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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Lipid Formulations for Patients Requiring Parenteral Nutrition: A Review of Clinical and Cost-Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	July 19, 2017
Report Length:	66 Pages

CADTH

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Cite As: Lipid formulations for patients requiring parenteral nutrition: a review of clinical and cost-effectiveness and guidelines. Ottawa: CADTH; 2017 Jul. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Context and Policy Issues

Parenteral nutrition (PN) is required in patients who cannot meet their nutritional needs through oral or enteral routes. In total PN, all essential nutrients are delivered intravenously. Examples of patients who may require PN include the critically ill, patients with chronic intestinal failure, and patients with small bowel obstruction.[1] Pediatric populations requiring PN also include preterm infants, very low birth weight infants, and infants with severe gastrointestinal malformations.[1]

The use of intravenous lipid emulsions (ILE) in PN provides a source of energy as well as essential fatty acids, preventing essential fatty acid deficiency.[2] Essential fatty acids cannot be produced in the human body and n-6 and n-3 (also known as omega-6 and omega-3) fatty acids should be provided as at least 2% and 0.5%, respectively, of daily calories to prevent essential fatty acid deficiency.[2] The two primary essential fatty acids are linoleic acid (an n-6 fatty acid) and alpha-linoleic acid (an n-3 fatty acid). Downstream metabolites of linoleic acid include pro-inflammatory mediators while alpha-linoleic is primarily metabolized to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which give rise to downstream anti-inflammatory mediators.[2,3]

The first generation of ILE for PN consisted of soybean-based lipids (long-chain triglycerides) which are abundant in n-6 fatty acids. Soybean oil has a high n-6 to n-3 fatty acid ratio and is rich in phytosterols which has been shown to result in decreased bile flow in animal models, which could contribute to liver disease.[2,3] While soybean oil emulsions continue to be used in patients, observations of liver complications with use of these emulsions prompted the development of alternative lipid emulsions for PN.[2,3] Medium-chain triglycerides, olive oil, and fish oil are all major components of these alternative lipid emulsions. Neither medium-chain triglycerides nor olive oil contain meaningful amounts of n-3 fatty acids.[3]

Of the newer lipid sources, fish oil is of great interest due to its relatively high levels of EPA and DHA and low levels of phytosterols, and because it is thought to exert a less pro-inflammatory effect than soybean oil.[2] There is also some evidence from observational studies that lipid emulsions containing fish oil may encourage reversal of PN-associated liver disease.[3] When used on its own, fish oil may not provide sufficient essential fatty acids and it is often found in combination with the aforementioned lipids.[2]

A previous CADTH report, published in 2009, entitled “n-3 Lipids for Patients on Total Parenteral Nutrition: A Review of the Clinical and Cost-Effectiveness”[4] summarized the results from 10 randomized controlled trials, four observational studies, and one economic evaluation.[4] The evidence indicated fish oil to be safe and well-tolerated with some randomized controlled trials showing reduced hospital stay and/or anti-inflammatory effects with the administration of n-3 fatty acids.[4] The economic evaluation did not support the cost-effectiveness of fish oil for PN. The current report aims to review the clinical effectiveness and cost-effectiveness of various lipid emulsions for PN in all patient populations requiring PN. This report also aims to review evidence-based guidelines pertaining to the use of various lipid ILEs in patients requiring PN.

Research Questions

1. What is the clinical effectiveness of lipid formulations in adult and pediatric patients requiring parenteral nutrition?
2. What is the cost-effectiveness of lipid formulations in adult and pediatric patients requiring parenteral nutrition?
3. What are the evidence-based guidelines associated with the use of lipid formulations in adult and pediatric patients requiring parenteral nutrition?

Key Findings

There is a lack of high-quality, large-scale randomized controlled trials (RCTs) comparing the effects of different parenteral lipid emulsions on clinical outcomes in patients receiving parenteral nutrition. Low to moderate quality evidence from eight RCTs and ten systematic reviews demonstrated that non-100% soybean emulsions, especially fish oil-containing emulsions, are no less safe than pure soybean emulsions and may confer clinical benefits. Safety parameters related to liver function, inflammation, and adverse events were not adversely affected by alternative lipid emulsions.

In preterm infants, the type of lipid emulsion did not affect mortality rate, growth parameters, or incidence rates of complications related to prematurity and neonatal ICU stay. One systematic review with substantial limitations found lowered rates of cholestasis and retinopathy of prematurity with fish oil-containing emulsions. A small-scale RCT in older infants with liver dysfunction and another in surgical neonates found reductions in bilirubin levels with SMOFlipid, a multicomponent emulsion with fish oil, compared with 100% soybean oil.

Administration of fish oil-containing lipid emulsions compared with non-fish oil emulsions consistently resulted in lower lengths of hospital and intensive care unit stay, lower nosocomial infection rates, and lower levels of pro-inflammatory markers in adult surgical and intensive care unit patients. Bilirubin and liver enzymes were sometimes reduced in these patients with fish oil-containing emulsions, but this effect was not consistent.

American guidelines were not able to make recommendations on alternative emulsions due to the lack of availability in the US. European guidelines suggest the use of fish-oil containing emulsions in adult patients, but refrain from making strong recommendations.

The economic evaluations demonstrated the cost-effectiveness of fish oil emulsion over soybean-based emulsions, with high likelihood of both improved clinical outcomes and lower costs in adult patients. However, there were substantial limitations in the economic analyses and the results should be interpreted with caution.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials,

economic studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 19, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients (including neonates) requiring parenteral nutrition (PN) in any setting (e.g., acute care/hospital, home, outpatients, clinics, etc.)
Intervention	Lipids for parenteral nutrition (e.g., but not limited to, n-3 lipids, n-3 lipid containing mixtures, n-3/n-6 lipid containing mixtures, etc.)
Comparator	Q1-2: Lipid formulations compared to each other Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., clinical benefits, improved patient outcomes, etc.) and safety (e.g. harms associated with use) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicate publications. Systematic reviews (SRs) were excluded if they did not provide meta-analyses exclusively based on randomized controlled trials (RCTs) or if their included studies completely overlapped with the included studies of another SR. Due to the volume of relevant SRs and RCTs identified from the literature search, articles reporting only biochemical outcomes or published prior to 2012 were excluded. Guidelines that were superseded by updated versions were excluded. References for articles of potential interest that were excluded are provided in Appendix 5. These comprise articles excluded on the basis of publication date and guidelines that may have been relevant but were outdated or not evidence-based.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using AMSTAR,[5] RCTs were critically appraised using the Downs and Black checklist,[6] economic studies were assessed using the Drummond checklist,[7] and guidelines were assessed with the AGREE II instrument.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Reporting of Study Outcomes

Although articles reporting only biochemical outcomes were excluded, safety-related biochemical data was extracted for this report. Outcomes were classified under “clinical effectiveness” if they were non-biochemical (with the exception of adverse events) or if they involved the interpretation of a biochemical marker (e.g. cholestasis defined as serum conjugated bilirubin >2 mg/dL). Direct measurements of biochemical markers related to liver function, kidney function, and inflammatory state, in addition to adverse events, were classified under “safety”.

Summary of Evidence

Quantity of Research Available

A total of 291 citations were identified in the literature search. Following screening of titles and abstracts, 208 citations were excluded and 83 potentially relevant reports from the electronic search were retrieved for full-text review. Twenty-six potentially relevant publications were retrieved from the grey literature search and manual searching of guidelines produced by the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism. Of these potentially relevant articles, 85 publications were excluded for various reasons, while 24 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart[9] of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are presented by study type in Appendix 2.

Study Design

Ten SRs were identified regarding the clinical effectiveness of PN in pediatric[10-14] and adult[15-19] populations. The 10 SRs included in this report searched databases from the time of database inception to the literature search dates, which ranged from 2012 to 2016 for pediatric populations[10-14] and from 2011 to 2014 for adult populations.[15-19] One SR[10] included both RCTs and observational studies and only subgroup analyses of RCTs were included in this report. Another SR[12] studied both timing of intravenous lipid emulsion (ILE) administration and type of ILE and only the latter objective was included in this report. The SRs did not report whether the included RCTs were single-centre or multi-centre studies, with two exceptions.[13,18] One study in an adult population[18] stated that five out of 21 RCTs were multi-centre studies while another study in a pediatric population[13] had only one multi-centre study among its 15 RCTs and quasi-RCTs. There was overlap in the studies included in the SRs (Appendix 6).

Eight RCTs regarding the clinical effectiveness of PN in adult[20-23] and pediatric[24-27] populations were identified.

Two economic studies that utilized cost-effectiveness analysis (discrete event simulation models) were included.[28,29] Both studies incorporated probabilistic sensitivity analysis, modelling clinical inputs as distributions rather than fixed values.[28,29]

Four evidence-based guidelines[30-33] were identified. All the guidelines indicated that a systematic literature search was performed. Although the level of detail provided varied between guidelines, they all provided ratings for the quality of the evidence and the strength of the recommendations. Expert consensus was reached based on consideration of the evidence, with one committee using the standards of the Guidelines International Network.[32]

Country of Origin

The SRs were led by authors in Australia,[13] Canada,[10] China,[14,15,18] Croatia,[11] Italy,[16] the Netherlands,[12] Scotland,[19] and South Korea.[17]

The RCTs were conducted in Canada,[25] England,[26] Spain,[20] Sweden,[24] Taiwan,[21] Thailand,[27] and the US.[23] One of the RCTs[22] was performed in 11 centres in seven countries: Australia, Denmark, France, Israel, Netherlands, Poland, and the UK.

One of the economic studies was conducted in China using clinical outcomes and costs from Chinese hospital data.[28] The other cost-effectiveness study was conducted in Italy using clinical outcomes from Italian and international data combined with costs specific to Italy, France, Germany, and the UK.[29] Both studies used clinical effectiveness data from the SR that was conducted in Italy and included international data.[16]

Two of the guidelines were produced by the American Society for Parenteral and Enteral Nutrition[31,33] and two were produced by the European Society for Clinical Nutrition and Metabolism.[30,32]

Patient Population

The systematic reviews and randomized controlled trials were evenly split between pediatric and adult patient populations.

Five of the SRs[10-14] surveyed pediatric populations. All of these SRs studied preterm infants (defined as gestational age <32[10] to <37[13] weeks) receiving partial or total PN containing ILE. One SR[10] included infants with gestational age <32 weeks or birth weight less than 1,500 g and noted that most of the included RCTs excluded infants with major congenital malformations and infections. Another SR[12] excluded infants with birth weight higher than 1,500 g as well as those with congenital abnormalities.

Five of the SRs[15-19] studied adult populations. Four[15-18] of these five SRs examined elective surgical patients receiving partial or total PN containing ILE in the post-operative period. The remaining SR[19] examined critically ill patients and excluded elective surgery patients routinely admitted to the intensive care unit (ICU).

Four of the RCTs[24-27] were conducted in pediatric populations, with two single-centre[24,27] and two multi-centre[25,26] studies. Two of the studies were in preterm infants at gestational age of less than 28 weeks[24] or 31 weeks,[26] excluding those with major congenital malformations[24] or those with life-threatening abnormalities.[26] One study was conducted in surgical neonates with intestinal malformations[27] and another was conducted in infants of less than 24 months of age with liver dysfunction and either short bowel syndrome or intestinal failure.[25]

The other four RCTs were conducted in adult populations, with one single-centre[21] and three multi-centre[20,22,23] trials. Mean ages ranged from 45[22] to 63[21] years. RCTs were conducted in ICU patients,[20,23] and in- and out-patients who were unable to sustain

adequate enteral food intake, and in patients who underwent elective radical surgery for gastric and colorectal cancer.[21].

Both of the cost-effectiveness evaluations were based on adult populations, with one study examining ICU patients[28] and the other study looking at two different populations: medical and surgical patients with an ICU stay and surgical patients without an ICU stay.[29] Simulated patient data was based on data collected from a specific hospital ICU,[28] nationwide ICU data,[29] or international trials in non-ICU patients.[29]

Three of the guidelines targeted adult populations[30,32,33] while one targeted children with PN-dependent intestinal failure and children at risk of PN-associated liver disease (PNALD).[31] One guideline targeted adults surgical patients,[32] another targeted adults with chronic intestinal failure due to benign disease,[30] and the third targeted adult critically ill patients expected to require a stay in the medical ICU of more than 2 days or a stay in the surgical ICU of more than 3 days.[33] Intended users were only specified in the critical care guideline and included all health care providers involved in nutritional therapy of the critically ill.[33]

Interventions and Comparators

In SRs in pediatric populations, two SRs[10,14] compared ILEs with fish oil (FO) versus without FO, and three SRs[11-13] compared non-100%-soybean oil (SO) ILEs against pure SO ILE. Where reported, PN with ILE started within the first week of life[10,12,13] and daily doses of 0.5 to 3.5 g/kg of ILE depending on the day of life were administered.[10,11,13] The duration of ILE administration ranged from 3 to 60 days,[11,13,14] but was not reported in two SRs.[10,12] Oral or enteral nutrition accompanying PN was not mentioned in any of the SRs.

Within the SRs studying adult populations, all the intervention groups received ILEs containing FO.[15-19] Control ILEs were a mixture of SO, SO/olive oil (OO), and SO/medium-chain triglyceride (MCT). Where reported, daily doses ranged from 0.14 to 0.28 g/kg of FO or 0.08 to 0.3 g/kg of n-3 fatty acids,[17-19] and the duration of ILE administration ranged from 3 to 10 days.[15,17-19] None of the SRs conducted in adults mentioned oral or enteral nutrition.

RCTs in pediatric populations all administered SMOFlipid (SO/MCT/OO/FO or SMOF ILE) in the intervention arm. Control ILEs were either Intralipid (SO ILE)[25-27] or Clinoleic (SO/OO ILE).[24] Preterm infants[24,26] and surgical neonates[27] received PN with ILE on day 1 of life, starting with a dose of 0.5 g/kg,[27] 1 g/kg,[24] or 2 g/kg[26] daily of SMOFlipid and increasing to a maximum 2 g/kg,[24] 3 g/kg,[26] or 3.5 g/kg[27] daily for at least seven days,[27] up to 28 weeks,[24] or until milk tolerance was achieved.[26] Infants with hepatic dysfunction received up to 3 g/kg of SMOFlipid daily for up to 12 weeks.[25] Aside from one study in which it was specified that >40% of calories were obtained through PN,[25] amounts of enteral nutrition were unclear.

RCTs in adult populations used SMOFlipid,[22] LipoPlus (SO/MCT/FO ILE),[20,21] or Clinoleic[23] in the intervention arm. Control ILEs were all non-FO-containing ILEs: Lipofundina or Lipofundin (50% MCT, 50% SO)[20,21] or Intralipid (SO ILE)[22,23]. Maximum daily doses of ILE ranged from 1.5 to 4 g/kg,[20-22] and treatment duration, where reported, ranged from 7 to 28 days.[21-23] One study allowed up to 50% of calories from enteral nutrition[20] and another study restricted enteral nutrition to clear liquid.[21] The amount of enteral nutrition was not described in the other studies.

Costs and benefits for PN in the economic studies were based on a comparison between Omegaven (pure FO ILE) and standard, non-FO-containing ILEs.[28,29] PN doses were

calculated based on body weight, with either lipid intake[29] or caloric intake[28] matched between groups. The only differences in clinical input parameters between the intervention and control arms were incidence of infection, hospital length of stay (LOS), and ICU LOS. These differences were based on results from an SR[16] for ICU patients and international clinical trial data for non-ICU patients.[29]

All the guidelines considered parenteral and enteral nutrition interventions, in addition to several other aspects of nutritional support.

Outcomes

The pediatric SRs evaluated clinical outcomes such as mortality[12-14], duration of ventilation,[12,13] physical growth,[12-14] and complications relevant to prematurity and neonatal ICU stay, including retinopathy of prematurity (ROP),[10,13] bronchopulmonary dysplasia (BPD),[10,13] cholestasis,[10,11,13] necrotizing enterocolitis (NEC),[10,13] and sepsis.[10,12] With respect to safety, common measures were bilirubin and liver enzyme levels.[11,14] In the adult populations, the outcomes considered in SRs were mortality,[16-19] infection rate,[16-19] hospital LOS,[15-19] and ICU LOS.[16,17,19] Regarding safety parameters, four of the SRs evaluated liver[15-18] and inflammatory[15-18] markers.

