Summary of proceedings and expert consensus statements from the international summit 'Lipids in Parenteral Nutrition'

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Abstract

Background: the 2018 Lipids in Parenteral Nutrition Summit involved a panel of experts in clinical nutrition, lipid metabolism, and pharmacology, to assess the current state of knowledge and develop expert consensus statements regarding the use of intravenous lipid emulsions in various patient populations and clinical settings. The main purpose of the consensus statements is to assist healthcare professionals by providing practical guidance on common clinical questions related to the provision of lipid emulsions as part of parenteral nutrition.

Methods: the summit was designed to allow interactive discussion and consensus development. The resulting consensus statements represent the collective opinion of the members of the expert panel, which was informed and supported by scientific evidence and clinical experience.

Results: the current article summarizes the key discussion topics from the summit and provides a set of consensus statements designed to complement existing evidence-based guidelines. Lipid emulsions are a major component of parenteral nutrition, serving as a condensed source of energy and essential fatty acids. In addition, lipids modulate a variety of biologic functions, including inflammatory and immune responses, coagulation, and cell signaling. A growing body of evidence suggests that lipid emulsions containing omega-3 fatty acids from fish oil confer important clinical benefits via suppression of inflammatory mediators and activation of pathways involved in the resolution of inflammation.

Conclusions: this article provides a set of expert consensus statements to complement formal parenteral nutrition guideline recommendations.

Keywords: parenteral nutrition; lipid; soybean oil; fish oil; fatty acid; omega-3; inflammation; immunomodulation

Clinical relevancy statement

There is a need for up-to-date practical guidance for healthcare professionals in the field of parenteral nutrition. The Lipids in Parenteral Nutrition summit is summarized in this article. Moreover, this article includes consensus statements that were formulated and voted on at the meeting, based on clinical and scientific evidence, and on expert practical clinical experience. The discussions from the meeting summarized here and the consensus recommendations are clinically relevant as they bridge the gap between formal guideline recommendations from nutrition societies and the practical use of lipid emulsions in everyday clinical practice.

Introduction

The Lipids in Parenteral Nutrition Summit was held on November 2–4, 2018, in Miami, Florida. The summit brought together expert clinicians and scientists from five continents to evaluate the current state of knowledge and offer practical guidance on the use of intravenous (IV) lipid emulsions in various patient populations and clinical settings, with a particular focus on the role of lipid emulsions containing omega-3 fatty acids. The main goal of the summit was to develop consensus statements to address common clinical questions related to the following six topics: (1) biologic effects of lipids; (2) hospitalized adults requiring parenteral nutrition (PN); (3) adults requiring home PN; (4) neonates requiring PN; (5) pediatric patients requiring home PN; and (6) practical handling aspects. In addition, because the cost effectiveness of therapy is an increasingly important topic, pharmacoeconomic considerations were addressed as a separate topic for discussion.

The format of the summit was designed to allow interactive discussion and consensus development. The resulting consensus statements represent the collective opinion of the members of the expert panel, which was informed and supported by scientific evidence and clinical experience. Importantly, the expert panel is not a formal guideline committee or sanctioned voting body. Thus, the consensus statements are not intended to be viewed as formal guidelines, but rather to complement existing evidence-based guidelines and position statements from national and international nutritional societies, so assisting healthcare professionals by bridging the gap between published guideline recommendations and practical questions that are commonly encountered in routine clinical practice.

The current article summarizes the highlights and consensus statements from the summit. A complete list of consensus statements and corresponding voting results is provided in Table 1. A more detailed review of the relevant clinical considerations for each topic area can be found in the accompanying articles in the current supplement.

Methods

Healthcare professionals with significant expertise in clinical nutrition, lipid metabolism, pharmacology, and health economic outcomes research, were invited to participate in an international consensus development conference to address common clinical questions related to the use of lipid emulsions. The overall objective of the conference was to offer practical guidance and expert consensus opinion on the use of lipid emulsions in various patient populations and clinical settings.

Consensus statements were developed using an adapted version of the Delphi technique, a widely used group communication process that aims to achieve a convergence of opinion through the collection of information regarding a specific topic within the participants' domain of expertise.[1] For each topic area, expert presentations summarizing the current state of knowledge and relevant recommendations from existing guidelines were followed by a panel discussion focused on the identification of priority issues and the development of corresponding draft consensus statements. At the conclusion of each round of discussion, panel members were asked to indicate by anonymous vote the degree to which they agreed with each consensus statement by selecting one of the following responses: agree, do not agree, do not wish to answer. Votes were recorded electronically to ensure anonymity. The voting results for each consensus statement are reported as the percentage of agreement, as well as the number of respondents for each of the three possible response categories.

