and 20% lipid emulsions, especially in their phospholipid content; phospholipid/triglyceride ratio is higher in 10% lipid ILE compared with 20% (66). Administration of 20% ILE leads to significantly faster triglyceride clearance compared to 10% ILE (67,68). Therefore, in most paediatric patients, only 20% emulsions are used (69). Infants who received 10% ILE had lipoprotein X–like particles in the low-density lipoprotein fraction, which has previously been shown to be associated with cholestasis (67). There is currently no evidence suggesting that different lipid concentrations have an influence on cholestasis.

Dose Reduction

With the aim of preventing or treating cholestasis associated with PN, some centres have attempted to modify lipid administration by reducing the amount of lipid (70), cycling PN (71,72), or temporarily completely removing lipids from PN in children on prolonged PN (21,73) based on the assumption that a dose of 1 $g \cdot kg^{-1} \cdot day^{-1}$ or less may be effective in preventing PN-associated cholestasis (PNAC) in both infants and children (11,21,74–76). A small, randomized controlled trial (RCT) performed by Rollins et al (77) found that reduction of the dose of SO ILE (1 $g \cdot kg^{-1} \cdot day^{-1}$ vs standard dose 3 $g \cdot kg^{-1} \cdot day^{-1}$) lowered the conjugated bilirubin in 28 neonates who underwent surgery and who were on PN for at least 4 weeks (77). In contrast, a recently published retrospective study failed to demonstrate that reduction of SO ILE to 1 $g \cdot kg^{-1} \cdot day^{-1}$ could delay the onset of cholestasis in 61 neonates (78). Moreover, although there is some evidence that lipid restriction may be beneficial and appropriate for patients with PNALD, the unknown long-term effects on growth and neurodevelopment remain a concern especially in premature infants (77).

Source of ILE

There is emerging evidence that the lipid source in ILE may have a role in PNALD. Several case-control studies have reported efficacy of FO as monotherapy (1 g/kg) in the treatment of PNALD in infants and children (79–88). Similarly, resolution of cholestasis was also found when multicomponent FO-containing ILE were introduced (89,90). These promising new results elicited numerous review articles and recommendations from different authorities on which ILE should be used (13,38,91). Although this emerging data suggest that lipid source could have a role in the prevention/treatment of cholestasis, a comprehensive assessment of available data is lacking. The aim of the present study is to perform a systematic review of the available RCT on the role of different ILE in the pathogenesis of cholestasis and PNALD in infants and children.

MATERIALS AND METHODS

A systematic review of the literature using defined search criteria was performed. A PubMed, EMBASE, and Cochrane Central Register of Controlled Trials CENTRAL search up to March 2015 was conducted. The following key terms were used (words in the title or abstract of the manuscript): (''lipid'' OR ''fat'' OR ''fatty acid'' OR ''oil'') AND (''parenteral'' OR ''intravenous'' OR ''infusion'') AND (''liver disease'' OR ''parenteral nutrition–associated liver disease'' OR ''intestinal failure associated liver disease'' OR ''liver disease'' OR ''cholestasis'' OR ''liver enzymes'' OR ''bilirubin''). The searches were limited to human studies. An age filter to restrict the search to children (0–18 years) and a filter for clinical studies were applied. The search was limited to English language manuscripts and only published data were considered. The reference lists of identified studies and key review articles, including previously published reviews, were also searched.

The primary outcome measure was the incidence of cholestasis defined as an elevated serum conjugated bilirubin ≥2 mg/dL (34.2 μmol/L). Secondary outcomes were the levels of total and conjugated bilirubin and liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], and γ-glutamyltransferase [GGT]) after the use of ILE.

Studies were included if they met all of the following criteria: RCT design in infants and children who needed PN and received parenteral lipid emulsion. No restriction on the dose or duration of administration of lipid infusion was applied. Studies with other designs (cohort studies, case series, case reports) were not included in the analysis.

The level of evidence for selected studies was graded using the Oxford Centre for Evidence-Based Medicine ''Levels of Evidence'' methodology and disagreements were resolved by discussion (92).

The data were analysed using Review Manager (RevMan) version 5.3. The primary outcome (binary measure) was presented as the risk of event (cholestasis) in experimental and control groups. Secondary outcomes were continuous and were given as the mean with standard deviation (SD). When data were presented as the standard error of the mean, the SD was recalculated. If data were presented as a median with the range, the authors were contacted to provide us with the mean values and SD. Data that were reported only as median values and no mean values were provided by the authors (93) were not included in the analysis due to nonsymmetrical distribution of the median.

In order to avoid heterogeneity, secondary outcome measures were levels reported at the end of the study but at a maximum of 14 days (range 6–14 days). Cholestasis rate was taken into account when reported although the time varied between studies (the longest follow-up was 6 weeks). Only studies those used SO ILE as control were included. Subgroup analysis was performed for specific experimental ILE (OO/SO and multicomponent FO-containing ILE).

Heterogeneity of the data was tested by visual assessment of the forest plot and by using the I^2 statistic in which levels of more than 50% were considered as showing substantial heterogeneity.

RESULTS

Search Results

Twenty-three of 493 potential studies on the effects of parenteral lipid emulsions on clinical outcomes met our predefined inclusion criteria. A flow chart of the search results is provided in Figure 1. Included studies were divided into 3 groups based on the age of participants and duration of the study: neonates including premature infants—short-term and long-term use, short-term use in older infants and children; and long-term use (defined as ≥4 weeks of PN) in infants and children.

Evaluation of Identified RCTs

Characteristics of included studies are reported in the supplementary table (*http://links.lww.com/MPG/A610*. Seventeen studies were performed in premature infants, 2 studies in older children (>1 year of age) on short-term PN, 3 studies in infants and children

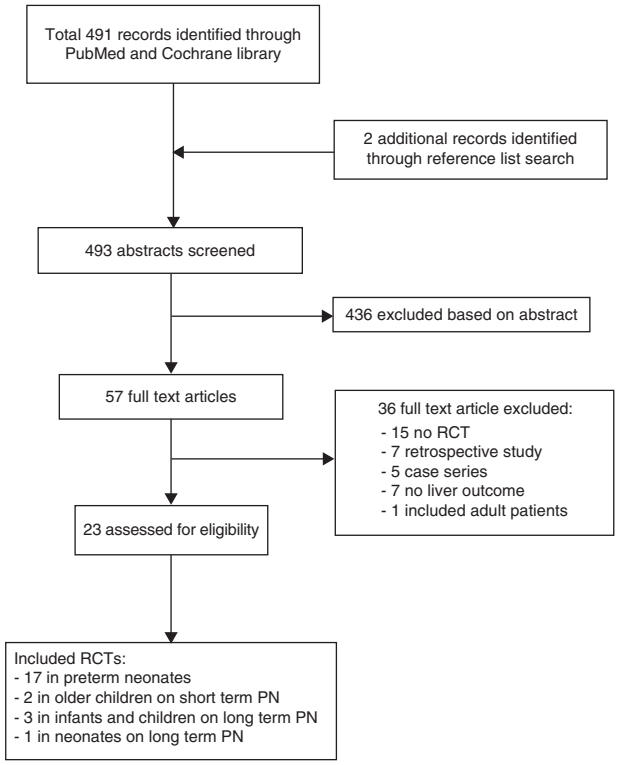

FIGURE 1. Flow chart of search results. PN, parenteral nutrition; RCT, randomized controlled trial.