RCTs in pediatric population evaluated clinical outcomes such as physical growth,[24-27] time to achievement of full enteral tolerance,[25,26] duration of PN,[24,27] complications related to prematurity or neonatal ICU stay,[24] body composition,[26] mortality,[26] and hospital LOS.[26] The most common safety parameters were bilirubin [25-27] and liver enzyme[25,27] levels. In the adult populations, common clinical outcomes in the RCTs were duration of PN,[20-23] nosocomial infections,[20,23] mortality,[20,23] hospital LOS,[20,23] and ICU LOS.[20,23] With respect to safety, outcomes included adverse events,[20-22] liver markers,[21,22] and inflammatory markers.[21-23]

The cost-effectiveness studies reported total LOS,[28,29] ICU LOS,[28] ward LOS,[28] infections,[28,29] and total costs accumulated during hospital,[28,29] ICU,[28] and ward[28] stays in renminbi[28] and euros.[29] The total costs included costs associated with hospital,[28,29] ICU,[28] and ward[28] stays as well as costs associated with PN and episodes of infection.[28,29] Incremental cost-effectiveness ratios were also found for days of hospital stay[29] and infections avoided.[28]

In the guidelines, outcomes of interest were broad, and included: biomedical, multidimensional, health economy and quality of life outcomes;[32] or a range of clinical outcomes such as sepsis and pancreatitis.[31,33] The guidelines targeting adult patients with chronic intestinal failure did not specify outcomes of interest.[30]

Summary of Critical Appraisal

Systematic Reviews

The SRs were generally well-conducted overall. Strengths common to all 10 SRs included: *a priori* establishment of research questions and inclusion criteria, provision of a list of included studies, description of important characteristics of included studies, and disclosure of conflicts of interest for the SR authors where applicable.[10-19] A comprehensive literature search including multiple online databases was conducted in all but one[16] SR that included a limited search of only PubMed. Study selection and data extraction were done at least in duplicate in eight SRs,[10,12-15,17-19] but methods for study selection and data extraction were unclear in the remaining two SRs.[11,16]

Studies were combined in meta-analyses using random-effect models in the presence of high heterogeneity in nine SRs.[10-12,14-19] One SR[13] used fixed-effects models regardless of heterogeneity but took heterogeneity into account when assigning quality of evidence to outcomes. None of the SRs mentioned whether clinical appropriateness or predetermined heterogeneity criteria affected the decision to pool study data. The likelihood of publication bias was assessed in six SRs.[10,12-14,17,18] The scientific quality of the evidence from individual studies was assessed and used appropriately in formulating conclusions in seven SRs.[12-15,17-19] In the other three SRs, quality of individual studies was assessed but not appropriately considered in forming conclusions,[10] or quality assessment was not mentioned.[11,16] In terms of limitations, only two SRs[13,18] included grey literature searches, and these were limited to searches of trial registries. In two SRs, publication language (i.e., in English) was an inclusion criterion,[11,17] and in four SRs it was unclear whether this was the case.[10,14,16,18] Characteristics of study populations were not well described in four SRs.[10,11,16,17] One of the SRs provided a list of excluded studies,[13] and none of the 10 SRs reported any conflicts of interest for the included primary studies.[10-19] In two of the SRs, some SR authors disclosed receipt of honoraria or funding from manufacturers of lipid emulsions.[11,16] The remaining SRs declared no conflicts of interest.[10,12-15,17-19]

Randomized Controlled Trials

The eight RCTs[20-27] were generally well-reported overall, with clearly described: study objectives; inclusion and exclusion criteria; characteristics of included patients, interventions, and outcomes; and main findings. Strengths common to the eight RCTs were: provision of statistical estimates of variability in the data, consideration and report of adverse events, report of actual probability (p-values), and the absence of retrospective (unplanned) analyses.[20-27] In all eight RCTs, patients were randomized to treatment groups, and the treatment groups were matched on important characteristics, however whether treatment allocation was concealed was unclear in four RCTs.[21,23,24,27] Outcome assessors were blinded in seven RCTs;[20-26] the eighth RCT was open-label, and no attempt was made to blind the patients, treating physicians, or investigators.[27]

In six of the included RCTs the patients were representative of the population from which they were recruited.[20-23,26,27] In the other two RCTs, characteristics of those who were recruited and declined participation were not reported.[24,25] All but one[27] RCT included *a priori* power calculations. The final sample size in one RCT was slightly smaller than the targeted sample size however this did not appear to influence the findings,[24] and in two RCTs some relationships approached (but did not reach) statistical significance and this may have been due to inadequate power since sample size calculations were based solely on the primary outcome variable.[20,23]

In terms of limitations, in four RCTs the interventions and comparators were insufficiently described (e.g., inconsistent reporting throughout the study, or inadequate details on nutrients aside from lipids) or had variable components titrated at the individual level (e.g., amount and/or content of enteral nutrition in addition to PN) such that their dosing protocols could not be replicated.[22-24,27] In one study, the numerical values reported in the abstract did not match those in the results section; however, this did not impact the clinical interpretation.[25] In another RCT, inappropriate statistical analysis was used; however, this likely did not impact the conclusions drawn from the resulting statistical output.[27] Two RCTs deviated from intent-to-treat analysis.[21,22] There was incomplete reporting in three of the RCTs, in the form of: some outcomes included in the methods not being reported in the results,[21] findings being reported only in a table and not included in the results or discussion,[25] and main findings only being reported as the number and proportion of

patients meeting certain criteria without providing absolute values to enable assessment of severity.[24] Lastly, the inclusion criteria in two RCTs were quite broad, leading to study populations that were not well-characterized; therefore, it is unclear to whom the results apply.[22,23]

Economic Evaluations

There were two economic evaluations that utilized cost-effectiveness analysis.[28,29] Both used discrete event simulation models, with clinical effectiveness data from the same systematic review[16] in combination with cost data specific to the local context in China[28] or four European countries (Italy, France, Germany, and the UK).[29]

Strengths of the economic studies included: clear methods of estimating quantities and unit costs, description of the discrete event simulation model structure, application of probabilistic sensitivity analysis, and presentation of major outcomes in both disaggregated and aggregated forms. Both studies considered many aspects of ward and ICU care in their cost estimates and both isolated costs due to nosocomial infections alone.[28,29] Additionally, the study by Wu et al.[28] estimated costs from a single hospital data set, reflecting actual costs for that hospital, and compared the model results against the observed hospital data. The study by Pradelli et al.[29] included clinical data from extensive primary data collection and several sources of cost data including prospective case-control studies, national reports, and patient data management systems. Additionally, Pradelli et al. included deterministic sensitivity analysis and threshold analyses to test the reliability of the results.[29]

In terms of limitations, neither economic study provided a rationale for using cost-effectiveness analysis, and primary outcome measures were not clearly stated *a priori*.[28,29] In the study by Wu et al.,[28] the viewpoint of the analyses (patients and their families) was not justified. Additionally, the rationales for the type of simulation[28,29] and for the choice and fitting of distributions for clinical input parameters were not described,[28] and sensitivity analyses were not comprehensive.[28] In the study by Pradelli et al.,[29] actual values and/or justification for model input parameters were unclear, and inflation rates for converting to 2011 costs were not provided.

Guidelines

Strengths common to the four evidence-based guidelines were: a clearly defined scope and purpose, the use of systematic methods to search for evidence, mention of the strengths and limitations of the body of evidence, consideration of both benefits and risks, and an explicit link between the recommendations and the supporting evidence.[30-33]

However, there were several limitations. None of the guidelines sought the views and preferences of the target population, described the criteria for screening studies and selecting the evidence, or described the methods for formulating the recommendations in sufficient detail.[30-33] No aspects of applicability were addressed in any of the four guidelines (i.e., discussion of barriers and facilitators to application of the guideline, advice or tools regarding implementation, resource implications, or provision of monitoring and/or auditing criteria). For one guideline,[32] it was unclear whether the guideline development group included individuals from all relevant professional groups, and the target users of the guideline were explicitly defined in only one[33] of the four guidelines. Two of the guidelines were externally reviewed by experts prior to publication.[31,33]

Regarding a procedure for updating the guidelines, in one of the guidelines it was indicated that they would be updated every three to five years,[33] and in another it was stated that a

revision was planned for 2018,[31] however no further details were provided and there was no mention of a procedure for updating the other two guidelines.[30,32] There was evidence of editorial independence in three of the guidelines,[30,32,33] but in the fourth there was no information provided on the source of funding or on real or perceived competing interests of the guideline development group members.[31]

Summary of Findings

Detailed summaries of the findings are presented in Appendix 4. Numerical results are only reported in the tables for secondary outcomes if findings were statistically significant.

What is the clinical effectiveness of lipid formulations in adult and pediatric patients requiring total parenteral nutrition?

Many studies reported levels of liver markers such as serum bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase (GGT) alongside clinical outcomes. High levels of conjugated bilirubin may indicate impaired bile flow (cholestasis) as well as contribute to high levels of total bilirubin. While an abnormally elevated liver markers may suggest liver damage or dysfunction, consideration of a panel of liver tests with other forms of clinical assessment is needed to determine clinical significance.

Pediatric populations

Among the SR meta-analyses conducted in pediatric populations, there were no significant differences in clinical outcomes[10-14] or safety parameters[11,14] between the various ILE comparisons, with two exceptions. First, one SR reported lower ROP and cholestasis rates with FO-containing ILEs compared with SO or SO/OO ILEs.[10] However, the meta-analysis included a study which was weighted strongly and was noted in another SR[13] as having much higher incidences of ROP and cholestasis in the control group (31.4% and 28.5%) when compared with the other studies (2.3% and 4.6%), and findings are not in agreement with two SRs[11,13] that found no difference in cholestasis rate and one SR[13] that found no difference in ROP incidence with any of the ILE comparisons. Second, another SR reported a higher AST level with SMOFlipid versus SO ILE, but these results were from a single study with only 96 patients.[11] One SR described individual results from small studies in other subpopulations, though actual values were not reported.[11] In children on home PN, there was a significantly greater decrease in total bilirubin in the SMOFlipid versus the SO ILE group.[11] In infants with cholestasis on prolonged PN, there were significantly greater decreases in bilirubin and ALT in the FO ILE group compared with the SO ILE group.

In two of the pediatric RCTs,[25,27] lower bilirubin levels were observed in the SMOFlipid group compared to the SO ILE control group while no significant difference was found in another RCT.[26] One pilot RCT with 24 patients[25] found that in patients with liver dysfunction the SMOFlipid group had significantly lower serum conjugated bilirubin level at trial completion compared to SO ILE (mean difference= -47 µmol/L; 95% confidence interval [CI], -21 to -17) and were more likely to experience a decrease in conjugated bilirubin to 0 µmol/L (hazard ratio = 10.6; 95% CI, 1.3 to 86.9). Mean baseline conjugated bilirubin was similar between the SMOFlipid and SO ILE groups (35 µmol/L and 36 µmol/L, respectively).[25] The other RCT[27] was an open-label study in surgical neonates showing significantly lower total (mean ± standard deviation [SD]: 0.99 ± 0.79 mg/dL versus 3.21 ± 1.99 mg/dL, $P < 0.001$) and direct bilirubin levels (mean ± SD: 0.58 ± 0.52 mg/dL versus 2.54 ± 1.75 mg/dL, $P < 0.001$) in the SMOFlipid group at day 22. Both aforementioned

RCTs[25,27] compared bilirubin levels at multiple time points using t-tests rather than tests more suited to repeated measures. Of the three RCTs measuring liver enzymes, the only significant finding was higher GGT level (mean difference = 114 U/L; 95% CI, 3 to 226) in the SMOFlipid versus SO ILE groups in the pilot study.[25] Where reported, there were no differences in growth or duration of PN in any of the RCTs.[24-27]

Adult populations

All five of the SRs[15-19] in adult populations reported shorter hospital LOS in the FO-containing ILE groups versus the non-FO-containing ILE groups, with differences ranging from 1.81[17] to 9.49.[19] Regarding ICU LOS, a shorter ICU LOS was reported in one SR in the FO- versus non-FO-containing ILE group among any patients with an ICU stay,[16] while the other SR reporting this outcome did not find a significant difference between groups although patients with elective surgery who were routinely admitted to the ICU were excluded.[19] In three SRs,[16-18] rates of infection were found to be lower in FO- versus non-FO containing ILE groups[16-18] in at least one ILE comparison, while one SR found no difference.[19] Odds ratios for infection in FO- versus non-FO containing ILE groups ranged from 0.42[17,18] to 0.52[18] and risk ratios ranged from 0.53[16] to 0.61.[16] Out of the SRs analyzing liver enzymes,[15,16,18] all reported lower ALT, AST, ALP, and/or GGT in groups receiving FO-containing ILEs compared with groups receiving non-FO-containing ILEs (often the comparisons with the largest sample size). Of the two SRs reporting bilirubin, one reported lower total bilirubin in the SO/MCT/FO versus SO/MCT ILE groups[18] while the other found no difference between FO-containing and non-FO-containing ILE groups.[16] Three SRs reported on inflammatory markers[16-18] and any differences found favoured reduced inflammation in the FO-containing- versus the non-FO-containing ILE group. Specifically, tumour necrosis factor-alpha (TNF-α) was lower with FO-containing ILEs in two SRs,[17,18]and two SRs reported lower IL-6[18] or greater IL-6 reduction.[16] Where analyzed, leukotriene B5 (LTB5) level was higher[16,18] and leukotriene B4 (LTB4) level[16] and LTB5/LTB4 ratio[16] were lower.

Findings from the four RCTs[20-23] indicated that the mean duration of PN was not significantly different between treatment groups. Two RCTs studied surgical and ICU patients,[20,21] comparing FO-containing ILE against non-FO-containing ILE. In the first RCT, fewer nosocomial infections were observed in ICU patients in the FO- compared to non-FO groups (21.0% for SO/MCT/FO ILE versus 37.2% for SO/MCT ILE group, $P = 0.04$) in addition to a longer time free of infection (mean ± standard deviation: 21 ± 2 vs. 16 ± 2 days, $P = 0.03$), but no differences were found in mortality or LOS.[20] In the second RCT, no differences in liver function or inflammatory markers were observed between SO/MCT/FO and SO/MCT ILE groups.[21]

In an RCT of patients receiving long-term PN,[22] lower ALT (30.3 ± 19.1 U/L for SMOFlipid vs. 48.7 ± 50.8 U/L for SO ILE, $P < 0.05$), lower AST (26.5 ± 10.9 U/L vs. 41.0 ± 33.7 U/L, $P = 0.03$), lower total bilirubin (9.5 ± 6.5 µmol/L vs. 15.7 ±15.9 µmol/L, $P = 0.04$), and lower number of patients with a severe adverse event (5.9% vs. 20.5%, $P = 0.03$) were observed after four weeks of PN with SMOFlipid compared with SO ILE. Lastly, one RCT compared ClinOleic (SO/OO ILE) against SO ILE in ICU patients and found no differences in LOS, mortality, nosocomial infections, acute renal failure, and inflammatory markers.[23]

What is the cost-effectiveness of lipid formulations in adult patients requiring total parenteral nutrition?

Both of the cost-effectiveness studies found that PN with Omegaven (FO ILE) dominated PN with standard ILE, showing lower overall costs[28,29] in conjunction with lower hospital LOS[29] and fewer infections[28] in 88% of ICU patients. The study conducted in China from the patient's perspective found a 6.5 day (standard error [SE] = 4.0) decrease in total LOS, a decrease in 614 infections per 10,000 patients (SE = 362), and a 10,617 renminbi (SE = 7,202) decrease in total cost per patient in the Omegaven arm versus the standard (non-FO-containing) ILE arm.[28]

The European study from the health care provider's perspective using clinical outcomes from Italian ICUs found the Omegaven arm had a decrease in total LOS of 4.55 days (95% CI, 4.29 to 4.79), a decrease in infections per 10,000 patients of 259 (95% CI, 178 to 480), and a decrease in total costs of €4,679 (95% CI, 3,372 to 6,121).[29] Using clinical outcomes for non-ICU patients from international clinical trials, the decreases in the Omegaven arm were: 1.58 days (95% CI, 1.49 to 1.61) in total LOS, 1,189 infections per 10,000 patients (95% CI, 645 to 1511), and €1,025 (95% CI, 1,540 to 546) in total costs.[29] Similar results were shown when estimating costs in France, Germany, and the UK.[29] Hospital and ICU LOS had the largest impact on costs, but input values for LOS and infection rate were not given for the Omegaven arm and it is difficult to assess the appropriateness of the effectiveness assumptions.[29]

The significance of lower LOS and infection rate as outcomes of the model is unclear since LOS and infection rate as input parameters were defined to be lower in the Omegaven arm relative to the control arm.

What are the evidence-based guidelines associated with the use of lipid formulations in adult and pediatric patients requiring total parenteral nutrition?

Recommendations in the guidelines related to ILE composition in PN were scarce and generally weak. The American Society for Parenteral and Enteral Nutrition (ASPEN) notes that only SO ILE is available for use in the United States (US) and declines to make recommendations concerning alternative ILEs.[31,33] The ASPEN guidelines recommend restriction of SO ILE dose to a maximum of 1 g/kg/day in children with PNALD[31] and a maximum of 100 g/week during the first week of PN in critically ill adults where essential fatty acid deficiency is a concern,[33] but these recommendations are based on very low quality evidence. The ASPEN guidelines also recommend against the use of specialty high-fat/low-carbohydrate PN formulations in ICU patients with acute respiratory failure, based on very low quality evidence.[33] The European Society for Clinical Nutrition and Metabolism (ESPEN) provides a moderate recommendation for the use of n-3 fatty acid-containing ILEs in adult postoperative patients requiring PN, based on evidence from observational studies.[32] The ESPEN guidelines also suggest as weak recommendations at least 1 g/kg/week of ILE to prevent essential fatty acid deficiency in long-term home PN, a limit of 1 g/kg/day of SO ILE for long-term home PN patients with chronic intestinal failure, and a decrease in the total amount or the n-6 to n-3 fatty acid ratio of the lipid component of PN in adults with intestinal failure-associated liver disease.[30]

Limitations

Despite the lack of non-biochemical outcomes was used as an exclusion criterion, safety-related biochemical outcomes were included in the present report. As a result, biochemical outcomes reported here may not be representative of the sources of literature searched. In the absence of interpretation of biochemical measurements, the clinical significance of these outcomes remains unknown.

The quality of evidence from the SRs suffered from the small number of studies available for each outcome and the small sample sizes in the included studies. The included studies were small-scale, single-centre trials. Almost all of the SRs stated the need for larger, high-quality RCTs. Given the small number and scale of studies available, publication bias was difficult to assess.

Each SR had some variation in the ILEs compared and the dosages and durations of PN. Details on enteral nutrition alongside PN were not reported in the SRs and were unevenly reported in the RCTs, so contributions of enteral nutrition to within and between study heterogeneity are unclear. Also, it is unclear how generalizable these findings are to patient populations completely relying on PN for nutritional intake.

Many primary studies were included in more than one SR and some SRs used very similar sets of RCTs, especially in the pediatric populations. Details on the RCTs whose outcomes were analyzed in each SR are presented in Appendix 6. The extensive overlap between SRs likely means there is uneven representation among the primary studies.

The effects of long-term PN are difficult to assess since the studies all focused on short-term PN. One RCT studied out-patients and even that study's duration was 28 days.

All of the outcomes analyzed in the SRs and RCTs were relatively short-term and many authors mentioned the need for studies with long-term follow-up, especially in pediatric populations.