A draft manuscript summarizing the key discussion topics and corresponding consensus statements was prepared for each topic area and circulated among the members of the expert panel for review and comment.

Biological aspects of lipid administration

It is now well established that individual fatty acids have unique functional properties; therefore, when prescribing lipid emulsions, it is important to understand the biological properties of the constituent fatty acids.[2] The article by Calder et al.[3] in the current supplement highlights evidence from molecular studies that has led to important insights regarding the differential biological effects of individual fatty acids as well as the specific pathways through which these

effects are mediated. Consensus statements related to the biological aspects of lipid administration are presented in Table 1 (consensus statements 1–4).

Role of lipids

Lipid emulsions are an integral component of PN. In addition to serving as an energy-dense source of energy and essential fatty acids, lipids facilitate the delivery of lipid-soluble vitamins and modulate several biologic functions, including inflammatory and immune responses, coagulation, and cell signaling.[4,5]

The influence of fatty acid composition on the biological effects of lipid emulsions

A wide variety of commercial lipid emulsions are now available for use in PN.[4] Soybean oil is the traditional lipid source in IV lipid emulsions[6]; however, based on concerns that an excessive supply of omega-6 fatty acids might be associated with inflammatory and immunosuppressive effects, subsequent generations of lipid emulsions include lipids derived from alternative oil sources as well as composite lipid emulsions containing a mixture of lipids from different oil sources.[7] Fish oil has become an important component of modern, composite lipid emulsions, owing in part to a growing body of evidence suggesting favorable effects on a variety of key biologic functions.[5,6]

The biological effects of lipid emulsions are strongly influenced by their fatty-acid composition.[4,5–10] Pure soybean oil emulsions contain high concentrations of the omega-6 polyunsaturated fatty acid (PUFA) linoleic acid, which is converted to arachidonic acid, a precursor to eicosanoids that promote inflammation and suppress cell-mediated immunity.[5,11] In

contrast, lipid emulsions containing fish oil are rich in omega-3 PUFAs such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which exhibit anti-inflammatory, immunomodulatory, and anti-oxidative properties in preclinical models.[4,5,12] Medium-chain triglycerides (derived from coconut oil or palm kernel oil) and olive oil are generally regarded as less inflammatory than soybean oil.[4,8,13]

Biological effects of fish oil

The recent characterization of a novel superfamily of lipid mediators known as specialized pro-resolving mediators (SPMs) has led to important insights regarding the biological effects of fish oil. SPMs include resolvins, protectins, and maresins.[4,5,14] Synthesized directly from the omega-3 fatty acids DHA and EPA, SPMs initiate signaling cascades that activate pathways involved in the resolution of inflammation.[15,16] Specifically, SPMs promote cessation of leukocyte infiltration, stimulate macrophage uptake of apoptotic cells, and facilitate clearance of cellular debris.[15,16] In addition, SPMs inhibit the synthesis of inflammatory mediators, including cytokines, adhesion molecules, cyclooxygenase-2, and inducible nitric oxide synthase.[4,15] Emerging evidence from clinical studies suggests that the biological effects of lipid emulsions containing omega-3 fatty acids confer meaningful clinical benefits, particularly in patients with clinical conditions characterized by a hypermetabolic or hyperinflammatory state.[8,12]

Hospitalized adults requiring PN

There is a growing body of evidence suggesting that differences in the fatty-acid composition of lipid emulsions can influence clinical outcomes in hospitalized adults who require PN.[17] The article by Mayer et al.[18] in the current supplement reviews the evidence from clinical studies

evaluating lipid emulsions in adult critically ill and surgical patients and presents consensus statements related to the use of lipid emulsions in hospitalized adults. Consensus statements related to the provision of lipid emulsions to adult critically ill (consensus statements 5–13) and surgical patients (consensus statements 14–25) are presented in Table 1.