(>1 month of age) on long-term PN (longer than 4 weeks), and 1 study in neonates on long-term PN.

From all the available studies meta-analysis could be performed only in the preterm infants and neonates who were on short-term PN. Overall, 11 studies reported at least 1 outcome, which was used in the meta-analysis (37,60,93–101); all these studies used SO ILE as a comparison. The meta-analysis did not include 5 studies (102–106), which reported no exact values for tested parameters and 1 study in which SO ILE was not used as a comparison (107). Overall 11 studies reported incidence of the cholestasis at baseline (93,95–103,107) from which 6 studies included only preterm infants/neonates with cholestasis at the baseline (93,96–100).

Neonates Including Preterm Infants

Short-Term Use in Neonates Including Preterm Infants

There were 17 RCT in total, which reported the influence of ILE on bilirubin or liver enzymes in preterm infants or critically ill neonates (Table 2). Six studies included children who had cholestasis at the time of the study (93,96–100). Only 2 studies determined bilirubin levels as a primary endpoint (105,106). Duration of the intervention was short (median/mean duration 3–27 days).

OO/SO Versus SO ILE

Six studies examined the difference between OO/SO (20% ClinOleic; Baxter, France) and SO (20% Intralipid; Fresenius Kabi, Germany) ILE (95–97,101–103). Five studies were performed in preterm infants; 4 studies found no difference in the bilirubin and/or liver enzymes between groups (95,97,102). The largest study, however, found significantly lower direct bilirubin 7 days after intervention with OO/SO ILE, although there was no difference in total bilirubin and liver enzymes (101). A study performed in critically ill neonates found lower levels of GGT in children who received OO/SO ILE (103).

MCT/SO Versus SO ILE

Two studies compared short-term use of SO (20% Intralipid) versus MCT/SO-based (20% Lipofundin; B. Braun, Germany) emulsions with no significant difference between interventions (105,106).

None of the mentioned studies were suitable for meta-analysis because there were no reported values for bilirubin levels or liver enzymes.

Multicomponent FO-Containing (SO, MCT, OO, and FO) Versus SO ILE

Six studies compared multicomponent FO-containing ILE, a physical mixture of 30% SO, 30% MCT, 25% olive oil, and 15% FO (SMOFlipid 20%) to SO (20% Intralipid) emulsion (37,93,94,98–100).

Two studies found a significantly greater decrease in bilirubin levels in the multicomponent FO-containing ILE group (98,99), whereas a third one found lower GGT in the multicomponent FO-containing ILE group, but no difference in bilirubin levels (100). Three studies found no difference in the cholestasis rate between groups (37,93,94).

Multicomponent FO-Containing (SO, MCT, FO) Versus MCT/SO ILE

One small pilot study compared a mixture of 10% FO, 50% MCT, and 40% SO to MCT/SO ILE and found no difference in total bilirubin levels at the end of intervention and 6 weeks after the intervention between groups (107). Because the present study did not use SO ILE as a comparison it was not included into the meta-analysis.

Comparison of Different ILEs

The largest study included 144 premature infants randomized into 5 arms (SO based [20% Intralipid], MCT/SO based [20% Lipofundin], multicomponent FO-containing ILE [SO, MCT, and FO] [20% Lipidem; B. Braun, Germany], OO/SO [20% ClinOleic], and multicomponent FO-containing ILE [SMOFlipid 20%]) and found no difference in bilirubin levels and liver enzymes between groups (60). Unfortunately, as the present study presented outcome values only 6 weeks after the introduction of ILE, it could not be included into meta-analysis for secondary outcomes.

Meta-Analysis

Primary Outcome

Six studies reported on the incidence of cholestasis at the end of the study (37,60,93,94,101,104). Pooled meta-analysis found no difference in incidence in any experimental mixed ILE compared to solely SO ILE (Fig. 2). The study by Pawlik et al (104) was not included in the analysis due to the control group (which was not SO ILE); the present study tested mixed FO-containing ILE (50% OO/SO ILE [20% ClinOleic] + 50% FO ILE [10% Omegaven]) compared to OO/SO ILE (20% ClinOleic) and found a significantly higher incidence of cholestasis in the group who received OO/SO ILE compared to multicomponent FO-containing ILE (320/70 vs 3/60; $P = 0.001$).

Secondary Outcomes Related to the Liver

All studies included in the meta-analysis reported total bilirubin levels 6 to 14 days after the intervention (57,92–100) and found no difference in overall effect and subgroup analysis

TABLE 2. Randomized controlled trials performed in premature infants and critically ill neonates

Author (year)	Subjects	Cholestasis before intervention	Intervention	Maximal daily dose, $g \cdot kg^{-1} \cdot day^{-1}$	Duration of intervention, days	Authors conclusions regarding liver function tests/bilirubin levels
Demirel (2012) (102)	40 VLBW premature infants (≤32 wk, <1500 g)	Not present; exact bilirubin values not reported	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	3	14	Liver enzymes were similar in two groups
Deshpande (2009) (95)	50 Premature infants (<28 wk) (44 completed the study)	Not present; exact bilirubin values not reported	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	3	5	Liver enzymes were not significantly different and within normal range in both groups
Koksal (2011) (97)	64 Premature infants (≤34 wk)	Present; total bilirubin levels in OO/SO group 7.4 ± 0.5 mg/L; SO group 6.2 ± 0.5 mg/dL	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	3	7	It was found that ALT and bilirubin decreased in both groups; no statistically significant difference was found between groups
Webb (2008) (103)	78 Critically ill neonates (≥25 wk of gestation, <7 days of age)	Not present; exact bilirubin values not reported	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	3	5	GGT was lower in the OO/SO group; not significant for bilirubin levels
Wang (2015) (101)	103 Premature infants (<2000 g)	Not present	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	3	Mean 27 and 23 days (at least 14 days)	The serum direct bilirubin was significantly higher in SO group after 7 days of PN; no difference between groups in regard to: AST, ALT, GGT, total bilirubin, and the incidence of cholestasis
Gobel (2003) (96)	45 Premature infants (28–37 wk) (33 completed the study)	Present; total bilirubin levels in OO/SO group 147.4 ± 6.6 μmol/L and SO group 138.6 ± 7.5 μmol/L	OO/SO (20% ClinOleic) vs SO (20% Intralipid)	2	7	No difference between groups for bilirubin and liver enzymes
Rayyan (2012) (98)	53 Premature infants (<34 wk)	Present; total bilirubin levels in multicomponent FO-containing group 127.6 ± 70.82 μmol/L and SO 115 ± 47.26 μmol/L	Multicomponent FO-containing (SMOFlipid 20%) vs SO (20% Intralipid)	3.5	7–14	Significantly higher decrease in total and direct bilirubin in the multicomponent FO-containing group
Skouroliakou (2010) (99)	38 Premature infants (<32 wk, <1500 g)	Present; total bilirubin levels in multicomponent FO-containing group 7.21 ± 2.39 mg/dL and SO 6.79 ± 2.18 mg/L	Multicomponent FO-containing (20% SMOFlipid) vs SO (20% Intralipid)	3	>14 days until discharge (not reported)	Bilirubin significantly decreased in the multicomponent FO-containing group (discharge comparing to baseline)
D'ascenzo (2011) (107)	48 Premature infants (500–1249 g)	Not present	Mixture of 10% FO, 50% MCT, and 40% SO vs MCT/SO	2.5	Up to 18 days	No significant difference in bilirubin levels
D'ascenzo (2014) (94)	80 Premature infants (500–1249 g)	Not reported	Multicomponent FO-containing (20% SMOFlipid) 2.5 and 3.5 $g \cdot kg^{-1} \cdot day^{-1}$ vs SO (20% Intralipid) 2.5 and 3.5 $g \cdot kg^{-1} \cdot day^{-1}$	2.5 and 3.5	7	No significant difference in total bilirubin levels between groups; the area under the curve of total bilirubin was significantly lower with multicomponent FO-containing than with soya bean oil.