Both economic studies[28,29] used effectiveness data comparing various FO-containing ILEs against non-FO-containing ILEs to model outcomes for pure FO ILE (Omegaven). The effectiveness data used in both economic studies[28,29] for the evaluation of ICU patients came from the same SR[16] which did not assess the quality of the individual studies. The effectiveness data from international clinical trials was not provided.[29] Absolute reductions in hospital and ICU LOS were converted to relative risks without commenting on the validity of this change.[29]

The Chinese economic study combined Chinese costs and patient outcomes with international effectiveness data.[28] The European economic study combined costs in Italy, France, Germany and the UK with Italian clinical outcomes data and international effectiveness data to evaluate cost-effectiveness in the specified countries.[29] It is unclear how generalizable these results are to the Canadian setting.

While the economic studies reported LOS[29] and infection rate[28] as outcomes, the reported improvements in clinical outcomes were likely inevitable given that LOS and infection rate as input parameters were defined to be lower in the Omegaven arm versus the control arm.

The European economic study[29] was partially funded by the manufacturer of Omegaven, Fresenius Kabi. One of the authors was an employee of Fresenius Kabi while the lead author was co-owner of the private research firm receiving this funding. The latter author was also an author in the Chinese study.[28]

Weak recommendations regarding the most appropriate ILEs to use in PN were sparse and based on low quality evidence.[30-33] Two of the guidelines originated from the US where only SO ILEs are available for PN.[31,33]

Conclusions and Implications for Decision or Policy Making

A total of 24 relevant publications, comprising 10 SRs,[10-19] eight RCTs,[20-27] two economic studies,[16,29] and four evidence-based guidelines,[30-33] were identified. Five SRs,[10-14] four RCTs,[24-27] and one guideline[31] examined pediatric populations (mainly preterm infants), while five SRs,[15-19] four RCTs,[20-23] two economic studies,[16,29] and three guidelines[30,32,33] were in adult populations (mainly elective surgery and critically ill patients).

Due to the lack of high-quality evidence for the comparison of clinical outcomes between patients receiving PN with different ILEs, it is not possible to draw any conclusions with a high level of confidence. However, there were consistent trends among studies, including evidence that administering PN is no less safe with non-100% SO ILEs versus SO ILEs or with FO-containing ILEs versus non-FO-containing ILEs. None of the meta-analyses showed an increase in adverse events, bilirubin or liver enzymes with non-100% SO ILEs and in RCTs where bilirubin or a single liver enzyme was higher in the non-100% SO versus the SO ILE groups, the finding was not accompanied by elevations in other liver markers.

In preterm infants, outcomes such as mortality rate, growth parameters, incidence rates of complications related to prematurity, and liver markers did not differ in comparisons between non-100% SO ILEs and SO ILEs or between FO-containing ILEs versus non-FO-containing ILEs. Isolated findings of lower rates of cholestasis and ROP with FO-containing ILEs were heavily influenced by a study with an anomalous population.[10] A small pilot study in older infants (up to 24 months of age) with liver dysfunction found lower conjugated bilirubin levels with SMOFlipid compared with SO ILE.[25] An RCT in surgical neonates found lower total and direct bilirubin levels, also with SMOFlipid versus SO ILE.[27] One SR[11] described small RCTs comparing FO-containing ILES with SO ILE: an RCT in children on home PN found greater decreases in bilirubin with SMOFlipid while an RCT in infants with cholestasis on long-term PN found greater decreases in bilirubin and ALT with FO ILE.

There was evidence of clinical benefits with FO-containing ILEs compared to non-FO-containing ILEs in adult populations, especially in surgical and ICU patients. Shorter hospital LOS,[16-19] shorter ICU LOS,[16] and lower rates of infection were commonly reported in the SRs. One RCT reported a reduced rate of nosocomial infection as well as longer time free of infection.[20] Bilirubin[18] and liver enzyme levels[15,16,18] were lower with FO-containing ILEs, though this effect was not consistently demonstrated. Levels of inflammatory markers favoured a less pro-inflammatory state in surgical and ICU patients.[16-18,21] The RCT comparing SO/OO ILE with SO ILE did not show differences in clinical outcomes or safety parameters.[23]

The economic evaluations supported the cost-effectiveness of FO ILE (Omegaven) over SO ILEs, demonstrating high probabilities of the following: lower LOS and costs in adult ICU and non-ICU surgical patients;[29] lower infection rates and costs in adult ICU patients.[28] ICU and hospital LOS were the main cost drivers and anticipated reductions in LOS with Omegaven more than compensated for its higher cost when costs were estimated for patients in China[29] and health care providers in European countries.[28] However, substantial limitations in the economic analyses mean that the results should be interpreted with caution.

The American Society for Parenteral and Enteral Nutrition guidelines were not able to make a recommendation on ILEs other than SO ILE due to their issues of availability in the US.[31,33] Therefore, the recommendations are limited to restricting SO ILE dose in children

with PNALD[31] and critically ill adults.[33] The European Society for Clinical Nutrition and Metabolism gives a recommendation of moderate strength for the use of n-3 fatty acid-containing ILEs in adult postoperative patients requiring PN.[32] It also suggests restricting dose of SO ILE for long-term home PN patients and decreasing the total amount or the n-6 to n-3 fatty acid ratio of ILEs in PN in adults with intestinal failure-associated liver disease.[30]

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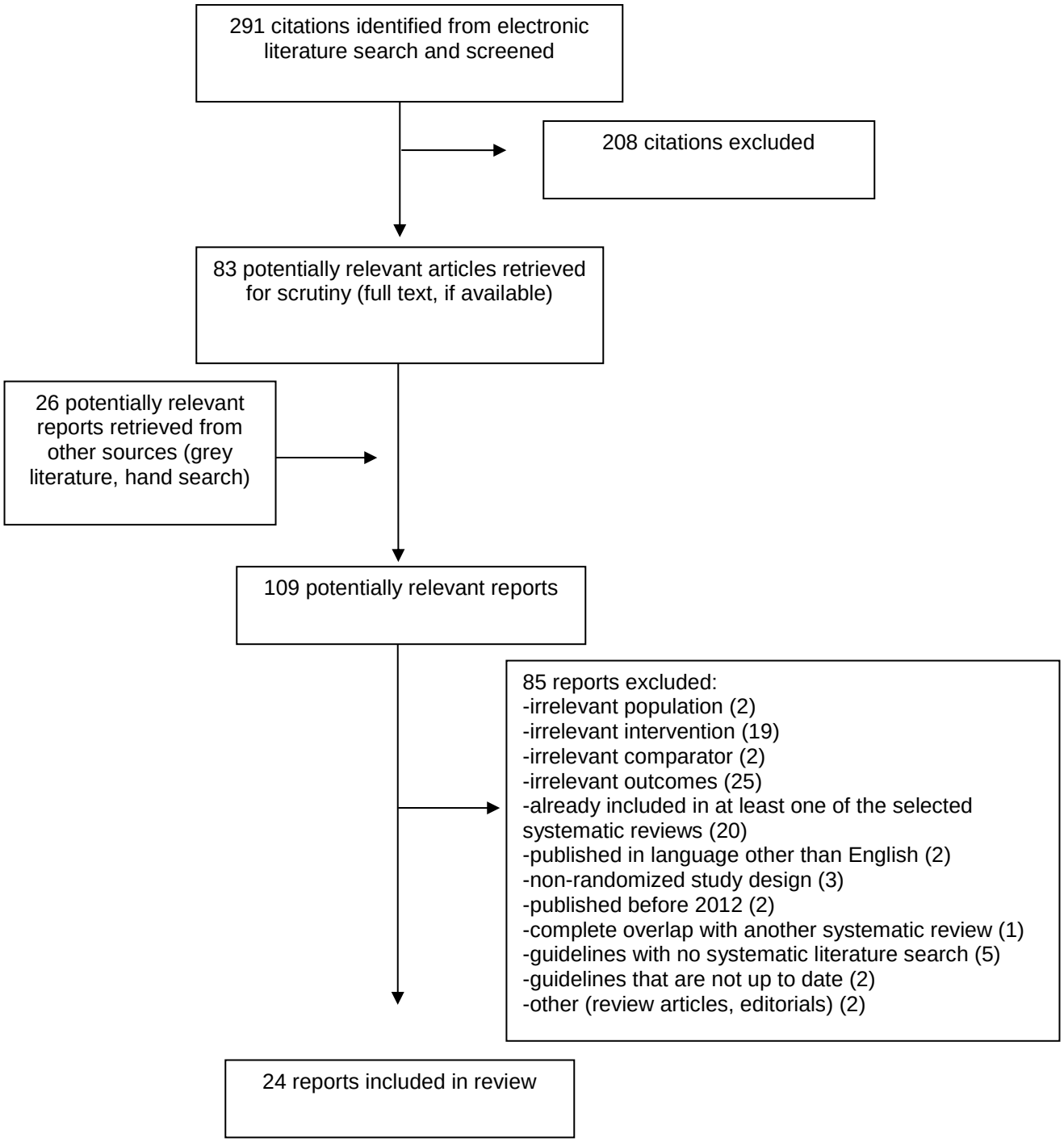
Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPD	bronchopulmonary dysplasia
CI	confidence interval
DHA	docosahexaenoic acid
EFA	essential fatty acids
EN	enteral nutrition
EPA	eicosapentaenoic acid
FO	fish oil
GGT	gamma-glutamyl transferase
ICU	intensive care unit
ILE	intravenous lipid emulsion
LCT	long-chain triglycerides
LOS	length of stay
LTB4	leukotriene B4
LTB5	leukotriene B5
MCT	medium chain triglycerides
MD	mean difference
NEC	necrotizing enterocolitis
OO	olive oil
OR	odds ratio
PN	parenteral nutrition
PNALD	parenteral nutrition-associated liver disease
RCT	randomized controlled trial
ROP	retinopathy of prematurity
RR	risk ratio
SMOF	soybean oil, medium chain triglycerides, olive oil, and fish oil
SO	soybean oil
SR	systematic review
TPN	total parenteral nutrition

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

Author, Publication Year, Country, Literature Search Period	Number and Type of Primary Studies Included	Population Characteristics, Total N (if applicable)	Intervention(s)	Comparator(s)	Main Outcomes
Pediatric Populations					
Vayalthrikkovil et al. 2017[10] **Canada** **Search: up to February 2016**	Six primary studies included: RCT (n = 4), observational (n = 2) Subgroup analysis was performed for each study design	Preterm infants of <32 weeks gestational age or birth weight <1500 g, without major comorbidities, receiving either FO-containing ILEs or SO-based ILEs within 24 hours of birth N ranged from 176 to 421 for outcomes in RCTs	FO-containing ILEs Duration: not reported Dose: 0.5 to 3.5 g/kg daily of ILE depending on day of life	SO or SO/OO ILE	*Clinical effectiveness:* ROP stage 3 and above or requiring laser therapy, cholestasis (defined as serum conjugated bilirubin >1 mg/dL), BPD, NEC stage II and above, intraventricular hemorrhage, sepsis, mortality
Hojsak et al. 2016[11] **Croatia (for the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee)** **Search: up to March 2015**	23 RCTs included	Pediatric patients requiring short- or long-term total or complementary PN: 17 RCTs in preterm infants or critically ill neonates with short-term PN 2 RCTs in older children (>1 year of age) with short-term PN 1 RCT in neonates with long-term (≥4 weeks) PN 3 RCTs in infants and children (>1 month of age) receiving long-term PN	Non-100% SO ILEs <u>Neonates or infants with short-term PN</u> Dose: maximum of 2 to 3.5 g/kg daily of ILE Duration: 3 to median ≈ 20 days <u>Children with short-term PN</u> Dose: maximum of 1-1.5 g/kg daily of ILE Duration: 14 to 76 days <u>Infants and children with long-term PN</u> Dose: maximum of 1.5 to 2 g/kg	SO ILE	*Clinical effectiveness:* incidence of cholestasis (defined as serum conjugated bilirubin ≥2 mg/dL) *Safety:* total and conjugated bilirubin, liver enzymes

Author, Publication Year, Country, Literature Search Period	Number and Type of Primary Studies Included	Population Characteristics, Total N (if applicable)	Intervention(s)	Comparator(s)	Main Outcomes
			daily or 4 to 5 times/week of ILE Duration: 10 days to 2 months		
Kapoor et al. 2015[13] **Australia** **Search: up to July 2015**	15 RCTs or quasi-RCTs	Preterm infants of <37 weeks gestational age receiving ILE as part of total or partial PN within the first week of life and for a minimum of 5 days N ranged from 57 to 623 depending on the primary outcome	SMOF, SO/MCT/FO, OO/SO, SO/MCT, FO, SO/borage oil, or structured SO/MCT ILE All FO-containing ILEs All alternative ILEs Duration: ≥5 days Dose: 0.5 to 3.5 g/kg daily of ILE depending on day of life	SO ILE	*Clinical effectiveness:* Primary: mortality, physical growth, BPD/chronic lung disease Secondary: duration of ventilation, duration of supplemental oxygen, need for home oxygen therapy, sepsis, NEC, significant jaundice, ROP, intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, air leaks, pulmonary hemorrhage, thrombocytopenia, PN-associated liver disease
Zhao et al. 2015[14] **China** **Search: up to June 2014**	8 RCTs included	Preterm infants of <34 weeks gestational age, without congenital abnormalities, admitted to a neonatal ICU N ranged from 45 to 483 depending on clinical outcome	SMOF or SO/MCT/FO ILE Duration: 7 to 60 days Dose: not reported	SO, SO/OO, or SO/MCT ILE	*Clinical effectiveness:* infant growth, mortality, complications *Safety:* laboratory parameters on the 8th day of treatment
Vlaardingerbroek et al. 2012[12] **Netherlands**	10 RCTs included for comparison of different ILEs (secondary objective)	Preterm infants of birth weight <1500 g admitted to a neonatal ICU receiving PN ILE within the first days	SO/MCT or SMOF ILE Duration and dose: not reported	SO ILE	*Clinical effectiveness:* rate of weight gain, death before discharge, duration of respiratory

Author, Publication Year, Country, Literature Search Period	Number and Type of Primary Studies Included	Population Characteristics, Total N (if applicable)	Intervention(s)	Comparator(s)	Main Outcomes
Search: up to February 2012		of life N ranged from 92 to 174 depending on the outcome			support, sepsis
Adult Populations					
Bae et al. 2017[17] **South Korea** **Search: up to August 2014**	19 RCTs included	Adult surgical patients receiving ≥3 days of PN in a hospital N ranged from 169 to 1,064 depending on the outcome	FO-containing ILEs Duration: 3 to 9 days Dose: 0.08 to 0.3 g/kg daily of n-3 fatty acids	SO, SO/MCT, or SO/OO ILE	*Clinical effectiveness:* infectious morbidity, mortality, hospital and ICU LOS *Safety:* liver function, inflammatory markers
Li et al. 2014[18] **China** **Search: up to September 2012**	21 RCTs included	Adult major elective surgery patients receiving total PN post-operatively N ranged from 126 to 765 depending on the outcome	FO-containing ILEs Duration: 5 to 7 days Dose: 1.0 to 1.5 g/kg ILE (0.14 to 0.28 g/kg fish oil) daily depending on post-operative day	SO or SO/MCT ILE	*Clinical effectiveness:* mortality, hospital LOS, post-operative infection rate *Safety:* liver function, inflammatory markers
Palmer et al. 2013[19] **UK** **Search: 1996 to June 2011**	9 RCTs included 3 of the included RCTs were from abstracts	Adult critically ill patients receiving PN Elective surgical patients routinely admitted to the ICU were excluded N ranged from 117 to 391 depending on the outcome	FO-containing ILEs Duration: 5 to 10 days where reported Dose: 0.08 to 0.2 g/kg daily of n-3 fatty acids where reported	SO or SO/MCT ILE where reported	*Clinical effectiveness:* mortality, infection rate, ICU and hospital LOS
Tian et al. 2013[15] **China** **Search: up to August 2012**	6 RCTs included	Adult elective abdominal or thoracic surgery patients receiving total PN immediately following surgery	SMOF ILE Duration: 4 to 6 days Dose: not reported	SO, SO/MCT or OO/SO ILE	*Clinical effectiveness:* hospital LOS Safety: adverse events, liver function, C-reactive protein

Author, Publication Year, Country, Literature Search Period	Number and Type of Primary Studies Included	Population Characteristics, Total N (if applicable)	Intervention(s)	Comparator(s)	Main Outcomes
		N ranged from 20 to 267 depending on the outcome			
Pradelli et al. 2012[16] **Italy** **Search: up to August 2011**	23 RCTs included	Adult ICU or elective surgery patients receiving PN N ranged from 27 to 1169 depending on the outcome	FO-containing ILEs Subgroup analysis based on ICU (any ICU stay) vs. non-ICU patients Duration and dose: not reported	SO, SO/MCT, or OO/SO ILE	*Clinical effectiveness:* mortality, infection rate, hospital and ICU LOS *Safety:* liver function, inflammatory markers

BPD = bronchopulmonary dysplasia; FO = fish oil; ICU = intensive care unit; ILE = intravenous lipid emulsion; LOS = length of stay; MCT = medium-chain triglycerides; NEC = necrotizing enterocolitis; OO = olive oil; PN = parenteral nutrition; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; ROP = retinopathy of prematurity; SMOF = soybean oil, medium-chain triglycerides, olive oil and fish oil; SO = soybean oil.