Critically ill patients

Role of lipid emulsions in critically ill adults requiring parenteral nutrition

Lipid emulsions are an integral component of nutrition therapy in hemodynamically stable, critically ill adults requiring PN.[19,20] Lipid emulsions provide a concentrated supply of energy and essential fatty acids (EFA), thereby reducing the risks of carbohydrate overload and EFA deficiency.[6]

Critical illness is associated with a systemic inflammatory response that markedly increases metabolic demands, leading to an increased risk of infection, increased length of stay in the intensive care unit (ICU), and increased mortality rates.[21–25] There is evidence that omega-3 fatty acids such as DHA and EPA attenuate the systemic inflammatory response and support immune function.[4,5] Evidence from studies in critically ill adults suggests that the anti-inflammatory and immunomodulatory properties of omega-3 fatty acids confer significant clinical benefits, including reduced risk of infection,[26–29] reduced duration of mechanical ventilation,[30,31] and decreased length of stay in the ICU [29,31,32] and in the hospital.[26,27,32,33]

Use of lipid emulsions containing fish oil in critically ill adults

The results of recently published clinical studies and meta-analyses demonstrate that lipid emulsions containing fish oil are associated with significant clinical benefits compared with standard lipid emulsions (i.e. without fish oil) in critically ill adults who require PN.[26–31] Based on these findings, it is the consensus opinion of the expert panel that there is sufficient scientific evidence to support the use of lipid emulsions containing fish oil in critically ill adult patients requiring PN (consensus statements 6 and 7, Table 1).

Certain groups of high-risk patients may benefit from early administration of lipid emulsions containing omega-3 fatty acids, including patients with sepsis, trauma, acute respiratory distress syndrome, and other states of acute stress that can result in conditions such as systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), or persistent inflammation, immunosuppression, and catabolism syndrome (PICS).[34–37]

Lipid requirements in critically ill adults

In critically ill adults, the dose of lipids should be sufficient to prevent EFA deficiency. The total lipid dose should not exceed 1.5g/kg/day, including lipids from non-nutritive sources such as propofol.[19] Based on the available clinical data,[38] 0.1–0.2g fish oil/kg/day should be administered as part of the IV lipid emulsion (consensus statement 9, Table 1).[4] When using an all-in-one admixture, the preferred duration of infusion is 24 hours (consensus statement 11, Table 1).

Monitoring

Serum triglyceride concentrations should be assessed at baseline and monitored routinely throughout the duration of PN therapy.[39] Serum triglyceride levels should be within the ranges

recommended by local or regional guidelines and generally should not exceed 400mg/dL (4.5mmol/L) during infusion (consensus statement 10, Table 1).

Surgical patients

Role of lipid emulsions in adult surgical patients requiring PN

In adult surgical patients, the primary indication for PN is intestinal failure, defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients, water, or electrolytes, such that intravenous supplementation is required to maintain health or normal growth.[40] In surgical patients who require PN, IV lipid emulsions are an integral part of nutrition therapy (consensus statement 14, Table 1).

Use of lipid emulsions containing fish oil in adult surgical patients

Evidence from clinical studies and meta-analyses demonstrates that lipid emulsions containing fish oil offer several clinical advantages compared with those containing no fish oil in adult surgical patients, including reduced risk of infectious complications,[28,29,41–44] decreased length of stay in the ICU,[29,32,41,42] and decreased length of stay in the hospital.[28,29,32,42–44] According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on clinical nutrition in surgery, postoperative PN including omega-3 fatty acids should be considered only in patients who cannot be adequately fed enterally and thus require PN (Grade of recommendation B – majority agreement [65%]).[45]

Based on the findings from clinical studies, systematic reviews, and meta-analyses, there is no evidence that lipid emulsions containing fish oil increase the risk of coagulopathy or bleeding abnormalities compared with standard lipid emulsions that do not contain fish oil.[4]

Lipid requirements in adult surgical patients

In adult surgical patients who require PN, the dose of lipids should be sufficient to prevent EFA deficiency.[21] The total lipid dose should not exceed 1.5g/kg/day, including lipids from non-nutritive sources (consensus statement 17, Table 1). Based on clinical data,[38] 0.1–0.2g fish oil/kg/day should be given as part of the lipid emulsion.[4]

Monitoring

Consistent with recommendations for patients with critical illness, serum triglyceride levels should be assessed at baseline and monitored routinely throughout the duration of PN therapy.[39] Serum triglyceride levels should be within the ranges recommended by local or regional guidelines, and generally should not exceed 400mg/dL (4.5mmol/L) during infusion (consensus statement 21, Table 1).

Adults requiring home PN

Home PN is a life-saving therapy in adult patients with chronic intestinal failure.[46] However, patients with intestinal failure who require long-term PN are at risk of developing intestinal failure associated liver disease (IFALD). The accompanying article by Mundi et al.[47] examines factors that may contribute to IFALD and discusses lipid management strategies in adult patients

at risk for IFALD. Consensus statements related to the provision of lipid emulsions to adults requiring home PN are presented in Table 1 (consensus statements 26–28).