(continued)

TABLE 2. *(continued)*

Author (year)	Subjects	Cholestasis before intervention	Intervention	Maximal daily dose, $g \cdot kg^{-1} \cdot day^{-1}$	Duration of intervention, days	Authors conclusions regarding liver function tests/bilirubin levels
Tomsits (2010) (100)	60 Premature infants	Present; total bilirubin levels in multicomponent FO-containing group 194.03 ± 68.49 μmol/L and SO 176.10 ± 57.00 μmol/L	Multicomponent FO-containing (20% SMOFlipid) vs SO (20% Intralipid)	2	7–14	At study end GGT was lower in the multicomponent FO-containing group; no difference in bilirubin levels
Beken (2014) (93)	80 VLBW infants	Present; total bilirubin levels in multicomponent FO-containing group 3.1 ± 1.3 mg/dL and SO 3.5 ± 1.6 mg/L	Multicomponent FO-containing (20% SMOFlipid) vs SO (20% Intralipid)	3	Median 14 days	No difference in cholestasis rate
Vlaardingerbroek (2014) (37)	96 VLBW infants	Not reported	Multicomponent FO-containing (20% SMOFlipid) vs SO (20% Intralipid)	3	Median 11 and 12 days	No differences between the groups in bilirubin (total and direct), ALT and cholestasis rate
Pawlik (2013) (104)	130 VLBW infants	Not reported	50% OO/SO (20% ClinOleic) + 50% FO (10% Omegaven) vs OO/SO (20% ClinOleic)	3.5	Mean ≈20 days (range 5–95 days)	Cholestasis was diagnosed 6 times more frequently in the OO/SO group
Rubin (1991) (105)	30 Premature infants	Not reported	SO (20% Intralipid) vs MCT/SO-based (20% Lipofundin) emulsions	3	3	Bilirubin levels decreased in both groups – no difference; unbound bilirubin was significantly lower in MCT/SO-based ILE group
Rubin (1995) (106)	49 Premature infants	Not reported	Paediatric fat emulsion (PFE 4501) vs SO (20% Intralipid) vs MCT/SO-based (20% Lipofundin) emulsions	2.5	6	Bilirubin plasma levels decreased significantly in all groups; no significant difference between the groups
Savini (2013) (60)	144 Premature infants	Not reported	SO (20% Intralipid) vs MCT/SO (20% Lipofundin) vs SMF (20% Lipidem) vs OO/SO (20% ClinOleic) vs multicomponent FO-containing (SMOFlipid 20%)	3	≈20	No significant difference between the groups regarding liver enzymes and bilirubin levels

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; FO, fish oil; GGT, γ-glutamyltransferase; ILE, intravenous lipid emulsions; MCT, medium-chain triglycerides; OO, olive oil; SMF, soya bean oil, MCT, and fish oil; SMOFlipid, soya bean oil, MCT, olive, and fish oil; SO, soya bean oil; VLBW, very low birth weight.

