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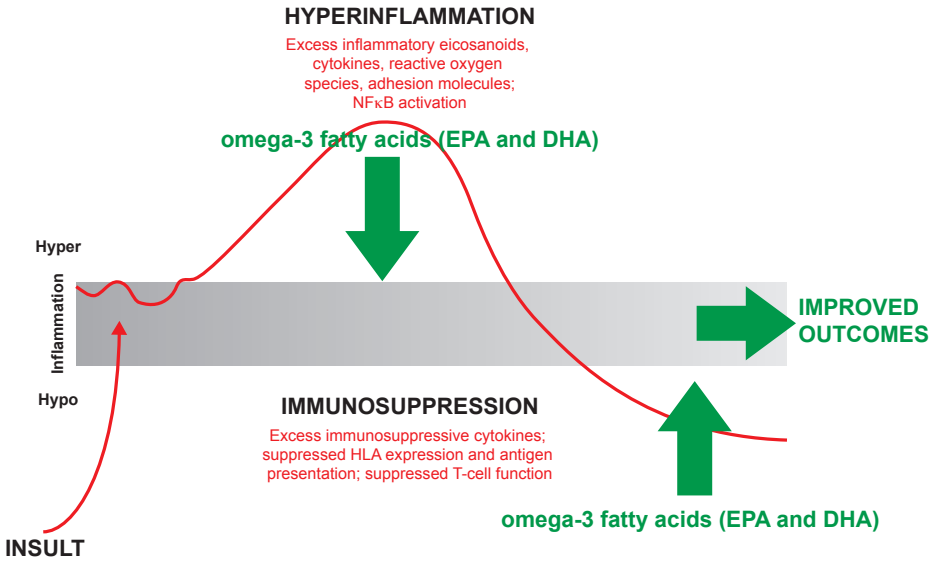

LIPIDS IN PARENTERAL NUTRITION: TRANSLATING GUIDELINES INTO CLINICAL PRACTICE

COMMENTARY

REVIEWS

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Cover Art Note: In this supplement, a panel of leading global experts with significant experience in the provision of nutrition parenteral and intravenous lipid emulsions review evidence-based literature and guidelines to assist clinicians to bridge the gap between the recommendations and their practical application in the provision of lipid emulsions via the parenteral route. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HLA, human leukocyte antigen; NFκB, nuclear factor κ B.

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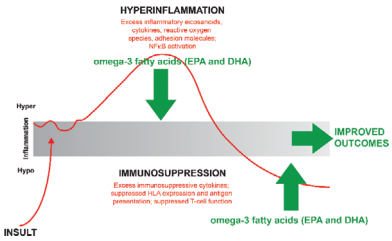

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Cover image credit: Figure adapted from Calder PC, Waitzberg DL, Klek S, Martindale RG. Lipids in parenteral nutrition: biological aspects. *JPEN J Parenter Enteral Nutr*. 2020;44(Suppl 1):S21-S27. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HLA, human leukocyte antigen; NFκB, nuclear factor κ B.

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Lipids in Parenteral Nutrition: Introduction

Robert G. Martindale, MD, PhD[1]; and Stanislaw Klek, MD, PhD[2]

Keywords
consensus; fish oil; lipids; omega-3; parenteral nutrition

Introduction

Thank you for reading this supplement, Lipids in Parenteral Nutrition, which is based upon the international summit "Lipids in Parenteral Nutrition" held on November 2–4, 2018 (Miami, FL, USA). A total of 18 international nutrition and metabolism experts participated in the summit, presenting and discussing topics concerning lipid emulsions in parenteral nutrition.[1] The purpose of the summit was to bridge the gap between formal guideline recommendations from several nutrition societies and the practical use of lipid emulsions as part of parenteral nutrition in everyday clinical practice. The summit format allowed for the rapid elucidation of practical and clinical issues, with a range of international multidisciplinary experts presenting on a variety of topics, followed by the formulation of related statements that were voted on anonymously using a Likert-type scale. The statements were based on clinical and scientific evidence, and on the practical clinical experience of the experts when evidence was lacking. Thus, the consensus statements complement formal recommendations, and represent the opinion of the experts, not those of a national or international nutrition society or formal guideline committee.

The topics covered by the summit encompassed the general role of lipids in parenteral nutrition, and with a particular focus on their clinical use in different patient populations, including adult and pediatric age groups, and various settings (hospitals and home parenteral nutrition). Although all lipid emulsions were discussed, the topic of lipid emulsions containing fish oil was of special interest because of recent popularity of research in this area and its expanded availability in many countries. Other non-clinical presentations at the summit concerned a review of the biological science of lipid emulsions, the practical handling of lipid emulsions in parenteral nutrition, and the pharmacoeconomics of ω-3 fatty-acid containing lipid emulsions. The summary of proceedings and expert consensus statements from the summit forms the first article in this supplement.[1] Thereafter, other reviews have been included based on presentations at the summit, including additional information from the literature. These are: lipids in parenteral nutrition: biological aspects,[2] lipid use in hospitalized adults requiring parenteral nutrition,[3] the use of lipids in adult patients requiring parenteral nutrition in the home setting,[4] use of lipids in neonates requiring parenteral nutrition,[5] lipid emulsion use in pediatric patients requiring long-term parenteral nutrition,[6] pharmacoeconomics of parenteral nutrition with ω-3 fatty acids in hospitalized adults,[7] and the use of intravenous lipid emulsions with parenteral nutrition: practical handling aspects.[8]

From the [1]Department of Surgery, Oregon Health and Science University, Portland, Oregon, USA; and the [2]Department of General and Oncology Surgery with Intestinal Failure Unit, Stanley Dudrick's Memorial Hospital, Skawina, Poland.

Financial disclosure: Fresenius Kabi Deutschland GmbH provided financial support to organize and invite experts to participate as speakers and discussants, based on knowledge and international reputation in the areas of clinical nutrition and more specifically lipid metabolism, to the international summit "Lipids in Parenteral Nutrition" from November 2–4, 2018 (Miami, FL, USA), as well as financial support for the development of this article. Fresenius Kabi Deutschland GmbH had no involvement in the writing of the manuscript; nor any decision on whether to submit the manuscript for publication. KFG Scientific Communications (Austin, TX, USA) provided technical support, and Dr Martina Sintzel (mcs medical communication services, Erlenbach ZH, Switzerland) and Dr Richard Clark (freelance medical writer, Dunchurch, Warwickshire, UK) provided consultancy services; all were funded by Fresenius Kabi GmbH. These services complied with international guidelines for Good Publication Practice (GPP3).

Conflicts of interest: R. G. Martindale has received honoraria from Abbott, Baxter, Fresenius Kabi, and Nestlé, and acted as an advisory board member for Nestlé. S. Klek has received speaker's honoraria from Baxter, Braun, Fresenius Kabi, Nestlé, Nutricia, Shire, and Vipharm, and acted as an advisory board member for Fresenius Kabi, Shire, and Tracheron.

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It is hoped that reviewing these areas and formulating these recommendations will help to guide international practice regarding the use of lipid emulsions in parenteral nutrition. Although these recommendations complement rather than take the place of formal nutrition guidelines, we trust that this information may help clinicians and other healthcare professionals to improve the safety and effectiveness of parenteral nutrition. Finally, we would like to thank Fresenius Kabi Deutschland GmbH (Bad Homburg, Germany) for their generosity in funding the international summit, Lipids in Parenteral Nutrition.

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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 (PN). *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 PN, 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 ω-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 PN guideline recommendations. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S7–S20)

Keywords

fatty acids; fish oil; immunomodulation; inflammation; lipids; omega-3; parenteral nutrition

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 because 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, USA. The summit brought together expert clinicians and scientists from 5 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 ω-3 fatty acids. The main goal of the summit was to develop consensus statements to address common clinical questions related to the following 6 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 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 nutrition societies, thus 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

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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 ω-3 polyunsaturated FAs, especially EPA and DHA, and include anti-inflammatory and immunomodulatory and anti-oxidative properties (94% agreement; 16 agree, 0 do not agree, 1 does 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, 0 do not agree, 1 does 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 1.5 g lipids/kg/d 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 0.1–0.2 g fish oil/kg/d, 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 400 mg/dL (4.5 mmol/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 h (82% agreement; 14 agree, 0 do not agree, 3 do not wish to answer).
	12.	In high-risk, critically ill, adult patients (eg, 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 (eg, 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/d (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).

(*continued*)

Table 1. (continued)

Topic	Consensus Statements
	18. Based on currently available clinical data, we recommend 0.1–0.2 g fish oil/kg/d, 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 400 mg/dL (4.5 mmol/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 g/kg/d 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: 1 g/kg/d, day 2: 2 g/kg/d, day 3 onwards: 3 g/kg/d • infants, children and pre-adolescent patients: up to 3 g/kg/d (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 (eg, DHA), which are critical in neonatal neurodevelopment and vision • anti-inflammatory effects due to ω-3 PUFA content • a well-balanced ω-6:ω-3 ratio • provision of medium-chain fatty acids (100% agreement; 16 agree, 0 do not agree, 0 do not wish to answer)

(*continued*)

Table 1. (continued)

Topic	Consensus Statements
	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 GGT) routinely (in hospital: weekly and HPN: at least every 3 months) • fatty-acid profiles should be determined if there is a specific clinical question, eg, 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. Data from clinical cohort studies and clinical experience indicate that cholestasis can be reversed by using fish-oil containing lipid emulsions together with the management of other risk factors, especially catheter-related or SIBO-related infections. (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 fish-oil containing ILEs, he/she should receive fish-oil composite ILEs as a first-line of treatment. If conjugated or direct bilirubin continues to rise above 2 mg/dL, 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 using all-in-one admixtures, the preferable maximum infusion duration is 24 hours (100% agreement; 14 agree, 0 do not agree, 0 do not wish to answer). 43. If using repacked ILEs, eg, 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; GGT, gamma-glutamyl transferase; 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; PUFA, polyunsaturated fatty acid; SIBO, small-intestinal bacterial overgrowth; SPM, specialized proresolution mediator; TG, triglyceride.

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 1 of the following responses: agree, do not agree, or 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 3 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 (EFAs), 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 ω-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.[4-10] Pure soybean-oil emulsions contain high concentrations of the ω-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 ω-3 PUFAs such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which exhibit anti-inflammatory, immunomodulatory, and antioxidative 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 ω-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 ω-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 PN. 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 EFAs, 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 ω-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 ω-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 (ie, 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 ω-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 1.5 g/kg/d, including lipids from non-nutritive sources such as propofol.[19] Based on clinical data,[38] 0.1–0.2 g fish oil/kg/d 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 400 mg/dL (4.5 mmol/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 IV 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 ω-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 1.5 g/kg/d, including lipids from non-nutritive sources (consensus statement 17, Table 1). Based on clinical data,[38] 0.1–0.2 g fish oil/kg/d 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 400 mg/dL (4.5 mmol/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 emulsions at doses higher than 1 g/kg/d.[46,48,49] Based on the risk of liver complications, current guidelines indicate that the dose of soybean oil emulsions should not exceed 1 g/kg/d 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 ω-6 PUFA and phytosterol content, increased ω-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 nutrition 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 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 nonprotein energy in fully parenterally fed neonates, and total lipid intake should not exceed 4 g/kg/d.[2] To prevent EFA deficiency, the lipid dose should be sufficient to provide a minimum linoleic acid intake of 0.25 g/kg/d in preterm neonates and 0.1 g/kg/d 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 ω-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 ω-6 fatty acids and high concentrations of the ω-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 PN

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 3 g/kg/d 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 lipid emulsions at doses higher than 1 g/kg/d 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 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 ω-6 and increased ω-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 multicomponent lipid emulsions containing fish oil reduce the risk of cholestasis and improve biochemical measures of hepatobiliary function compared with soybean 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 (>2 mg/dL [>34 μmol/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 ≈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 United States and the United Kingdom recommend the use of a filter for PN admixtures.[113,114] For lipid-containing emulsions, 1.2-μm 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 ω-3 fatty acids with standard lipid emulsions in critically ill and surgical populations have shown that using IV lipid emulsions containing ω-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 ω-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 ω-3 fatty acids in other patient populations.

Statement of Authorship

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Review

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Lipids in Parenteral Nutrition: Biological Aspects

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Abstract

Lipid emulsions are an integral part of parenteral nutrition, and traditionally have been regarded as an energy-dense source of calories and essential fatty acids. For many years, lipids used in parenteral nutrition have been based on vegetable oils (eg, soybean-oil emulsions). However, soybean-oil emulsions may not have an optimal fatty-acid composition under some circumstances when used as the only lipid source, as soybean oil is particularly abundant in the ω-6 polyunsaturated fatty acid (PUFA), linoleic acid. Hence, a progressive series of more complex lipid emulsions have been introduced, typically combining soybean oil with 1 or more alternative oils, such as medium-chain triglycerides (MCTs) and/or olive oil and/or fish oil. The wide range of lipid emulsions now available for parenteral nutrition offers opportunities to alter the supply of different fatty acids, which potentially modifies functional properties, with effects on inflammatory processes, immune response, and hepatic metabolism. Fish oil has become an important component of modern, composite lipid emulsions, in part owing to a growing evidence base concerning its biological effects in a variety of preclinical models. These biological activities of fish oil are mainly attributed to its ω-3 PUFA content, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA and EPA have known mechanisms of action, anti-inflammatory, immunomodulatory, and antioxidative properties. Specialized proresolving mediators, such as resolvins, protectins, and maresins, are synthesized directly from DHA and EPA, are key for the resolution of inflammation, and improve outcomes in many cell- and animal-based models and, recently, in some clinical settings. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S21–S27)

Keywords

fatty acids; fish oil; immunomodulation; inflammation; lipids; omega-3 fatty acids; parenteral nutrition; soybean oil; specialized pro-resolving mediator

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Table 1. Consensus Statements From The Lipids In Parenteral Nutrition–International Summit (November 2–4, 2018, Miami, FL, USA), Relevant to this Article.[1].

Statement Number	Consensus Statement	Expert Voting Results
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 ω-3 polyunsaturated FAs, especially EPA and DHA, and include anti-inflammatory and immunomodulatory and antioxidative 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 adds considerably to our understanding of the biological characteristics of fish oil. Specialized pro-resolution mediators (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, 0 do not agree, 1 does not wish to answer).

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; ILE, intravenous lipid emulsion; PN, parenteral nutrition; SPM, specialized pro-resolution mediators.

Introduction

This manuscript is based upon presentations given at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al[1] that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the use of lipid emulsions in parenteral nutrition and, as such, complement formal nutrition society guidelines on this subject.

Lipid emulsions are an integral component of parenteral nutrition, providing a major source of non-protein energy and lowering the amount of carbohydrate that needs to be provided as part of nutrition support.[2,3] Lipids provide the building blocks for cell membranes, and supply essential fatty acids, thus preventing essential fatty-acid deficiency.[4,5] Moreover, they allow the delivery of fat-soluble vitamins.[4] In humans, the ω-6 polyunsaturated fatty acid (PUFA) linoleic acid and the ω-3 PUFA α-linolenic acid are termed essential fatty acids, as their de novo synthesis is not possible, and so they must be supplied exogenously.[6] These fatty acids are synthesized in plants, and so many plant ('vegetable') oils (eg, soybean oil) are rich sources of essential fatty acids.[5] The types of lipids used in parenteral nutrition are primarily triglycerides, with either medium-chain fatty acids (caprylic, capric, lauric, and myristic acids), long-chain fatty acids (palmitic, oleic, linoleic, and α-linolenic acids), or very long-chain fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as their major components.[4] Fatty acids differ by chain length and the presence, number, and position of double bonds. These factors can affect fatty-acid properties, influencing processes such as metabolism, inflammation, immune response, oxidative stress, blood coagulation, organ function, and wound healing.[4,7] Importantly, the different fatty-acid compositions of lipid emulsions can result in a range of biologic effects, which may translate into changes in clinical outcomes.[4,8]

The blend of lipids used in clinical nutrition therapy has evolved over time. A pure soybean oil lipid emulsion has been used worldwide since its introduction in 1962, but a potential disadvantage of using only soybean-oil emulsions is their relatively high ω-6 PUFA content: over 50% of the fatty-acid content consists of linoleic acid.[3,4] Following concerns that an excessive supply of ω-6 PUFA might be inflammatory and immunosuppressive, more complex blends of lipid emulsions were developed using a mixture of different oil sources.[9] A wide variety of commercially available lipid emulsions is now available for use in parenteral nutrition (Table 2).[4] Differences in fatty-acid supply can influence functional properties (biological activity), including regulation of membrane structure and function;

Table 2. Typical Fatty Acid Compositions (% of Total) of Commercially Available Lipid Emulsions for Use in Parenteral Nutrition.