Role of lipids in adults requiring home PN

In patients who require long-term home PN, lipid emulsions are an integral part of nutrition therapy. At a minimum, patients who require home PN should receive IV lipids at a dose sufficient to prevent EFA deficiency (consensus statement 26, Table 1).

Lipid management in adult patients at risk for IFALD

Patients with intestinal failure who require long-term PN are at risk at risk of developing IFALD. IFALD can develop as a consequence of physiological or anatomical abnormalities related to the underlying disease as well as metabolic complications related to PN.[46,48] PN-related factors include catheter-related sepsis, continuous PN infusion, excessive glucose intake, and the use of soybean oil lipid emulsions at doses higher than 1g/kg/day.[46,48,49] Based on the risk of liver complications, current guidelines indicate that the dose of soybean oil lipid emulsions should not exceed 1g/kg/day in adults who require long-term (>6 months) home PN.[48]

Evidence from clinical trials suggests that the risk of liver complications may be reduced in adult home PN patients by using lipid emulsions containing fish oil.[47,50] Lipid emulsions containing fish oil offer several potential advantages compared with pure soybean oil emulsions, including reduced omega-6 PUFA and phytosterol content, increased omega-3 PUFA content, and increased amounts of α-tocopherol, an isoform of vitamin E that exhibits strong antioxidant effects.[11,51,52] Based on the reduced risk of hepatic injury, lipid emulsions containing fish oil are

preferred over lipid emulsions derived exclusively from soybean oil in adult home PN patients at risk for liver complications (consensus statement 27, Table 1).

Lipid management in adult patients with existing IFALD

Limited data are available to guide lipid management strategies in adults with existing IFALD. A recent observational study in adults with soybean oil intolerance receiving home PN showed a reduction in glucose intake and an improvement in measures of liver function after switching from a pure soybean oil emulsion to a mixed lipid emulsion containing fish oil.[53] This suggests that fish-oil containing lipid emulsions may be beneficial in adult home PN patients with IFALD. Additional data from prospective randomized studies are required to evaluate the potential benefit of fish-oil containing lipid emulsions in adult patients with IFALD.

Neonates requiring PN

Neonates have unique nutritional needs owing to factors ranging from high metabolic demands to limited nutrient reserves, and insufficient nutrient intake during the postnatal period can adversely affect long-term growth and neurocognitive development.[2] The article by Deshpande et al.[54] in the current supplement reviews the role of lipids in early development and summarizes findings from meta-analyses and clinical studies evaluating the effects of various lipid emulsions in neonates requiring PN. Consensus statements related to the provision of lipid emulsions to neonates are presented in Table 1 (consensus statements 29–32).

Role of lipids in neonates requiring PN

In neonates who require PN, lipid emulsions are an indispensable component of nutrition therapy.[2] Lipids serve as a concentrated source of energy and EFAs and modulate key metabolic pathways, including inflammatory and immune responses, coagulation, and cell signaling.[2,5] In preterm neonates, early administration of lipids is associated with improvements in long-term outcomes such as growth and intellectual development.[2]

According to current international guidelines, parenteral lipid intake should generally provide 25–50% of non-protein energy in fully parenterally fed neonates, and total lipid intake should not exceed 4g/kg/day.[2] To prevent EFA deficiency, the lipid dose should be sufficient to provide a minimum linoleic acid intake of 0.25g/kg/day in preterm neonates and 0.1g/kg/day in term neonates.[2]

Use of lipid emulsions containing fish oil in neonates

Neonates, particularly preterm neonates, are born with limited antioxidative capacity and an immature immune system, making them susceptible to oxidative stress and infection.[55,56] Lipid emulsions derived exclusively from soybean oil are rich in omega-6 fatty acids and can therefore potentially increase lipid peroxidation, oxidative stress, and inflammation.[2] Composite lipid emulsions containing fish oil have low concentrations of omega-6 fatty acids and high concentrations of the omega-3 fatty acids DHA and EPA and the antioxidant α-tocopherol.[2,5,11]