Table A2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Pediatric Populations					
Najm et al. 2017[24] **Sweden**	Open-label RCT Randomized in blocks of 20, adjusting for gestational age	Infants with gestational age <28 weeks, without major congenital malformations, admitted to neonatal intensive care SMOFlipid, n = 41 Mean gestational age ± SD = 25.5 ± 1.3 wk Clinoleic, n = 37 Mean gestational age ± SD = 25.6 ± 1.6 wk	SMOFlipid (15% fish oil with n-3 LCPUFAs) started 6-12 h after birth at a rate of 1 g/kg/d with daily increases up to 2 g/kg/d plus enteral nutrition (maternal or donor breastmilk with individualized fortification) for up to 28 days after birth	Clinoleic (olive oil-based) started 6-12 h after birth at a rate of 1 g/kg/d with daily increases up to 2 g/kg/d plus enteral nutrition (maternal or donor breastmilk with individualized fortification) for up to 28 days after birth	*Clinical effectiveness:* amount and duration of PN, growth (weight, length, head circumference) from birth to postmenstrual age 36 wk, cholestasis, ROP, BPD, NEC, PDA, sepsis (verified by culture and/or C-reactive protein)
Diamond et al. 2016[25] **Canada**	Multi-centre RCT Randomized using a number sequence with blocks of variable size	Infants <24 mo of age with short bowel syndrome or intestinal failure and hepatic dysfunction without sepsis who obtained >40% of total calories parenterally SMOFlipid, n = 11 Mean age: 6.5 wk (range, 4.3 to 8.7 wk) Intralipid, n = 13 Mean age: 5.3 wk (range, 3.5 to 7.2 wk)	SMOFlipid (30% soybean oil, 30% MCT, 25% olive oil, 15% fish oil) for up to 12 wk, unless enteral tolerance was achieved sooner	Intralipid (soy-based) for up to 12 wk, unless enteral tolerance was achieved sooner	*Clinical effectiveness:* time to achievement of full enteral tolerance, growth (weight, height, head circumference) *Safety:* Conjugated bilirubin, unconjugated bilirubin, albumin, INR, AST, ALT, ALP, GGT, AEs
Uthaya et al. 2016[26] **England**	Multi-centre RCT Randomized using minimization with a random element and stratification by gestational age, birth weight, and study centre	Preterm infants (born at <31 wk gestation) without life-threatening abnormalities who could receive PN within 24 h of birth Imm-RDI/SMOF, n = 43	SMOF (2 g/kg/d on day 1, increased to 3g/kg/d from day 2) and immediate recommended daily intake (Imm-RDI) of amino acids (Vaminolact; 3.6 g/kg/d from day 1)	Intralipid (soybean based lipid emulsion [SO]; 2 g/kg/d on day 1, increased to 3g/kg/d from day 2) and incremental delivery of animo acids (Inc-AA; Vaminolact; 1.7	*Clinical effectiveness:* time to achieve enteral tolerance, growth from premature birth to term (weight, length, head circumference), body composition

		Mean gestational age ± SD = 27.8 ± 2.1 wk Inc-AA/SO, n = 42 Mean gestational age ± SD = 27.8 ± 1.9 wk Inc-AA/SMOF, n = 42 Mean gestational age ± SD = 27.5 ± 2.4 wk Imm-RDI/SO, n = 41 Mean gestational age ± SD = 28.1 ± 2.1 wk	*or* SMOF and Inc-AA Trial PN ceased when 150 ml milk/kg/d was tolerated for ≥ 24 h Note: Intervention groups pooled in the analyses	g/kg on day 1, 2.1 g/kg on day 2, and a maximum of 2.7 g/kg/d from day 3) *or* SO and Imm-RDI Trial PN ceased when 150 ml milk/kg/d was tolerated for ≥ 24 h Note: Comparator groups pooled in the analyses	(non-adipose mass, total adiposity, adipose tissue depots), insulin sensitivity (quantitative insulin sensitivity check index), total and regional brain volumes, incidence of conjugated hyperbilirubinemia, length of hospital stay, sepsis incidence, mortality *Safety:* BUN, intrahepatocellular lipid, total and conjugated bilirubin
Ariyawangso et al. 2014[27] **Thailand**	Open-label RCT Randomized in blocks of 4	Surgical neonates with gastroschisis, omphalocele, jejuno-ilea atresia or duodenal atresia requiring PN for at least 7 consecutive days SMOFlipid, n = 21 Gestational age: <37 wk, n = 14 (51.9%); 37-42 wk: n = 13 (48.1%) Intralipid, n = 21 Gestational age: <37 wk: n = 14 (51.9%); 37-42 wk: n = 13 (48.1%)	SMOFlipid 20% (30% soybean oil, 30% MCT, 25% olive oil, 15% FO) for at least 7 days; 0.5 g/kg/d on day 1 and increased daily up to 3 and 3.5 g/kg/d for term and pre-term neonates respectively until it reached 50% of total energy intake	Intralipid 20% for at least 7 days; 0.5 g/kg/d on day 1 and increased daily up to 3 and 3.5 g/kg/d for term and pre-term neonates respectively until it reached 50% of total energy intake	*Clinical effectiveness:* duration of PN, growth (weight, length, head circumference) *Safety:* ALT, AST, ALP, GGT, total bilirubin, direct bilirubin, BUN, creatinine, complications, SAEs
Adult Populations					
Grau-Carmona et al. 2015[20] **Spain**	Multi-centre RCT Randomization using an allocation program to balance groups on prognostic factors (APACHE score) and presence of sepsis on admission	Patients ≥ 18 y of age admitted to ICU with APACHE II ≥ 13 who were expected to require TPN for ≥ 5 d MCT/LCT/FO: n = 81 Mean age ± SD = 60.7 ± 17.3 y MCT/LCT:	MCT/LCT/FO: Lipoplus (50% MCT, 40% soybean oil [LCT] and 10% FO) up to 1.5 g/kg/day Enteral nutrition up to 50% of caloric requirements was allowed	MCT/LCT: Lipofundina (50% MCT, 50% LCT) up to 1.5 g/kg/day Enteral nutrition up to 50% of caloric requirements was allowed	*Clinical effectiveness:* duration of TPN, prevalence of nosocomial infections during 28 days of ICU stay, number of antibiotic-free days, time free of infection, length of ICU stay, length of hospital stay, ICU

		n = 78 Mean age ± SD = 60.6 ± 16.4 y			mortality, hospital mortality, 6-mo mortality, prevalence of cholestasis, liver necrosis, and mixed liver injury *Safety:* AEs
Ma et al. 2015[21] **Taiwan**	RCT Randomization in two blocks of 60; patients allocated 1:1	Patients ≥ 18 y of age following elective radical surgery for gastric and colorectal cancer MCT/LCT/n-3: n = 51 Mean age ± SD = 61.6 ± 9.8 y MCT/LCT: n = 48 Mean age ± SD = 62.9 ± 10.1 y	MCT/LCT/n-3: 20% Lipoplus; 0.8 to 1.5 g/kg/day from 1 day before surgery to 7-days post-operation Enteral nutrition restricted to clear liquid	MCT/LCT: 20% Lipofundin; 0.8 to 1.5 g/kg/day from 1 day before surgery to 7-days post-operation Enteral nutrition restricted to clear liquid	*Clinical effectiveness:* duration of TPN *Safety:* Post-operative inflammatory markers (IL-6, CRP, TNF-α, PCT), liver parameters (AST, ALT, GGT, bilirubin, PTT), albumin, INR, AE and SAEs
Klek et al. 2013[22] **Australia, Denmark, France, Israel, Netherlands, Poland, United Kingdom**	Multi-centre RCT Randomization performed by electronic data processing using a seed depending random number generator	In- and out-patients aged 18 to 85 y unable to sustain adequate enteral food intake for ≥ 4 wk and in need of PN SMOFlipid, n = 30 Mean age ± SD = 53.2 ± 14.6 y Intralipid 20%, n = 32 Mean age ± SD = 45.2 ± 13.6 y	SMOFlipid 20%; 1-2 g fat/kg/d for 4 wk	Intralipid 20%; 1-2 g fat/kg/d for 4 wk	*Clinical effectiveness:* PN duration *Safety:* liver parameters (ALP, GGT, total and conjugated bilirubin), INR,inflammatory markers (IL-6, sTNF-RII, CRP), AE and SAEs
Umpierrez et al. 2012[23] **USA**	Multi-centre RCT Randomization by computer-generated randomization table	Medical-surgical ICU patients aged 18 to 80 y who were expected to require PN for > 5 d by conventional criteria ClinOleic, n = 51 Mean age ± SD = 46 ± 19 y Intralipid, n = 49	Intralipid (100% soybean oil, plus egg yolk phospholipids, glycerin, and water) to a maximum of 28 d	ClinOleic (80% olive oil, 20% soybean oil plus glycerol, purified egg phospholipids, sodium oleate, sodium hydroxide, and water) to a maximum of 28 d	*Clinical effectiveness:* PN duration, nosocomial infections and non-infectious complications, acute renal failure, ICU and hospital length of stay, glycemic control, ICU and hospital mortality

		Mean age ± SD = 51 ± 15 y			*Safety:* inflammatory markers (CRP, IL-6, TNF-α) and oxidative stress markers (cysteine, glutathione, glutathione disulfide, glutathione redox potential, cysteine redox potential)

AE = adverse event; APACHE II = Acute Physiology and Chronic Health Evaluation II; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPD = bronchopulmonary dysplasia; BUN = blood urea nitrogen concentration; CRP = C-reactive protein; d = day; FO = fish oil; GGT = gamma-glutamyl transferase; ICU = intensive care unit; IL-6 = interleukin-6; Imm-RDI = immediate recommended daily intake; INR = international normalized ratio; Inc-AA = incremental introduction of amino acid; LCPUFA = long-chain polyunsaturated fatty acids; LCT = long-chain triglycerides; MCT = medium-chain triglycerides; mo = month; n-3 = n-3 polyunsaturated fatty acids; NEC = necrotizing enterocolitis; PCT = procalcitonin; PDA = patent ductus arteriosis; PN = parenteral nutrition; PTT = partial thromboplastin time; RCT = randomized controlled trial; ROP = retinopathy of prematurity; SAE = serious adverse event; SMOF = soybean oil, medium-chain triglycerides, olive oil and fish oil; SO = soybean-based lipid emulsion; sTNF-RII = soluble tumour necrosis factor receptor II; TNF-α = tumor necrosis factor-alpha; TPN = total parenteral nutrition; wk = week; y = year.

Table A3: Characteristics of Included Economic Analyses

First Author, Publication Year, Country	Type of Analysis, Perspective	Study Population	Intervention, Comparator	Time Horizon	Main Assumptions
Wu et al. 2015[28] **China**	Cost-effectiveness analysis using discrete event simulation from the perspective of the patient and their family	Patient Characteristics, Resource Consumption, Unit Costs: Chinese ICU patients at the Department of General Surgery, Zhongshan Hospital Clinical Effectiveness Data: adult ICU or elective surgery patients receiving PN[16]	PN with Omegaven (FO ILE) vs. standard emulsions (assumed to be non-FO-containing ILEs) Outcomes: ICU and ward LOS, costs, incremental cost per infection avoided	Duration of hospital stay	• Clinical effectiveness data from SR[16] on various FO-containing ILEs vs. non-FO-containing ILEs was assumed to be similar to clinical effectiveness of Omegaven and applicable to Chinese standards of care • All other relevant input parameters were the same in both arms • Total cost of antibiotics was modelled as linear combination of ward LOS, ICU LOS, and occurrence of infection to separate out antibiotic costs for prophylaxis vs. treatment of infection
Pradelli et al. 2014[29] **Italy (includes analyses for France, Germany, UK)**	Cost-effectiveness analysis using discrete event simulation from the perspective of the health care provider	Patient Characteristics: data collected from over half of all ICUs in Italy for ICU patients and international clinical trial data for non-ICU patients Resource Consumption, Unit Costs: Italian ICU data and national report (Italy) for ward data Clinical Effectiveness Data: adult ICU or elective surgery patients receiving PN[16] for ICU patients and international clinical trial data for non-ICU patients	PN with Omegaven (FO ILE) vs. standard emulsions (assumed to be non-FO-containing ILEs) Outcomes: hospital LOS, costs, incremental cost per day of stay avoided	Duration of hospital stay	• Clinical effectiveness data from SR[16] on various FO-containing ILEs vs. non-FO-containing ILEs was assumed to be similar to clinical effectiveness of Omegaven and applicable to Italian and other European standards of care • All other relevant input parameters were the same in both arms • Omegaven-associated reduction in LOS can be modeled with a risk ratio • Patient population and outcomes do not vary between the countries studied

FO = fish oil; ICU = intensive care unit; ILE = intravenous lipid emulsion; LOS = length of stay; PN = parenteral nutrition.

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Target Population, Intended Users	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Pediatric Populations						
Wales et al. 2014[31]						
Target population: children with PN-dependent intestinal failure; children at risk of PNALD **Intended users:** health professionals	Ethanol lock, fat emulsion strategies, enteral UDCA, multidisciplinary intestinal rehabilitation teams	Examples provided (e.g., clinical outcomes, bloodstream infection) but not a comprehensive list	"*Rigorous search of the published literature*" p. 540; details not provided for search strategy, screening, or evidence synthesis	Evidence rated using the GRADE approach (grades "high" to "very low" quality)	Expert consensus based on consideration of evidence (risks and benefits)	Internal and external peer review
Adult Populations						
Weimann et al. 2017[32]						
Target population: surgical patients at nutritional risk; patients undergoing major surgery (e.g., for cancer); patients developing severe complications despite best perioperative care **Intended**	Nutritional support, including enteral and parenteral nutrition	Biomedical, multidimensional, health economy, quality of life	Electronic database searches (from 2010, updated to October 31, 2016) and hand-searching of RCTs, meta-analyses, and systematic reviews; methods for screening and evidence synthesis not indicated	Evidence graded using SIGN (Grades A [highest], B, 0, or GPP ["good practice points", based on expert opinion])	Expert consensus based on review of literature using the standards of the Guideline International Network	None indicated

users: not specified						
Pironi et al. 2016[30]						
Target population: adult patients with chronic intestinal failure due to benign disease **Intended users:** not specified	Home PN; PN formulation; intestinal rehabilitation, medical therapies, non-transplant surgery; intestinal transplantation; prevention/treatment of infection or occlusion/thrombosis related to central venous catheter; liver disease, gallbladder sludge and stone, renal failure, and metabolic bone disease associated with intestinal failure	Not specified	Electronic search in PubMed (dates and search strategy not specified); methods for screening and evidence synthesis not indicated	Evidence rated using the GRADE approach (grades "high" to "very low" quality)	Expert consensus (Delphi rounds and votes) based on opinions, balance of risks and benefits, costs, and review of evidence	None indicated
Taylor et al. 2016[33]						
Target population: adult critically ill patients expected to require a length of stay >2 or 3 days in a medical or surgical ICU **Intended users:** all healthcare providers involved in nutrition therapy of the critically ill (e.g., primary physicians, nurses, dietitians, pharmacists)	Nutrition, enteral, parenteral, tube feeding	Examples provided (e.g., pancreatitis, sepsis) but not a comprehensive list	Electronic database searches through to December 31, 2013, including ePub publications; method for screening not indicated; data extraction in duplicate and meta-analyses performed where possible	Evidence rated using the GRADE approach (grades "high" to "very low" quality)	Expert consensus based on consideration of evidence (risks and benefits); "consensus" defined as 70% agreement	Internal and external peer review

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PN = parenteral nutrition; PNALD = parenteral nutrition-associated liver disease; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; UDCA = ursodeoxycholic acid.

Appendix 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
Pediatric Populations	
Vayalthrikkovil et al. 2017[10]	
• Research questions and inclusion criteria established *a priori* • Multiple databases (MEDLINE, EMBASE, PubMed, Scopus, Web of Sciences, and CINAHL) and the Pediatric Academic Societies' annual meeting abstracts were searched; search strategy with key words was provided. • Study selection done by four independent reviewers • Data extraction done by two independent reviewers • List of included studies provided • Important characteristics of included studies provided • Quality of individual studies assessed using the van Tulder scale • Studies were combined in the meta-analysis using an appropriate method (fixed-effects models used following assessment of heterogeneity with I^2) • Likelihood of publication bias was assessed using funnel plots, but unclear which outcome was described in the included funnel plot • SR authors declared no conflicts of interest	• Grey literature not searched • Unclear whether studies were limited by language in the literature search • List of excluded studies not provided • Study populations not well described • Analysis and conclusions did not consider scientific quality of included studies beyond concealed randomization • Retinopathy of prematurity and cholestasis rates were much higher in one out of the four studies, yet this was not addressed • Retinopathy of prematurity risk ratio may have been improperly calculated for one study • Conflicts of interest not reported for the included studies
Hojsak et al. 2016[11]	
• Research questions and inclusion criteria established *a priori* • Multiple databases (PubMed, EMBASE, and Cochrane CENTRAL) searched; search strategy with key words provided • List of included studies provided • Characteristics of the included studies provided • Studies were combined in the meta-analyses using an appropriate method (fixed-effects models used following assessment of heterogeneity with I^2) • SR authors reported conflicts of interest	• Unclear if study selection and data extraction were done in duplicate • Grey literature not searched • Studies were limited to English language manuscripts • List of excluded studies not provided • Study populations not well described • Quality assessment of included studies not mentioned • Analysis and conclusions did not consider scientific quality of included studies • Likelihood of publication bias not assessed • Some authors of the systematic review received honoraria or funding from manufacturers of lipid emulsions. • Conflicts of interest not reported for the included studies
Kapoor et al. 2015[13]	
• Research questions and inclusion criteria established *a priori* • Multiple databases (MEDLINE, EMBASE, Cochrane CENTRAL, CINAHL, Ovid Nursing Database, and Maternity and Infant Care), reference lists of all included studies, abstracts (Biological Abstracts, Pediatric Academic Societies, and Web of Science), and trials registries (www.clinicaltrials.gov, www.controlled-trials.com, and the	• Grey literature search limited to trial registries • Studies were not combined in the meta-analysis using an appropriate method (fixed-effects model used for all outcomes regardless of heterogeneity) • Conflicts of interest not reported for the included studies