	Pure SO[a]	SO/MCT-Oil Blend[b]	Restructured SO/MCT-Oil Blend[c]	Pure FO[d]	OO/SO Blend[e]	FO Blend 1[f]	FO Blend 2[g]
Lipid source	100% SO	50% SO, 50% MCT	64% SO, 36% MCT	100% FO	20% SO, 80% OO	40% SO, 50% MCT, 10% FO[j]	30% SO, 30% MCT, 25% OO, 15% FO[c]
SFA	15	58	46	21	14	49	37
MUFA[h]	24	11	14	23	64	14	33
PUFA	61	31	40	56	22	37	30
n-3 PUFA:	8	4	5	48	3	10	7
ALA	8	4	5	1	3	4	2
EPA	–	–	–	20	–	3.5	3
DHA	–	–	–	19	–	2.5	2
n-6 PUFA[i]	53	27	35	5	19	27	23

ALA, **α**-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FO, fish oil; LCT, long-chain triglyceride; MCT, medium-chain trigylceride; MUFA, monounsaturated fatty acid; OO, olive oil; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SO, soybean oil. Reprinted from Calder et al, 2018. Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. *Clin Nutr*. 2018;37(1):1–18,[4] with permission from Elsevier.

[a]Intralipid.
[b]Lipofundin MCT/LCT.
[c]Structolipid.
[d]Omegaven.
[e]ClinOleic.
[f]Lipoplus/Lipidem.
[g]SMOFlipid.
[h]Mainly oleic acid.
[i]Mainly linoleic acid.
[j]The fatty-acid composition of FO is more variable than that of vegetable oils so that the precise contribution of different fatty acids may differ in different batches. Note that the FO used in Lipolus is more concentrated in EPA and DHA than that used in SMOFlipid so that 10% FO in Lipoplus provides more EPA and DHA than 15% FO in SMOFlipid.

regulation of intracellular signaling pathways, transcription factor activity, and gene expression; and regulation of the production of bioactive lipid mediators.[7] Modulating the supply of fatty acids can influence health, well-being, and risk of disease states.[7] Other lipid emulsion components include phytosterols (cholesterol-like structures present in plant oils, known to inhibit bile flow); **α**-tocopherol (vitamin E) that acts as an antioxidant to prevent oxidative lipid damage; and phospholipids, usually phosphatidylcholine (sometimes called lecithin) used as an emulsifier.[2,4,6]

Soybean Oil, *ω*-6 PUFA, and Inflammation

Soybean oil has traditionally been used as the lipid emulsion of choice for parenteral nutrition.[2] Although soybean oil consists of about 53% linoleic acid, it also contains *ω*-3 fatty acids (≈8% **α**-linolenic acid), and so its *ω* 6:*ω*-3 fatty-acid ratio is about 7:1. However, it is important to differentiate between the plant-derived *ω*-3 fatty acid, **α**-linolenic acid, and the *ω*-3 fatty acids DHA and EPA, usually derived from marine (ie, fish) sources. The main metabolic role of **α**-linolenic acid is to be converted into DHA and EPA, but as conversion to DHA is poor, **α**-linolenic acid cannot act as a substitute for DHA.[7] In the body, the *ω*-6 fatty acid linoleic acid is converted by the action of elongase and desaturase enzymes to form arachidonic acid. Arachidonic acid is the key *ω*-6 substrate for the eicosanoid pathway involved in inflammation, immunosuppression, and thrombosis.[6] Arachidonic acid is converted into eicosanoids, such as 2-series prostaglandins (PGs) and thromboxanes (TXs), 5-hydroxy-eicosatetraenoic acid (HETE), and 4-series leukotrienes (LTs), thus participating in inflammatory processes and potentially suppressing cell-mediated immunity.[3] The *ω*-3 and *ω*-6 fatty acids share the same biosynthetic pathways involving the same desaturases and elongases (Figure 1).[6,10] Thus, conversion of **α**-linolenic acid to EPA (and onwards to DHA) competes with the conversion of linoleic acid to arachidonic acid, and because the same enzymes are used, excess linoleic acid can inhibit DHA and EPA biosynthesis.[10] Overall, a high exogenous supply of *ω*-6 fatty acids may create a less optimal inflammatory, immunosuppressive, and coagulatory environment

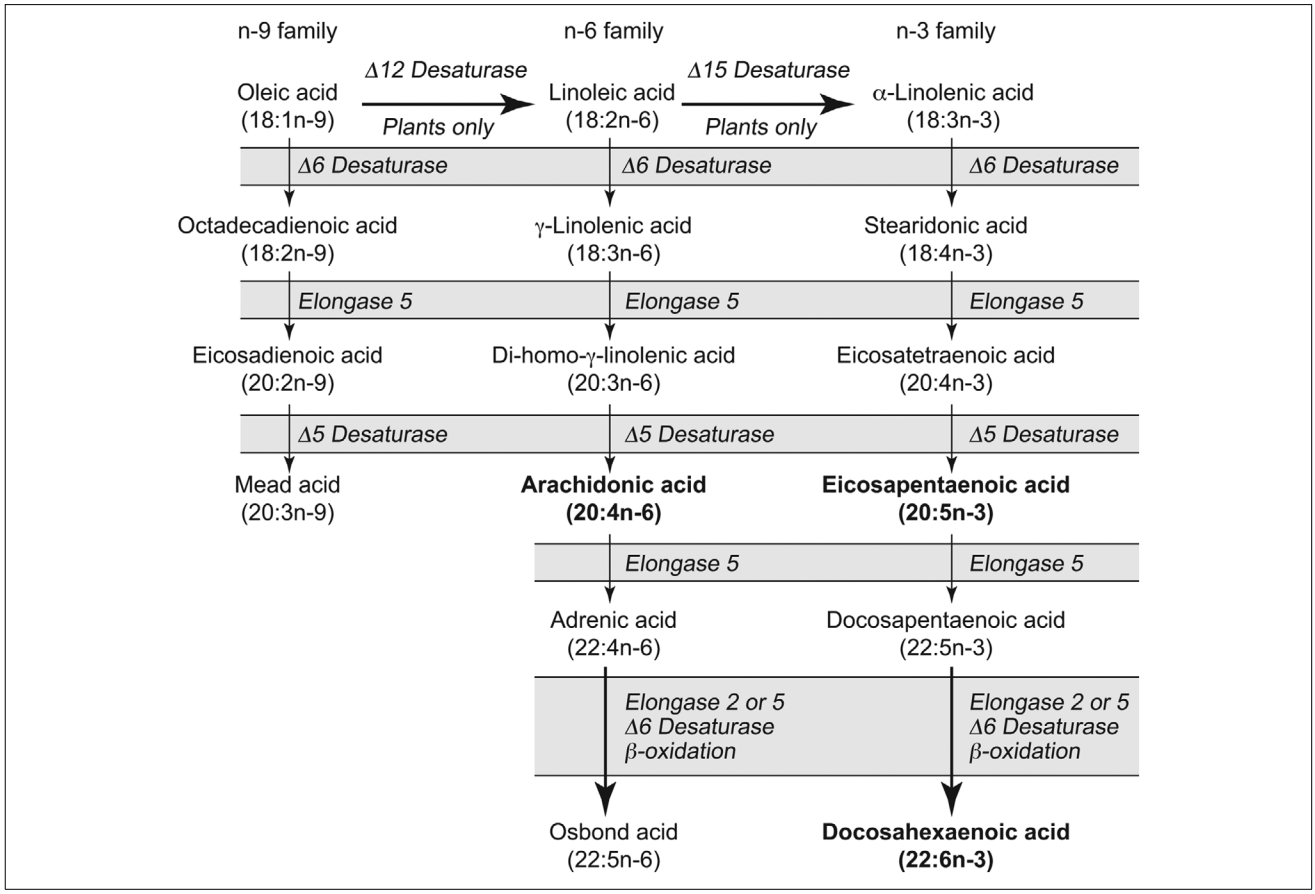

Figure 1. Metabolic processing of ω-3 (n-3), ω-6 (n-6), and ω-9 (n-9) polyunsaturated fatty acids by shared elongases and desaturases. Fatty acids in bold are key intermediates: arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenic acid (DHA).

and can lead to poor outcomes.[11] A preponderance of ω-6 fatty acids may worsen the biphasic immuno-inflammatory response to a traumatic insult (Figure 2), characterized by increased generation of inflammatory mediators and then a shift toward a hyperinflammatory yet immunosuppressed state. Thus, there is growing consensus that lipid emulsions based entirely on soybean oil should be avoided in favor of parenteral lipid emulsions in which the linoleic acid and **α**-linolenic acid content may be partially replaced by medium-chain triglycerides (MCTs), olive-oil-providing monounsaturated fatty acids (MUFAs), and/or fish-oil-providing EPA and DHA.[8,12] Using such alternative lipid emulsions may be particularly valid for critically ill hypermetabolic patients in highly inflammatory states, such as following major surgery, trauma, burns, and those with sepsis.[8,12]

Alternatives to Pure Soybean-Oil Emulsions

A range of lipid emulsions other than those containing pure soybean oil are available in many countries, and all of these reduce the proportion of fatty acids supplied as ω-6 PUFAs (Table 2).[4] These alternatives contain different proportions of fatty acids, such as MCTs (caprylic, capric, lauric, and myristic acids), oleic acid, DHA, and EPA, and thus they have at least the potential to deliver different bioactivities. For example, MCTs, derived from purified coconut oil or palm kernel oil, are a readily available energy source that is ketogenic, protein sparing, and relatively resistant to peroxidation, while not affecting blood triglyceride levels.[4,8] MCTs are absorbed and metabolized rapidly with little tendency to deposit as body fat.[13] Furthermore, MCTs are generally regarded as relatively "immune neutral" in comparison with pure soybean-oil lipid emulsions.[8]

Oleic acid, an ω-9 MUFA, is the main fatty acid supplied by olive oil and considered to have less potential impact on immune function, inflammation, and blood coagulation than lipid emulsions with a higher ω-6 PUFA content.[4,14] Lipid peroxidation may be a potential problem for PUFAs, as they contain multiple carbon double bonds (which are peroxidation targets), whereas MUFAs such as oleic acid only have 1 such bond.[8] Thus, because of its high MUFA content, olive oil is thought to be more resistant to peroxidation and oxidative stress than soybean oil.[8] Lipid emulsions

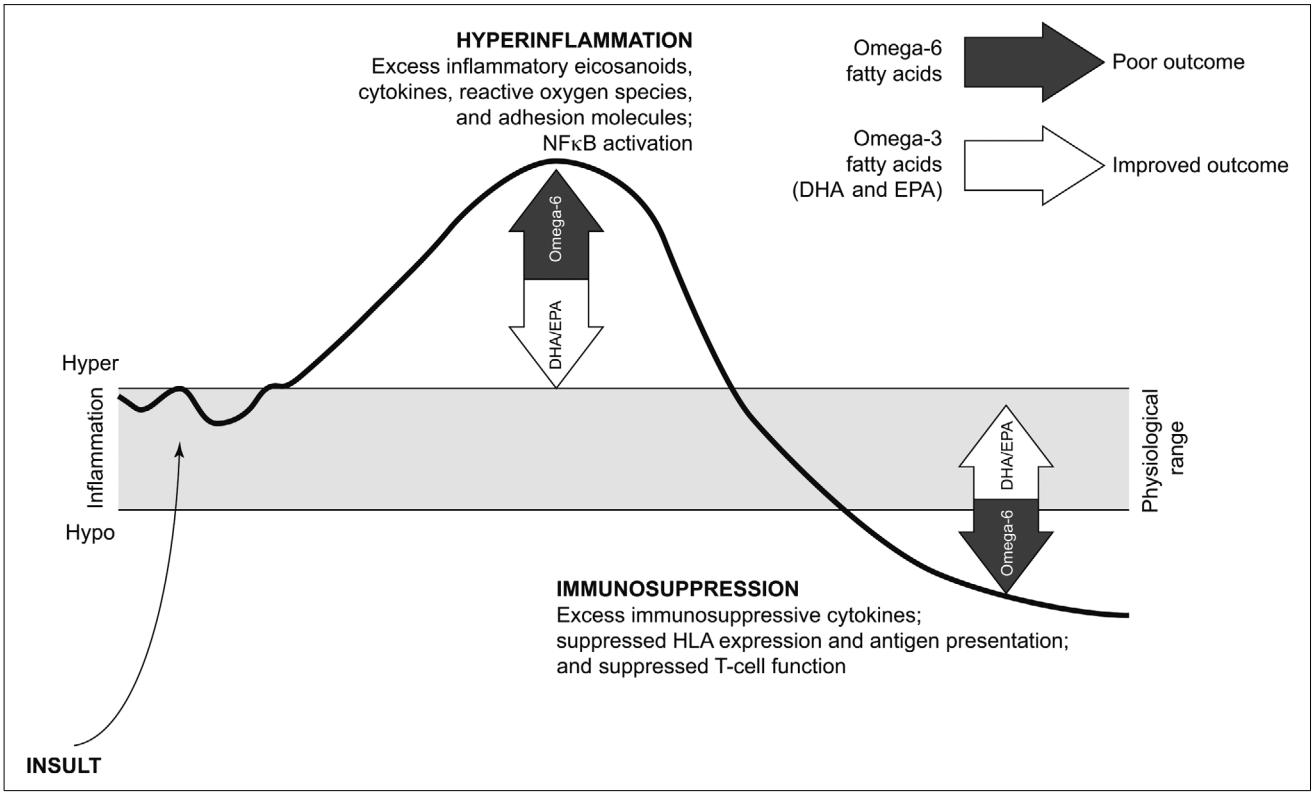

Figure 2. The biphasic immuno-inflammatory response to a traumatic insult, characterized by increased generation of inflammatory mediators and then a shift towards an anti-inflammatory immunosuppressed state, may be further worsened by a preponderance of ω-6 fatty acids but improved by the presence of ω-3 fatty acids DHA and EPA. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HLA, human leukocyte antigen; NFκB, nuclear factor κ B.

rich in olive oil may have less potential effect on host immune response than pure soybean or MCT/soybean-oil lipid emulsions, with little effect on lymphocytes, natural killer cells, and neutrophils.[8,15] However, ex vivo experimental model studies for ulcers and necrosis colitis have shown that olive-oil/soybean-oil lipid emulsions may cause more unfavorable effects than soybean oil or soybean oil/MCT.[16] The effects of parenteral nutrition incorporating fish oil, in particular DHA and EPA, are covered in the following section.

Focus on Lipid Emulsions Containing Fish Oil

There is growing evidence that standard lipid emulsions based solely on soybean oil should be avoided in some clinical situations in favor of lipid emulsions containing alternatives such as fish oil, which is rich in the very long-chain fatty acids DHA and EPA.[12] In general, ω-3 fatty acids work by opposing and so modulating the actions of ω-6 fatty acids (Figure 2), with DHA and EPA exerting beneficial effects on blood lipids, blood coagulation, inflammation, hepatic metabolism, endothelial function, and cardiovascular disease.[3,4] Not only does the inclusion of fish oil decrease the provision of potentially oxidative, inflammatory/immunosuppressive, and prothrombotic ω-6 fatty acids, but DHA and EPA have biologic effects including anti-inflammatory, immunomodulatory, and antioxidative properties, and seem likely to reduce the risk of infections and length of hospital or intensive care unit stay.[4,12,17,18] These potential clinical benefits may occur by a range of mechanisms, with DHA and EPA acting via changes in the composition of cell membranes (Figure 3).[19]

Just as enzymatic conversion of the ω-6 PUFA arachidonic acid gives rise to bioactive eicosanoids (see earlier), EPA is converted to 3-series PGs and TXs and 5-series LTs using the same pathways. The EPA-derived mediators are typically less potent than the mediators derived from arachidonic acid.[3] Moreover, the discovery of potent specialized pro-resolving mediators (SPMs) has provided an additional molecular basis for the many health benefits attributed to the ω-3 fatty acids.[20,21] EPA and DHA give rise to SPMs such as resolvins (both EPA and DHA), protectins, and maresins (DHA only), which play a key role in resolution of inflammation, reduction of tissue injury, and promotion of wound healing.[4,22] SPMs can control the extent and duration of inflammation and speed the return

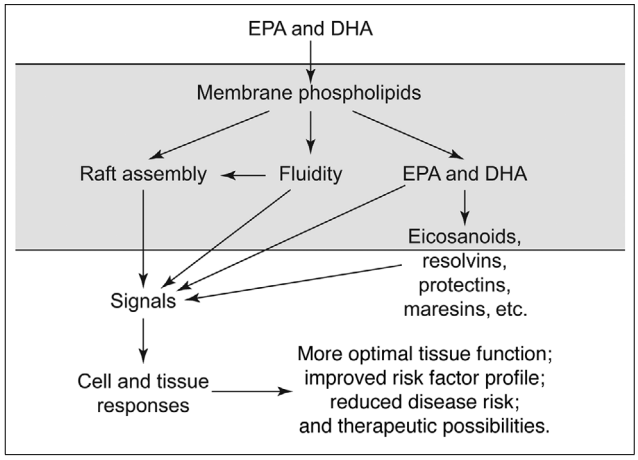

Figure 3. Mechanisms by which docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) act via changes in the composition of cell membranes (area shaded gray), potentially leading to beneficial clinical outcomes. Figure reproduced with permission from Calder, PC. Intravenous lipid emulsions to deliver bioactive ω-3 fatty acids for improved patient outcomes. *Mar Drugs.* 2019;17(5):274.[19]

to homeostasis.[22,23] A summary of the anti-inflammatory actions attributed to ω-3 PUFAs and the likely mechanisms involved are shown in Table 3.[24]

The paradigm for an acute inflammatory response can now be viewed as consisting of 2 stages: initiation (productive and transition phases) and resolution.[25] Traditionally, there has been a view that excess inflammatory mediator production underlies chronic inflammation, but, increasingly, evidence shows that disruptions in production of endogenous SPMs may be at least as equally important, as they not only actively terminate the production of inflammatory mediators but also directly stimulate macrophage phagocytosis of both apoptotic cells and bacteria, promote egress of phagocytes from sites of inflammation, regulate polymorphonuclear neutrophil (PMN) apoptosis, promote chemokine scavenging, and stimulate tissue repair and regeneration.[26] Thus, SPMs have been shown to improve outcomes in many cell- and animal-based models, limiting neutrophilic infiltration and enhancing macrophage resolution responses, and, consequently, may have an important role in conditions characterized by excessive, uncontrolled inflammation.[3] It is also important to note that some chronic inflammatory diseases are associated with defects in production of SPMs.[26] Furthermore, administration of DHA or EPA increases resolvin production in animal models of inflammation, and human studies have shown that ω-3 PUFA intake increases the concentration of resolvins and their biosynthetic pathway markers in plasma or serum.[26,27] EPA and DHA may also exert anti-inflammatory effects by acting via other pathways, including suppression of nuclear factor κB signaling and activation of peroxisome proliferator-activated receptor γ, thus inhibiting production of inflammatory cytokines, adhesion molecules, cyclooxygenase-2, inducible nitric oxide synthase, and matrix metalloproteinases.[4]

Table 3. Summary of the Anti-Inflammatory Actions Attributed To Marine ω-3 Polyunsaturated Fatty Acids and the Likely Mechanisms Involved.