Evidence from randomized clinical trials in neonates requiring PN indicate that composite lipid emulsions containing fish oil reduce markers of lipid peroxidation and improve antioxidant status compared with lipid emulsions without fish oil (olive oil/soybean or soybean oil alone).[57–67] In

preterm neonates, evidence from randomized clinical trials demonstrates that composite lipid emulsions containing fish oil offer significant clinical benefits compared with lipid emulsions without fish oil, including reduced risk of bronchopulmonary dysplasia,[67,68] retinopathy of prematurity,[69–71] and cholestasis,[59,66,72] and a shorter duration of mechanical ventilation.[65]

Pediatric patients requiring PN

The ability to deliver nutrients via PN has markedly improved the prognosis of infants and children with intestinal failure; however, long-term administration of PN may be associated with complications such as IFALD.[73–75] The article by Goulet et al.[76] in the current supplement examines emerging insights regarding the role of lipid emulsions in the management of PN-dependent pediatric patients, with a particular focus on the prevention and treatment of IFALD. Corresponding consensus statements are presented in Table 1 (consensus statements 29–38).

Role of lipids in pediatric patients requiring parenteral nutrition

IV lipid emulsions are an integral component of pediatric PN. According to current international guidelines, parenteral lipid intake in children should be limited to a maximum of 3g/kg/day and should generally provide 25–50% of non-protein energy in fully parenterally fed pediatric patients.[2]

The most common indications for long-term PN in children are primary digestive diseases causing intestinal failure, including short bowel syndrome, neuromuscular disorders, and mucosal intestinal diseases.[77,78] Children with intestinal failure who require long-term PN are at risk for the development of IFALD.[79] The use of soybean oil lipid emulsions at doses higher than

1g/kg/day has been identified as a risk factor for IFALD.[11,74,79,80] Potential mechanisms for lipid-mediated liver injury in patients receiving long-term PN with soybean oil lipid emulsions include increased oxidative stress, phytosterol accumulation, and activation of the reticuloendothelial system.[11,74]

Lipid management in pediatric patients at risk for IFALD

Lipid emulsions containing fish oil offer several potential advantages compared with lipid emulsions derived purely from soybean oil, including decreased omega-6 and increased omega-3 PUFA content, higher α-tocopherol levels, and reduced phytosterol content.[2,5,11] Studies in PN-dependent infants and children at risk for IFALD have shown that multi-component lipid emulsions containing fish oil reduce the risk of cholestasis and improve biochemical measures of hepatobiliary function compared with soybean oil lipid emulsions.[81–83]

Lipid management in pediatric patients with existing IFALD

In PN-dependent children with existing IFALD, cholestasis can be reversed by using fish-oil containing lipid emulsions along with management of other risk factors, especially catheter-related infections and small intestinal bacterial overgrowth.[84–96]

Pure fish oil lipid emulsions have been shown to be a valuable short-term rescue treatment in cholestatic pediatric patients who require PN but should not be used as the sole source of lipids over a long period.[2] Based on evidence from clinical studies, administration of a composite lipid emulsion containing fish oil should be considered as first-line treatment for infants and children with existing cholestasis.[90,91] If elevated levels of conjugated or direct bilirubin (>2mg/dL

[>34μmol/L]) persist, short-term rescue therapy with a pure fish oil lipid emulsion should be considered (consensus statement 37, Table 1).

Practical handling aspects

The safe handling of IV lipid emulsions is an important aspect of PN therapy. The article by Boullata et al.[97] in the current supplement reviews the main considerations in the handling of lipid emulsions and offers practical recommendations for the preparation and administration of PN admixtures containing lipid emulsions. Consensus statements related to practical handling aspects are presented in Table 1 (consensus statements 39–43).

Minimizing the risk of medication errors

PN is a major source of medication errors, and approximately 20–30% of PN-related medication errors involve IV lipid emulsions.[98–101] In accordance with major guidelines and consensus recommendations, standardization of the PN process (including prescription, review, preparation, and administration) is recommended to minimize the potential risks associated with PN.[102–105]

Lipid emulsions can be given separately or as part of a total nutrient admixture. Total nutrient admixtures, including commercial multi-chamber bags and pharmacy compounded bags, reduce line manipulations, infection risk, and cost compared with multi-bottle systems.[106] In addition, commercial multi-chamber PN products are associated with fewer medication errors.[107] When compounding is necessary, clinicians should ensure that the prescribed formulation is reviewed and prepared under the supervision of a pharmacist with expertise in compounding PN admixtures (consensus statement 40, Table 1).