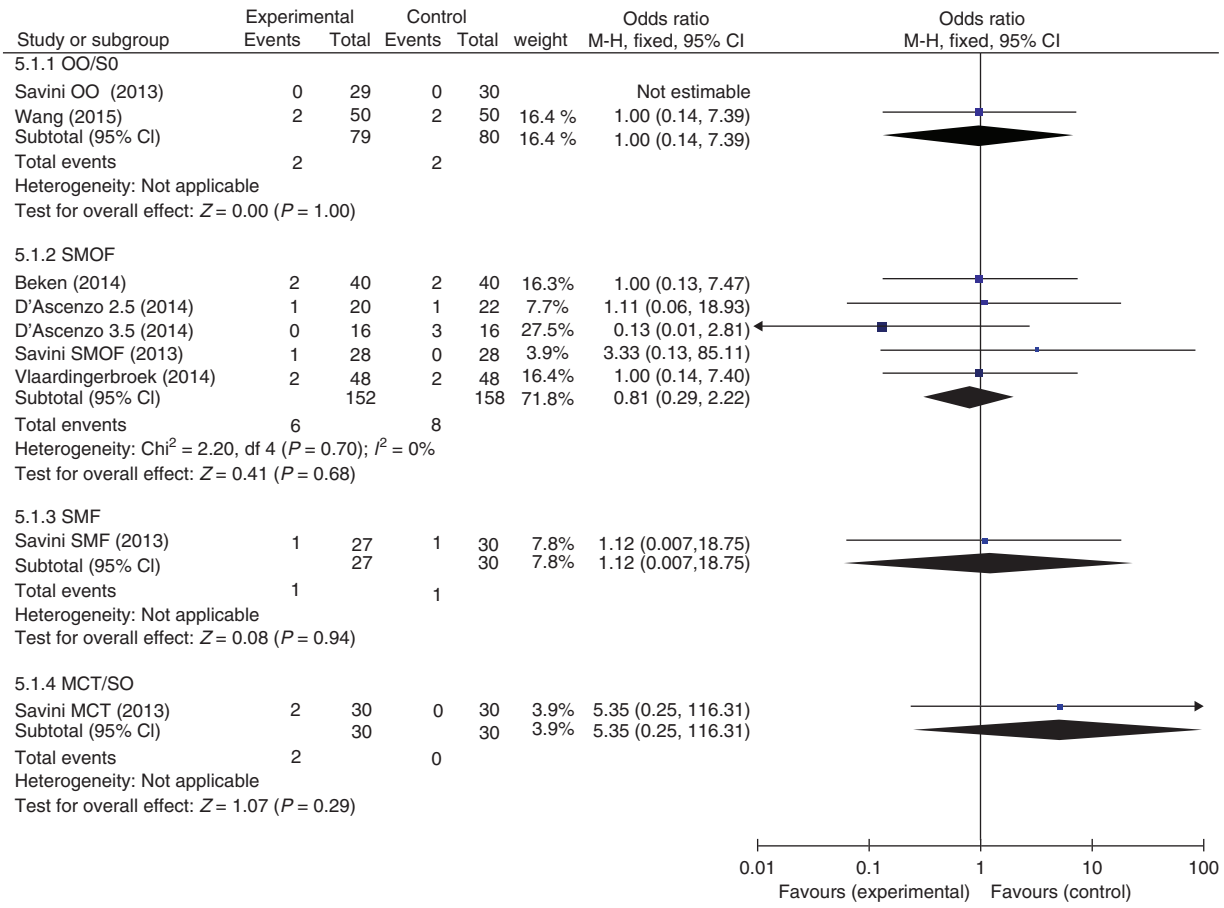

FIGURE 2. Effect of mixed intravenous lipid emulsions on cholestasis rate in comparison to pure soya bean–based lipid emulsion in neonates including preterm infants. CI, confidence interval; MCT/SO, medium-chain triglycerides and SO-based lipid emulsion; OO/SO, olive oil– and SO-based lipid emulsion; SO, soya bean oil–based lipid emulsion; SMF, multicomponent intravenous lipid emulsion (SO, MCT, fish oil [FO]); SMOF, multicomponent FO-containing intravenous lipid emulsion (SO, medium-chain triglycerides, OO, and FO).

(Fig. 3). Similarly, no difference was found for conjugated bilirubin assessed by 5 studies (37,95,96,98,101), ALP assessed by 4 studies (96,97,100,101), and GGT assessed by 6 studies (95–98,100,101) (Figs. 4–6). AST was assessed by 4 studies (37,96,97,101) (Fig. 7). ALT was assessed by 8 studies (37,93,95–98,100,101); however, due to high heterogeneity 1 study (97) was excluded from the meta-analysis. Overall results and separate results for OO/SO ILE and multicomponent FO-containing ILE found no difference comparing to solely SO ILE (Fig. 8).

Long-Term Use in Neonates

Only 1 RCT (108) evaluated the use of FO ILE (10% Omegaven) compared to SO ILE (20% Intralipid) on cholestasis incidence in young neonates who required long-term (more than 4 weeks) PN. Unfortunately, due to the low incidence of cholestasis, the study was terminated prematurely. Overall 19 neonates were included and the study failed to demonstrate any difference in direct bilirubin and liver function tests between groups (Table 3).

Infants and Children

Characteristics of included studies are reported in the supplementary table (*http://links.lww.com/MPG/A610*. Two studies were performed in older children (>1 year of age) on short-term PN and 3 studies in older infants or children (>1 month of age) on long-term PN (longer than 4 weeks).

Children With Short-Term PN

Two studies evaluated the safety and efficacy of different ILE in children older than 1 year of age (Table 4) (111,112). None of the studies evaluated the influence of different ILE on liver function tests or bilirubin levels as a primary outcome measure, and none reported cholestasis rate. One study was performed in children after abdominal/oesophageal surgery (111) comparing MCT/SO (10% Lipofundin MCT/SO) versus SO ILE (10% Lipofundin S) and reported a decrease in bilirubin levels in MCT/SO ILE, whereas in the SO group concentrations remained elevated (108). Another study included children after bone marrow transplantation and compared MCT/SO (20% Lipofundin) and OO/SO ILE (20% ClinOleic) (112). That study found no difference between groups in bilirubin levels and liver function tests.

Infants and Children With Long-Term PN

There are 3 RCTs which examined long-term administration of ILE (Table 3). Two studies were performed in a single centre

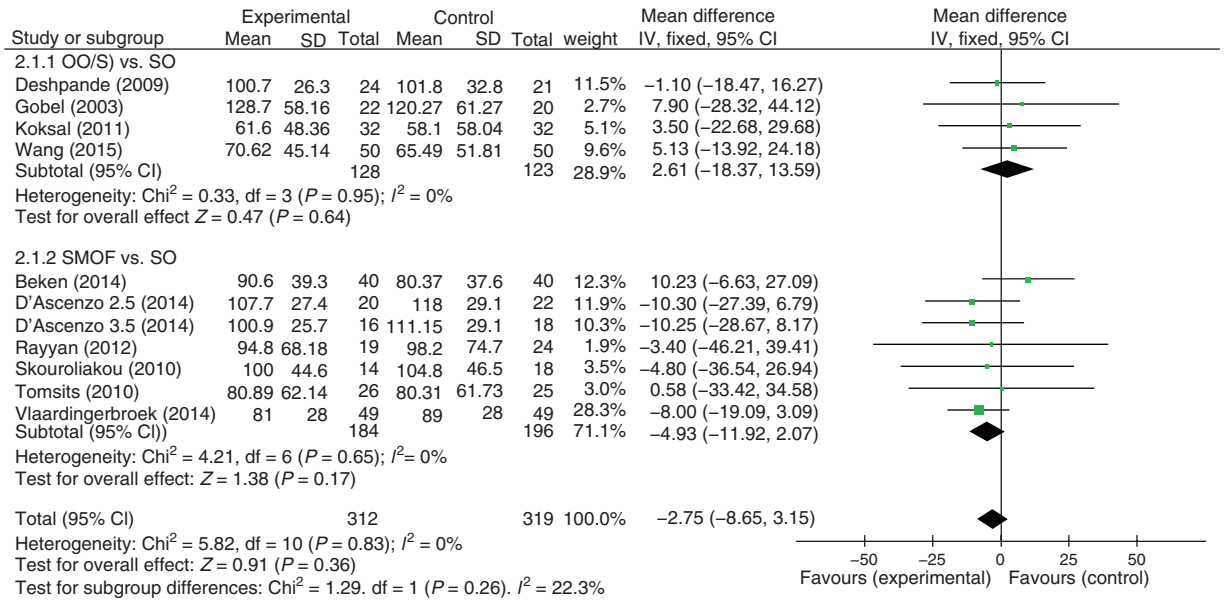

FIGURE 3. Effect of mixed intravenous lipid emulsions on total bilirubin levels (μmol/L) in comparison to pure SO-based lipid emulsion in neonates including preterm infants. CI, confidence interval; OO/SO, olive oil– and SO–based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