Anti-Inflammatory Effect	Likely Mechanism Involved
Reduced leukocyte chemotaxis	Decreased production of some chemoattractants (eg, LTB4); down-regulated expression of receptors for chemoattractants
Reduced adhesion molecule expression and decreased leucocyte–endothelium interaction	Down-regulated expression of adhesion molecule genes (via NFκB, NR1C3 [ie, PPAR-γ], etc)
Decreased production of eicosanoids from arachidonic acid	Lowered membrane content of arachidonic acid; inhibition of arachidonic acid metabolism
Decreased production of arachidonic-acid-containing endocannabinoids	Lowered membrane content of arachidonic acid
Increased production of "weak" eicosanoids from EPA	Increased membrane content of EPA
Increased production of anti-inflammatory EPA- and DHA-containing endocannabinoids	Increased membrane content of EPA and DHA
Increased production of pro-resolution resolvins and protectins	Increased membrane content of EPA and DHA; presence of aspirin
Decreased production of inflammatory cytokines	Down-regulated expression of inflammatory cytokine genes (via NFκB, NR1C3 [ie, PPAR-γ], etc)
Decreased T-cell reactivity	Disruption of membrane rafts (via increased content of EPA and DHA in specific membrane regions)

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LTB, leukotriene B; NFκB, nuclear factor κ B; NR1C3, nuclear receptor subfamily 1, group C, member 3; PPAR, peroxisome proliferator-activated receptor.
Reproduced with permission from Calder, PC. ω-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol*. 2013;75(3):645–662.[24]

In summary, EPA and DHA are direct precursors of potent SPMs (resolvins, protectins, and maresins), have desirable bioactivities with known mechanisms of action, and are likely to exert any clinical benefits via anti-inflammatory and pro-resolution pathways. Thus, there appears to be a firm biologic basis for fish oil in particular, alongside other alternative lipid emulsions, to partially replace soybean oil as a component of parenteral nutrition.

Statement of Authorship

P. C. Calder, D. L. Waitzberg, S. Klek, and R. G. Martindale equally contributed to the conception and design of the research; P. C. Calder, D. L. Waitzberg, S. Klek, and R. G. Martindale contributed to the acquisition, analysis, and interpretation of the data; R. Clark drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Lipid Use in Hospitalized Adults Requiring Parenteral Nutrition

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Abstract

In hospitalized patients, lipid emulsions are an integral part of balanced parenteral nutrition. Traditionally, a single lipid source, soybean oil, has been given to patients and was usually regarded as just a source of energy and to prevent essential fatty-acid deficiency. However, mixtures of different lipid emulsions have now become widely available, including mixtures of soybean oil, medium-chain triglycerides, olive oil, and fish oil. Fish oil is high in the ω-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). There is a growing body of evidence that these ω-3 fatty acids can exert beneficial immunomodulatory, anti-inflammatory, and inflammation-resolution effects across a wide range of patient groups including surgical, cancer, and critically ill patients. At least in part, these effects are realized via potent specialized pro-resolution mediators (SPMs). Moreover, parenteral nutrition including ω-3 fatty acids can result in additional clinical benefits over the use of standard lipid emulsions, such as reductions in infection rates and length of hospital and intensive care unit stay. Clinical and experimental evidence is reviewed regarding lipid emulsion use in a variety of hospitalized patient groups, including surgical, critically ill, sepsis, trauma, and acute pancreatitis patients. Practical aspects of lipid emulsion use in critically ill patients are also considered, such as how to determine and fulfill energy expenditure, how and when to consider parenteral nutrition, duration of infusion, and safety monitoring. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S28–S38)

Keywords

fish oil; infections; inflammation; intensive care unit; lipids; meta-analyses; omega-3; parenteral nutrition; specialized pro-resolving mediator; surgery

Introduction

This manuscript is based upon presentations given at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al[1] that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the use of lipid emulsions in parenteral nutrition and, as such, complement formal nutrition society guidelines on this subject.

Lipid emulsions are a principle part of parenteral nutrition,[2,3] minimizing dependence on glucose as a major source of non-protein energy and preventing essential fatty acid deficiency (EFAD).[3] Lipid oil sources can also be characterized by their relative range of inflammatory effects: soybean oil, which contains a high concentration of linoleic acid, is more inflammatory than either medium-chain triglycerides (MCTs) or olive oil, while fish oil is even less inflammatory and possibly even anti-inflammatory.[4,5] Access to lipid emulsions is variable: ranging from a full spectrum of lipid emulsions available in parts of Europe, to the situation in the United States where pure soybean oil lipid emulsions were the only lipid emulsions available until August 2016.[4,6] The wide range of lipid emulsions obtainable is reviewed elsewhere.[4,6,7] Now that alternatives are available, the transition away from pure soybean oil emulsions is occurring rapidly.[7] However, in some locations a relatively slow transition away from pure soybean oil lipid emulsions is occurring for complex reasons that may reflect differences in healthcare systems. This was discussed by 1 of the authors in his presentation at this meeting, when he detailed the complex process of trying to add SMOFlipid (Fresenius Kabi, Bad Homberg, Germany), a multi-component intravenous lipid emulsion containing 30% soybean oil, 30% MCTs, 25% olive oil, and 15% fish oil (henceforth referred to as SMOF) to the hospital formulary at the Ohio State University in the United States.[8] However, this situation may not be uniform across US healthcare, as other universities' medical centers have accepted SMOF rapidly.

In this article, we discuss the use of lipid emulsions as part of parenteral nutrition in adult hospitalized patients,

with a particular emphasis on comparisons between lipid emulsions containing ω-3 fatty acids and other standard lipid emulsions without fish oil, to reflect recent clinical research in this field. While all commercially available lipid emulsions suffice as an energy supply and contain enough essential fatty acids to prevent EFAD, those containing only soybean oil as a lipid source have a high ω-6:ω-3 fatty-acid ratio and abundance of phytosterols, raising concerns about their inflammatory and hepatotoxic potential in some patients.[6] Conversely, there is a growing body of evidence that ω-3 fatty acids can exert beneficial immunomodulatory, anti-inflammatory, and resolution of inflammation effects across a wide range of patient groups including surgical, cancer, and critically ill patients.[9-11] In addition, lipid emulsions based on fish oil contain high levels of the antioxidant vitamin E,[7] which may help to reduce oxidative stress during inflammatory conditions. These potential advantages can translate into clinical benefits such as reductions in infection rates and length of hospital and intensive care unit (ICU) stay, as will be discussed in the following sections.

Surgical Patients

Several changes within the field of parenteral nutrition have emerged that can potentially stimulate changes in clinical practice for surgical patients. These include a closer attention to glycemic control and a broader availability of lipid emulsions in recent years, particularly mixes of lipids containing soybean oil, olive oil, MCT, and fish oil. In addition, we realize that fish oil has anti-inflammatory and immunomodulatory effects, and it contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), now known to be direct precursors of endogenously produced specialized pro-resolution mediators (ie, resolvins, protectins, and maresins) that improve outcomes in many animal disease models.[11,12] Moreover, the resolvins and protectins can promote better macrophage and neutrophil killing without increasing the inflammatory response,[13] which may be of particular benefit in some groups such as those with hyperdynamic septic shock. This has been illustrated by the use of intravenous fish oil to blunt the physiological stress response in healthy volunteers to intravenous endotoxin, which induces a transient inflammatory condition mimicking aspects of sepsis.[14] Fish oil significantly reduced fever, adrenocorticotropic hormone (ACTH), and cortisol plasma levels, but without affecting the inflammatory response (eg, tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], and C-reactive protein [CRP] levels).[14]

Overall, major guidelines are broadly supportive concerning the use of alternatives to pure soybean oil lipid emulsions in surgical patients. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for clinical nutrition in surgery stated that postoperative parenteral nutrition including ω-3 fatty acids should be considered in patients that require parenteral nutrition if they cannot be fed adequately via the enteral route.[15]

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Table 1. Consensus Statements From the International Summit *Lipids in Parenteral Nutrition* on November 2–4, 2018 (Miami, FL, USA), Relevant to This Article.[1]

Statement Number	Consensus Statement	Expert Voting Results
	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 1.5 g lipids/kg/d 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 0.1–0.2 g fish oil/kg/d, 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 (TGs) in serum should be within local or regional guidelines, and should, in general, not exceed 400 mg/dL (4.5 mmol/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 h.	82% agreement (14 agree, 0 do not agree, 3 do not wish to answer)
12	In high-risk, critically ill, adult patients (eg, sepsis, ARDS, PICS), we recommend using fish-oil containing ILEs as part of the PN.	82% agreement (15 agree, 0 do not agree, 2 do not wish to answer)
13	In high-risk, critically ill, adult patients (eg, sepsis, ARDS, and 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)
	Adult 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 1.5 g/kg/d (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 0.1–0.2 g fish oil/kg/d, 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)

(*continued*)

Table 1. (continued)

Statement Number	Consensus Statement	Expert Voting Results
21	Serum TG levels should be within the ranges recommended by local or regional guidelines; in general, they should not exceed 400 mg/dL (4.5 mmol/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 nutrition 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. *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.*	100% agreement (15 agree, 0 do not agree, 0 do not wish to answer)
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)

ARDS, acute respiratory distress syndrome; EFA, essential fatty acid; FA, fatty acid; ILE, intravenous lipid emulsion; PICS, persistent inflammation, immunosuppression, and catabolism syndrome; PN, parenteral nutrition; TG, triglyceride.

Furthermore, an ESPEN expert group stated that parenteral nutrition including fish oil appears to be well tolerated and confers additional clinical benefits, particularly in surgical ICU patients, owing to its anti-inflammatory and immune-modulating effects.[9] Guidelines for nutrition support therapy from Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) for adult critically ill patients also extend to a target patient population including surgical patients (eg, trauma, traumatic brain injury, open abdomen, burns, sepsis, and postoperative major surgery), and thus are relevant to this discussion.[16] This guideline was produced before SMOF was approved in the United States, so although it states that alternatives to soybean-oil intravenous lipid emulsions may provide outcome benefits, the authors could not make a recommendation owing to a lack of availability of alternative lipid emulsions. However, the guideline specified that when alternatives (SMOF, MCTs, olive oil, and fish oil) become available in the United States, based on expert opinion, their use should be considered in the critically ill patient who is an appropriate candidate for parenteral nutrition.[16]

In this section the clinical data from systematic reviews and meta-analyses will be considered regarding the use of parenteral nutrition enriched with ω-3 fatty acids in a range of hospitalized patients, including surgical patients. Since 2010, at least 11 meta-analyses have been published concerning parenteral nutrition with and without ω-3 fatty acids (Table 2).[17-27] These meta-analyses have covered surgical patients,[18,19,21,23,25] a mixture of ICU and non-ICU (surgical) patients,[20,26,27] and ICU and/or critically ill patients.[17,22,24] Overall, 9 out of 11 meta-analyses found at least 1 significant clinical benefit in those given ω-3 fatty acids,[18-20,22-27] but none favored standard parenteral nutrition for any clinical outcome.

The meta-analyses show the following clinical benefits for parenteral nutrition with ω-3 fatty acids rather than standard lipid emulsions:

- infectious complications were significantly reduced in non-ICU/surgical patients,[18-20,23,25,26] ICU patients,[24,26] and a mixed population of ICU and non-ICU (surgical) patients[20,27]
- significantly shorter hospital length of stay[19,20,22-27]
- significantly shorter ICU length of stay.[18-20,27]

It is notable that the 2 meta-analyses showing no significant differences included the fewest trials (6 in each case) and very few (<400) patients.[17,21]

Results from the largest and most comprehensive meta-analysis published to date, including 49 randomized controlled trials (RCTs) and 3641 patients,[27] showed that the use of ω-3 fatty acids was associated with 40% fewer infections (relative risk [RR] 0.60; 95% confidence interval [CI], 0.49–0.72; $P < .00001$), ≈2 days shorter hospital stay (2.14 days; 95% CI, 1.36–2.93; $P < .00001$), and ≈2 days shorter ICU stay (1.95 days; 95% CI, 0.42–3.49; $P = .01$), and sepsis was reduced by 56% (RR 0.44; 95% CI, 0.28–0.70; $P = .0004$). In addition, this meta-analysis also

Table 2. Meta-Analyses Comparing Clinical Outcomes for PN Enriched With Ω-3 Fatty Acids vs Standard PN (ie, Containing Only MCT/LCT Emulsions, Olive/Soybean Oil Emulsion or Soybean Oil Emulsions).

Authors	Patient Types(s), Number Of Trials (N) and Patients (n)	Significant Differences Detected in Favor of Parenteral Nutrition Enriched With ω-3 Fatty Acids[a]
Wei et al, 2010	Surgery (postoperative) N = 6 n = 611	Significantly fewer infections: RR 0.49; 95% CI, 0.26–0.93; $P = .03$. Significant reduction in ICU LOS: −2.07 mean days' difference; 95% CI −3.47 to −0.67; $P = .004$.
Chen et al, 2010	Major abdominal surgery N = 13 RCTs n = 892	Significantly fewer infections: OR 0.56; 95% CI, 0.32–0.98; $P = .04$. Significant reduction in hospital LOS: WMD −2.98 days; 95% CI, −4.65 to −1.31 days; $P < .001$. Significant reduction in ICU LOS: WMD −1.80 days; 95% CI, −3.04 to −0.56 days; $P = .004$.
Pradelli et al, 2012	ICU and non-ICU (surgical) patients N = 23 RCTs n = 1502	Significantly fewer infections: RR 0.61; 95% CI, 0.45–0.84; $P = .002$. (Note: results were also significant for non-ICU but not ICU subpopulation.) Significant reduction in hospital LOS: −3.29 mean days' difference; 95% CI, −5.13 to −1.45; $P = .0005$. (Note: results were also significant for both ICU and non-ICU subpopulations.) Significant reduction in ICU LOS: −1.92 mean days' difference; 95% CI, −3.27 to −0.58; $P = .005$.
Tian et al, 2013	Surgery (postoperative) N = 6 RCTs n = 306	No significant differences detected in hospital LOS in the 2 studies reporting this parameter.
Palmer et al, 2013	ICU N = 9 studies n = 431	Significant reduction in hospital LOS: −9.49 days' difference; 95% CI, −16.51 to −2.47; $P = .008$.
Manzanares et al, 2014	ICU N = 6 RCTs n = 390	No significant differences found in mortality rates, infections, ICU LOS, or duration of mechanical ventilation.
Li et al, 2014	Surgery (postoperative) N = 21 RCTs n = 1487	Significantly fewer infections: OR 0.53; 95% CI, 0.35–0.81; $P = .003$. Significant reduction in hospital LOS: −2.14 mean days' difference; 95% CI, −3.02 to −1.27; $P < .00001$.
Manzanares et al, 2015	ICU N = 10 RCTs n = 733	Significantly fewer infections: RR 0.64; 95% CI, 0.44–0.92; $P = .02$. Significant reduction in hospital LOS for in 4 higher-quality trials: WMD −7.42 days; 95% CI, −11.89 to −2.94; $P = .001$.
Bae et al, 2017	Surgery N = 19 RCTs n = 1167	Significantly fewer infections: OR 0.44; 95% CI 0.30–0.65; $P < .0001$ Significant reduction in hospital LOS: WMD −1.81 days; 95% CI −2.89 to −0.74 days; $P = .0009$
Kreymann et al, 2018	RCTs in critically ill (N = 3 for infection rates; N = 3 for ICU LOS), surgical patients (N = 1 for infection rates), surgical patients with cancer (N = 14 for infection rates; N = 13 for hospital LOS) Patient numbers not reported.	Even though very few trials were included in each category, there were significant benefits for PN enriched with ω-3 fatty acids vs standard PN for: - critically ill patients (fewer infections) - surgical patients (fewer infections) - surgical patients with cancer (fewer infections and reduced hospital LOS)
Pradelli et al, 2019	ICU and non-ICU (surgical) patients N = 49 RCTs n = 3641	Significantly fewer infections: RR 0.60; 95% CI, 0.49–0.72; $P < .00001$. Significant reduction in hospital LOS: −2.14 mean days' difference; 95% CI, −1.36 to −2.93; $P < .00001$. Significant reduction in ICU LOS: −1.95 mean days' difference; 95% CI −0.42 to −3.49; $P = .01$. Significant reduction in sepsis: RR 0.44; 95% CI, 0.28–0.70; $P = .0004$.