Prevention of lipid peroxidation and contamination

IV lipid emulsions with a high PUFA content are particularly prone to lipid peroxidation, which can lead to cellular damage and liver injury. Data from *in vitro* studies suggest that concomitant administration of multivitamins containing ascorbic acid with an IV lipid emulsion via light-protected tubing is an effective method for preventing lipid peroxidation and limiting vitamin loss.[2]

Repackaging of IV lipid emulsions, a practice typically used to reduce the volume of lipid infusions for neonatal and pediatric patients, increases the risk of contamination.[108–111] The risks of contamination should be weighed against the benefits of smaller lipid volumes.[112] Repackaging should be avoided if possible; if repackaging is performed, it should be under aseptic conditions and the IV lipid emulsion should be used within 12 hours (consensus statements 41 and 43, Table 1).

To prevent the risks associated with infusion of microprecipitates and particulate matter, guidelines from the US and the UK recommend the use of a filter for PN admixtures.[113,114] For lipid-containing emulsions, 1.2µm filters should be used.[113,115–117] However, the routine use of in-line filters is not widespread in Europe, Japan, or Australia.[113,118–120] In several countries, guidelines recommend the use of in-line filters in at-risk groups such as neonates, children, immunocompromised patients, and patients who require intensive PN therapy, but not in all patients.[113,115,116] For instance, European guidelines on pediatric PN state that PN admixtures may be administered through a terminal filter.[117]

Pharmacoeconomic considerations

The management of patients who require PN represents a substantial source of healthcare resource consumption. Thus, the cost effectiveness of various IV lipid emulsions is an important consideration when assessing therapeutic options,[121,122] and so these pharmacoeconomic aspects have also been reviewed in this supplement.[123] Discrete event simulation models that incorporate evidence-based clinical data and cost estimates derived from local sources are recognized as a useful method for evaluating health economic outcomes.[124,125]

Pharmacoeconomic evaluations comparing lipid emulsions containing omega-3 fatty acids with standard lipid emulsions in critically ill and surgical populations have shown that using IV lipid emulsions containing omega-3 fatty acids is a cost-effective strategy in patients who require PN.[121,122,126] According to findings from discrete event simulation models using clinical outcomes data from meta-analyses and cost data from regional sources as model inputs, in critically ill and surgical patients who require PN the acquisition cost of omega-3 fatty-acid containing lipid emulsions is more than offset by the cost savings from reductions in length of hospital and/or ICU stay and less antibiotic use.[121,122,126] Additional studies may be beneficial to evaluate the potential pharmacoeconomic benefits of lipid emulsions containing omega-3 fatty acids in other patient populations.

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Table 1. Consensus statements from the Lipids in Parenteral Nutrition International Summit (November 2–4, 2018, Miami, FL, USA).

Topic	Consensus Statements
Biological aspects	1. We recognize that lipid emulsions are an integral part of PN. Originally, lipid emulsions were an energy-dense source of calories and provided essential FAs *(100% agreement;16 agree, 0 do not agree, 0 do not wish to answer).* 2. Subsequent generations of lipid emulsions include combinations of various lipid components, predominantly with the aim of improving the safety profile of ILEs. Each lipid has its own FA composition and biological effects, which may be more or less beneficial on, for example, pro- or anti-inflammatory, immune-stimulating or modulating properties *(100% agreement; 17 agree, 0 do not agree, 0 do not wish to answer).* 3. An important component of modern composite lipid emulsions is fish oil. The group recognizes that the biological effects of fish oil are increasingly characterized in preclinical studies (different models). The biological effects of fish oil can mainly be attributed to omega-3 polyunsaturated FAs, especially EPA and DHA, and include anti-inflammatory, immunomodulatory, and anti-oxidative properties (*94% agreement; 16 agree, 1 does not agree, 0 do not wish to answer).* 4. In the view of the group, the latest findings regarding the role of specialized pro-resolution mediators (SPMs) in immune modulation add considerably to our understanding of the biological characteristics of fish oil. SPMs are a new class of mediators, which are produced directly from EPA and DHA, and are increasingly recognized as key mediators in the resolution of inflammation *(94% agreement; 16 agree, 1 does not agree, 0 do not wish to answer).*
Hospitalized adults requiring PN: critically ill patients	5. In stable, critically ill, adult patients requiring PN, ILEs are an integral part of PN *(100% agreement; 17 agree, 0 do not agree, 0 do not wish to answer).* 6. In our view, there is sufficient scientific evidence to justify the indication of fish-oil containing ILEs as part of PN in critically ill, adult surgical patients requiring PN *(100% agreement; 17 agree, 0 do not agree, 0 do not wish to answer).*