(24,109). One study investigated the difference between OO/SO (20% ClinOleic) and SO ILE (20% Intralipid) in children with prolonged PN (>3 months) due to short bowel syndrome, intractable diarrhoea, or intestinal pseudo-obstruction (24). That study found no difference in the liver enzymes, bilirubin, and biliary acids between groups. The more recent study investigated the difference between multicomponent FO-containing ILE (20% SMOFlipid) and SO ILE (20% Intralipid) during a 29-day period in children on home PN with short bowel syndrome, intestinal pseudo-obstruction, or congenital disease of the intestinal mucosa and reported a significant difference in the change in bilirubin levels from baseline to day 29 between groups (109). The present study found a decrease in the bilirubin levels in the multicomponent FO-containing group and an increase in the SO group; however, bilirubin levels in both groups were low and did not reach cholestatic levels (109). A recent study examined the influence of FO ILE (10% Omegaven) versus SO ILE (20% Intralipid) on cholestasis reversal in young infants with prolonged PN (110). The present study included only 16 patients and found no difference in the age at which an improvement in cholestasis occurred; however, only in the FO-based group did proportion (3 out of 9) of infants recover from cholestasis while still on PN. The present study also showed a significant decrease in

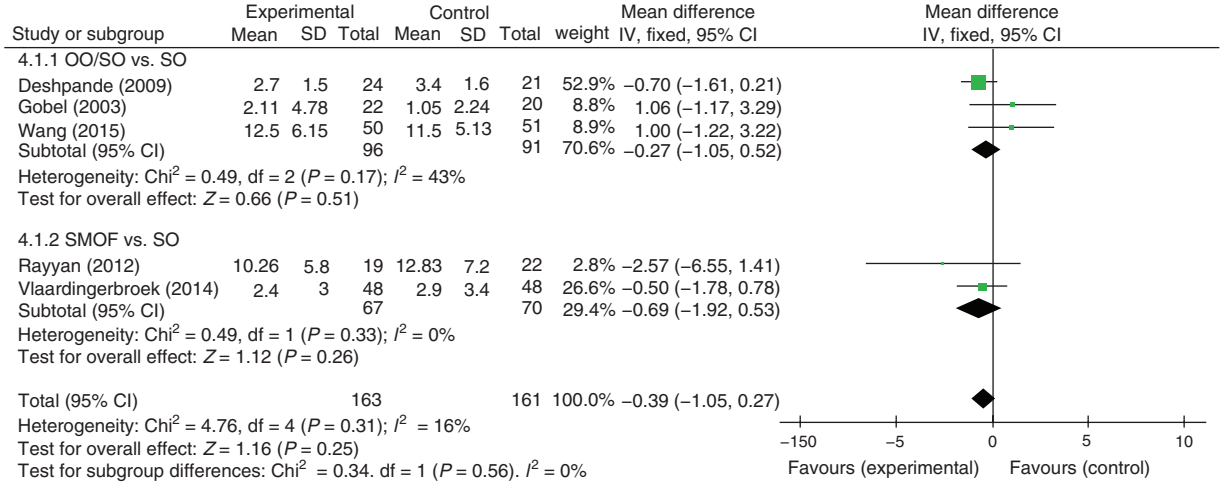

FIGURE 4. Effect of mixed intravenous lipid emulsions in comparison to pure soya bean oil (SO)-based lipid emulsion in neonates including preterm infants on conjugated bilirubin levels (μmol/L). CI, confidence interval; OO/SO, olive oil– and SO-based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

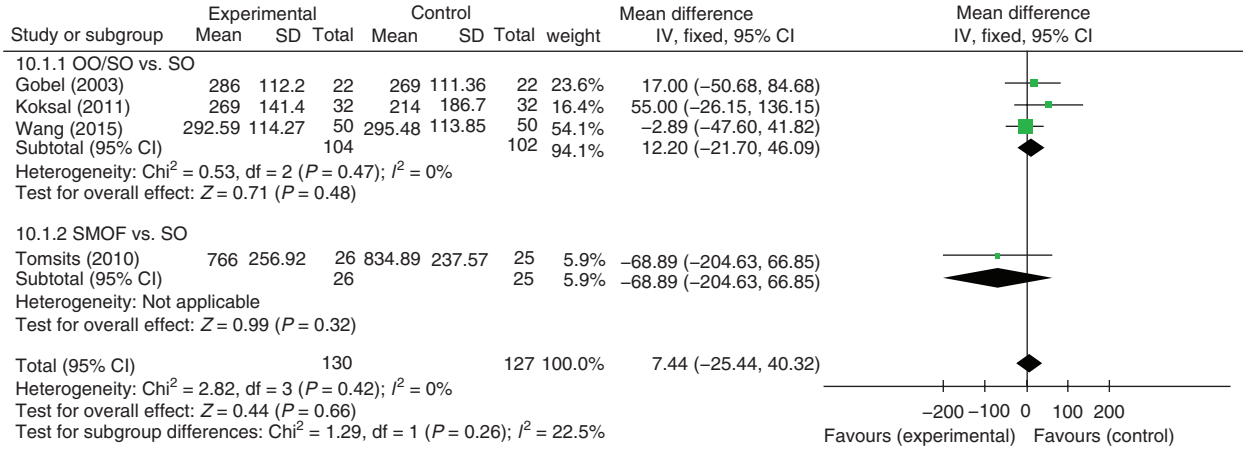

FIGURE 5. Effect of mixed intravenous lipid emulsions in comparison to pure soya bean oil (SO)-based lipid emulsion in neonates including preterm infants on alkaline phosphatase (ALP). CI, confidence interval; OO/SO, olive oil– and SO-based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

progression in conjugated bilirubin and ALT levels in infants on FO compared with those on SO. Moreover, this is the first study which compared the same dose of FO-based ILE and SO-based ILE (both groups received 1.5 $g \cdot kg^{-1} \cdot day^{-1}$).

DISCUSSION

This systematic review found a limited number of RCTs, which evaluated the short and long-term effect of ILE on bilirubin or liver enzyme levels. The majority of the available RCTs were performed in premature neonates (more than 1200 infants included) in whom ILE were administered for a short period of time. None of the ILEs were found to be significantly more efficacious in the prevention of cholestasis and decrease in bilirubin levels and liver enzymes. It should, however, be noted that all studies had different primary endpoints and did not evaluate the same parameters. Some studies did not mention exact bilirubin or liver enzyme levels, which prevented further analysis (102,105,106). The number of studies in infants and children (130 infants/children included) on long-term PN is limited. This systematic review identified only 3 RCTs (24,109,110), which all used different ILE and 1 study on prolonged PN in neonates (108) which compared FO to SO ILE. A study which assessed OO/SO ILE versus SO ILE found no difference in bilirubin levels (24). On the contrary, the same group of authors found that the use of multicomponent FO-containing ILE significantly decreased bilirubin levels (109). Both of these studies were, however, performed in children without cholestasis, and the bilirubin levels were not elevated even after the study. The study performed in infants evaluated the role of FO in infants with cholestasis and found a positive effect on the decrease in bilirubin (110). Because all 3 RCTs used different ILE it was not possible to perform a meta-analysis. The only study investigating prolonged PN in neonates assessed the difference between FO and SO (used in the same dosage—1 mg/kg) on the incidence of cholestasis (108).