CI, confidence interval; ICU, intensive care unit; LOS, length of stay; MCT/LCT, medium-chain triglycerides/long-chain triglycerides; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; RR, relative risk; WMD, weighted mean difference.

[a]Results showed significant differences in favor of ω-3 fatty acids in 8 out of 11 studies. No significant differences were detected in favor of standard PN in any meta-analyses.

showed a potential hepatoprotective effect by ω-3 fatty acids, with significant benefits in marker liver enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transferase [GGT] levels), as well as higher levels of the antioxidant α-tocopherol, and lower levels for markers of inflammation such as TNF-α.[27]

Previous to the 2019 meta-analysis, a 2012 meta-analysis by the same group had similar clinical outcome results,[20] and these have been used in pharmacoeconomic analyses showing that the use of ω-3 fatty acids can also be cost-effective (ie, they improve patient outcomes while saving money, with the acquisition cost of ω-3 fatty acids being completely offset by reductions in hospital-stay costs and antibiotic costs).[28-30] Thus, parenteral nutrition regimens including ω-3 fatty acids were cost-effective vs standard parenteral nutrition for Italian, French, German, and UK hospitals for ICU and non-ICU patients,[28] and for Chinese ICU patients.[29,30]

Taken together, there appears to be sufficient clinical and laboratory data available to conclude that lipid emulsions containing ω-3 fatty acids are a valuable parenteral nutrition component for surgical patients, including surgical ICU patients. Some of these advantages are covered in the ESPEN expert group publication.[9] Additional points made in this publication are that doses of fish oil between 0.1 and 0.2 g/kg/d are needed to show clinical benefits such as decreased length of hospital/ICU stay and lower antibiotic requirements. Moreover, concerns that ω-3 fatty acids might cause an increased incidence of bleeding events have not been substantiated when evaluating the incidence of coagulation abnormalities.[20,27]

In summary, lipid emulsions containing ω-3 fatty acids offer a number of advantages in surgical patients. These include increased safety and tolerability, less inflammation, and a more hepatoprotective effect vs soybean oil emulsions.[4,10,31] Moreover, lipid emulsions containing ω-3 fatty acids can decrease the risk of cholestasis, as well as improve a number of clinical outcomes discussed previously (eg, decreased infections and decreased length of hospital/ICU stay).[4] In practice, the use of lipid emulsions containing ω-3 fatty acids could eliminate the practice of withholding intravenous (soybean oil) lipid emulsions for some groups such as hyperdynamic patients (surgical and mixed ICU patients) and in stable patients with sepsis, and could decrease the incidence of hypertriglyceridemia and the resultant need to discontinue or decrease the supply of intravenous lipid emulsions.

Critically Ill Patients

As mentioned briefly in the previous section, SCCM/ASPEN guidelines acknowledge the potential risk of using pure soybean oil emulsions in critically ill patients by recommending withholding or limiting their use during the first week after starting parenteral nutrition.[16] Furthermore, a consensus statement regarding critically ill patients at the current summit, with experts from around the globe, stated that based on currently available clinical data, there is no need to withhold or limit (for safety concerns) the use of fish-oil containing lipid emulsions during the first week of parenteral nutrition (Table 1). Moreover, other consensus statements agreed that in high-risk, critically ill, adult patients (eg, sepsis; acute respiratory distress syndrome [ARDS]; persistent inflammation, immunosuppression, and catabolism syndrome [PICS]), fish-oil containing lipid emulsions should be used as part of parenteral nutrition, particularly during the first week of parenteral nutrition (Table 1).

ESPEN guidelines for parenteral nutrition in ICU patients recommend that the administration of intravenous lipid emulsions should be generally a part of parenteral nutrition and that lipid emulsions enriched with EPA and DHA (fish oil dose 0.1–0.2 g/kg/d) can be provided in patients receiving parenteral nutrition.[2] The authors at the current lipid meeting were also in agreement with this dose range, for stable, critically ill, adult patients requiring parenteral nutrition (Table 1). The ESPEN guidelines[2] report that evidence of ω-3 enriched emulsions in non-surgical ICU patients is not sufficient to mention this as a stand-alone recommendation, referencing the 2018 review by the ESPEN expert group.[9] This review stated that fish-oil enriched parenteral nutrition was well tolerated and confers additional clinical benefits, particularly in surgical patients, but that the evidence in non-surgical ICU patients is less clear.[9] Although this is an excellent review, it may require updating because the meeting was held before the more recent data noted below.

When considering evidence to inform healthcare decisions, some consider meta-analyses to be the most powerful methods, forming the highest level of the evidence-based medicine hierarchy,[32] whereas others believe that large RCTs represent the highest level of evidence. Currently, the evidence is limited because few large RCTs are available for studying the mixed-oil lipid emulsions, so we must rely on meta-analyses to make evidence-based clinical decisions. The previous section summarized meta-analyses assessing the effectiveness of ω-3 fatty acids for parenteral nutrition in a variety of hospitalized patients, including critically ill patients (Table 2). Of these meta-analyses, the largest published up to 2019 included 13 trials (n = 762 patients) covering the ICU population.[20] While there was not a significant decrease in mortality with ω-3 fatty-acid enriched emulsions, they were associated with significant reductions in the infection rate (RR 0.61; 95% CI, 0.45–0.84; $P = .002$) and the length of stay, both in the ICU (-1.92 days; 95% CI, -0.58 to -3.27; $P = .005$) and in hospital overall (-3.29 days; 95% CI, -1.45 to -5.13;

$P = .0005$). Moreover, there were beneficial improvements in many laboratory parameters including AST and ALT, suggesting a potential hepatoprotective effect, as well increases in DHA and EPA, and a positive effect on inflammation such as reductions in CRP and IL-6 levels, increases in leukotriene (LTB)5, and better LTB5:LTB4 ratio.[20] Furthermore, based on the aforesaid results,[20] ω-3 fatty-acid enriched parenteral nutrition was shown to be cost-effective vs standard parenteral nutrition as increases in (direct) acquisition cost are offset by savings through reduced length of stay and antibiotic requirements.[28] These savings were €3972–€4897 per ICU patient and €561–€1762 per non-ICU patient.[28]

Some meta-analyses have considered the use of ω-3 fatty acids in the subgroup of critically ill patients with sepsis, 1 including 11 studies (7 parenteral nutrition, 5 enteral nutrition; 808 patients)[33] and the other 17 clinical trials (10 parenteral nutrition, 7 enteral nutrition studies; 1239 patients).[34] They found that ω-3 nutrition supplementation reduced ICU length of stay by ≈4 days[34] and duration of mechanical ventilation by ≈2–4 days,[33,34] but were cautious about generalizing from these results because of small sample size, a relatively high degree of heterogeneity, and low quality of evidence.[33,34]

When considering those RCTs that are available in critically ill patients, Grau-Carmona et al performed a randomized controlled double-blind study involving 159 critically ill medical and surgical patients in 17 Spanish ICUs over a period of 4 years.[35] Patients were randomized to receive either a lipid emulsion containing 50% MCT, 40% soybean oil, and 10% fish oil or 50% MCT/50% soybean oil. Forty percent of energy intake was covered by lipids up to a total of 1.5 g/kg/d, with parenteral nutrition given for at least 5 days, but as long as required. The number of patients with nosocomial infections (primary outcome) was significantly reduced in the fish-oil group compared with the control (no fish oil) group (21% vs 37.2%, respectively; $P = .03$), and the predicted time free of infection was greater in the fish-oil group (21 ± 2 vs 16 ± 2 days, respectively; $P = .03$) (Figure 1). While the length of hospital stay was not significantly different between groups, it did approach the point of significance (medians of 25 vs 37 days, respectively, for fish-oil and control groups; $P = .059$).

Finally, a review of the evidence surrounding the use of ω-3 fatty acids in parenteral nutrition, including critical care, stated that there is a strong scientific rationale for using ω-3 polyunsaturated fatty acids in parenteral nutrition: they improve outcomes in critically ill patients as well as a wide variety of other groups.[10] Moreover, lipid emulsions containing fish oil have a proven safety and tolerability profile and represent a cost-effective component of parenteral nutrition regimens.[10] Importantly, a consensus statement at the current meeting stated that based on clinical studies, systematic reviews, and meta-analyses, there

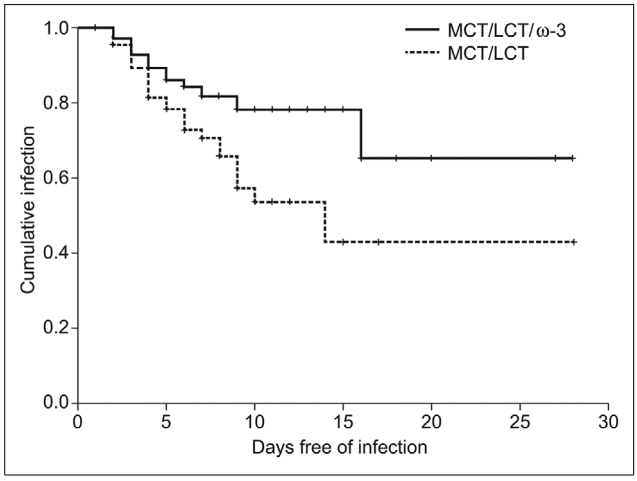

Figure 1. Time free of infection (TFI) for patients given parenteral nutrition containing 50% medium-chain triglycerides (MCTs), 40% soybean oil (LCT),10% fish oil (ω-3) (n = 68) vs those given 50% MCT/50% LCT (n = 71). TFI was significantly longer in the MCT/LCT/ω-3 group (21 vs 16 days, respectively; $P = .03$). LCT, long-chain triglyceride. Reproduced with permission from Grau-Carmona et al, 2015. Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU Lipids Study. *Crit Care Med.* 2015;43(1):31-39.[35]

is no evidence that fish-oil containing lipids increase the risk of coagulopathy or bleeding abnormalities (Table 1).[1] Nevertheless, controversy remains regarding the use of ω-3 fatty-acid enriched parenteral nutrition. This is not only because of the quality of some RCTs, but also as there are some conflicting results from previous reviews and meta-analysis.[36] Some controversy continues, but it seems likely that this may be because of a low concordance in source data (ie, references selected). Factors contributing to this might be differences in selection of keywords and search methods, and perhaps intellectual conflicts of interest for some authors. In conclusion, and on balance, this consensus of the expert group was that there is sufficient scientific evidence to justify the use of ω-3 fatty acids in the parenteral nutrition of surgical and non-surgical (septic) critically ill patients.

Specific Groups: Trauma and Acute Pancreatitis

Several additional groups of patients may benefit from ω-3 enriched lipid emulsions. These include patients with sepsis (as discussed in the previous section), trauma or emergency surgery patients. Under these conditions of acute stress, a myriad of metabolic responses can occur that can result in conditions such as systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response

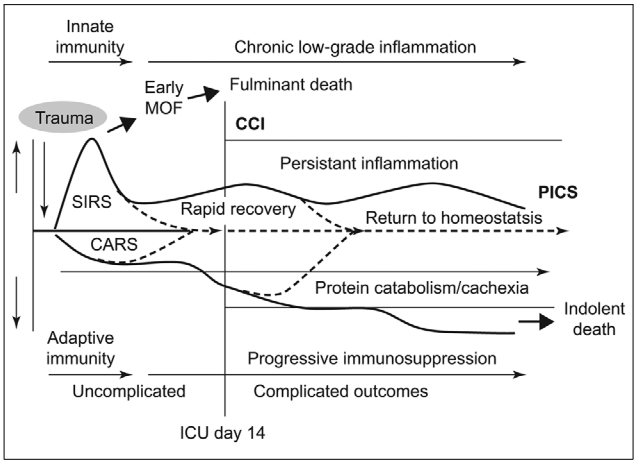

Figure 2. Response after traumatic injury. CARS, compensatory anti-inflammatory response syndrome; CCI, chronic critical illness; ICU, intensive care unit; MOF, multiple organ failure; PICS, persistent inflammation, immunosuppression and catabolism syndrome; SIRS, systemic inflammatory response syndrome. Reproduced with permission from Vanzant et al, 2014. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg*. 2014;76(1):21-29.[37]

syndrome (CARS), or PICS (Figure 2).[37] RCTs are nearly impossible to do in these populations, but one can make inferences from research in other fields in which parenteral nutrition including ω-3 fatty acids has proven beneficial, such as major elective surgery or sepsis, which involves similar stress responses to injury. As ω-3 fatty acids are known to be effective in modulating immune response, they may have a key role in treating these inflammatory conditions arising from trauma. Thus, when patients sustain major injuries, and are critically ill they can enter a constant dynamic state of SIRS, and compelling evidence supports both immune- and metabolic-response modulation by specific nutrients, including ω-3 fatty acids.[38] Early diagnosis of these immune disorders and systemic hypermetabolic states, and the use of appropriate nutrition therapy including immune- and metabolic-modulating nutrients, can potentially reduce the incidence of complications, length of hospital stay, and mortality rates.[39]

The epidemiology of chronic illness after severe trauma has been explored in a prospective observational study involving 135 trauma ICU patients with hemorrhagic shock who survived beyond 48 hours after injury.[40] Of those surviving 48 hours, relatively few patients (3 patients, 2%) died within 7 days, 107 (79%) exhibited rapid recovery, but 25 (19%) progressed to chronic critical illness (CCI). Patients who developed CCI rather than recovering tended to be those who had an infection during the first 7 days of hospitalization (64% vs 28%, respectively; $P = .0019$). In addition, 56% of those developing CCI either died prior to discharge or had a poor discharge disposition (discharge to skilled nursing or long-term acute care facility) associated with poor outcomes. At 4 months, CCI patients had higher mortality rates than patients who had a rapid recovery (16% vs 1.9%, respectively; $P < .05$), with survivors also scoring lower for general health measures ($P < .005$). Thus, while early mortality is low after severe trauma, CCI is a common course in survivors and is associated with poor long-term outcomes. To prevent this response to injury, early identification may allow targeted interventions to change the trajectory of this morbid phenotype.[40] As we know that catabolism is driven by a persistent inflammatory response, it seems reasonable to use parenteral nutrition enriched with ω-3 fatty acids that may help to resolve inflammation and thus decrease the likelihood of CCI/PICS.

When associated with pancreatic necrosis, severe acute pancreatitis (SAP) continues to be associated with high mortality rates, and is characterized by marked nutrition depletion so nutrition support is required. SAP is a biphasic disease: the early stage is characterized by an inflammatory response resulting in SIRS, which can progress to early multiple-organ dysfunction syndrome (MODS), while the late phase involves a transition to an anti-inflammatory response and potential development of secondary infections of necrotic tissue, that can result in sepsis and late MODS.[41] Some of these patients may be required to be fed parenterally when attempts at enteral feeding have failed or been insufficient to meet their needs, particularly as gastrointestinal dysmotility is common in SAP, and so the parenteral route becomes the only option for macronutrient delivery.[41]

Lipid emulsions containing ω-3 fatty acids may have a role in the parenteral nutrition of patients with SAP owing to their anti-inflammatory, inflammation-resolving, and immunomodulatory characteristics. As an example, a small RCT involving 40 patients with SAP compared parenteral nutrition including 2 different lipid emulsions: pure soybean oil or soybean oil supplemented with fish oil.[42] The group given fish oil had a significantly higher blood EPA concentration ($P < .01$), lower CRP level ($P < .05$), and better oxygenation index ($P < .05$) after 5 days of parenteral nutrition. Furthermore, patients in the fish-oil group had fewer days of continuous renal replacement therapy than the control group ($P < .05$).[42] Overall, these results suggest that ω-3 fatty-acid enriched parenteral nutrition may attenuate the systemic response to pancreatic and organ injury in this group of patients. However, large-scale RCTs are still needed to prove whether or not this strategy can reduce organ failure and mortality rates associated with SAP.