Strengths	Limitations
WHO International Clinical Trials Registry Platform) searched; search strategies with key words provided • Study selection and data extraction performed independently by two reviewers • Studies not limited by language in the search • Lists of included and excluded studies provided • Characteristics of the included studies provided in great detail, including study populations • Quality of individual studies assessed using Cochrane Neonatal Review Group standard methods (similar to Cochrane Risk of Bias Tool) • Multiple reports of a single study identified to avoid double counting • GRADE used to assess quality of evidence for each outcome • Quality of individual studies used appropriately in formulating conclusions • Heterogeneity assessed with I^2 was considered in assigning quality of evidence for each outcome • Sensitivity analysis conducted for outlying studies • Funnel plots not used due to few studies for each outcome • SR authors declared no conflicts of interest	
Zhao et al. 2015[14]	
• Research questions and inclusion criteria established *a priori* • Study selection and data extraction performed independently by two reviewers • Multiple databases (PubMed, EMBASE, Ovid, and Cochrane Library), related textbook chapters, and conference presentations searched and key words provided; reference lists of relevant publications manually searched • List of included studies provided • Characteristics of included studies provided, including study populations A 7-point Jadad scale factoring in allocation concealment was used to assess quality of individual studies; all studies included in the analysis had a Jadad score of ≥4 • Studies were combined in the meta-analysis using appropriate methods based on assessment of heterogeneity with I^2 • Quality of individual studies used appropriately in formulating conclusions • Likelihood of publication bias assessed using funnel plots • SR authors declared no conflicts of interest	• Grey literature not searched • Unclear whether studies were limited by language of publication • List of excluded studies not provided • Conflicts of interest not reported for the included studies
Vlaardingerbroek et al. 2012[12]	
• Research questions and inclusion criteria established *a priori* • Study selection and data extraction were performed independently by two reviewers • Multiple databases (PubMed, EMBASE, and Cochrane	• Grey literature not searched • List of excluded studies not provided • Conflicts of interest not reported for the included studies

Strengths	Limitations
Library) were searched and key words were provided; reference lists of relevant publications were manually searched • Studies not limited by language in the search • List of included studies provided • Characteristics of the included studies well described, including study populations • Quality of individual studies assessed using a 5-point Jadad scale • Sensitivity analysis for an outcome was performed if included publications of low quality • Quality of individual studies used appropriately in formulating conclusions • I^2 for heterogeneity was evaluated and **s**tudies were combined in the meta-analysis using an appropriate method (random-effects model) • Likelihood of publication bias assessed using funnel plots and Begg and Eggers tests (for symmetry of funnel plots) not performed due to few studies • SR authors declared no conflicts of interest	
Adult Populations	
Bae et al. 2017[17]	
• Research questions and inclusion criteria established *a priori* • Study selection and data extraction performed independently by two reviewers • Multiple databases (MEDLINE, EMBASE, and Cochrane CENTRAL) searched and search strategy with key words provided • List of included studies provided • Important characteristics of the included studies provided • Quality of individual studies assessed using Cochrane Risk of Bias Tool • Studies with incomplete outcomes reporting excluded from analysis • Quality of individual studies used appropriately in formulating conclusions • Studies were combined in the meta-analysis using an appropriate method (random-effects model) • Likelihood of publication bias assessed with funnel plots and Egger's regression test • SR authors declared no conflicts of interest	• Grey literature not searched • Studies limited to English language • List of excluded studies not provided • Study populations and outcomes not well described • Conflicts of interest not reported for the included studies
Li et al. 2014[18]	
• Research questions and inclusion criteria established *a priori* • Study selection and data extraction performed independently by two reviewers • Multiple databases (MEDLINE, EMBASE, Cochrane CENTRAL, and Web of Science) and the WHO International Clinical Trials Registry Platform searched and search strategy with key words provided; relevant journals and	• Grey literature search limited to trials registries • Unclear whether studies were limited by language of publication • List of excluded studies not provided • Conflicts of interest not reported for the included studies

references were manually searched • List of included studies provided • Characteristics of the included studies well described, including study populations • Quality of individual studies assessed using Cochrane Risk of Bias Tool • GRADE used to assess quality of evidence for each outcome • Quality of individual studies used appropriately in formulating conclusions • Studies were combined in the meta-analysis using appropriate methods based on assessment of heterogeneity with I^2 (fixed-effects model for $I^2 \leq 50\%$ and random-effects model for $I^2 > 50\%$ or low number of studies) • Likelihood of publication bias was assessed using funnel plots • SR authors declared no conflicts of interest	
Palmer et al. 2013[19]	
• Research questions and inclusion criteria established ***a priori*** • Study selection and data extraction performed independently by two reviewers • Multiple databases (MEDLINE, EMBASE, and Cochrane CENTRAL) and abstracts from the 2005 to 2010 meetings of the British Association for Parenteral and Enteral Nutrition, European Society for Clinical Nutrition and Metabolism, and the American Society for Parenteral and Enteral Nutrition searched; search strategy with key words provided • Studies not limited by language of publication in the search • List of included studies provided • Characteristics of the included studies very well described, including study populations • Quality of individual studies assessed according to nine criteria (randomization, blinding, analysis, patient selection, comparability of groups at baseline, follow-up, treatment protocol, co-interventions, and outcomes) • Quality of individual studies used appropriately in formulating conclusions • Studies were combined in the meta-analysis using an appropriate method (random-effects model) • SR authors declared no conflicts of interest	• Grey literature not searched • List of excluded studies not provided • Likelihood of publication bias not assessed • Conflicts of interest not reported for the included studies
Tian et al. 2013[15]	
• Research questions and inclusion criteria established *a priori* • Study selection and data extraction performed independently by two reviewers • Multiple databases (PubMed, EMBASE, the Cochrane Library, Web of Science, the China Journal Full-text Database, Chinese Biomedical Literature Database, and the Chinese Scientific Journals Full-text Database) and search strategy with key words provided; reference lists of retrieved RCTs and systematic reviews meeting the	• Grey literature not searched • List of excluded studies not provided • Assessment of likelihood of publication bias not described; may have been part of quality of evidence assessment • Conflicts of interest not reported for the included studies

inclusion criteria manually searched • Studies were not limited by language of publication • List of included studies provided • Characteristics of the included studies well described, including study populations • Quality of individual studies assessed using Cochrane Risk of Bias Tool • GRADE used to assess quality of evidence for each outcome and subgroup comparison • Subgroup analysis performed for each control ILE to minimize heterogeneity • Quality of individual studies used appropriately in formulating conclusions • Studies were combined in the meta-analysis using appropriate methods based on assessment of heterogeneity with I^2 • SR authors declared no conflicts of interest	
Pradelli et al. 2012[16]	
• Research questions and inclusion criteria established *a priori* • Reference lists of relevant publications manually searched, key words were provided • List of included studies provided • Important characteristics of the included studies were provided • Studies were combined in the meta-analysis using an appropriate method (random-effects model) • SR authors reported conflicts of interest	• Grey literature not searched • Unclear if study selection and data extraction done in duplicate • Only the PubMed database searched • Unclear whether studies were limited language of publication • List of excluded studies not provided • Study populations and interventions not well described • Quality assessment of included studies was not mentioned • Analysis and conclusions did not consider scientific quality of included studies • Likelihood of publication bias not assessed • Some authors of the systematic review received honoraria or funding from manufacturers of lipid emulsions • Conflicts of interest not reported for the included studies • Authors of included studies were not contacted for further data and inappropriate method used to impute missing data (i.e., missing standard deviations were replaced with the average standard deviation/mean ratio for each outcome)

GRADE = Grading of Recommendations Assessment, Development and Evaluation; SR = systematic review.

Table A6: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist[6]

Strengths	Limitations
Pediatric Populations	
Najm et al. 2017[24]	
• Clearly described: study objective, inclusion and exclusion criteria, outcomes • All patients recruited from the same hospital; staff, places, and facilities where patients were treated were representative of the treatment of the majority of patients • Patients randomized to treatment groups, and treatment groups matched on important characteristics • Important adverse events considered and reported • Outcome assessors blinded to treatment groups • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported	• Unclear whether included patients were representative of the population from which they were recruited; 90/138 eligible patients participated, but characteristics of those recruited and declined were not reported • Whether treatment allocation was concealed was not reported • Intervention and comparator inconsistently described in the methods as "*up to 2 g/kg/d*" or "*2-3 g/kg body weight every 24 h*" p. 19 • Main findings clearly described, but only reported as number and proportion of participants meeting certain criteria (e.g., BPD, NEC) without providing absolute values to enable assessment of severity • Characteristics of those lost to follow-up (due to mortality; 13%) not described • To achieve 80% power at alpha 0.05, it was calculated that a sample size of 80 was needed; the final sample size was slightly smaller (n = 78)
Diamond et al. 2016[25]	
• Clearly described: study objective, inclusion and exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients invited to participate were representative of the population from which they were recruited; patients at all participating sites were identified by examining all patients who met the inclusion criteria • Patients randomized to treatment groups with allocation concealment, and treatment groups matched on important characteristics • Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive • Patients, treating clinicians, and investigators were blinded to treatment group assignment • Main outcome measures valid and reliable • Two patients achieved full tolerance of enteral feeds early in the trial and as per protocol were not include in the analysis; no patients were lost to follow-up • Main findings clearly described for primary outcomes • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings	• Unclear whether included patients were representative of the population from which they were recruited; 18 patients were eligible but refused participation, and characteristics of those who declined were not reported • Numerical values for mean difference in conjugated bilirubin between groups reported in abstract did not match those in results section, however the clinical interpretation was not different • Findings for some secondary outcomes (e.g., indicators of growth) only included in a table and not included in the results or discussion

• Actual probability values (p-values) reported • No retrospective, unplanned analyses reported • The study was sufficiently powered; it was powered to detect a clinically-meaningful difference in the primary outcome (conjugated bilirubin) with 24 participants	
Uthaya et al. 2016[26]	
• Clearly described: study objective, inclusion and exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups with allocation concealment, and treatment groups matched on important characteristics • Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive • Patients, treating clinicians, and investigators were blinded to treatment group assignment • Main outcome measures valid and reliable • Few patients lost to follow-up and reasons provided • Main findings clearly described • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Adequate adjustment for confounding in the analyses • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported • The study was sufficiently powered	• Characteristics of patients lost to follow-up not completely described, however very few patients lost to follow-up
Ariyawangso et al. 2014[27]	
• Clearly described: study objective, inclusion and exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups, and treatment groups matched on important characteristics • Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive • Main outcome measures valid and reliable • No patients lost to follow-up after randomization • Main findings clearly described • Important adverse events considered and reported • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported	• No attempt was made to blind patients, treating clinicians, or investigators to treatment group assignment (open-label study) • Whether treatment allocation was concealed was not reported • Other components of nutrition (i.e., intervention and comparator), aside from lipid dosing, inadequately described • Inappropriate statistical tests used (independent t-tests and Man-Whitney or Wilcoxon signed-ranks test for between- and within-group comparisons, respectively) • Power calculation not performed

Adult Populations	
Grau-Carmona et al. 2015[20]	
• Clearly described: study objective, inclusion and exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups with allocation concealment, and were matched on important characteristics (except for prevalence of pancreatitis, which was higher in the MCT/LCT/FO group) • Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive • Patients, treating clinicians, and investigators were blinded to treatment group assignment • Main outcome measures valid and reliable • Few patients lost to follow-up and proportion was balanced between groups • Main findings clearly described • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported	• Some relationships approached, but did not reach, statistical significance; this may have been due to inadequate power since sample size calculations were based solely on the primary outcome variable (nosocomial infections)
Ma et al. 2015[21]	
• Clearly described: study objective, inclusion and exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups by an independent investigator, and were matched on important characteristics • Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive • Patients, treating clinicians, and investigators were blinded to treatment group assignment (except for the investigator who coordinated group assignment) • Main outcome measures valid and reliable • Acceptable number of patients lost to follow-up and proportion was balanced between groups • Main findings clearly described for most outcomes • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported • The study was sufficiently powered	• Unclear whether treatment allocation was concealed • Analysis was conducted as per protocol, and not as intent-to-treat • Some outcomes included in the methods were not included in the results (e.g., platelet- and erythrocyte-count, INR, PTT)

Klek et al. 2013[22]	
• Clearly described: study objective, exclusion criteria, characteristics of included patients, outcomes, and interventions • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups with allocation concealment, and were matched on important characteristics • Patients, treating clinicians, and investigators were blinded to treatment group assignment • Main outcome measures valid and reliable • Acceptable number of patients lost to follow-up and proportion was balanced between groups • Main findings clearly described for main outcomes • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported • The study was sufficiently powered	• Inclusion criteria were broad (in- or out-patients unable to sustain adequate enteral food intake for at least 4 wk and in need of PN) and external validity is unclear • Unclear whether staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive; treatment location for out-patients not described • Other components of nutrition (i.e., intervention and comparator), aside from lipid dosing, inadequately described • Results reported as “intent-to-treat” analysis, however two patients (one per group) that did not receive the allocated intervention were excluded from the analysis
Umpierrez et al. 2012[23]	
• Clearly described: study objective, exclusion criteria, characteristics of included patients, and outcomes • Patients were representative of the population from which they were recruited • Patients randomized to treatment groups, and were matched on important characteristics • Patients, treating clinicians, and investigators were blinded to treatment group assignment; however, details of blinding not described • Main outcome measures valid and reliable • No patients lost to follow-up • Main findings clearly described for main outcomes • Important adverse events considered and reported • Appropriate statistical tests used to assess main outcomes • Statistical estimates of variability in the data provided for main findings • Actual probability values (p-values) reported • No retrospective, unplanned analyses reported • The study was sufficiently powered for most outcomes	• Inclusion criteria were vague (“medical and surgical ICU patients”) and external validity is unclear • Unclear whether treatment allocation was concealed • Unclear intervention dosing (total energy intake described, but not lipid dose and schedule) • The study was not powered to detect differences in mortality between treatment groups

BPD = bronchopulmonary dysplasia; FO = fish oil; INR = international normalized ratio; LCT = long-chain triglycerides; MCT = medium-chain triglycerides; NEC = necrotizing enterocolotis; PTT = partial thromboplastin time.

Table A7: Strengths and Limitations of Economic Studies using Drummond[7]

Strengths	Limitations
Wu et al. 2015[28]	
• Economic importance of the research question was stated • Systematic review[16] was referenced as the source of effectiveness data • All costs were estimated from the same hospital data set and should accurately reflect actual costs for that hospital • Methods of estimating quantities and unit costs were described • Discrete event simulation model structure was well-described • Probabilistic sensitivity analysis allows simultaneous estimation of effects of uncertainty around multiple input parameters by modeling them as distributions • Outcomes were broken down into major costs, ICU LOS, ward LOS, and infection rate • Model results were compared against observed hospital data	• The choice of Chinese patients and their families as the viewpoint was not discussed and may not be relevant for policy makers • The rationale for using cost-effectiveness analysis was not stated • Primary outcome measure was not clearly stated a priori • Choice and fitting of distributions for clinical input parameters were not described • The rationale for using discrete event simulation was not stated • Additional sensitivity analysis was not performed to see which inputs had the greatest impact or how robust they were to variations in input parameters and how they were derived • Sensitivity analysis was not done to support conclusion about LOS driving costs
Pradelli et al. 2014[29]	
• Economic importance of the research question was stated • The research question was stated and viewpoint was justified • ICU clinical inputs were based on extensive data collected throughout Italian ICUs • Systematic review[16] was referenced as the source of effectiveness data • Methods of estimating quantities and unit costs were described • Sources of cost data included prospective case-control studies, national reports, cost studies, and patient data management systems • Use of discrete event simulation was justified by the authors • Discrete event simulation model structure was well-described • Probabilistic sensitivity analysis allows simultaneous estimation of effects of uncertainty around multiple input parameters by modeling them as distributions • Deterministic sensitivity analysis was done to see which inputs had the greatest impact on incremental total cost and LOS • Threshold analyses were done to determine the values of cost and effectiveness parameters at which the cost difference would disappear • Outcomes were broken down into major costs, total LOS, and infection rate • Conclusions follow from the data reported	• The rationale for using cost-effectiveness analysis was not stated • Primary outcome measure was not clearly stated a priori • Selection of sources (clinical trials) of non-ICU clinical input parameters was not justified • Actual effectiveness values used were not specified • Statistically insignificant risk ratio for infection in ICU patients[16] was used without specifying whether distribution was based on confidence interval or 20% uncertainty • Inflation rates were not given for converting to 2011 costs

ICU = intensive care unit; LOS = length of stay.

Table A8: Strengths and Limitations of Guidelines using AGREE II[8]

Item	Guideline			
	Pediatric	Adult		
	Wales et al. 2014[31]	Weimann et al. 2017[32]	Pironi et al. 2016[30]	Taylor et al. 2016[33]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓	✓	✓
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	✓	X	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	X	X	X	X
6. The target users of the guideline are clearly defined.	X	X	X	✓
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	✓	✓	✓	✓
8. The criteria for selecting the evidence are clearly described.	X	X	X	X
9. The strengths and limitations of the body of evidence are clearly described.	✓	✓	✓	✓
10. The methods for formulating the recommendations are clearly described.	X	X	X	X
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	✓	✓	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓	✓	✓	✓
13. The guideline has been externally reviewed by experts prior to its publication.	✓	X	X	✓
14. A procedure for updating the guideline is provided.	✓	X	X	✓

Item	Guideline			
	Pediatric	Adult		
	Wales et al. 2014[31]	Weimann et al. 2017[32]	Pironi et al. 2016[30]	Taylor et al. 2016[33]
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	X	X	X	X
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X	X	X	X
20. The potential resource implications of applying the recommendations have been considered.	X	X	X	X
21. The guideline presents monitoring and/or auditing criteria.	X	X	X	X
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	X	✓	✓	✓
23. Competing interests of guideline development group members have been recorded and addressed.	X	✓	✓	✓

✓ = yes; X = no or unclear.