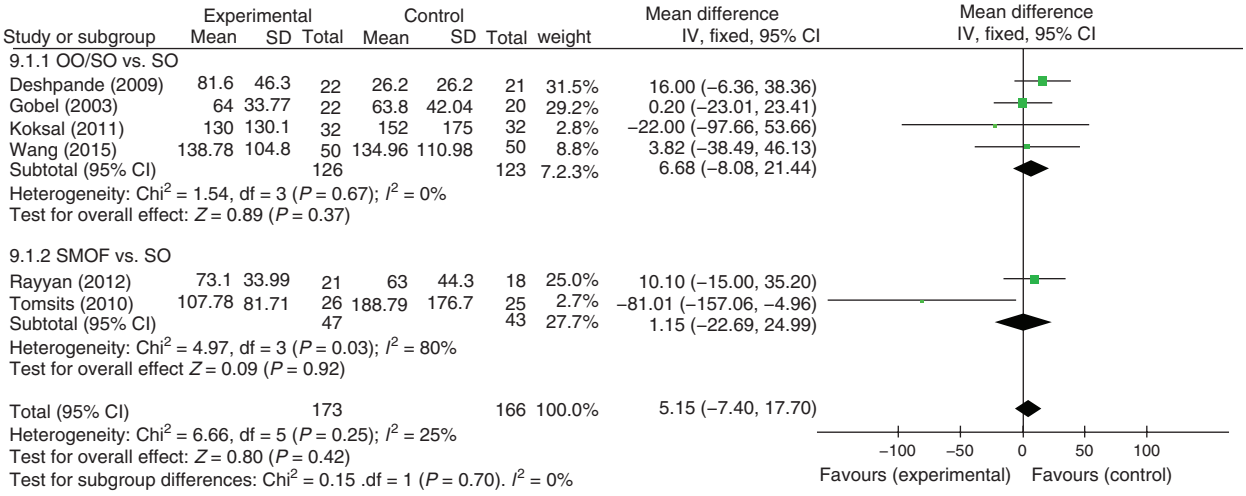

FIGURE 6. Effect of mixed intravenous lipid emulsions in comparison to pure soya bean oil (SO)-based lipid emulsion in neonates including preterm infants on γ-glutamyltransferase (GGT). CI, confidence interval; OO/SO, olive oil– and SO-based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

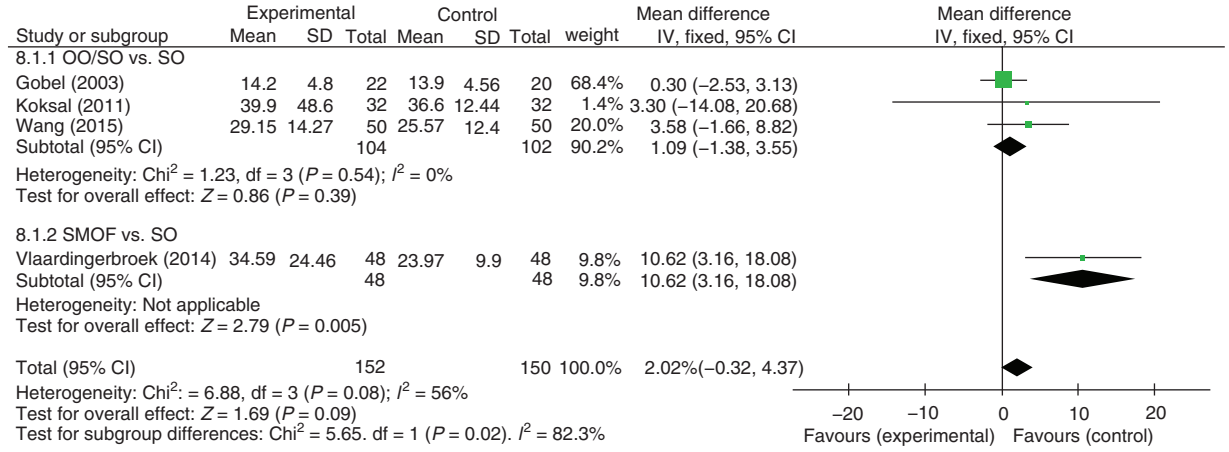

FIGURE 7. Effect of different intravenous lipid emulsions in comparison to pure soya bean oil (SO)-based lipid emulsion in neonates including preterm infants on aspartate transaminase (AST). CI, confidence interval; OO/SO, olive oil– and SO-based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

The present study terminated prematurely due to low incidence in cholestasis in both groups; furthermore, all other liver-related parameters did not differ between groups.

The role of a pure SO ILE on PNALD is well recognized and because of that, expectations after the introduction of MCT- and OO-containing ILE were high. Available evidence does not support their superiority over solely SO for short-term use. RCTs that evaluated the difference between SO-based and OO/SO ILE (95–97,102,103) and MCT/SO-based ILE (105,106) found no difference in liver function tests and bilirubin levels. Furthermore, meta-analysis found no difference in bilirubin levels and liver enzymes between OO/SO and SO ILE. All of these studies were performed in premature neonates and did not evaluate the effect on the liver as a primary outcome. There are also 2 RCTs performed in older children; 1 study, which included children after surgery found a decrease in liver function test in the group of children on MCT/SO-based ILE; however, the present study included only 10% lipid emulsions not recommended for children (111). The other study was performed in children after bone marrow transplantation and found no effect comparing OO/SO ILE to MCT/SO-based ILE (112). Those studies were performed in children who had not had gut resections and did not have severe liver disease, and therefore evaluated only the possible hepatotoxic effect of different ILE in the short term. OO/SO ILE, however, did not show an advantage over SO ILE even in children on long-term PN (24). The potential advantages of OO/SO ILE are to decrease the risks related to an excessive intake of PUFAs, such as increased peroxidation and also to decrease the plant sterol load, and may also be beneficial due to naturally high vitamin E content (27,28). Clinical studies, however, have not proven that the use of these ILE result in improvement in