Critically Ill Adult Patients: Practical Aspects

A number of practical aspects are worth considering when using lipid emulsions as part of parenteral nutrition, such

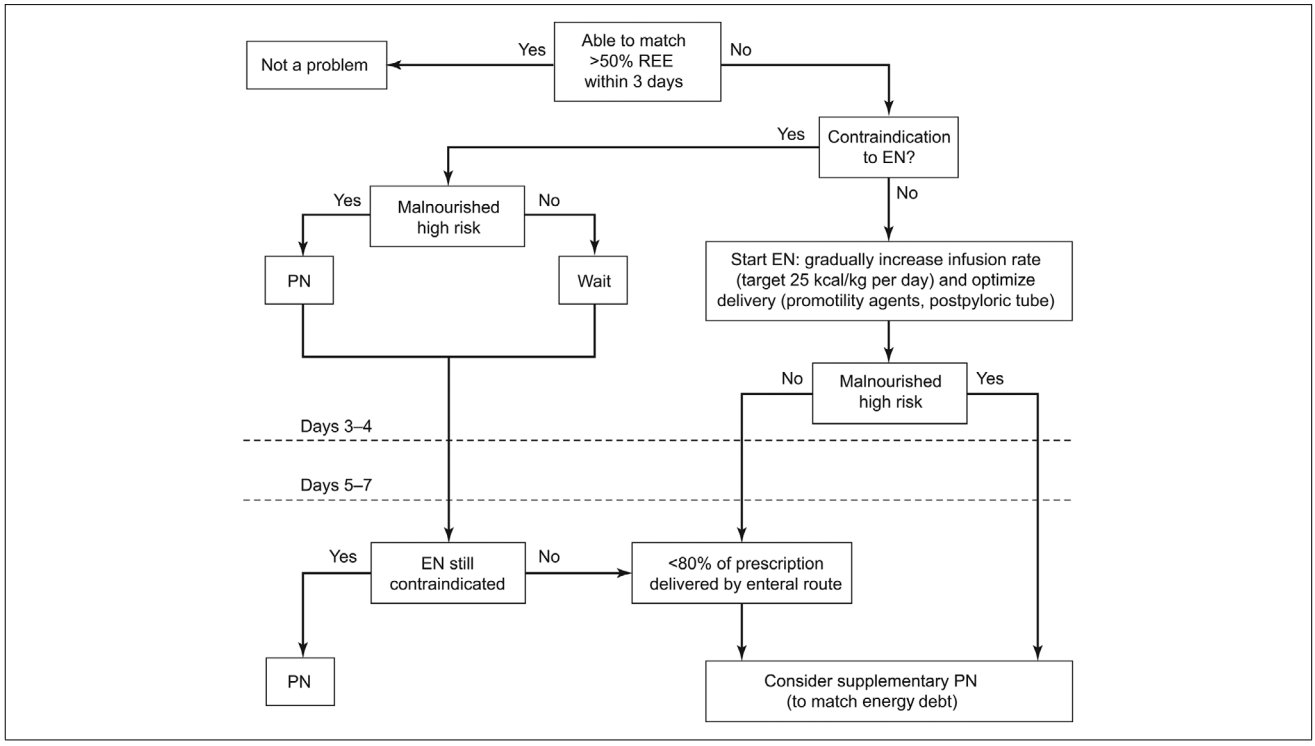

Figure 3. Algorithm for starting PN in severely ill patients. EN, enteral nutrition; PN, parenteral nutrition; REE, resting energy expenditure. Reproduced with permission from Weimann A, Singer P. Avoiding underfeeding in severely ill patients. *Lancet*. 2013;381(9880):1811.[46]

as the optimum duration of infusion, monitoring safety, how and when to consider parenteral nutrition, whether to consider parenteral nutrition as a supplement to enteral nutrition or alone, and how to determine/fulfill energy expenditure.

A randomized controlled crossover study compared slow (24 hours) and fast (6 hours) soybean oil intravenous lipid emulsion infusions alongside parenteral nutrition in patients with ARDS (n = 8) or severe sepsis (n = 10).[43] For patients with ARDS, the fast but not the slow infusion was associated with a significant deterioration in hemodynamics and the partial pressure arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio, potentially because of increased arachidonic acid derived prostaglandins and thromboxane synthesis.[43,44] Thus, in clinical practice, it seems preferable to give lipid emulsions over 12–24 hours as part of parenteral nutrition. This was also agreed as a consensus statement, which stated that if all-in-one admixtures are used, the preferable infusion duration is 24 hours (Table 1).[1]

Monitoring of clinical nutrition is required as it has become an important part of critical care, evolving from a support tool into a therapy that requires close attention and monitoring.[45] An ESPEN guideline group produced a consensus document that looked into what should be monitored, with particular attention toward triglycerides and energy delivery.[45] Hypertriglyceridemia in the ICU may be caused by sepsis, administration of propofol, lipid emulsions, or overfeeding. Thus, it is important to monitor triglycerides, with the ESPEN guideline group setting an upper limit of 500 mg/dL (5.6 mmol/L) for critically ill patients.[45] To some this limit might seem somewhat high. For example, the consensus at the current meeting was that serum triglyceride levels should be within the ranges recommended by local or regional guidelines, and in general, they should not exceed 400 mg/dL during infusion (Table 1).[1] The ESPEN guideline group also agreed that energy and substrate delivery should preferably be monitored using computerized systems in order to ensure the inclusion of energy from all routes and sources, including non-nutritional supplies such as propofol and citrate.[45]

How and when to consider using parenteral nutrition is also an area of concern. It is important that local institutions develop their own decision-making protocols that can perhaps be summarized as an algorithm. One example is shown in Figure 3.[46] Another topic to consider is the determination of energy expenditure. The use of indirect calorimetry for determining energy expenditure is highly recommended in the ESPEN guidelines for critically ill patients.[2] However, this is not always available, and in these instances the guidelines recommend calculating energy expenditure using oxygen consumption (VO_2) from

a pulmonary arterial catheter or carbon dioxide production (VCO_2) derived from the ventilator, and that these methods will give a better estimate of energy expenditure than predictive equations.[2] However, in the absence of indirect calorimetry, VO_2, or VCO_2 measurements, these guidelines recommend the use of simple weight-based equations (such as 20–25 kcal/kg/d), and that "the simplest option may be used."[2] It is clear that under- and overfeeding can both be harmful, and that the optimal energy supply is estimated to be between 70% and 100% of measured energy expenditure.[2,47] The SCCM/ASPEN nutrition guidelines for the ICU recommend using predictive equations when indirect calorimetry is not available.[16]

Conclusions

The use of lipid emulsions in hospitalized adult patients requiring parenteral nutrition continues to evolve: from the use of traditional lipid emulsions containing only soybean oil as a lipid source, to now moving to those containing multiple lipid components in many groups of patients. There is currently considerable interest in ω-3 fatty-acid enriched lipid emulsions and their comparison with other standard lipid emulsions without fish oil, and studies comparing these lipid emulsions are being published. The current globally represented expert consensus group and the ESPEN expert group hold the view that fish-oil enriched parenteral nutrition confers additional clinical benefits over other, particularly single-source, lipid emulsions.[9] The potential benefits include reductions in infection rates and length of hospital and ICU stay.[27] As discussed in this review, it is clear that such clinical benefits can extend over a wide range of patients, such as surgical, critically ill, and severe trauma patients, as well as those with acute pancreatitis. Moreover, some practical aspects of administering lipid emulsions are particularly important to consider. These include optimum duration of infusion, monitoring safety, as well as how and when to consider parenteral nutrition.

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Statement of Authorship

K. Mayer, S. Klek, A. Garcia-de-Lorenzo, M.D. Rosenthal, A. Li, D.C. Evans, M. Muscaritoli, and R.G. Martindale, equally contributed to the conception and design of the research; K. Mayer, S. Klek, A. Garcia-de-Lorenzo, M.D. Rosenthal, A. Li, D.C. Evans, M. Muscaritoli, and R.G. Martindale, contributed to the acquisition, analysis, and interpretation of the data; R. Clark drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Use of Lipids in Adult Patients Requiring Parenteral Nutrition in the Home Setting

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Abstract

It is estimated that over 25,000 Americans receive home parenteral nutrition (HPN), mostly because of intestinal failure (IF). Although there is significant variability in the fluid and energy needs of patients receiving HPN, intravenous lipid emulsions (ILEs) are an essential part of the macronutrient composition, serving as an excellent source of non-protein energy, as well as supplying essential fatty acids. However, the long-term use of ILEs in particular may be associated with some detrimental health effects, such as intestinal failure associated liver disease (IFALD). Although there is lack of unifying diagnosis, IFALD can present as cholestasis, steatosis, or fibrosis, with a prevalence that ranges between 5% and 43%. The development of IFALD tends to be multifactorial. Risk factors of IFALD can include those related to IF, inflammation/infection, and long-term parenteral nutrition. Some studies have shown a link between development of IFALD and ILE dose, especially if the dose is >1 g/kg/d, with high ω-6:ω-3 polyunsaturated fatty acid (PUFA) ratio and phytosterol content being theorized as some contributing factors. Thus, efforts have been made to use alternative oils (olive oil, medium-chain triglycerides, and fish oil) to reduce the soybean-oil content of ILE, which tends to be high in ω-6 PUFA and phytosterols. Although additional long-term clinical data are emerging, this strategy, as reviewed in the current manuscript, has shown to provide some benefit in both prevention and treatment of IFALD and other sequelae of HPN. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S39–S44)

Keywords

fatty acid; fish oil; home parenteral nutrition; intestinal failure; intestinal failure associated liver disease; intravenous lipid emulsion; omega-3; phytosterol; soybean oil

Introduction

This review is based upon presentations given at a meeting (Lipids in Parenteral Nutrition – International Summit, November 2–4, 2018, Miami, FL, USA). Statements from the consensus document that are most relevant to this article are shown in Table 1. Note: the full consensus document is also available as part of this supplement. These consensus

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Table 1. Consensus Statements From the International Summit Lipids in Parenteral Nutrition on November 2–4, 2018 (Miami, FL, USA), Relevant to This Article.

Statement Number	Consensus Statement	Expert Voting Results
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 receiving long-term PN (>6 months), soybean ILEs dose should not exceed 1.0 g lipids/kg/d 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).

EFA, essential fatty acid; IFALD, intestinal failure associated liver disease; ILE, intravenous lipid emulsion; PN, parenteral nutrition.

statements provide practical advice regarding the use of lipid emulsions in parenteral nutrition (PN) and, as such, complement formal nutrition society guidelines on this subject.

Prevalence of Home Parenteral Nutrition

Intestinal failure (IF) has been defined as a reduction in gut function below the minimal necessary for the absorption of macronutrients and/or water and electrolytes, requiring intravenous supplementation.[1] IF can be further subclassified based on functional classifications with type I (acute) patients typically receiving PN short-term in the hospital. Type II (prolonged acute) and type III (chronic) require PN over weeks to months or months to years, respectively, and typically receive PN at home. Given lack of active worldwide registries, it is difficult to know how many patients receive home parenteral nutrition (HPN), and the prevalence of HPN is likely to be underreported. Published prevalences vary widely based on country or region of residence. In the United States, a recent study utilized data from Medicare combined with insurance provider data from 3 of the largest infusion providers to estimate that over 25,000 Americans (79 per million) were receiving HPN in 2013.[2] This was a significant reduction from an analysis published in 1995 that reported 40,000 Americans (157 per million) were receiving HPN.[3] Registry-based data from countries in Europe have shown lower prevalence of HPN. The British Artificial Nutrition Survey from 2005 noted HPN prevalence in adults of 11.1 per million for England, 14.6 per million for Scotland, 5.4 per million for Ireland, and 5.4 per million for Wales.[4] Similarly, data from the Italian Society for Parenteral and Enteral Nutrition showed an HPN prevalence of 25.6 per million.[5] Other countries in Europe have reported HPN prevalence of 0.65–12.7 for adults and 0.34–8.92 in pediatric populations.[6,7] The period prevalence of HPN across 16 European countries has also been reported as an extremely wide range (3.25–66 patients per million).[8]

Essential Fatty-Acid Deficiency

Within the HPN population there can be wide variability in terms of fluid and energy needs depending on the etiology of IF. Despite this variability, experts in the field of nutrition and guidelines from major nutrition societies tend to agree that intravenous lipid emulsions (ILEs) are an integral part of PN.[1,9-11] Most recent guidelines on chronic IF (CIF) recommend that patients totally dependent on HPN should receive a minimum of 1 g/kg/wk of ILE containing essential fatty acids (EFAs) in order to prevent EFA deficiency (EFAD).[9] Linoleic acid (18:2ω-6) and α-linolenic acid (18:3ω-3) cannot be synthesized by humans and play key roles, such as in cellular signaling and the structural stability of membranes.[12] In the era of ILE-free PN in the United States, a number of patients developed EFAD, which tended to present biochemically with elevations of mead acid (20:3ω-9), a triene/tetraene ratio >0.4, and a fall in linoleic and α-linolenic acid levels. The triene/tetraene ratio refers to the mead acid:arachidonic acid ratio. Typically, 18-carbon fatty acids are metabolized by elongase and desaturase enzymes, which tend to prefer ω-3 and ω-6 fatty acids to ω-9.[13] However, in the absence of EFAs, oleic acid (18:1ω-9) is metabolized by these enzymes to mead acid, thus increasing this ratio. These biochemical changes were noted after only 2 weeks of ILE-free PN in infants and up to 4 weeks in adults.[14-16]

Clinical manifestations typically occur after 2–6 months of ILE-free PN and include scaly and dry skin, hair loss, and abnormal liver function tests. Long-term sequelae of EFAD included reduced growth, hair loss, dermatitis, liver dysfunction, neurological manifestations, and increased susceptibility to infections.[17,18] EFAs are synthesized in plants, and typically plant seeds or seed oils such as soybean oil (SO) tend to be an excellent source. In patients with EFAD, most required 1.2–2.4 g/kg of ILE twice weekly to normalize EFA levels.[19]

Intestinal Failure Associated Liver Disease

Unfortunately, despite the benefit of being an excellent source of EFA and non-protein energy, SO ILE can also be associated with detrimental health effects such as intestinal failure associated liver disease (IFALD). The most frequently used definition of IFALD was created by Cavicchi et al.[20] According to this group of authors, IFALD is a liver injury due to factors related to IF and/or to PN and no other evident cause.[20] It is difficult to describe the prevalence of IFALD because there is no single, unified definition.[21,22] Presentation of IFALD can include cholestasis, cholelithiasis, hepatic steatosis, and hepatic fibrosis. Although rare, IFALD can progress to liver cirrhosis and failure, especially in neonates and children. Cavicchi et al prospectively followed 90 consecutive patients receiving HPN and noted that 58 (65%) developed chronic cholestasis after a median of 6 months and 37 (41%) developed "complicated HPN-related liver disease" after a median of 17 months.[20] Multivariate analysis revealed that both cholestasis and IFALD were associated with ILE dose >1 g/kg/d. Other studies have noted that IFALD can occur in 30%–60% of children and 15%–40% of adults requiring long-term HPN.[23-25]

Risk factors of IFALD can be divided into those related to IF, inflammation/infection, and long-term PN. One of the factors attributed to the correlation between SO ILE and IFALD is the fact that SO has a high ratio of ω-6:ω-3 polyunsaturated fatty acid (PUFA). Metabolism of ω-6 PUFA (linoleic acid) gives rise to arachidonic acid and inflammatory eicosanoids (2-series prostaglandins and thromboxanes as well as 4-series leukotrienes).[12] Metabolism of ω-3 PUFA, on the other hand, tends to generate eicosapentaenoic acid (EPA) and less inflammatory 3-series prostaglandins and thromboxanes as well as 5-series leukotrienes.[12,26] Additionally, EPA and docosahexaenoic acid (DHA) may give rise to E-series and D-series resolvins that dampen acute leukocyte responses and facilitate resolution of inflammation.[27,28]

IFALD has also been linked with the relatively high phytosterol content of SO ILE.[29-31] Clinical evidence is very limited, and results on the correlation between phytosterols and cholestasis are controversial. There is evidence that reduced enterohepatic circulation of bile acids in short-bowel syndrome (SBS) and increased levels of phytosterols, which are contained in many parenteral lipid emulsions, might increase the risk of cholestasis in pediatric patients or patients receiving long-term PN.[30,32,33] Over time, the phytosterol content in ILE can exceed the body's capacity for disposal via biliary secretion and loss from skin and gut mucosa, leading to increased phytosterol content of plasma lipoproteins and cell membranes—especially in children. This affects membrane-bound transporters and membrane fluidity, and also inhibits cholesterol 7α-hydroxylase, reducing bile-acid synthesis.[29] The combination of lower bile-acid content and higher levels of phytosterols, which are less soluble than bile acids, leads to decreased bile flow and sludge.