Appendix 4: Main Study Findings and Author's Conclusions

Table A9: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusions
Pediatric Populations	
Vayalthrikkovil et al. 2017[10]	
FO-containing ILEs vs. SO and SO/OO ILEs: Clinical Effectiveness • ROP stage ≥3 incidence significantly lower in intervention group; RR = 0.40 (95% CI, 0.22 to 0.76), N = 307; based on results from three studies; one study's RR may be improperly calculated • Cholestasis incidence significantly lower in intervention group; RR = 0.31 (95% CI 0.15 to 0.68), N = 386 • No significant difference in: ○ Mortality; RR = 1.34 (95% CI, 0.87 to 2.06), N = 404 ○ Sepsis; RR = 1.00 (95% CI, 0.71 to 1.41), N = 386 ○ BPD; RR = 0.93 (95% CI, 0.66 to 1.30), N = 386 ○ Intraventricular hemorrhage grade ≥3; RR = 1.17 (95% CI, 0.44 to 3.09), N = 176 ○ NEC stage ≥2; RR = 1.13 (95% CI, 0.60 to 2.12), N = 386	*"In this systematic review, we demonstrated that parenteral FLE [fish oil lipid emulsion] reduced the incidence of severe ROP [retinopathy of prematurity] in preterm infants <32 weeks of gestation. Nevertheless, there is insufficient evidence to strongly recommend routine use of FLE in preterm infants."* p.714
Hojsak et al. 2016[11]	
Short-term PN in neonates and preterm infants: **SMOF ILE vs. SO ILE:** Clinical Effectiveness • No significant difference in cholestasis incidence; OR = 0.81 (95% CI, 0.29 to 2.22), N = 310 Safety • AST significantly higher in intervention group; MD = 10.62 U/L (95% CI, 3.16 to 18.08), N = 96 (single study) • No significant difference in total bilirubin, conjugated bilirubin, AP, GGT, and ALT **OO/SO ILE vs. SO ILE:** • No significant difference in total bilirubin, conjugated bilirubin, AP, GGT, AST, and ALT **SMOF and OO/SO ILEs vs. SO ILE:** • No significant difference in total bilirubin, conjugated bilirubin, AP, GGT, AST, and ALT ***Meta-analyses were not available for the other populations and reported outcomes may not be complete for the following results:***	*"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[based on Oxford Centre for Evidence-Based Medicine "Levels of Evidence" methodology])."* p.789

Main Study Findings	Author's Conclusions
Short-term PN in children >1 year of age: **Safety** • information on statistical significance was not available • SO/MCT vs. SO ILE: decrease in bilirubin with SO/MCT vs. sustained elevation in bilirubin with SO ILE, N = 40 (single study) • SO/MCT vs. SO/OO ILE: no difference in bilirubin or liver function tests, N = 19 (single study) **Long-term PN in infants and children:** **Clinical Effectiveness** • FO vs. SO ILE: no significant difference in median age of cholestasis resolution, 3 of 9 in FO group vs. 0 of 7 in SO group recovered from cholestasis while on PN (statistical significance unknown), N = 16 (single study) Safety • FO vs. SO ILE: significantly greater decrease in conjugated bilirubin and ALT in intervention group, N = 16 (single study) • SMOF vs. SO ILE: significantly different change in bilirubin from baseline to day 29--decrease in SMOF group vs. increase in SO group, N = 28 (single study) • SO/OO vs. SO ILE: no significant difference in bilirubin, liver enzymes, or biliary acids, N = 18 (single study)	
Kapoor et al. 2015[13]	
SMOF vs. SO ILE: Clinical Effectiveness • No significant difference in: ○ Death before discharge; RR = 1.26 (95% CI, 0.68 to 2.31), N = 369 ○ Days to regain birth weight; MD = 1.12 days (95% CI, -0.17 to 2.41), N = 234 ○ Rate of weight gain; MD = -0.71 g/kg/day (95% CI, -0.17 to 1.60), N = 347 ○ BPD/chronic lung disease; RR = 1.02 (95%CI, 0.70 to 1.49), N = 314 ○ Duration of ventilation, duration of supplemental oxygen, culture positive sepsis, any sepsis, NEC, duration of phototherapy, ROP, intraventricular hemorrhage, periventricular leukomalacia, or patent ductus arteriosus **SO/MCT/FO vs. SO ILE (single study):** Clinical Effectiveness • No significant difference in: ○ Death before discharge; RR = 5.0 (95% CI, 0.25 to 99.95), N = 60 ○ Days to regain birth weight; MD = -1.0 day (95% CI, -3.6 to 1.6), N = 57	*"there were no statistically significant differences in clinically important outcomes including death, growth, BPD, sepsis, ROP ≥ stage 3, and PNALD with the use of newer alternative LE [lipid emulsion] versus the conventional pure soy oil based LE (GRADE QoE [Quality of Evidence] ranged from 'low' to 'very low'). Currently there is insufficient evidence to recommend any alternative LE over S-LE [SO ILE] or vice versa in preterm infants."* p.2

Main Study Findings	Author's Conclusions
○ Rate of weight gain; MD = -1.67 g/kg/day (95% CI, -7.01 to 3.67), N = 57 ○ BPD/chronic lung disease; RR = 1.39 (95%CI, 0.42 to 4.65), N = 57 ○ Any sepsis, NEC, or patent ductus arteriosus **SO/OO vs. SO ILE:** <u>Clinical Effectiveness</u> • No significant difference in: ○ Death before discharge; RR = 1.0 (95% CI, 0.21 to 4.82), N = 224 ○ Days to regain birth weight; MD = -0.19 day (95% CI, -2.00 to 1.62), N = 223 ○ Rate of weight gain; MD = -0.42 g/kg/day (95% CI, -5.15 to 4.30), N = 123 ○ BPD/chronic lung disease; RR = 0.69 (95%CI, 0.46 to 1.04), N = 261 ○ Duration of ventilation, duration of supplemental oxygen, duration of home oxygen therapy, culture positive sepsis, any sepsis, NEC, jaundice requiring treatment, duration of phototherapy, intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, PNALD/cholestasis, hypertriglyceridemia, or hyperglycemia **SO/MCT vs. SO ILE (single study):** <u>Clinical Effectiveness</u> • No significant difference in: ○ Death before discharge; risk difference = 0.0 (95% CI, -0.06 to 0.06), N = 60 ○ Days to regain birth weight; MD = 1.0 day (95% CI, -1.53 to 3.53), N = 60 ○ Rate of weight gain; MD = -2.67 g/kg/day (95% CI, -8.20 to 2.86), N = 60 ○ BPD/chronic lung disease; RR = 1.0 (95%CI, 0.28 to 3.63), N = 60 ○ Any sepsis, NEC, patent ductus arteriosus, or PNALD/cholestasis **FO-containing ILEs vs. SO ILE:** <u>Clinical Effectiveness</u> • No significant difference in: ○ Death before discharge; RR = 1.28 (95% CI, 0.69 to 2.35), N = 399 ○ Days to regain birth weight; MD = 0.81 days (95% CI, -0.43 to 2.05), N = 261 ○ Rate of weight gain; MD = 0.69 g/kg/day (95% CI, -0.19 to 1.57), N = 374 ○ BPD/chronic lung disease; RR = 1.02 (95% CI, 0.70 to 1.49), N = 341 ○ Duration of ventilation, duration of supplemental oxygen, culture positive sepsis, any sepsis, NEC,	

Main Study Findings	Author's Conclusions
duration of phototherapy, ROP, intraventricular hemorrhage, periventricular leukomalacia, any patent ductus arteriosus, or patent ductus arteriosus requiring treatment **All non-100% SO ILEs vs. SO ILE:** Clinical Effectiveness • No significant difference in: ○ Death before discharge; RR = 1.17 (95% CI, 0.66 to 2.07), N = 623 ○ Days to regain birth weight; MD = 0.53 days (95% CI, -0.52 to 1.58), N = 484 ○ Rate of weight gain; MD = 0.68 g/kg/day (95% CI, -0.19 to 1.55), N = 497 ○ BPD/chronic lung disease; RR = 0.84 (95%CI, 0.63 to 1.12), N = 602 ○ Duration of ventilation, duration of supplemental oxygen, culture positive sepsis, any sepsis, NEC, jaundice requiring treatment, duration of phototherapy, ROP, intraventricular hemorrhage, periventricular leukomalacia, any patent ductus arteriosus, patent ductus arteriosus requiring treatment, air leaks, or PNALD/cholestasis **Note**: Cholestasis data for SMOF vs. SO ILE was already reported by Hojsak et al. 2015[11]	
Zhao et al. 2015[14]	
FO-containing ILEs vs. non-FO-containing ILEs: Clinical Effectiveness • No significant difference in: ○ Mean weight on the 8th day; MD = 26.52 g (95% CI, -52.32 to 105.36), N = 145 ○ Mortality during the trial period; RR = 1.19 (95% CI, 0.65 to 2.18), N = 283 ○ Overall complications rate; RR = 0.80 (95% CI, 0.58 to 1.10), N = 127 Safety • No significant difference in direct bilirubin, CRP, creatinine (all on the 8th day) **Notes:** • One of the studies in the meta-analyses for mortality, complications rate, and CRP was described by Vlaardingerbroek as not reporting clinical outcomes; reason for discrepancy is unclear • Most of the studies included in the above analyses were also included in Kapoor et al. 2015[13]	*"Owing to the limited data, we were not able to demonstrate any clinical benefits or detrimental effects on using the fish oil-containing lipid emulsions."* p. 715

Main Study Findings	Author's Conclusions
Vlaardingerbroek et al. 2012[12]	
SO/MCT and SMOF ILEs vs. SO ILE: Clinical Effectiveness • No significant difference in rate of weight gain; MD = 0.05 g/kg/day (95% CI, -2.46 to 2.56), N = 164 **Note**: all other relevant results were reported in the review by Kapoor et al. 2015;[13] findings are not repeated here (see Appendix 6 for overlap between systematic reviews).	*"beneficial effects on growth could not be shown for […] the type of lipid emulsion."* p. 255
Adult Populations	
Bae et al. 2017[17]	
FO-containing vs. non-FO-containing ILEs: Clinical Effectiveness • Infectious morbidity significantly lower in intervention group; OR = 0.44 (95% CI, 0.30 to 0.65), N = 1,064 • Hospital LOS significantly shorter in intervention group; MD = -1.81 days (95% CI, -2.89 to -0.74), N = 809 • No significant difference in mortality events; OR = 1.20 (95% CI, 0.46 to 3.12), N = 505 Safety • TNF-α on post-operative days 6 to 8 significantly lower in intervention group; weighted MD = -1.46 (95% CI, -2.33 to -0.60, units unclear), N = 247 • No significant difference in IL-6 on post-operative days 6 to 8; weighted MD = -9.90 (95% CI, -21.24 to 1.43, units unclear), N = 219; high heterogeneity (I^2 = 93%) **FO-containing vs. SO ILE:** Clinical Effectiveness • Infectious morbidity significantly lower in intervention group; OR = 0.42 (95% CI, 0.25 to 0.72), N = 715 • Hospital LOS significantly shorter in intervention group; MD = -2.70 days (95% CI, -3.60 to -1.79), N = 642 **FO-containing vs. SO/MCT ILE:** Clinical Effectiveness • No significant difference in: ○ Infectious morbidity; OR = 0.57 (95% CI, 0.30 to 1.06), N = 322 ○ Hospital length of stay; MD = -0.61 days (95% CI, -2.02 to 0.81), N = 169 **SO/OO/FO vs. SO/OO ILE (single study):** **Clinical Effectiveness** • **Infectious morbidity** significantly lower in intervention group; OR = 0.08 (95% CI, 0.01 to 0.50), N = 27	*"The results of the meta-analysis indicated that FO-containing IVFEs [ILEs] could improve infectious morbidity and LOS. The overall effect of reducing infectious morbidity and LOS was found to be the greatest in comparison with the SO-based IVFEs."* p. 916

Main Study Findings	Author's Conclusions
Li et al. 2014[18]	
SO/FO ILE vs. SO ILE: Clinical Effectiveness • Infectious complications significantly lower in intervention group; OR = 0.42 (95% CI, 0.19 to 0.93), N = 1,463 (participants × types of infectious diseases) • Hospital LOS significantly shorter in intervention group; MD = -2.17 days (95% CI, -3.50 to -0.84), N = 345 Safety • IL-6 significantly lower in intervention group; MD = -5.79 (95% CI, -9.60 to -1.97, units unclear), N = 301 • No significant difference in AST, ALT, GGT, and total bilirubin (all from a single study) • No significant difference in TNF-α **SO/MCT/FO ILE vs. SO ILE (single study):** Clinical Effectiveness • Hospital LOS significantly shorter in intervention group; MD = -4.70 days (95% CI, -8.30 to -1.37), N = 256 • No significant difference in: ○ Mortality; Peto OR = 2.84 (95% CI, 0.70 to 11.59), N = 256 ○ Infectious complications; OR = 0.50 (95% CI, 0.17 to 1.48), N = 512 (calculated from participants × types of infectious diseases) Safety • LTB5 l significantly higher in intervention group; standard MD = 0.87 (95% CI, 0.63 to 1.12), N = 286 **SMOF ILE vs. SO ILE:** Clinical Effectiveness • Hospital LOS significantly shorter in intervention group; MD = -3.21 days (95% CI, -5.73 to -0.68), N = 232 • No significant difference in mortality; Peto OR = 0.73 (95% CI, 0.16 to 3.26), N = 249 ILE (single study) Safety • ALT significantly lower in intervention group; MD = -8.25 U/L (95% CI, -15.91 to -0.59), N = 219 • No significant difference in AST, GGT, and total bilirubin (single study) **SO/MCT/FO ILE vs. SO/MCT ILE:** Clinical Effectiveness • No significant difference in: ○ Infectious complications; OR = 0.60 (95% CI, 0.34 to 1.05), N = 878 (calculated from participants × types of infectious diseases)	*"Because fish oil is likely to reduce the length of hospital stay and the occurrence of infectious events, […] fish oil may be a safe and preferable choice for patients post-surgery."* p. 237

Main Study Findings	Author's Conclusions
○ Hospital LOS; MD = -1.32 days (95% CI, -2.73, 0.09), N = 218 Safety • Total bilirubin significantly lower in intervention group; MD = -4.83 µmol/L (95% CI, -8.49 to -1.18), N = 145 • TNF-α significantly lower in intervention group; standard MD = -0.77 (95% CI, -1.05 to -0.48), N = 205 • No significant difference in AST, ALT, and GGT (all from a single study) **FO-containing ILEs vs. SO and SO/MCT ILEs:** Clinical Effectiveness • Infectious complications significantly lower in intervention group; OR = 0.52 (95% CI, 0.34 to 0.80), N = 2,853 (calculated from participants × types of infectious diseases) • Hospital LOS significantly shorter in intervention group; MD = -2.14 days (95% CI, -3.02 to -1.27), N = 1,051 • No significant different in mortality; Peto OR = 1.50 (95% CI, 0.54 to 4.19), N = 826 Safety • ALT significantly lower in intervention group; MD = -6.35 U/L (95% CI, -11.75 to -0.94), N = 550 • GGT significantly lower in intervention group; MD = -11.01 U/L (95% CI, -20.77 to -1.25), N = 620 • Total bilirubin significantly lower in intervention group; MD = -2.06 µmol/L (95% CI, -3.6 to -0.52), N = 685 • TNF-α significantly lower in intervention group; standard MD = -0.43 (95% CI, -0.61 to -0.26), N = 506 • IL-6 significantly lower in intervention group; MD = -7.69 (95% CI, -11.55 to -3.82, units unclear), N = 552 • LTB5 significantly higher in intervention group; standard MD = 1.03 (95% CI, 0.38 to 2.72), N = 415 • No significant difference in AST Quality of evidence for outcomes was rated as follows: • High: mortality, infectious complications, length of hospital stay, liver enzymes, and LTB5 • Moderate: total bilirubin and TNF-α • Low: TNF-α for SO/MCT/FO ILE vs. SO/MCT ILE	
Palmer et al. 2013[19]	
FO-containing ILEs vs. SO and SO/MCT ILEs: Clinical Effectiveness • Hospital LOS significantly lower in intervention group; MD = -9.49 days (95% CI, -16.51 to -2.47), N = 117; author notes that 2 of the 3 studies are problematic due to potentially biased reporting of outcomes in one study and much larger standard deviation in the control group in the other study • No significant difference in: ○ Mortality; RR = 0.83 (95% CI, 0.57 to 1.20), N = 391	*"In conclusion, there is insufficient evidence to recommend the supplementation of PN in critically ill adult patients with ω-3 FA [fatty acids] except as an intervention being investigated in the setting of a RCT. Although ω-3 [n-3] FA appear to reduce hospital LOS, the poor methodology of the included studies and the absence of other outcome improvements means that this result must be interpreted with caution."* p. 315

Main Study Findings	Author's Conclusions
○ New infections; RR = 0.78 (95% CI, 0.43 to 1.41), N = 337 ○ ICU LOS; MD = -0.57 days (95% CI, 0.-5.05 to 3.90), N = 305	
Tian et al. 2013[15]	
SMOF ILE vs. SO ILE: <u>Safety</u> • AST significantly lower in intervention group; MD = -5.25 U/L (95% CI, -8.52 to -1.98), N = 219 • ALT significantly lower in intervention group; MD = -8.92 U/L (95% CI, -14.23 to -3.60), N = 219 • GGT significantly lower in intervention group; MD = -23.46 U/L (95% CI, -40.13 to -6.79), N = 219 • ALP significantly lower in intervention group; MD = -19.56 U/L (95% CI, -29.85 to -9.28), N = 219 • No significant difference in adverse events; RR = 1.00 (95% CI, 0.64 to 1.56), N = 267 • No difference in LOS, CRP (single study) **SMOF ILE vs. SO/OO ILE:** <u>Safety</u> • No difference in AST and ALT (single study) **SMOF ILE vs. SO/MCT ILE:** <u>Safety</u> • No significant difference in: ○ Adverse events; RR = 2.00 (95% CI, 0.41 to 9.71), N = 40 (single study, Ma 2012) ○ AST, ALT, GGT (single study), and ALP (single study) **Note**: • GRADE quality of evidence ranged from "low" to "moderate" • LOS analyses already reported by Bae et al. 2017[17] and Li et al. 2014[18]; findings are not repeated here (see Appendix 6 for overlap between systematic reviews)	*"The results of the present meta-analysis indicate that for postoperative patients receiving parenteral nutrition SMOFlipid20% [SMOF ILE] may be less toxic to the liver than either Lipoven20% [SO ILE] or ClinOleic20% [SO/OO ILE] and there are no significant differences between SMOFlipid20% and MCT/LCT20% [SO/MCT ILE].* *However, the data available are so limited that some of the reported findings could not be confirmed. Based on the GRADE approach, the quality of evidence for almost all of the outcomes investigated was moderate for the trials of Lipoven20% and low for the trials investigating ClinOleic20% and MCT/LCT20%."* p. 821
Pradelli et al. 2012[16]	
FO-containing vs. non-FO-containing ILEs in ICU patients: <u>Clinical Effectiveness</u> • Hospital LOS significantly shorter in intervention group; MD = -5.17 days (95% CI, -8.35 to -1.99), N = 615 • ICU LOS significantly shorter in intervention group; MD = -1.92 days (95% CI, -3.27 to -0.58), N = 615 • No significant difference in: ○ Mortality; RR = 0.94 (95% CI, 0.61 to 1.45), N = 547 ○ Infection rate; RR = 0.71 (95% CI, 0.45 to 1.12), N = 524	*"In conclusion, these results confirm previous findings in surgical patients and extend them to the ICU population: the body of available evidence indicates that the use of n-3 PUFA-enriched [ie. FO-enriched] parenteral nutrition is safe and effective in reducing the infection rate and hospital/ ICU stay in surgical patients, and that these benefits also apply to ICU patients. Other beneficial effects included reduced markers of inflammation,[…] liver function,[…] and a trend towards less impairment of kidney function."* p. 9