	7. In our view, there is sufficient scientific evidence to justify the indication of fish-oil containing ILEs as part of PN in non-surgical, critically ill (sepsis), adult patients requiring PN *(94% agreement; 17 agree, 1 does not agree, 0 do not wish to answer).* 8. In stable, critically ill, adult patients, the total lipid dose should not exceed 1.5g lipids/kg/day of ILEs (including non-nutritive lipid sources). A minimum dose of ILE should be given to at least prevent EFA deficiency *(89% agreement; 16 agree, 1 does not agree, 1 does not wish to answer).* 9. Based on currently available clinical data, we recommend 0.1–0.2g fish oil/kg/day, provided by lipid emulsions containing fish oil, for stable, critically ill, adult patients requiring PN *(100% agreement; 18 agree, 0 do not agree, 0 do not wish to answer).* 10. The concentrations of triglycerides (TG) in serum should be within local or regional guidelines, and should, in general, not exceed 400mg/dL (4.5mmol/L) during infusion. If the level is high, ensure the blood sample was drawn from an appropriate location. We recommend assessing serum TG at the baseline in all patients *(100% agreement; 17 agree, 0 do not agree, 0 do not wish to answer).* 11. If you are using all-in-one admixtures, the preferable infusion duration is 24 hours *(82% agreement; 14 agree, 0 do not agree, 3 do not wish to answer).* 12. In high-risk, critically ill, adult patients (e.g. sepsis, ARDS, PICS), we recommend using fish-oil containing ILEs as part of PN *(82% agreement; 15 agree, 0 do not agree, 2 do not wish to answer).* 13. In high-risk, critically ill, adult patients (e.g. sepsis, ARDS, PICS), we recommend including fish-oil containing ILEs as part of PN in the first week of PN *(94% agreement; 16 agree, 0 do not agree, 1 does not wish to answer).*
Hospitalized adults requiring PN: surgical patients	14. In adult surgical patients requiring PN, ILEs are an integral part of PN *(100% agreement; 13 agree, 0 do not agree, 0 do not wish to answer).* 15. There is sufficient scientific evidence from clinical trials, systematic reviews, and meta-analyses to demonstrate that fish-oil containing ILEs have advantages over standard ILEs (without fish oil) when used in adult surgical patients requiring PN *(100% agreement; 13 agree, 0 do not agree, 0 do not wish to answer).*

	16. When PN in adult surgical patients is required, consider including fish-oil containing ILEs, where possible *(94% agreement; 15 agree, 0 do not agree, 1 does not wish to answer).* 17. In adult surgical patients, the intravenous lipid dose should not exceed 1.5g/kg/day (including non-nutritional lipid sources). A minimum dose of ILEs should be given to at least prevent EFA deficiency *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 18. Based on currently available clinical data, we recommend 0.1–0.2g fish oil/kg/day, provided by lipid emulsions containing fish oil, for adult surgical patients requiring PN *(93% agreement; 14 agree, 0 do not agree, 1 does not wish to answer)).* 19. Based on currently available clinical data, there is no need to withhold or limit (for safety concerns) the use of fish-oil containing ILEs for PN during the first week of PN *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 20. Based on clinical studies, systematic reviews, and meta-analyses, there is no evidence that fish-oil containing lipids increase the risk of coagulopathy or bleeding abnormalities *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 21. Serum TG levels should be within the ranges recommended by local or regional guidelines; in general, they should not exceed 400mg/dL (4.5mmol/L) during infusion. If the level is high on initial testing, ensure that the blood sample was drawn from an appropriate location. We recommend serum TG levels be measured at the baseline in all patients being considered for PN *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 22. We recommend considering early initiation of PN in low-risk surgical patients if it is anticipated that the patient will be unable to attain 50–60% of goal energy and proteins within the first 5 days *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 23. We recommend considering early initiation of PN in malnourished/high nutritional risk surgical patients if enteral or oral nutrition is contraindicated or insufficient *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).* 24. In surgical patients, the main indication for PN is intestinal failure *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).*