Phytosterol level elevation in plasma is highly variable between patients, and some might be more susceptible to develop IFALD than others. Clayton et al noted that children with IFALD had marked elevations in plasma phytosterol concentrations and phytosterols comprised approximately 25% of total plasma sterols instead of <2.5% seen normally.[29] They further revealed that a reduction in weekly ILE dose resulted in a fall in plasma phytosterol concentration and improvement in liver function studies in 2 patients. Llop et al explored this correlation in adults and noted that plasma phytosterol concentrations in HPN patients with SBS tended to be higher than non-HPN controls, and that patients with the highest plasma phytosterol concentrations tended to present with liver dysfunction.[30] In this cohort, linear regression showed a correlation between total phytosterol levels and liver function tests, which was strongest for total bilirubin and aspartate aminotransferase. Another cohort of 24 adult patients with SBS also noted higher phytosterol levels in patients receiving PN, as well as a correlation between phytosterol levels and alkaline phosphatase levels that was limited in significance, possibly owing to a small sample size.[31] Furthermore, among children with IF, parenteral phytosterols tend to accumulate in the liver, reflecting their increased serum levels, and are associated with biochemical liver injury, portal inflammation, and liver fibrosis.[34]

A number of strategies, including use of cyclic PN, avoidance of hepatotoxic agents, and avoidance and timely management of sepsis, are employed to prevent or minimize the risk of developing IFALD.[9,21] One additional strategy has been to minimize the dose of ILE, especially SO ILE. Overall, ILE should amount for 15%–30% of total energy supplied and approximately 30%–50% of non-protein energy.[9] In patients receiving long-term HPN, the current recommendation is that the SO ILE should not exceed 1 g/kg/d in order to prevent liver complications associated with PN.[9,20]

Once IFALD develops, strategies including avoidance of overfeeding, reduction of SO ILE to <1 g/kg/d, and a reduction of ω-6/ω-3 PUFA ratio should be implemented.[21]

At times, this strategy is implemented in our practice and in many other centers in the United States by reducing the SO ILE frequency to <3 times per week. However, as the ILE component of PN is reduced, a higher percentage of non-protein energy is derived from dextrose, a strategy that can have its own detrimental effects. This dilemma is highlighted nicely by the recently published case of a 32-year-old male with CIF owing to a history of intestinal dysmotility and pseudo-obstruction, who subsequently developed IFALD.[35] Initially, after development of IFALD, his SO ILE was reduced from 50 g provided 3 times per week to 50 g once every 2 weeks. With this change, in order to maintain body weight, his daily dextrose dose was increased to >500 g/d, leading to elevations in insulin levels and pancreatitis. Similar sequelae of high-dextrose PN were reported previously by Meguid et al in a study that randomized 88 patients admitted to surgical wards to either ILE-free PN or PN in which 33% of dextrose energy was replaced by an ILE.[36] They noted that in patients who did not undergo surgery, insulin levels increased by 300% in the ILE-free PN group compared with 130% in the ILE-containing group.

Another strategy to prevent or decrease these potential negative sequelae of HPN has been to reduce the amount of SO in ILE through the use of alternative sources, such as medium-chain triglycerides (MCTs), olive oil (OO), and fish oil (FO). Although alternative ILEs have been available worldwide for many years, in the United States, the predominant ILE has been SO ILE until the 2016 approval and availability of mixed-oil (MO) ILE in 2016. As opposed to older generations of ILEs, such as a 50:50 combination of MCT:SO ILE or 80:20 combination of OO:SO, MO ILE available in the United States uses a mixture of 4 oils (30% SO, 30% MCT, 25% OO, and 15% FO) in order to improve the ω-6 to ω-3 fatty-acid ratio and decrease phytosterol content.

Clinical Data

Although there is a lack of data from larger long-term randomized controlled trials (RCTs) within the HPN population, published clinical data does highlight some benefits to using MO ILE. Klek et al randomized 73 patients with CIF to either MO ILE or SO ILE for 4 weeks.[37] They targeted 1–2 g/kg/d of ILE and noted that mean intake was similar in both groups (approximately 1.3 g/kg/d). The authors noted that there was a slight increase in alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin in the SO ILE group, whereas the MO ILE group experienced a significant decline in all 3 of these parameters. In a follow-up study, Klek et al randomized 88 CIF patients to 1 of 4 available ILEs (MCT/SO, OO/SO, MO, and SO), and patients were followed up for over a year.[38] At the time of analysis, 23 patients were lost to follow-up (4 in MCT/SO, 5 in OO/SO, 6 in MO, and 8 in SO ILE groups). With long-term follow-up, they noted that liver function tests tended to stabilize and improve in all 4 groups, with no significant differences.

Instead of starting with adult patients who are newer to HPN, another beneficial approach has been to use MO ILE in patients who may have developed intolerance to SO ILE, such as those with liver abnormalities.[35,39,40] This was the approach taken in the case study of a patient with IFALD, as discussed previously.[35] After development of IFALD, reduction in ILE dose and corresponding increase in dextrose dose was complicated by development of pancreatitis. Attempts were made to increase oral intake and provide enteral nutrition support, but without success. Pure FO ILE was also attempted, but as this required a separate pump for infusion due to lack of compatibility data, he reported that he was not able to sleep well and developed chronic fatigue. After MO ILE was available in the United States, we were able to add to his PN as a 3:1 admixture utilizing the same pump, and the patient was slowly transitioned up to a dose of 70 g/d, 7 d/wk. With this increase, his weight rebounded and his total bilirubin decreased from 2.4 to 0.8 mg/dL after the first month, and his AST and ALT levels normalized.[35]

Another manuscript described a similar approach in 64 SO ILE intolerant patients.[40] Out of the 64, 17 patients had used MO ILE for >12 months at the time of analysis and were described in detail. These patients were noted to be intolerant of SO ILE, and at the time of transition to MO ILE, they were receiving 66% ± 8% of total energy on average from dextrose and just 8% ± 8% of energy from SO ILE. After 12 months of MO ILE, the mean proportion of energy from ILE was increased to 22% ± 8%, whereas energy from dextrose was reduced to 54% ± 5%. Even though energy from the ILE was increased, these patients experienced a significant decrease in median AST (55–39 U/L), ALT (66–52 U/L), and total bilirubin (1.1–0.6 mg/dL).

α-Tocopherol

In addition to impact in liver function tests (LFTs), MO ILE use also tends to result in significantly higher α-tocopherol levels.[37] α-tocopherol is an isoform of vitamin E, which can also occur as other isoforms (β-, γ-, and δ-) depending on the number and position of the methyl groups attached to the chromanol ring.[41] As opposed to the other isoforms, α-tocopherol is the most biologically active and typically found in the highest concentration in human tissues. FO-based ILEs tend to have higher α-tocopherol levels (approximately 200 mg/L) than other lipid emulsions, including pure soybean lipid emulsions (approximately 38 mg/L),[42] leading to higher plasma concentrations compared with SO ILE.[13] α-tocopherol is an antioxidant that is capable of scavenging free radicals that form owing to peroxidation of lipids such as PUFA. This antioxidant capability may be a possible

mechanism for benefit in terms of liver function, given that free radicals can result in cell damage and death.[43] Similar increases were noted in long-term HPN patients switching from SO ILE to MO ILE.[40]

Conclusions

Overall, ILEs remain an integral part of PN for patients with CIF and are an excellent source of non-protein energy and EFAs. In most HPN patients, especially those with no oral intake, a minimum dose of ILE should be given to prevent development of EFAD. However, this dose should not exceed 1 g/kg/d if SO ILEs are utilized in long-term HPN patients owing to concerns over development of complications such as IFALD. Although larger RCTs are needed in HPN patients, clinical data are emerging that suggest risk of developing IFALD may be reduced with use of MO ILEs. Additionally, patients who develop liver abnormalities while receiving SO ILE may better tolerate MO ILE, allowing for less reliance on dextrose as a source of non-protein energy. Certainly, as more data become available and larger RCTs are conducted, the availability of FO-containing ILEs may allow for a paradigm shift in the approach to macronutrient composition of PN, as well as the prevention and management of complications such as IFALD.

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Statement of Authorship

All authors equally contributed to the conception and design of the research; all authors contributed to the acquisition, analysis, and interpretation of the data; M. S. Mundi drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Use of Lipids in Neonates Requiring Parenteral Nutrition

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Abstract

Neonates have limited antioxidative capacity and are at increased risk of infection and inflammation—a situation that is exacerbated in preterm neonates. Together, oxidative stress and inflammation are implicated in many serious conditions affecting neonates, such as bronchopulmonary dysplasia and periventricular leukomalacia. Neonates requiring parenteral nutrition have certain nutritional requirements. For example, very long-chain ω-3 polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are regarded as conditionally essential with critical roles during early retinal and brain development, and may also have other benefits such as anti-inflammatory effects. Because of these factors, the choice of lipid emulsion used as part of parenteral nutrition support may influence clinical outcomes in neonates. There are concerns that lipid emulsions based purely on soybean oil may increase lipid peroxidation, oxidative stress, and inflammation because of their high ω-6 PUFA and low ω-3 PUFA concentrations. Composite fish-oil containing lipid emulsions may provide advantages for neonates owing to their high DHA and EPA content and high antioxidant (α-tocopherol) levels. Here, we discuss clinical trials of lipid emulsions in preterm and term neonatal populations, with a particular emphasis on markers of oxidative stress and DHA and EPA levels. Olive oil/soybean oil lipid emulsions have shown few advantages in neonates over other lipid emulsions. However, compared with either pure soybean or soybean/olive-oil based emulsions, composite fish-oil containing lipid emulsions reduce oxidative stress/lipid peroxidation and also increase DHA and EPA levels. These advantages may translate into clinical benefits for neonates requiring parenteral nutrition. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S45–S54)

Keywords

fish oil; inflammation; lipids; neonate: oxidative stress; omega-3; omega-6; parenteral nutrition; pediatric; soybean oil

Introduction

This manuscript is based on presentations and discussions among the experts at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al[1] that are most relevant to this article are shown in Table 1. Note: the full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the use of lipid emulsions

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Table 1. Consensus Statements From the International Summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA), Relevant to This Article.[1]

Statement Number	Consensus Statement	Expert Voting Results
29	In pediatric patients requiring PN, ILEs are an integral part of PN.	100% agreement (14 agree, 0 do not agree, and 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: 1 g/kg/d, day 2: 2 g/kg/d, day 3 onwards: 3 g/kg/d. • infants, children and pre-adolescent patients: up to 3 g/kg/d.	76% agreement (13 agree, 0 do not agree, and 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 essential LC-PUFAs (eg, DHA), which are critical in neonatal neurodevelopment and vision • anti-inflammatory effects due to the ω-3 PUFA content • a well-balanced ω-6:ω-3 ratio • provision of medium-chain fatty acids.	100% agreement (16 agree, 0 do not agree, and 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 GGT) routinely (in hospital: weekly and HPN: at least every 3 months) • fatty-acid profiles should be determined if there is a specific clinical, question, eg, patients on fish-oil rescue therapy.	100% agreement (16 agree, 0 do not agree, and 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, and 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, and 0 do not wish to answer).
35	Data from clinical cohort studies and clinical experience indicate that cholestasis can be reversed by using fish-oil containing lipid emulsions together with the management of other risk factors, especially catheter-related or SIBO-related infections.	100% agreement (15 agree, 0 do not agree, and 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, and 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 fish-oil containing ILEs, he/she should receive fish-oil composite ILEs as a first-line of treatment. If conjugated or direct bilirubin continues to rise above 2 mg/dL, pure fish-oil emulsion is recommended until resolution.	100% agreement (16 agree, 0 do not agree, and 0 do not wish to answer).

ALT, alanine transaminase; AST, aspartate aminotransferase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GGT, gamma-glutamyl transferase; HPN, home parenteral nutrition; IFALD, intestinal failure–associated liver disease; ILE, intravenous lipid emulsion; LC-PUFA, long-chain polyunsaturated fatty acid; PN, parenteral nutrition; SIBO, small-intestine bacterial overgrowth.

in parenteral nutrition and, as such, complement formal nutrition society guidelines on this subject.

Lipid emulsions are recommended as an integral part of parenteral nutrition for pediatric patients, either exclusively or complementary to enteral feeding, and lipid emulsions can be started immediately after birth in preterm infants requiring parenteral nutrition.[2] Lipid emulsions can provide a concentrated source of non-carbohydrate energy, essential fatty acids (EFAs; linoleic acid and **α**-linolenic acid), and very long-chain polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In fact, sufficient lipids should be given to provide about 25%–50% of total non-protein energy requirements.[2]

Various lipid emulsions are available for use as part of parenteral nutrition. These include conventional lipid emulsions consisting of pure soybean oil, mixed lipid emulsions consisting of soybean oil plus medium-chain triglycerides (MCTs) and/or olive oil, and most recently, SMOFlipid

(Fresenius Kabi, Germany), a multicomponent intravenous lipid emulsion containing 30% soybean oil, 30% MCTs, 25% olive oil, and 15% fish oil (henceforward referred to as "SMOF"). Another lipid emulsion containing fish oil (10%), soybean oil (40%), and MCT (50%) (Lipidem/Lipoplus; B Braun, Germany) is also available. Omission of lipid emulsions from parenteral nutrition results can result in EFA deficiency (EFAD) within a few days in infants.[2,3] To prevent EFAD in preterm and term infants, a minimum linoleic acid intake of 0.25 and 0.1 g/kg/d, respectively, should be given, which also supplies adequate quantities of **α**-linolenic acid.[2] Soybean oil is a particularly rich source of the essential ω-6 PUFA linoleic acid, which accounts for about 50% of the fatty acids present.[4] However, soybean oil does not contain any very long-chain ω-3 PUFAs (DHA or EPA).[5] This is particularly important because these are regarded as conditionally essential in this age group and have critical roles during early retinal and brain development.[2,6] Concerns developed that soybean-based lipid emulsions could promote inflammation and suppress immune function, perhaps because of their high ω-6 PUFA and low ω-3 PUFA concentrations.[4,7,8] Therefore, subsequent generations of lipid emulsions have introduced combinations of various lipid components, predominantly with the aim of improving the safety profile and reducing soybean oil content.

Although lipid emulsions containing soybean oil as the sole lipid source are still commonly used, many neonatal units around the world, including Australian units, have switched to using modern olive-oil based or composite lipid emulsions.[9] One of the alternatives to pure soybean lipid emulsions is a lipid emulsion composed of 80% olive oil and 20% soybean oil (ClinOleic, Baxter S.A., Lessines, Belgium), which is rich in the monounsaturated fatty acid (MUFA) oleic acid and has a reduced ω-6 PUFA content, but does not contain DHA or EPA.[4,10] SMOF contains olive oil and MCT to help reduce ω-6 PUFA content, and fish oil to provide the very long-chain ω-3 PUFAs, DHA and EPA. SMOF also contains approximately 200 µg/mL of α-tocopherol (vitamin E), which is a considerably higher level than that found in other lipid emulsions such as ClinOleic (≈30 µg/mL) or pure soybean lipid emulsions (≈15 µg/mL), which may help to reduce oxidative stress and lipid peroxidation.[5,9,11]

There is growing interest in lipid emulsions containing fish oil, as this is rich in very long-chain ω-3 PUFAs (DHA and EPA) associated with potential anti-inflammatory and immunomodulatory benefits.[12-15] Differential effects on inflammatory processes by ω-6 and ω-3 fatty acids are mediated via modification of eicosanoid production and by directly or indirectly modifying intracellular signal transduction pathways, including the alteration of gene transcription.[14,16,17] Moreover, EPA and DHA are direct precursors of specialized pro-resolving mediators (SPMs), a new class of lipid mediators including 3 major families: resolvins, protectins, and maresins.[17] In many animal disease models, SPMs have been shown to control the duration and magnitude of inflammation and accelerate the return to tissue homeostasis after infection.[18,19]

Lipid Emulsions in the Parenteral Nutrition of Neonates

Parenteral nutrition is widely used in preterm neonates in the initial period after birth, providing a relatively safe means of preventing nutrient deficits.[20] Even short periods of inadequate nutrition and reduced growth at this age may have profound effects, such as poor neurodevelopmental outcomes, and provision of adequate parenteral nutrition during the first weeks of life may limit these negative consequences.[21] Thus, parenteral nutrition is now considered "standard of care" for most very low birth weight preterm infants over the first few postnatal days.[20] Meta-analyses have shown outcome benefits for the inclusion of fish oil as part of parenteral nutrition, as it significantly reduces the likelihood of severe retinopathy of prematurity (ROP) in preterm neonates,[22] and was significantly more likely to reverse parenteral nutrition associated cholestasis in neonates than other lipid emulsions that did not contain fish oil.[23] Furthermore, a recent clinical trial has shown that neonates given parenteral nutrition including a fish-oil containing lipid emulsion (SMOF) were significantly less likely to have severe bronchopulmonary dysplasia and had a shorter mean duration of non-invasive ventilation than those given an olive oil/soybean oil lipid emulsion.[24] However, it is important to note that not all studies have shown additional clinical outcome benefits regarding the inclusion of fish oil, but given the short duration of many studies this is not particularly surprising.