Main Study Findings	Author's Conclusions
Safety • ALT significantly lower in intervention group; MD = -18.18 U/L (95% CI, -21.68 to -14.68), N = 109 • LTB5 significantly higher in intervention group; standard MD = 3.35 (95% CI, 0.54 to 6.16), N = 120 • LTB5/LTB4 ratio significantly higher in intervention group; MD = 0.11 (95% CI, 0.01 to 0.22), N = 100 • LTB4 significantly lower in intervention group; standard MD = -0.85 (95% CI, -1.42 to -0.27), N = 125 • No significant difference in CRP, AST, and serum bilirubin **FO-containing vs. non-FO-containing ILEs in non-ICU patients:** Clinical Effectiveness • Infection rate significantly lower in intervention group; RR = 0.53 (95% CI, 0.34 to 0.82), N = 395 • Hospital LOS significantly shorter in intervention group; MD = -1.86 days (95% CI, -3.13 to -0.59), N = 554 • No significant difference in mortality; RR = 0.58 (95% CI, 0.18 to 1.84), N = 300 Safety • AST significantly lower in intervention group; MD = -8.37 U/L (95% CI, -17.36 to 0.61), N = 283 • ALT significantly lower in intervention group; MD = -4.97 U/L (95% CI, -9.62 to 0.32), N = 373 • LTB5 significantly higher in intervention group; standard MD = 2.14 (95% CI, 0.42 to 3.85), N = 63 • LTB5/LTB4 ratio significantly higher in intervention group; MD = 0.06 (95% CI, 0.05 to 0.07), N = 100 = 63 • No significant difference in CRP, LTB4, and serum bilirubin **FO-containing vs. non-FO-containing ILEs in all patients:** Clinical Effectiveness • Infection rate significantly lower in intervention group; RR = 0.61 (95% CI, 0.45 to 0.84), N = 919 • Hospital LOS significantly shorter in intervention group; MD = -3.29 days (95% CI, -5.13 to -1.45), N = 1,169 • No significant difference in mortality; RR = 0.89 (95% CI, 0.59 to 1.33), N = 847 Safety • AST significantly lower in intervention group; MD = -10.05 U/L (95% CI, -18.81 to -1.29), N = 656 • ALT significantly lower in intervention group; MD = -9.85 U/L (95% CI, -17.49 to 2.21), N = 482 • LTB5 significantly higher in intervention group; standard MD = 2.86 (95% CI, 1.22 to 4.50), N = 183 • LTB5/LTB4 ratio significantly higher in intervention group; MD = 0.07 (95% CI, 0.05 to 0.09), N = 163 • IL-6 reduction over infusion period significantly higher in intervention group; MD = 37.70 pg/mL (95% CI, 20.23 to	

Main Study Findings	Author's Conclusions
55.16), N = 432 • No significant difference in CRP time, prothrombin time, partial thromboplastin time, platelet count, serum creatinine, and serum urea	

ALT = alanine transaminase; ALP = alkaline phosphatase; AST = aspartate transaminase; BPD = bronchopulmonary dysplasia; CI = confidence interval; CRP = C-reactive protein; FO = fish oil; GGT = gamma-glutamyl transpeptidase; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICU = intensive care unit; IL-6 = interleukin-6; ILE = intravenous lipid emulsion; LOS = length of stay; LTB4 = leukotriene B4; LTB5 = leukotriene B5; MCT = medium-chain triglycerides; MD = mean difference; NEC = necrotizing enterocolitis; OO = olive oil; OR = odds ratio; PN = parenteral nutrition; PNALD = PN-associated liver disease; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; ROP = retinopathy of prematurity; RR = risk ratio; SO = soybean oil; TNF-α = tumour necrosis factor-α.

Table A10: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Author's Conclusion
Pediatric Populations	
Najm et al. 2017[24]	
Baseline Characteristics • Treatment groups did not differ significantly in baseline characteristics Clinical Effectiveness • Treatment groups did not differ significantly in amount or duration of PN: ○ Median (min-max) amount of fat: Clinoleic, 72 (15-1558) mL; SMOFlipid, 92 (9-1384) mL ○ Median (min-max) duration: Clinoleic, 12 (2-92) d; SMOFlipid, 12 (2-72) d • Growth was not different between treatment groups: ○ Weight change SDS (mean ± SD): Clinoleic, -0.38 ± 1.2; SMOFlipid, -0.22 ± 1.1, *P* = 0.91 ○ Height change SDS (mean ± SD): Clinoleic, -1.62 ± 1.9; SMOFlipid, -0.75 ± 1.9, *P* = 0.25 ○ Head circumference change (mean ± SD): Clinoleic, -0.59 ± 1.2; SMOFlipid, -0.64 ± 1.4, *P* = 0.79 • Cholestasis was not different between treatment groups: Clinoleic, 2 (5.7%); SMOFlipid, 4 (9.8%), *P* = 0.39 • Measures of morbidity were not different between treatment groups (n, for Clinoleic vs. SMOFlipid respectively): ○ Any ROP: 28 (78%) vs. 33 (80%), *P* = 0.40 ○ Severe ROP: 13 (35%) vs. 18 (44%), *P* = 0.29 ○ BPD: 17 (42%) vs. 22 (58%), *P* = 0.18 ○ NEC: 1 (3%) vs. 4 (10%), *P* = 0.21 ○ PDA: 29 (79%) vs. 25 (61%), *P* = 0.08 ○ Sepsis: 11 (30%) vs. 19 (46%), *P* = 0.10	"*We found no association between the type of parenteral lipid emulsion and either postnatal morbidity or growth in extremely preterm infants. This might in part be due to the limited time period of parenteral nutrition and the variability in omega-3 [long-chain polyunsaturated fatty acids] content reported in breastmilk [which did not differ between groups in this study].*" p. 22
Diamond et al. 2016[25]	
Baseline Characteristics • Treatment groups did not differ significantly in baseline characteristics	"[Compared with Intralipid], o*ur results confirmed our hypothesis that SMOFlipid, provided at conventional dosing, lessens the risk of [intestinal failure associated liver disease] progression as quantified by serum [conjugated bilirubin], our primary clinical outcome.*" p. 10

Main Study Findings	Author's Conclusion
Clinical Effectiveness • Time to achievement of full enteral tolerance was not different between groups: HR = 1.3; 95% CI, 0.5 to 4.0, *P* = 0.59 • Growth was not significantly different between SMOFlipid and Intralipid groups (mean difference): ○ Weight: 0.2 kg, 95% CI, -0.5 to 0.9, *P* = 0.51 ○ Height: 0.5 cm, 95% CI, -3 to 4, *P* = 0.78 ○ Head circumference: -0.4 cm, 95% CI, -2 to 2, *P* = 0.65 Safety • After removal of one outlier (a patient who developed sepsis), the serum conjugated bilirubin at trial completion was significantly lower in the SMOFlipid vs. Intralipid group: between-group difference = -47 µmol/L, 95% CI, -17 to -21, *P* = 0.001 • Patients in the SMOFlipid group were more likely than those in the Intralipid group to have a decrease in conjugated bilirubin to 0 µmol/L: HR = 10.6; 95% CI, 1.3 to 86.9, *P* = 0.006 • GGT was significantly higher in the SMOFlipid group at trial completion: between-group difference = 114; 95% CI, 3 to 226, *P* = 0.04 • The following parameters were not significantly different between groups: unconjugated bilirubin, AST, ALT, ALP, INR, albumin • All patients experienced at least 1 adverse event, and the mean number of adverse events per patient was not significantly different between groups: SMOFlipid, 12.4; Intralipid, 9.2; *P* = 0.30 **Note:** Numerical values for mean difference in conjugated bilirubin between groups reported in the abstract do not match those reported in the results section. The more conservative estimates, from the results section, are reported here.	"*There was no difference in safety outcomes between the groups."* p. 1
Uthaya et al. 2016[26]	
Baseline and PN Characteristics • Gestational age and birth weight were not significantly different between the treatment groups Clinical Effectiveness • The median (IQR) number of days to achieve a milk intake of 150 mL/kg/d for ≥24 h was similar across the groups • Non-adipose mass was not significantly different between SMOF andSO groups (adjusted mean difference = -14 g, 95% CI, -114 to 86, *P* = 0.78) at term • The following outcomes were not significantly different between groups: weight, length, adiposity, insulin sensitivity, total and regional brain volumes, incidence of conjugated hyperbilirubinemia, length of hospital stay, sepsis incidence, mortality	"*We […] conclude that SMOF does not reduce intrahepatic lipid accumulation. We found that a standardized PN regimen was well accepted by clinicians and well tolerated by infants. […] Optimal amino acid intakes and intravenous lipid formulations for extremely preterm infants remain to be established."* p. 1451 "*Overall, our data support the conclusion […] that fish oil-based lipid emulsions do not prevent PN-associated cholestasis […], although we do not preclude the possibility that other formulations may be beneficial, including those with higher fish oil content."* p. 1451

Main Study Findings	Author's Conclusion
Safety • Intrahepatocellular lipid was not significantly different between SMOF and SO groups (adjusted mean difference = 0.89; 95% CI, 0.61 to 1.31, *P* = 0.57) • The following outcomes were not significantly different between groups: total bilirubin, conjugated bilirubin, urea, creatinine, ALT	
Ariyawangso et al. 2014[27]	
Baseline Characteristics • Treatment groups did not differ significantly in baseline characteristics Clinical Effectiveness • Mean duration of PN was not significantly different between groups (mean ± SD): SMOFlipid, 30.10 ± 7.64 d; Intralipid, 31.33 ± 11.14 d, *P* = 0.68 • Growth (weight, length, and head circumference) was not significantly different between groups or within groups on days 8, 15 and 22 Safety • No safety and efficacy outcomes were significantly different between groups on days 8 and 15 of the study • On day 22 of the study, the following outcomes were not significantly different between groups: AST, ALT, ALP, GGT, BUN, serum creatinine • On day 22, total bilirubin and direct bilirubin were significantly higher in the Intralipid vs SMOFlipid group: ○ Total bilirubin (mean ± SD): Intralipid, 3.21 ± 1.99 mg/dL; SMOFlipid, 0.99 ± 0.79 mg/dL, *P* < 0.001 ○ Direct bilirubin (mean ± SD): Intralipid, 2.54 ± 1.75 mg/dL; SMOFlipid, 0.58 ± 0.52 mg/dL, *P* < 0.001 • Four patients in each group experienced complications during the study period (e.g., NEC, sepsis) but all recovered completely and there were no SAEs	"*SMOFlipid 20% may provide benefit in preventing [parenteral nutrition associated liver disease.*" p. 207 *"It is concluded that SMOFlipid 20 % is safe and well tolerated without causing adverse events and that it can decrease plasma bilirubin which may indicate a potential beneficial effect on cholestasis."* p. 202
Adult Populations	
Grau-Carmona et al. 2015[20]	
Baseline Characteristics • Baseline characteristics were not significantly different between groups, except that the number of patients with acute pancreatitis was significantly higher in the MCT/LCT/FO group (n = 14, 17.5%) than the MCT/LCT group (n = 5, 6.4%; *P* = 0.049) Clinical Effectiveness • Mean duration of TPN was not different between groups: MCT/LCT/FO: 8.8 ± 6.0 d; MCT/LCT: 8.9 ± 5.4 d; *P* = 0.574 • The prevalence of nosocomial infections was significantly reduced in the MCT/LCT/FO vs MCT/LCT group: ○ MCT/LCT/FO, 17/81 (21.0%) patients; MCT/LCT, 29/78 (37.2%) patients; *P* = 0.04	"*[A]dministration of ~0.1 g FO/kg body weight per day in combination with MCT and LCT in a lipid emulsion reduces the risk of [nosocomial infections] and increases the predicted [time free of infections] in critically ill medical and surgical ICU patients. Length of hospital stay was reduced close to significance. The administration of a MCT/LCT/FO parenteral lipid emulsion in critically ill patients was shown to be safe.*" p. 37-38

Main Study Findings	Author's Conclusion
○ Nosocomial infection risk for patients in MCT/LCT/FO group: RR = 0.4, 95% CI: 0.19 to 0.86, *P* = 0.019 • Antibiotic-free days tended to be higher in the MCT/LCT/FO group but the difference was not statistically significant (1.7 ± 3.3 vs. 1.3 ± 2.2 d, *P* = 0.290) • Time free of infection was significantly longer in the MCT/LCT/FO vs. MCT/LCT group (21 ± 2 d vs. 16 ± 2 d, *P* = 0.03) • The following outcomes were not significantly different between groups: length of ICU stay, length of hospital stay, hospital mortality, 6-mo mortality, 6-mo survival, prevalence of cholestasis, liver necrosis, and mixed liver injury • ICU mortality tended to be greater among patients with pancreatitis in the MCT/LCT/FO group (n = 7, 36.8%) vs. the MCT/LCT group (n = 1, 20.0%), but the difference was not statistically significant (*P* = 0.338). • The Competing Risks Survival Analysis showed that the MCT/LCT/FO diet protected against infection regardless of the observed mortality: subdistribution HR = 0.51, 95% CI: 0.29 to 0.91, *P* = 0.023 <u>Safety</u> • No serious adverse reactions were reported	
Ma et al. 2015[21]	
<u>Baseline Characteristics</u> • Baseline characteristics were not significantly different between groups <u>Clinical Effectiveness</u> • Mean duration of TPN was not different between groups: MCT/LCT/n-3, 7.49 d; MCT/LCT, 7.17 d; *P* = 0.399 <u>Safety</u> • Inflammatory markers (IL-6, CRP, TNF-α, and PCT) were not significantly different between groups before surgery or at any follow-up time point (after surgery, at days 1, 3, and 7, and 30 days after the last treatment) • Number of patients with pre-treatment AEs were not different between groups: MCT/LCT/n-3, n = 2 (3.9%); MCT/LCT, n = 4 (8.3%); *P* = 0.371 • Number of patients with treatment-emergent AEs (e.g., injuries, poisoning, procedural complications and general disorders, administration site conditions) were not different between groups: MCT/LCT/n-3, n = 47 (92.2%); MCT/LCT, n = 41 (85.4%); *P* = 0.243 • There was one SAE in each treatment group; both patients were withdrawn from the study • The following outcomes were not different between groups before or after surgery: ALT, AST, GGT, albumin, bilirubin	"*In respect of efficacy, safety and tolerance both [intravenous fat emulsions] were comparable.*" p. 1 "*Both lipid emulsions exerted a comparable effect on the efficacy parameters chosen and n-3 [polyunsaturated fatty acids] had limited immunomodulation in normal subjects undergoing elective surgery for gastric and colorectal cancers.*" p. 10

Main Study Findings	Author's Conclusion
Klek et al. 2013[22]	
Baseline and PN Characteristics • Baseline characteristics were not different between groups, except that patients in the Intralipid group were significantly younger than those in the SMOFlipid group (mean ± SD: 45.2 ± 13.6 vs 53.2 ± 14.6 y respectively, *P* = 0.02) Clinical Effectiveness • Mean duration of PN was not significantly different between groups (mean ± SD): SMOFlipid, 26.8 ± 4.9 d; Intralipid, 25.6 ± 7.0 d, *P* = 0.40 Safety • In week 4, mean concentrations of the following liver parameters were significantly lower in the SMOFlipid vs. Intralipid groups, respectively (mean ± SD): ○ ALT: 30.3 ± 19.1 U/L vs. 48.7 ± 50.8 U/L, *P* < 0.05 ○ AST: 26.5 ± 10.9 U/L vs. 41.0 ± 33.7 U/L, *P* = 0.03 ○ Total bilirubin: 9.5 ± 6.5 µmol/L vs. 15.7 ± 15.9 µmol/L, *P* = 0.04 • The following liver outcomes were not significantly different between groups at baseline and the end of the study: ALP, GGT, conjugated bilirubin, INR • The following inflammatory indicators were not significantly different between groups at baseline and the end of the study: IL-6, sTNF-RII, CRP • The number of patients with at least one AE was not different between groups: SMOFlipid, n = 15 (44.1%); Intralipid, n = 21 (53.8%), *P* = 0.11; all had full recovery • The number of patients with a SAE was significantly greater in the Intralipid (n = 8; 20.5%) vs. SMOFlipid (n = 2; 5.9%) groups (*P* = 0.03); all had full recovery	"*The results of this study confirmed that a mixed lipid emulsion containing soybean oil, MCT, olive oil and fish oil [SMOFlipid] was safe and well tolerated in a large group of intestinal failure patients requiring parenteral nutrition for 4 weeks. […] improvements in parameters of liver function and cholestasis as well as in antioxidant defences were demonstrated.*" p. 230
Umpierrez et al. 2012[23]	
Baseline and PN Characteristics • Baseline characteristics were not different between groups Clinical Effectiveness • Mean duration of PN was not different between groups: ClinOleic, 12.8 ± 8 d; Intralipid, 13.1 ± 8 d, *P* = 0.87 The following outcomes were not significantly different between groups: • ICU length of stay: ClinOleic, 17.0 ± 18 d; Intralipid, 15.2 ± 14 d, *P* = 0.77 • Hospital length of stay: ClinOleic, 40.8 ± 36 d; Intralipid, 46.7 ± 48 d, *P* = 0.49 • Mortality during hospital stay: ClinOleic, n = 5 (9.8%); Intralipid, n = 8 (16.3%), *P* = 0.38 • Acute renal failure: ClinOleic, n = 9 (17.6%); Intralipid, n = 13 (26.5%), *P* = 0.34 • Nosocomial infections: ClinOleic, n = 29 (56.8%); Intralipid, n = 21 (42.8%), *P* = 0.16	"*In summary, our results indicate that the administration of PN containing soybean oil-based [Intralipid] and olive oil-based [ClinOleic] lipid emulsions results in similar overall rates of infectious and non-infectious complications, mortality, and ICU length of stay and no significant differences in metabolic, inflammatory, or immune markers in critically ill adults patients.*" p. 8