	Intestinal failure is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth. 25. Although enteral nutrition is considered as the first line of treatment in severe pancreatitis, if the patient requires PN, ILEs are an integral part of this PN *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).*
Adults requiring home PN	26. In patients requiring home PN, ILEs are an integral part of PN *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).* 27. There is sufficient scientific evidence from clinical trials to indicate that fish-oil containing ILEs are preferred over ILEs derived exclusively from soybean for adult home PN patients at risk of liver complications *(100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer).* 28. In patients on long-term PN (>6 months), soybean ILE doses should not exceed 1.0g/kg/day to prevent liver complications. The risk of liver complications in adult home PN patients may be reduced by using fish-oil containing lipid emulsions. A minimum dose of ILEs should be given to at least prevent EFA deficiency. Fish-oil containing ILEs may be beneficial in patients with IFALD *(93% agreement; 13 agree, 0 do not agree, 1 does not wish to answer).*
Pediatric patients requiring PN	29. In pediatric patients requiring PN, ILEs are an integral part of PN *(100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer).* 30. The group recommends the following dosing schedules for fish-oil containing ILEs (mixed ILEs, excludes pure fish oil): • neonates: day 1: 1g/kg/day, day 2: 2g/kg/day, day 3 onwards: 3g/kg/day • infants, children and pre-adolescent patients: up to 3g/kg/day *(76% agreement; 13 agree, 0 do not agree, 4 do not wish to answer)* 31. In the view of the group, evidence from clinical evaluations indicates that fish-oil containing ILEs have advantages over conventional ILEs in neonates and pediatric patients for numerous markers including: • reduced risk of cholestasis

	• reduced oxidative stress/lipid peroxidation • provision of LC-PUFAs (e.g. DHA), which are critical in neonatal neurodevelopment and vision • anti-inflammatory effects due to omega-3 PUFA content • a well-balanced omega-6:omega-3 ratio • provision of medium-chain fatty acids *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer)* 32. In both groups, neonates and pediatric patients, the following parameters should be monitored: • liver function tests (total, conjugate, direct bilirubin, conjugated bilirubin, ALT, AST, alkaline phosphatase and gamma-glutamyl transferase) routinely (in hospital: weekly and HPN: at least every 3 months). • fatty-acid profiles should be determined if there is a specific clinical question, e.g. patients on fish-oil rescue therapy. *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer)* 33. In pediatric patients requiring long-term PN, fish-oil containing ILEs serve to provide energy and help to prevent liver complications *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).* 34. Data from clinical study cohorts and clinical experience indicate that the risk of liver complications in pediatric PN can be prevented and reduced by using fish-oil containing lipid emulsions *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).* 35. Pure fish oil lipid emulsions have been shown to be a valuable rescue treatment for pediatric patients with IFALD with a good safety profile *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).* 36. Pure fish oil lipid emulsions have been shown to be a valuable rescue treatment for pediatric patients with IFALD with a good safety profile *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer)* 37. In cholestatic (IFALD) pediatric patients requiring PN, pure fish oil should be used as a rescue treatment but should not be used as a sole source of lipids over a longer period. If the patient is not already receiving a fish-oil containing ILE, he/she should receive a fish oil composite ILE as a first

	line of treatment. If conjugated or direct bilirubin continues to rise above 2mg/dL, a pure fish oil emulsion is recommended until resolution *(100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer).*
Practical handling aspects	38. In accordance with major guidelines, a higher rate of standardization of the PN process to minimize potential risks associated with PN (from prescription to administration) is advocated *(100% agreement; 15 agree, 0 do not agree, 0 do not wish to answer).* 39. The group recommends considering the use of commercially available multi-chamber bags or compounded bags, depending on local expertise and economic considerations *(86% agreement; 12 agree, 1 does not agree, 1 does not wish to answer).* 40. When compounding is necessary, ensure that the prescribed formulation is reviewed and prepared under the supervision of an expert pharmacist *(100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer).* 41. To reduce the risk of contamination, we recommend avoiding repackaging of ILEs into other bags or syringes. However, if this is necessary it should be under aseptic conditions *(100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer).* 42. If you are using all-in-one admixtures, the preferable infusion duration is no longer than 24 hours *(100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer).* 43. If you are using repacked ILEs, e.g. transferred into syringes or other bags, the infusion duration should not exceed 12 hours to minimize the risk of contamination *(57% agreement;8 agree, 2 do not agree, 4 do not wish to answer).*

ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; DHA, docosahexaenoic acid; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FA, fatty acid; HPN, home parenteral nutrition; IFALD, intestinal failure-associated liver disease; ILE, intravenous lipid emulsion; LC-PUFA, long-chain polyunsaturated fatty acid; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; PN, parenteral nutrition; SIBO, small intestinal bacterial overgrowth; SPM, specialized pro-resolution mediators; TG, triglycerides.