Neonates are also particularly vulnerable to oxidative stress owing to their limited antioxidative capacity, and suffer from an increased likelihood of infections and inflammation—a situation that is exacerbated in preterm neonates.[25,26] Together, oxidative stress and inflammation are implicated in many serious conditions affecting this age group (Fig. 1).[26] As such, the use of soybean oil as the sole lipid source in parenteral nutrition may be a particular concern in preterm neonates, as soybean oil is rich in ω-6 PUFAs such as linoleic acid and typically has a relatively low antioxidant content, and so can potentially increase lipid peroxidation, oxidative stress, and inflammation.[2] Thus, lipid emulsions with lower ω-6 PUFA content and including very long-chain ω-3 PUFAs from fish oil (DHA and EPA) could be beneficial for neonates. DHA and EPA supplies are also regarded as conditionally essential in preterm neonates, and deficits of DHA have been observed in smaller preterm infants who were given lipid emulsions not containing fish oil.[2,27] In order to avoid the potential adverse effects of

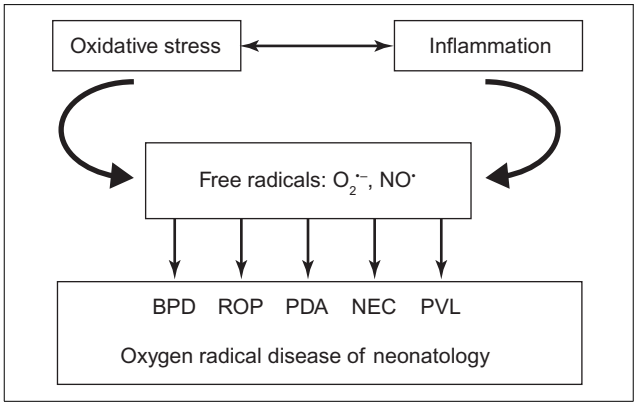

Figure 1. A schematic presentation of the relationship between oxidative stress, inflammation, and diseases of neonatology. BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity. Figure reproduced with permission from Saugstad OD. Oxidative stress in the newborn—a 30-year perspective. *Biol Neonate.* 2005;88(3):228-236.[26] Copyright © 2005, Karger Publishers, Basel, Switzerland.

pure soybean oil emulsions it would seem sensible to use lipid emulsions with reduced ω-6 PUFA content, inclusion fish oil to provide DHA and EPA, and enriched in the potent antioxidant α-tocopherol (vitamin E) to help reduce oxidative stress/lipid peroxidation.

Although evidence from clinical trials is still limited, in the remainder of this article we look at evidence from randomized controlled trials, particularly concerning the prevention of oxidative stress in preterm and near-term neonates, assessing various lipid emulsions (pure soybean emulsions, olive oil/soybean emulsion, and composite lipid emulsions containing fish oil), all given as part of parenteral nutrition.

Clinical Trials in Neonates

Olive Oil/Soybean Oil vs Pure Soybean Lipid Emulsions: Lipid Peroxidation/Oxidative Stress

As mentioned previously, reduction in oxidative stress is a key issue in neonates requiring parenteral nutrition. It has been proposed that lipid emulsions such as olive oil, that are high in MUFA, may be at lower risk of lipid peroxidation than lipids high in PUFA such as soybean oil.[10] Moreover, olive oil/soybean oil lipid emulsions such as ClinOleic have higher α-tocopherol levels than pure soybean lipid emulsions and are well tolerated in neonates.[6] There were no significant differences in markers of oxidative stress for olive oil/soybean oil lipid emulsions compared with soybean oil (Table 2).[11,28-32] These results are reasonably consistent across studies, whether using plasma F_2-isoprostane levels,[30] urinary malondialdehyde (MDA) excretion,[28] or exhaled pentane[29] as oxidative stress markers. Similarly, few trials in neonates have shown significant benefits in neonates for olive oil/soybean oil lipid emulsions compared with soybean oil for other parameters such as inflammation, immune function, infections, plasma cholesterol, triglycerides, or markers of liver function.[10]

Deshpande et al performed a double-blind randomized controlled trial conducted in very preterm neonates (between 23 and <28 weeks' gestation).[11] This assessed 5 days' parenteral nutrition with a lipid emulsion containing 80% olive oil and 20% soybean oil vs a pure soybean oil emulsion. The rationale for this study was that the olive oil might benefit preterm neonates by reducing oxidative injury. Plasma F_2-isoprostane levels were used as a marker of in vivo oxidative stress and lipid peroxidation, and are considered the "gold-standard" biomarker for this parameter.[33,34] Forty-four of 50 randomized participants completed the study. There were no significant differences between groups in total energy intake or proportion of enteral and parenteral administration. Both emulsions were well tolerated, and there were no significant differences between the groups in terms of safety/laboratory parameters. Alanine transaminase (ALT) and gamma-glutamyl transferase (GGT) were within normal ranges and not significantly different between groups, and there was no significant difference between full blood counts, including platelet count, or C-reactive protein (CRP) between groups. Levels of long-chain PUFA such as DHA and arachidonic acid (ARA) in plasma and red blood cell (RBC) membranes were similar for the 2 groups, despite the lower PUFA content of the olive oil emulsion. F_2-isoprostane levels were high at baseline (4323.4 vs 4240.5 pmol/L for the olive oil and soybean oil groups, respectively), indicating extreme oxidative stress in the immediate postnatal period. While F_2-isoprostane levels decreased significantly in both groups by the end of the study, there was no significant difference between the olive oil and soybean oil groups (3238.2 vs 3322.8 pmol/L, respectively; $P = .743$)—despite the olive oil lipid emulsion containing about double the α-tocopherol concentration of the pure soybean lipid emulsion (30.3 vs 14.5 μg/mL, respectively).[11]

The study by Deshpande et al (2009)[11] complements the results of 2 other trials performed in somewhat different neonatal populations.[28,30] Goebel et al[28] investigated 7 days' parenteral nutrition containing either soybean oil or 80% olive oil/20% soybean oil lipid emulsions in larger preterm neonates (n = 45; 28–<37 weeks). They found that the plasma α-tocopherol:total lipid ratio was higher in the olive oil/soybean oil group than those given soybean oil only (2.45 ± 0.27 vs 1.90 ± 0.08 μmol/mmol, respectively; $P < .001$), which may indicate a better antioxidant status with the olive oil emulsion. However, this failed to translate into a significant difference in oxidative stress (urinary MDA excretion) between groups. The trial by Webb et al[30] included 80 preterm and term neonates (≥25 weeks'

Table 2. Randomized Controlled Trials of PN Including Olive Oil/Soybean Oil Lipid Emulsions Compared With Soybean Oil Alone or Soybean Oil/MCT Lipid Emulsions in Neonates: Peroxidation/Oxidative Stress.[11,28-32]

Study	Gestational Age, Number (n) Randomized	Lipid Emulsions Given	Duration of PN	Outcomes
Gobel et al, 2003	28–<37 wk, n = 45	OO/SO or SO	7 d	No significant difference between groups in urinary MDA excretion.
Pitkanen et al, 2004	28–≤33 wk, n = 13	OO/SO or SO/MCT	2 d	Significant increases in exhaled pentane for both groups from baseline. There was no significant difference between groups in exhaled pentane.
Webb et al, 2008	≥25 wk–7 d old, n = 80	OO/SO or SO	5 d	No significant difference in F_2-isoprostane levels between groups.
Deshpande et al, 2009	23–<28 wk, n = 50	OO/SO or SO	5 d	No significant difference in F_2-isoprostane levels between groups.
Roggero et al, 2010	28–33 wk, n = 36	OO/SO or SO/MCT or SO	7 d	No significant differences in F_2-isoprostane or TRAP levels between groups.
Koksal et al, 2011	≤34 wk, n = 64	OO/SO or SO	7 d	No significant difference in TAC levels between groups. There was a significantly lower incidence of BPD in the OO/SO group ($P = .02$).

BPD, bronchopulmonary dysplasia; MCT, medium-chain triglyceride; MDA, malondialdehyde; OO/SO, olive oil–soybean oil lipid emulsion (ClinOleic); PN, parenteral nutrition; SO, soybean oil lipid emulsion; TAC, total antioxidant capacity; TRAP, total radical-trapping antioxidant potential.

gestation –7 days old) randomized to receive 5 days' parenteral nutrition containing either soybean oil or 80% olive oil/20% soybean oil lipid emulsions. Again, there was no significant difference between groups in terms of oxidative stress (as measured by F_2-isoprostane levels), but the olive oil/soybean oil group had higher levels of plasma phospholipid oleic acid and reduced levels of plasma phospholipid linoleic acid compared with the soybean oil group. There were no significant differences between groups in total energy intake, routine biochemical and hematologic parameters, including liver enzymes. Thus, none of these studies have shown marked differences between olive oil/soybean oil lipid emulsions and those containing soybean oil as the sole lipid source.

Composite Lipid Emulsions Containing Fish Oil vs Olive Oil/Soybean Oil or Soybean Oil: Lipid Peroxidation/Oxidative Stress and DHA/EPA Levels

A number of clinical trials have been performed to compare lipid peroxidation/oxidative stress and/or DHA/EPA levels for parenteral nutrition with a composite lipid emulsion containing fish oil (ie, SMOF) with other lipid emulsions (olive oil/soybean oil or soybean oil alone; Table 3).[9,24,35-43] These trials all show that neonates given composite lipid emulsions containing fish oil experience beneficial modulation of their fatty-acid profiles and/or reduced oxidative stress/lipid peroxidation than when given other lipid emulsions. Clinical trials have shown that neonates given composite lipid emulsions containing fish oil vs olive oil/soybean or soybean oil alone have greater increases in DHA and EPA levels,[35,36,38-41] or just EPA levels,[9] and beneficial changes in ω-3:ω-6 ratio.[36,38,40] Furthermore, trials in neonates investigating oxidative stress/lipid peroxidation have also shown significant and potentially beneficial reductions for composite lipid emulsions containing fish oil compared with other lipid emulsions, using a variety of methods,[9,24,35,37,42,43] with only 1 trial failing to show a significant difference in this parameter.[36] Administration of composite lipid emulsions containing fish oil has also been associated with higher vitamin E/**α**-tocopherol levels compared with other lipid emulsions.[9,37,40]

Deshpande et al conducted a double-blind randomized controlled trial comparing a composite lipid emulsion containing fish oil (SMOF) with an 80% olive oil/20%

Table 3. Randomized Controlled Trials of PN Including a Composite Lipid Emulsion Containing Fish Oil Compared With Other Lipid Emulsions Such as Olive Oil/Soybean Oil or Soybean Oil Alone in Neonates: Peroxidation/Oxidative Stress, DHA and EPA Levels, and Clinical Outcomes.[9,24,35-43]

Study	Gestational Age, Number (n) Randomized	Lipid Emulsions Given	Duration of PN	Outcomes
Tomsits et al, 2010	≤34 wk, n = 60	SMOF or SO	≥7 d but ≤14 d	Significantly higher EPA and **α**-tocopherol but not DHA concentrations for SMOF vs SO. The *ω*-3:*ω*-6 ratio also increased significantly for SMOF vs SO. Both groups had similar lipid peroxidation as measured by plasma MDA levels and similar increases in body weight.
Skouroliakou et al, 2010	<34 wk (<1500 g), n = 38	SMOF or SO	≥7 d	Significantly higher TAP for SMOF vs SO. Vitamin E levels increased significantly from baseline in the SMOF group but not the SO group. No significant differences between groups in growth or clinical outcomes.
Rayyan et al, 2012	<34 wk, n = 53	SMOF or SO	≥7 d but ≤14 d	Significantly higher DHA and EPA levels for SMOF vs SO. The *ω*-6:*ω*-3 ratio also decreased significantly for SMOF vs SO. Growth parameters were similar between groups.
Deshpande et al, 2013	>34 wk, n = 46	SMOF or OO/SO	7 d	Significant reduction in F_2-isoprostane for SMOF vs OO/SO and significant increases in DHA and EPA levels (in RBC and plasma) vs OO/SO.
Vlaardingerbroek et al, 2014	VLBW (<1500 g) preterm infants, n = 96	SMOF or SO	Until receiving full EN	Significantly higher EPA and DHA concentrations for SMOF vs SO. By discharge, the SMOF group had significantly greater weight gain, increase in weight *z*-score, and increase in head circumference *z*-score, than those given SO. Clinical outcomes and mortality rates did not differ significantly between groups.
Deshpande et al, 2014	23–30 wk, n = 34	SMOF or OO/SO	7 d	Significant reduction in F_2-isoprostane, significant increases in (RBC) EPA levels, and significantly greater increase in **α**-tocopherol level for SMOF vs OO/SO. There were no significant differences in clinical outcomes or growth parameters between groups.
Skouroliakou et al, 2016	26–32 wk, n = 60	SMOF or SO	≥15 d	The SMOF group had significantly higher **α**-tocopherol, DHA, and EPA levels, lower linolenic acid level, and a lower *ω*-6:*ω*-3 ratio compared with the SO group. There were no significant differences between groups in growth or morbidity.
Najm et al, 2017	<28 wk, n = 90	SMOF or OO/SO	Up to 92 d	The SMOF group had significantly higher EPA and DHA levels at postnatal days 7, 14, and 28 and PMA 32 wk compared with the OO/SO group. The SMOF group had a decreased ARA:DHA ratio from 1 wk after birth up to PMA 32 wk compared with the OO/SO group. There were no significant differences between groups in growth or morbidity.
Unal et al, 2018[a]	25–32 wk, n = 227	SMOF or OO/SO	7 d (median)	TAC was significantly higher in the SMOF group (day 7) than the OO/SO group. There were no significant differences in morbidity rates between the groups. However, there were (statistically insignificant) lower rates of ROP (9.4% vs 11.7%) and chronic lung disease (4.7% vs 6.7%) for the SMOF vs OO/SO groups.

(*continued*)

Table 3. (continued)

Study	Gestational Age, Number (n) Randomized	Lipid Emulsions Given	Duration of PN	Outcomes
Yildizdas et al, 2018	32 wk and/or weighing 1500 g, n = 75	SMOF or OO/SO	At least 7 d	TBARS levels were significantly lower (day 7) in the SMOF group than in the OO/SO group, but not after 28 d. However, SOD levels decreased over time in the SMOF group and were significantly lower than the OO/SO group by day 28. Cholestasis was significantly lower in SMOF group (0% vs 18.2%), and neonates regained birth weight earlier than in the OO/SO group. There was no significant difference in other morbidities.
Ozkan et al, 2019	<32 wk, n = 89	SMOF or OO/SO	14 d	TAC was significantly higher in the SMOF group (day 7). BPD was significantly lower in the SMOF group (14.1%) than the OO/SO group (31.2%), and the rate of severe BPD was also significantly lower in the SMOF group (7.1% vs 19.1%, respectively). The duration of mechanical ventilation was also significantly lower in the SMOF group (10.3 vs 18.5 d, respectively).