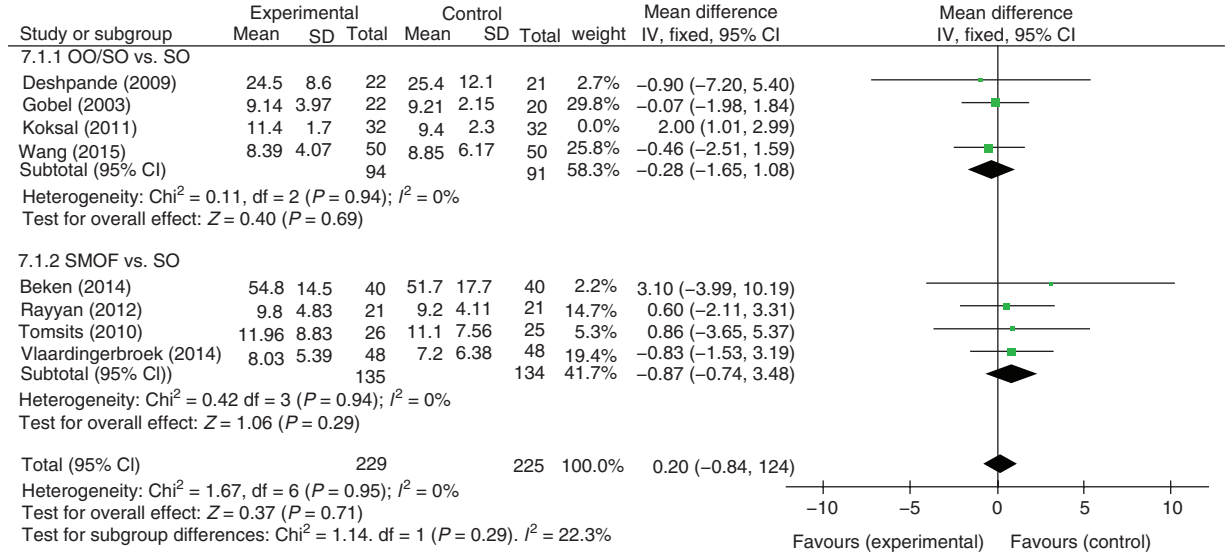

FIGURE 8. Effect of different intravenous lipid emulsions in comparison to pure soya bean oil (SO)-based lipid emulsion in neonates including preterm infants on alanine transaminase (ALT). CI, confidence interval; OO/SO, olive oil– and SO-based lipid emulsion; SD, standard deviation; SO, soya bean oil–based lipid emulsion; SMOF, multicomponent fish oil (FO)-containing intravenous lipid emulsion (SO, medium-chain triglycerides, olive oil, and FO).

TABLE 3. Randomized controlled trials performed in children on long-term parenteral nutrition

Author (year)	Subjects	Cholestasis before intervention	Intervention	Dose, $g \cdot kg^{-1} \cdot day^{-1}$	Duration of intervention	Primary outcome	Authors conclusions regarding liver function tests/bilirubin levels
Goulet (1999) (24)	18 Children with prolonged PN (>3 mo); patients with abnormal liver function were excluded (age 1–9 y)	Not present; total bilirubin levels in OO/SO group 10.9 ± 3.6 μmol/L and SO group 9.1 ± 3.0 μmol/L	30-Day equilibrium period with MCT/SO-based emulsion (medialipide 20%); randomization: OO/SO (20% ClinOleic) vs SO (20% Intralipid) emulsions	1.92 ± 0.17 (OO/SO) vs 1.69 ± 0.15 (SO)	2 mo	Primary outcome not mentioned; clinical and biological indices were measured	No significant difference between the groups regarding liver enzymes, bilirubin, and biliary acids
Goulet (2010) (109)	28 Children on HPN (age 5 mo–11 y)	Not present; total bilirubin levels in multicomponent FO-containing group 9.07 ± 10.84 μmol/L and SO group 8.75 ± 6.25 μmol/L	One-week equilibrium period with SO (20% Intralipid): randomization multicomponent FO-containing (20% SMOFlipid) vs SO (20% Intralipid) emulsions	4 or 5 times per week at a target dosage of 2.0 $g \cdot kg^{-1} \cdot day^{-1}$	4 wk	Primary outcome not mentioned; clinical and biological indices were measured	The mean changes in the total bilirubin concentration decreased in the multicomponent FO-containing ILE group and increased in the soya bean ILE group
Lam (2014) (110)	16 Young infants on prolonged PN (age 27–65 days)	Present; total bilirubin levels in FO group median 86 (42–163) and 92 (72–143) μmol/L in SO group	FO emulsion (10% Omegaven) vs SO (20% Intralipid) emulsion	Maximal dose 1.5 $g \cdot kg^{-1} \cdot day^{-1}$ in both groups	10–90 days	Reversal of PN-associated cholestasis	Median age of cholestasis resolution—NS; 3/9 infants in FO group vs 0/7 in SO group recovered from cholestasis during PN; total bilirubin and ALT significantly worsened in SO group, but not in FO group; the rate of bilirubin and ALT increase was significantly greater in SO group vs FO group
Nehra (2014) (108)	19 Neonates (age 2 days)	Not present; total bilirubin levels <1 mg/dL	FO emulsion (10% Omegaven) vs SO (20% Intralipid) emulsion	1	29–76 days	Cholestasis incidence	Overall very low cholestasis rate; no difference between groups in direct bilirubin and liver function tests

ALT, alanine transaminase; FO, fish oil; HPN, home parenteral nutrition; ILE, intravenous lipid emulsions; MCT, medium-chain triglycerides; OO, olive oil; PN, parenteral nutrition; SMOFlipid, soya bean oil, MCT, olive, and fish oil–based lipid emulsion; SO, soya bean oil.

TABLE 4. Randomized controlled trials performed in children on short-term parenteral nutrition older than 1 year of age

Author (year)	Subjects	Cholestasis before intervention	Intervention	Maximal daily dose, $g \cdot kg^{-1} \cdot day^{-1}$	Duration of intervention	Primary outcome	Authors conclusions regarding liver function tests/bilirubin levels
Lai (2000) (111)	40 Children after abdominal or oesophageal surgery (2–6 y)	Present; exact values not reported	MCT/SO-based (10% Lipofundin MCT/SO) vs SO-based (10% Lipofundin S)	1.5	14 days	Primary outcome not mentioned; nutritional indicators and side effects	Decrease in bilirubin levels in MCT/SO group, concentrations remained elevated in the SO group; normalization of the AST concentration in the MCT/SO but not in the SO group
Hartman (2009) (112)	28 Children after bone marrow transplantation (1–18 y)	Not present; total bilirubin levels in MCT/SO group 0.9 ± 0.3 mg/dL and OO/SO 0.6 ± 0.2 mg/dL	MCT/SO-based (20% Lipofundin) vs OO/SO (20% ClinOleic)	1.1 ± 0.2 vs 1.1 ± 0.1	≈19 days (assessment on day 14)	Primary outcome not mentioned; short-term safety and metabolic effects	No significant difference between the groups regarding serum bilirubin and transaminases at baseline or follow-up

AST, aspartate transaminase; MCT, medium-chain triglycerides; OO, olive oil; SO, soya bean oil.

liver function compared to the historical pure SO-based ILE (6,95,97,101,102).

Moreover, neither animal models (113) nor the observational clinical data have demonstrated clear superiority of MCT/SO or OO/SO ILE (24) over their SO ILE counterparts regarding prevention or recovery of cholestasis or PNALD (21,114,115).