Main Study Findings	Author's Conclusion
• Other infectious complications (pneumonia, urinary tract infection, bacteremia, wound infection) or cardiac complications (acute myocardial infarction, congestive heart failure, cardiac arrhythmia) Safety • Inflammatory markers (CRP, IL-6, TNF-α) were not significantly different between groups • Measures of oxidative stress (plasma cysteine, glutathione, glutathione disulfide, glutathione redox potential, and cysteine redox potential) were not significantly different between groups at baseline and on days 3 and 7 of PN infusion	

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BPD = bronchopulmonary dysplasia; BUN = blood urea nitrogen; CRP = C-reactive protein; FO = fish oil; GGT = gamma-glutamyl transferase; HR = hazard ratio; ICU = intensive care unit; IL-6 = interleukin-6; INR = international normalized ratio; IQR = interquartile range; LCT = long-chain triglycerides; MCT = medium-chain triglycerides; n-3 = n-3 polyunsaturated fatty acids; NEC = necrotizing enterocolitis; PCT = procalcitonin; PDA = patent ductus arteriosis; PN = parenteral nutrition; ROP = retinopathy of prematurity; SD = standard deviation; SDS = standard deviation scores; SMOF = soybean oil, medium-chain triglycerides, olive oil, and fish oil; SO = soybean-based lipid emulsion (Intralipid); sTNF-RII = soluble tumour necrosis factor receptor II; TNF-α = tumor necrosis factor-alpha; TPN = total parenteral nutrition.

Table A11: Summary of Findings of Economic Studies

Main Study Findings	Author's Conclusions
Wu et al. 2015[28]	
Effectiveness (Omegaven vs. Standard ILE, Omegaven – Standard ILE) • All values expressed as mean (standard error): • Total LOS including pre-ICU: 24 (4.0) vs. 30 (0.3) days, -6.5 (4.0) days • ICU LOS: 7.7 (1.6) vs. 10.6 (0.2) days, -2.9 (1.6) days • Ward LOS: 10.9 (3.6) vs. 14.5 (0.2) days, -3.6 (3.6) days • Infections per 10,000 patients: 1,348 (453) vs. 1,962 (427), -614 (362) Costs (Omegaven vs. Standard ILE, Omegaven – Standard ILE) • All values expressed as mean (standard error) in renminbi: • Total: 49,219 (7,256) vs. 59,836 (1,339), -10,617 (7,202) • ICU LOS: 17,960 (3,651) vs. 24,501 (1,112), -6,541 (3,582) • Ward LOS: 16,460 (5,644) vs. 22,095 (552), -5,635 (5,628) • Parenteral nutrition: 6,047 (526) vs. 4,254 (39), 1,793 (525) Probabilistic sensitivity analysis for incremental costs per days of infections avoided • 88% more effective at lower cost • 8% more effective at higher cost • 4% less effective at lower cost	*"In conclusion, the present results suggest that the appropriate use of omega-3 PUFA-enriched lipid emulsions in PN regimens given to Chinese surgical ICU patients may induce a pattern of faster recovery and subsequent hospitalization cost reduction"* p. 374 *"We therefore conclude that the extra costs of omega-3 PUFA-enriched lipid emulsions in the ICU population should not present a barrier to their use"* p. 374
Pradelli et al. 2014[29]	
The following tables are derivatives of tables (3, 4, 5) from Pradelli et al. 2014:[29] (This is an open access article under the CC BY-NC-SA license (**http://creativecommons.org/licenses/by-nc-sa/3.0/**). **Effectiveness in** | **Omegaven** | **Standard ILE** | **Difference**	*"In conclusion, the results of this modelling study strongly suggest that the addition of omega-3 fatty acids to standard PN is a clinically and economically attractive strategy, representing a 'win-win' scenario for both patients and healthcare providers. This is because supplementation of lipid emulsions with omega-3 fatty acids reduces*

Main Study Findings			Author's Conclusions
			infection rates and length of hospital stay in ICU and in non-ICU patients receiving PN. As a consequence, supplementary treatment costs are completely offset by the reduction in the cost of hospital stay and antibiotics. As such, the results of the model show that supplementation of lipid emulsions with omega-3 fatty acids is highly likely to lead to cost savings in Italian, French, German, and UK hospitals." p. 791

ICU patients **Mean (95% CI)**			**(Omegaven – Standard ILE)**
Total LOS (days)	18.59 (11.82, 19.38)	23.06 (22.11, 24.15)	-4.55 (-4.79, -4.29)
Infections/10,000 patients	827 (477, 1,135)	1,086 (674, 1,596)	-259 (-480, -178)

Effectiveness in non-ICU patients **Mean (95% CI)**	**Omegaven**	**Standard ILE**	**Difference (Omegaven – Standard ILE)**
Total LOS (days)	15.70 (15.65, 16.05)	17.29 (17.20, 17.60)	-1.58 (-1.61, -1.49)
Infections/10,000 patients	1,201 (754, 1686)	2,391 (1,410, 3,186)	-1,189 (-1,511, -645)

Costs in Italian ICU patients (€) **Mean (95% CI)**	**Omegaven**	**Standard ILE**	**Difference (Omegaven – Standard ILE)**
Total	19,825 (14,847, 25,191)	24,504 (18,266, 31,265)	-4670 (-6,121, -3,372)
ICU	7,575 (4,698, 10,607)	10,166 (6,389, 14,415)	-2,691 (-3,812, 1,688)
Ward	6,336 (3,799, 8,912)	8,531 (5102, 11,972)	-2,195 (-3,064, -1,300)
Infection	90 (37, 139)	119 (52, 196)	-28 (-58, -14)
Parenteral nutrition	1,605 (1,442, 1,627)	1,370 (1,232, 1,394)	235 (203, 240)

Costs in Italian non-ICU patients (€) **Mean (95% CI)**	**Omegaven**	**Standard ILE**	**Difference (Omegaven – Standard ILE)**
Total	13,595 (8,832, 18,663)	14,619 (9,383, 10,197)	-1,025 (-1,540, -546)
Ward	12,171 (7,560, 17,370)	13,399 (8,29, 19,086)	-1,228 (-1,709, -737)
Infection	131 (59, 212)	261 (110, 401)	-130 (-190, -50)
Parenteral nutrition	1,292 (1,132, 1,152)	959 (836, 848)	333 (293, 307)

Abbreviated results for other countries:

Main Study Findings	Author's Conclusions

Country	Difference in total costs (€) for Omegaven – Standard ILE Mean (95% CI)	
	ICU patients	Non-ICU patients
France	-4,897 (-6,287, -3,637)	-1,762 (-2,319, -1,123)
Germany	-3,972 (-5,084, -2,996)	-1,335 (-2,116, -498)
UK	-4,130 (-5,103, -3,326)	-478 (-510, -418)

Incremental costs per days of hospital stay avoided is dominant in all cases and sensitivity analyses.

Probabilistic sensitivity analysis

- Italy:
  - Omegaven dominates in 88% of ICU patients
  - Omegaven dominates in 68% of non-ICU patients
- France, Germany and UK:
  - Omegaven dominates 88-90% of ICU patients
  - Omegaven dominates in 71-73% of non-ICU patients

CI = confidence interval; ICU = intensive care unit; ILE = intravenous lipid emulsion; PN = parenteral nutrition.

Table A12: Summary of Recommendations in Included Guidelines

Findings and Recommendations	Quality of Evidence, Strength of Recommendation
Pediatric Populations	
Wales et al. 2014[31]	
"Since the only fat emulsion in the United States is soy oil fat emulsion (SOE), a suggestion is made to reduce the dose of SOE to ≤1 g/kg/d to treat cholestasis in children with PNALD. The quality of evidence supporting this recommendation is very low. Most studies are small observational studies. The desirable effect of the reduction of liver indices has to be considered in light of the unknown effects of poor growth and development when lipids are restricted."	Grade of Evidence: Very low Strength of Recommendation: Weak
"Fish oil fat emulsion (FOE) is available in the United States under a compassionate use protocol. Until it is approved by the Food and Drug Administration, no recommendation can be made for use in the United States. The evidence supporting the use of FOE is very low quality. Included studies are small observational studies that are confounded by current SOE dose reduction and advancement of enteral feedings. The desirable effect of the reduction of liver indices has to be considered in light of the unknown effects of poor growth and development when lipids are restricted."	Grade of Evidence: Further research needed Strength of Recommendation: No recommendation
"Fat emulsion with soy oil, medium-chain triglycerides, olive oil, and fish oil (SMOF) is not available in the United States. Until it is approved for use, no recommendation can be made for use in	Grade of Evidence: Further research needed Strength of Recommendation: No recommendation

Findings and Recommendations	Quality of Evidence, Strength of Recommendation
the United States. If available, the evidence supporting the use of SMOF for the treatment of cholestasis is very low quality. The randomized controlled trials are primarily safety and efficacy studies in preterm infants with the primary outcome variable of plasma phospholipid levels and safety."	
"Fat emulsion that contains a blend of refined olive and soy oil has been approved for adults receiving PN. It is not approved for infants or children. Until it is approved for use in children, no recommendation can be made for use in the United States."	Grade of Evidence: Further research needed Strength of Recommendation: No recommendation
Adult Populations	
Weimann et al. 2017[32]	
"Postoperative parenteral nutrition including omega-3-fatty acids should be considered only in patients who cannot be adequately fed enterally and, therefore, require parenteral nutrition."	Grade of Recommendation: B Majority agreement (65% agreement)
Pironi et al. 2016[30]	
"We suggest, in patients totally dependent on HPN, a minimal supply of 1 g/kg/week of intravenous lipid emulsion containing EFA, to prevent EFA deficiency."	Grade of Evidence: Very low Strength of Recommendation: Weak
"We suggest that most patients on long-term HPN for CIF without ongoing metabolic complications be safely treated with provision of no more than 1 g/kg/day of intravenous soybean-based lipid emulsion."	Grade of Evidence: Very low Strength of Recommendation: Weak
"We suggest for treatment of intestinal failure-associated liver disease: • to re-consider all the measures to prevent intestinal failure associated liver disease • to revise the lipid component of the PN admixture, in order to decrease the total amount and/or to decrease the ω6/ω3 PUFA ratio • to revise any potential inflammatory/infective foci"	Grade of Evidence: Low Strength of Recommendation: Weak
Taylor et al. 2016[33]	
"We suggest withholding or limiting SO-based IVFE [ILE] during the first week following initiation of PN in the critically ill patient to a maximum of 100 g/week (often divided into 2 doses/week) if there is concern for essential fatty acid deficiency."	Quality of Evidence: Very low
"Alternative IVFE [ILE] may provide outcome benefit over soy-based IVFE; however, we cannot make a recommendation at this time due to lack of availability of these products in the U.S. When these alternative IVFEs (SMOF, MCT, OO and FO) become available in the United States, based on expert opinion, we suggest that their use be considered in the critically ill patient who is an appropriate candidate for PN."	Quality of Evidence: Ungraded (considered a "good practice statement")
"We suggest that specialty high-fat/low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO_2 production NOT be used in ICU patients with acute respiratory failure."	Quality of Evidence: Very low

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; DHA = docosahexaenoic acid; EFA = essential fatty acids; EN = enteral nutrition; EPA = eicosapentaenoic acid; FO = fish oil; FOE = fish oil fat emulsion; GPP = good practice points; HPN = home parenteral nutrition; MCT = medium-chain triglycerides; OO = olive oil; PN = parenteral nutrition; PNALD = parenteral nutrition-associated liver disease; PUFA = polyunsaturated fatty acid; SMOF = soybean oil, medium-chain triglycerides, olive oil and fish oil; SO = soybean oil; SOE = soy oil fat emulsion; TBI = traumatic brain injury.

Appendix 5: Additional References of Potential Interest with Reason for Exclusion

1. Chen B, Zhou Y, Yang P, Wang HW, Wu XT. Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. J Parenter Enteral Nutr. 2010;34(4):387-94. (Pre-2012 study)

2. Xiong J, Zhu S, Zhou Y, Wu H, Wang C. Regulation of omega-3 fish oil emulsion on the SIRS during the initial stage of severe acute pancreatitis. Journal of Huazhong University of Science and Technology – Medical Science. 2009;29(1):35-8. (Pre-2012 study)

3. Ortiz LC, Montejo Gonzalez JC, Vaquerizo AC, Metabolism and Nutrition Working Group of the Spanish Society of Intensive Care Medicine and Coronary units. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUC-SENPE: septic patient. Nutr Hosp. 2011 Nov;26 Suppl 2:67-71, 2011 Nov:-71. (Pre-2012, guideline not evidence-based)

4. Plauth M, Cabre E, Campillo B, Kondrup J, Marchesini G, Schutz T, et al. ESPEN Guidelines on Parenteral Nutrition: hepatology. Clin Nutr. 2009;2894):436-44. (Pre-2012, guideline not evidence-based)

5. Singer P, Berger MM, Van den BG, Biolo G, Calder P, Forbes A, et al. ESPEN Guidelines on Parenteral Nutrition: Intensive care. Clinical Nutrition. 2009;28(4):387-400. (Pre-2012, guideline not evidence-based)

6. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, et al. ESPEN Guidelines on Parenteral Nutrition: Home Parenteral Nutrition (HPN) in adult patients. Clinical Nutrition. 2009;28(4):467-79. (Pre-2012, guideline not evidence-based)

7. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition. 2009;28(4):378-86. (Pre-2012, guideline not evidence-based and has since been updated)

8. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33(3):277-316. (Pre-2012, guideline has since been updated)

Appendix 6: Studies Included in Systematic Reviews

Table A13: Studies Included in Systematic Reviews of Pediatric Populations

RCT Author and Date	Vayalthrikkovil et al. 2017[10]	Hojsak et al. 2016[11]	Kapoor et al. 2015[13]	Zhao et al. 2015[14]	Vlaardingerbroek et al. 2012[12]
Beken 2014*	✓	✓	✓	✓	
D'Ascenzo 2014*	✓	✓	✓	✓	
D'Ascenzo 2011		✓		✓	
Demirel 2012			✓		
Deshpande 2014				✓	
Deshpande 2009		✓	✓		
Gawecka 2008			✓		
Gobel 2003		✓	✓		
Koksal 2011		✓	✓		
Lima 1988					✓
Pawlik 2014	✓				
Rayyan 2012*		✓	✓	✓	✓
Rubin 1995			✓		
Savini 2013		✓	✓		
Skouroliakou 2010*		✓	✓	✓	✓
Tomsits 2010*		✓	✓	✓	✓
Vlaardingerbroek 2014*	✓	✓	✓	✓	
Wang 2015		✓	✓		

RCT = randomized controlled trial

* RCT was included in ≥3 systematic reviews

Table A14: Studies Included in Systematic Reviews of Adult Populations

RCT Author and Date	Bae 2017[17]	Li 2014[18]	Palmer 2013[19]	Tian 2013[15]	Pradelli 2012[16]
Antébi 2004*		✓		✓	✓
Badia-Tahull 2010	✓				✓
Barbosa 2010			✓		✓
Berger 2008	✓				✓
De Miranda Torrinhas 2013	✓				
Friesecke 2008			✓		✓
Grecu 2003 (abstract)			✓		
Grimm 2006*	✓	✓			✓

RCT Author and Date	Bae 2017[17]	Li 2014[18]	Palmer 2013[19]	Tian 2013[15]	Pradelli 2012[16]
Hallay 2010		✓		✓	
Han 2012	✓	✓			
Heller 2004	✓				✓
Heller 2002		✓			
Ignatenko 2010 (abstract)			✓		
Jiang 2010*	✓	✓			✓
Klek 2005*	✓	✓			✓
Koeller 2003		✓			✓
Leiderman 2010 (abstract)			✓		
Liang 2008*	✓	✓			✓
Lin 2010				✓	
Ma 2012	✓			✓	
Makay 2011	✓				✓
Mayer, Fegbeutel et al. 2003			✓		
Mayer, Gokorsch et al. 2003			✓		
Mertes 2006*	✓	✓		✓	✓
Morlion 1996		✓			✓
Piper 2009				✓	✓
Sabater 2011					✓
Senkal 2007		✓			✓
Tao 2011		✓			
Wachtler 1997		✓			✓
Wang 2012	✓	✓			
Wang 2011		✓			
Wang 2009			✓		
Wang 2008			✓		✓
Wei 2014	✓				
Weiss 2002	✓				✓
Wichmann 2007*	✓	✓			✓
Wu 2012	✓				
Zhu MW 2012	✓	✓			
Zhu XH 2012	✓				

RCT = randomized controlled trial

* RCT was included in ≥3 systematic reviews