In 2005, the guidelines provided by the ESPGHAN and ESPEN experts stated that the use of commercial lipid emulsions based on LCT (SO or OO/SO) or physical mixtures of MCT/SO could be considered generally safe in infants and children and that there was currently no evidence (based on clinical outcome data) supporting the advantage of any of the ILE that were currently available (6). Based on the all available data, it seems that introduction of MCT or OO in ILE did not significantly contribute to the resolution or prevention of hepatotoxic effect of ILE, and that new data support previous guidelines regarding these ILEs.

Expectations for FO-based lipid emulsions were even higher. Good quality data are, however, lacking; there are only 2 RCTs available which compared FO to SO ILE in neonates (108) and infants on prolonged PN (110). Several case studies presented by the same team reported the efficacy FO as monotherapy (at a reduced dose—1 g/kg) in the treatment of PNALD in infants and children (79–86). In most of the studies, a high dose of SO emulsion was replaced by 1 g/kg of FO. Therefore, it is still not clear whether reversal of cholestasis was due to the effect of stopping the soya bean load or the effect of FO itself (including the high α-tocopherol load) or both. A meta-analysis of 2 of these observational studies (80,83) showed a significant decrease in plasma bilirubin in the children treated with pure FO ILE compared to those treated with SO ILE (38). Recently, other teams (87) also found a remarkable effect of FO-based ILE on severe cholestasis in preterm infants (88). Only 2 previously mentioned RCTs compared FO to SO, 1 in infants with cholestasis on long-term PN which found FO to be superior in the reduction of bilirubin and ALT levels (110) and the other in neonates without cholestasis on prolonged PN which found no difference in the cholestasis incidence and bilirubin levels between groups (108). The strength of both of these studies is that both arms (experimental and control) used the same lipid dose [$1.5\ mg \cdot kg^{-1} \cdot day^{-1}$ in 1 (110) and $1\ mg \cdot kg^{-1} \cdot day^{-1}$ in the other study (108)].

The newest ILE are multicomponent FO-containing ILE, which could have several theoretical advantages. Their effect was assessed by several RCTs in neonates and 1 RCT in children with long-term PN (37,60,93,98–100,109). Although some studies found that the use of multicomponent FO-containing lipid emulsions have positive effect on bilirubin levels in premature infants and neonates, meta-analysis found no superiority of these multicomponent FO-containing ILE compared to SO ILE. Regarding children on prolonged PN, 1 RCT found that multicomponent FO-containing ILE led to significant decrease of total bilirubin levels compared to SO ILE; however, in both groups bilirubin levels were not abnormal at the end of the study (109). There are also several nonrandomized cohort studies which found resolution of cholestasis after multicomponent FO-containing ILE was introduced (89,90). When interpreting these results the small sample size (8 and 9 patients) and design of the study should, however, be taken into account. Furthermore, in children with IF the pathogenesis of liver disease is extremely complex and intervention should not be limited only to different ILE. There is evidence indicating that just tailoring and adjusting PN in children on long-term PN could improve liver disease (116), meaning that the focus should not only be on the type of ILE.

Considering all these results it seems that addition of FO and reduction of SO could be beneficial in reducing cholestasis in children on long-term PN. The overall quality of the data is,

however, poor and well-designed RCTs including larger numbers of patients are lacking.

Furthermore, there are no RCTs that assess the role of ILE on liver fibrosis with some evidence showing persistent liver fibrosis even several years after PN discontinuation (117). A small adult study showed histologic improvement after 4 weeks of treatment with pure FO, with a so-called marked decrease in inflammation and cholestasis (27). Some animal and human studies suggest that fibrosis persists or even progresses despite normalization of cholestasis markers using FO (118–122). These studies underline the limitations of relying on cholestasis as the sole endpoint. Recently, Mercer et al (121) blindly examined liver biopsies in 6 children with cholestasis who were treated with FO ILE and although hyperbilirubinaemia reversed in all children, there was no influence on fibrosis in 5 of 6 children. Thus, it is still not clear whether a decrease in bilirubin levels is a good marker for improvement of liver damage.

Finally, when interpreting the results of this systematic review it should be emphasized that we only examined the effect of different ILE on cholestasis or PNALD other parameters, which could potentially be influenced by the use of different ILE, for example, nutritional adequacy, growth, development, nosocomial infections, and so on were not evaluated. ILE are an important noncarbohydrate source of energy and an integral part of paediatric PN. Furthermore, ILE in children, particularly in infants, are the main provider of essential fatty acids. EPA and DHA can be synthesized from α-linolenic acid, yet the capacity of the converting enzyme pathway is limited. Physiological DHA requirements are highest in the perinatal period and infants are dependent on dietary DHA intake from the mother's milk or formula (123). Therefore, there is a serious concern that the DHA supply in SO ILE may be limiting for infant development. On the contrary, exclusive FO lipid intake during the perinatal period resulted in growth retardation and delayed psychomotor development in rats (124). Therefore, the optimal n-3 fatty acid and FO intake (dosage and duration) in children who depend on PN lipid delivery should be better defined, especially in infants. Short-term studies showed that multicomponent FO-containing ILE was well tolerated in premature neonates with a modification of red blood cell phospholipid fatty acid pattern as compared with a group receiving an SO ILE (37,98,100).Long-term studies are, however, needed to assess the effects of prolonged administration of different fatty acid mixtures on fatty acid profile, growth, and neurodevelopment especially in children on prolonged PN.

CONCLUSIONS

The ESPGHAN Committee on Nutrition (CoN) concludes

- There is no evidence of a difference in bilirubin, conjugated bilirubin, AST, ALT, ALP, and GGT between short-term use of OO/SO and SO ILE in infants and children (level of evidence 2a).
- There is no evidence of a difference in bilirubin, conjugated bilirubin, AST, ALT, ALP, and GGT between short-term use of multicomponent FO-containing ILE and SO ILE in neonates (level of evidence 2a).
- The use of multicomponent FO-containing ILE may contribute to a decrease in total bilirubin levels in children with IF on prolonged PN (level of evidence 2b).
- Pure FO supply combined with a decrease or interruption of SO ILE may contribute to cholestasis recovery in children with PNALD (level of evidence 2b).

RECOMMENDATIONS

- Prevention and care of PNALD in children should not be focused exclusively on parenteral ILE intake.
- Because of their high phospholipid content, 10% ILE should no longer be used (GR B).
- Based on available evidence, the CoN cannot currently recommend the use of any specific ILE for short-term use in infants and children for the prevention and treatment of PNALD (GR B).
- For children in whom long-term use of PN is expected, it appears prudent to use multicomponent FO-containing ILE (GR C).
- The present evidence base is inadequate to determine the optimal strategy for intravenous lipid supply in both preterm and term infants and older children to prevent or treat liver complications.
- In particular, studies on both the prevention and treatment of PNALD should be conducted in high-risk infants and children who are likely to require long-term PN, and should also consider additional extrahepatic outcomes such as growth and cognition.

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