ARA, arachidonic acid; BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; MDA, malondialdehyde; OO/SO, olive oil/soybean oil lipid emulsion (ClinOleic); PMA, postmenstrual age; PN, parenteral nutrition; RBC, red blood cell; ROP, retinopathy of prematurity; SMOF, SMOFlipid (soybean oil/medium-chain triglycerides/olive oil/fish oil); SO, soybean oil lipid emulsion; SOD, superoxidase dismutase; TAC, total antioxidant capacity; TAP, total antioxidant potential; TBARS, thiobarbituric acid reactive substances; VLBW, very low birth weight.
[a]Observational study.

soybean oil lipid emulsion in very preterm neonates (gestation 23–30 weeks).[9] A total of 34 neonates were randomized, and 30 completed the study. There was no significant difference between groups in total energy intake or proportion of enteral and parenteral administration. Both emulsions were well tolerated, and there were no significant differences between the groups in terms of safety/laboratory parameters including liver enzymes (ALT and GGT), which were within normal ranges. F_2-isoprostane levels were reduced from baseline levels in the composite fish-oil group (2818.0 vs 2051.7 pmol/L, respectively, $P = .0312$), whereas in the olive oil/soybean oil group there was no significant change (2630.8 vs 2642.8 pmol/L, respectively, $P = .2274$). Moreover, there was a significant difference between groups (change from baseline) in F_2-isoprostane levels ($P = .0372$). EPA levels (given as percentage of total fatty acids) reduced significantly in the olive oil/soybean oil group from baseline to the end of the study (1.52% to 1.07%, respectively; $P = .0026$); however, in the composite fish-oil group, EPA levels increased (1.45% to 2.29%, respectively; $P = .0038$). Moreover, there was a significant difference between groups (change from baseline) in EPA levels ($P = .0001$). Other long-chain PUFA levels, including ARA and DHA, reduced significantly from baseline by the end of the study and were similar in both groups, whereas oleic acid and linoleic acid levels increased significantly in both groups with no significant between-group differences. α-tocopherol levels increased significantly in both the olive oil/soybean oil group (15.93 to 84.6 μmol/L; $P = .0007$) and the composite fish-oil group (13.00 to 123.25; $P = .0004$). Moreover, there was a significantly greater increase in α-tocopherol level (change from baseline) in the composite fish-oil group than in the olive oil group ($P = .0091$).

This trial showed that for high-risk, very preterm neonates, a composite lipid emulsion containing fish oil had beneficial effects in terms of a significant reduction in oxidative stress, and significantly increasing α-tocopherol levels as well as RBC EPA levels, which may be beneficial in reducing inflammation.[9] However, there was no significant difference between groups in RBC DHA levels despite the higher DHA content of the composite lipid emulsion containing fish oil, and the reasons for this are not clear. It may be because of relatively poor tissue uptake in preterm neonates, but there was not enough plasma to measure plasma DHA levels to test this hypothesis. Alternatively, very preterm neonates may have higher DHA requirements than previously thought, and this issue was investigated by another similar trial that investigated DHA and EPA levels in plasma and RBC in term or near-term neonates (>34 weeks' gestation, n = 46) randomized to receive 80%

olive oil/20% soybean oil or a composite lipid emulsion containing fish oil (SMOF) for 7 days as part of their parenteral nutrition.[35] EPA and DHA levels increased significantly more in the SMOF group than in the olive oil/soybean oil group in both plasma and RBC ($P = .0001$ for all comparisons).

One further study of note is a recently published randomized controlled trial conducted in a population of preterm neonates (<32 weeks; n = 89) randomized to receive parenteral nutrition including either SMOF or an 80% olive oil/20% soybean oil lipid emulsion.[24] This study was the first to suggest that parenteral nutrition with SMOF might decrease oxidative damage and oxidative-stress associated morbidities compared with olive oil/soybean oil emulsion in preterm infants. Thus, severe bronchopulmonary dysplasia was significantly less common in those given SMOF (3 of 42 patients, 7.1%) than in the olive oil/soybean oil group (9 of 47, 19.1%) ($P = .02$). Moreover, the mean duration of non-invasive mechanical ventilation was also lower in those given SMOF than in the olive oil/soybean oil group (10.3 vs 18.5 days, respectively; $P = .01$). These improvements in clinical outcome in the SMOF group corresponded with numerically higher total antioxidant capacity vs the olive oil/soybean oil group at all time points measured, with a significant increase by day 7 ($P = .001$). There is evidence that DHA may improve respiratory outcomes, including the prevention of bronchopulmonary dysplasia, in preterm neonates when given early in life when the immune system is still developing.[44] Nevertheless, the improvements in clinical outcomes observed by Ozkan et al require further trials in greater numbers of neonates to confirm these potential benefits.[24]

Discussion

There have been significant advances in the development of lipid emulsions over the last 50 years, and these developments may have a particular significance for neonatal patients owing to the particular vulnerabilities of this patient population. This includes requirements for DHA and EPA, regarded as conditionally essential in this age group with critical roles during early retinal and brain development.[2] Moreover, neonates have a limited antioxidative capacity and are thus very vulnerable to oxidative stress and suffer from an increased likelihood of infections and inflammation; together, this may result in the many serious conditions affecting this age group.[25,26]

Because of these special requirements in neonates, it seems logical to select a lipid emulsion that potentially addresses some of these issues when parenteral nutrition is required. To this end, clinical trials have assessed different types of lipid emulsions in preterm neonates. In clinical trials, the fish-oil containing composite lipid emulsion SMOF has shown potential advantages over other lipid emulsions (olive oil/soybean oil or pure soybean oil emulsions) in preterm and near-term neonates, including reduced oxidative stress/lipid peroxidation,[9,24,35,37,42,43] and beneficial modulation of fatty-acid profiles and/or improved vitamin E status.[9,35-41] Presumably, this is because SMOF has a well-balanced fatty-acid composition, relatively low ω-6:ω-3 ratio, and high vitamin E content.[36] Although not the subject of this review, by addressing these issues it seems likely that the use of composite lipid emulsions containing fish oil may have additional clinical benefits. These include reducing the likelihood of ROP,[22,44] reversing parenteral nutrition associated cholestasis,[23] and reducing the incidence of severe bronchopulmonary dysplasia and shortening the duration of noninvasive ventilation.[24] However, further larger long-term clinical trials are needed to investigate potential clinical benefits of using composite lipid emulsions containing fish oil in neonates.

The prevention of EFAD is another factor to be considered when choosing a lipid emulsion for neonates. SMOF and 80% olive oil/20% soybean oil are comparable regarding their EFA content, with SMOF containing slightly greater quantities of linoleic acid and α-linolenic acid, yet both emulsions are considerably lower in EFAs compared with a pure soybean lipid emulsion.[5] Nonetheless, all commercially available 20% intravenous lipid emulsions meet the recommended intakes of EFAs for preterm or term infants and children.[2]

In summary, the use of composite lipid emulsions containing fish oil such as SMOF have a well-balanced fatty-acid composition and high vitamin E content, which can lead to improvements in neonates such as increased levels of ω-3 very long-chain PUFAs DHA and EPA, improved vitamin E status, and reduced oxidative stress/lipid peroxidation, in comparison with other lipid emulsions. These biochemical and biologic benefits may contribute to protecting these most sensitive patients from increased levels of oxidative stress and also may be associated with improved infant development and the prevention of morbidity.

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Statement of Authorship

G. C. Deshpande and W. Cai equally contributed to the conception and design of the research; G. C. Deshpande and W. Cai contributed to the acquisition, analysis, and interpretation of the data; R. Clark drafted the manuscript.

All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Lipid Emulsion Use in Pediatric Patients Requiring Long-Term Parenteral Nutrition

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Abstract

The ability to deliver nutrients via parenteral nutrition (PN) has markedly improved the prognosis of infants and children with intestinal failure. Technical refinements and advances in knowledge have led to the development of highly sophisticated PN solutions that are tailored to meet the needs of pediatric patients. However, children who require long-term PN have an increased risk of complications such as catheter-related sepsis, liver disease, and bone disease. Although the pathogenesis of intestinal failure associated liver disease (IFALD) is multifactorial, studies have identified a possible link between the dose of lipid emulsions based on soybean oil and cholestasis, shown to occur with a significantly higher frequency in patients receiving >1 g lipids/kg/d. Potential contributing factors include oxidative stress, high ω-6 polyunsaturated fatty acid (PUFA) and phytosterol content, and relatively low α-tocopherol levels. Lipid emulsions containing fish oil offer potential advantages compared with traditional emulsions with a high soybean oil content, such as decreased ω-6 and increased ω-3 PUFA concentrations, high concentrations of α-tocopherol, and reduced phytosterol content. Studies in PN-dependent children at risk for IFALD have shown that lipid emulsions containing fish oil reduce the risk of cholestasis and improve biochemical measures of hepatobiliary function compared with pure soybean oil emulsions. This review summarizes evidence regarding the role of lipid emulsions in the management of pediatric patients with intestinal failure requiring long-term PN, with a particular focus on the prevention and treatment of IFALD. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S55–S67)

Keywords

fish oil; IFALD; intestinal failure; intravenous lipid emulsions; nutrition; parenteral nutrition; pediatrics; soybean oil

Introduction

The updated guidelines on pediatric parenteral nutrition (PN) from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the European Society for Clinical Nutrition and Metabolism (ESPEN), the European Society for Pediatric Research (ESPR), and the Chinese Society for Parenteral and Enteral

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Nutrition (CSPEN), all state that intravenous lipid emulsions are an integral component of pediatric PN.[1] In addition to serving as a non-carbohydrate source of energy, it provides essential fatty acids (EFAs) and facilitates the delivery of lipid-soluble vitamins.[1] Moreover, polyunsaturated fatty acids (PUFAs), in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), modulate key metabolic pathways, including inflammatory and immune response, coagulation, and cell signaling.[2] In addition, DHA is crucial for brain development (see the review of lipid emulsions in neonates also in this supplement).[3] According to current international guidelines, parenteral lipid intake in children should be limited to a maximum of 3 g/kg/d (level of evidence 3–4, grade of recommendation 0, conditional recommendation for, strong consensus) and should generally provide 25%–50% of non-protein energy in fully parenterally fed pediatric patients.[1]

The most common indications for long-term and home parenteral nutrition (HPN) in children are primary digestive diseases causing intestinal failure (IF), including short bowel syndrome, neuromuscular disorders, and mucosal intestinal diseases.[4,5] IF is characterized by the reduction of functional gut capacity below the minimum required for adequate digestion and absorption of nutrients to support normal growth.[6-8]

The ability to deliver nutrients via PN has markedly improved the prognosis of infants and children with IF; however, long-term administration of PN can be associated with complications, including catheter-related bloodstream infections, metabolic bone disease, growth failure, and liver disease.[9-12] The development of liver disease is recognized as a limiting factor in the long-term management of patients with IF and represents a major indication for intestinal transplantation or combined liver–intestinal transplantation.[9,10] Risk factors for the development of liver disease include factors related to the underlying IF and factors related to PN administration.[9,10,13] As suggested by Goulet,[9] based on the recognition of the multifactorial pathogenesis of liver disease in patients with IF, the ESPGHAN Working Group on Intestinal Failure and Intestinal Transplantation recently replaced the terms "PN-associated liver disease (PNALD)" and "PN-associated cholestasis (PNAC)" with the broader term "intestinal failure associated liver disease (IFALD)" to describe hepatobiliary dysfunction in the setting of IF.[13]

Better understanding of the pathogenesis of IFALD and the development of novel lipid emulsions derived from fish oil have resulted in substantial improvements in the prevention and treatment of cholestatic liver disease. The current review summarizes recent insights regarding the role of lipid emulsions in the management of pediatric patients with IF requiring long-term PN, particularly regarding IFALD.

This manuscript is based upon presentations given at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA). Statements from the consensus document by Martindale et al[14] that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[14] These consensus statements provide practical advice regarding the use of lipid emulsions in PN, and as such complement formal nutrition society guidelines on this subject.

Intestinal Failure Associated Liver Disease

IFALD is the most prevalent complication affecting children with IF receiving long-term PN.[9,13] Estimating the prevalence of IFALD in pediatric patients is complicated by the lack of consensus diagnostic criteria or data from large, well-designed studies.[10,13] Approximately 40%–60% of infants receiving long-term PN develop cholestasis.[15] In a systematic literature review of 23 studies in 3280 children receiving PN for at least 14 days, the incidence of IFALD was 49.8% (range, 23%–67%), with a correlation between IFALD and the length of PN, with no obvious change in the incidence of IFALD during the 40-year period covered by the review.[16] Such a high incidence should be interpreted with caution, as the difference between PNAC and IFALD is not established and the meta-analysis included premature infants—a population that likely has a higher risk of developing cholestatic liver disease.

The diagnosis of IFALD is usually based on the presence of cholestasis, generally defined as an elevation in conjugated serum bilirubin concentration ($\geq$2 mg/dL), in children with IF receiving long-term PN.[13,17]

The pathogenesis of IFALD is not completely understood, though multiple etiological factors have been identified. Liver disease can develop as a result of physiological and anatomical abnormalities related to the underlying cause of IF, as well as metabolic complications related to the composition of PN or the route of PN administration.[10,13] Risk factors for IFALD include prematurity, short bowel syndrome, lack of enteral intake, continuous vs cyclical PN, and recurrent episodes of catheter-related bloodstream infections.[10] Proposed mechanisms of liver injury include impaired enterohepatic circulation, intestinal stasis leading to small intestinal bacterial overgrowth and translocation, disruption of hepatobiliary transport pathways and/or biliary stasis, and hepatocellular injury owing to lipid peroxidation and phytosterol accumulation.[10,13]

Intestinal Failure

Loss of function of the distal ileum can occur because of disease or resection, and impairs bile absorption and recirculation, increasing the risk of cholestatic liver disease.[10]

Table 1. Consensus Statements From the International Summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA), Relevant to This Article.[14]

Statement Number	Consensus Statement	Expert Voting Results
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: 1 g/kg/d, day 2: 2 g/kg/d, day 3 onwards: 3 g/kg/d • infants, children, and pre-adolescent patients: up to 3 g/kg/d	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 (eg, DHA), which are critical in neonatal neurodevelopment and vision • anti-inflammatory effects due to ω-3 PUFA content • a well-balanced ω-6:ω-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 GGT) routinely (in hospital: weekly and HPN: at least every 3 months) • fatty-acid profiles should be determined if there is a specific clinical question, eg, 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	Data from clinical cohort studies and clinical experience indicate that cholestasis can be reversed by using fish-oil containing lipid emulsions together with management of other risk factors, especially catheter-related or SIBO-related infections.	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 fish-oil containing ILEs, he/she should receive fish-oil composite ILEs as a first-line of treatment. If conjugated or direct bilirubin continues to rise above 2 mg/dL, pure fish-oil emulsion is recommended until resolution.	100% agreement (16 agree, 0 do not agree, 0 do not wish to answer).

ALT, alanine aminotransferase; AST, aspartate amino transferase; DHA, docosahexaenoic acid; IFALD, intestinal failure associated liver disease; ILE, intravenous lipid emulsion; LC-PUFA, long-chain polyunsaturated fatty acid; PN, parenteral nutrition; PUFA, polyunsaturated fatty acid; SIBO, small intestinal bacterial overgrowth; GGT, γ-glutamyl transferase.

Lack of oral or enteral feeding promotes intestinal stasis, resulting in impaired bacterial clearance, small intestinal bacterial overgrowth,[18,19] increased intraluminal permeability,[20] and translocation of bacteria and toxic microbial products such as endotoxin and lipopolysaccharide from the portal vein to the liver.[18,21]

An observational study in 175 neonates with abdominal pathology requiring laparotomy, showed that patients with short bowel syndrome were more likely than those without this condition to develop cholestasis (62.5% vs 10.4%; relative risk [RR], 5.8; 95% confidence interval [CI], 3.4–9.9; $P < .0005$) and liver failure (25% vs 0.7%; RR, 5; 95% CI, 3.4–7.2; $P < .0005$).[22] Short bowel syndrome was also associated with an increased risk of Gram-positive sepsis (RR, 5.3; 95% CI, 2.6–10.9; $P < .0005$) and Gram-negative sepsis (RR, 3.6; 95% CI, 2.6–5.9; $P < .0005$).[22] The US Intestinal

Failure Consortium reported data from 272 infants (median gestational age of 34 weeks; range, 30–36 weeks) and a median birth weight of 2.1 kg (range, 1.2–2.7 kg).[23] The median duration of follow-up was 25.7 months (range, 11.2–40.9 months). Underlying diagnoses included necrotizing enterocolitis (26%), gastroschisis (16%), intestinal atresia (10%), midgut volvulus (9%), combinations of these diagnoses (17%), aganglionosis (4%), and other single or multiple diagnoses (18%). The cohort experienced 8.9 new catheter-related bloodstream infections per 1000 catheter days. The cumulative incidences of enteral autonomy, death, and intestinal transplantation were 47%, 27%, and 26%, respectively. The high rates of death and transplantation are explained by the high incidence of end-stage liver disease caused by catheter-related bloodstream infections and small intestinal bacterial overgrowth. Notably, pediatric surgeons in Finland reported evidence of a link between bowel dilatation, sepsis, and cholestatic liver disease.[24] In particular, they found a significant correlation between small bowel diameter ratio and the grade of cholestasis in children with short bowel syndrome ($r = 0.534$, $P = .001$), providing evidence of a direct relationship between liver disease, the underlying intestinal disease, and the occurrence of small intestinal bacterial overgrowth.

Sepsis, small intestinal bacterial overgrowth, and conditions such as necrotizing enterocolitis that induce a systemic inflammatory response are closely associated with IFALD, particularly in patients with short bowel syndrome.[10,25] Endotoxin and inflammatory cytokines released by activated hepatic macrophages such as Kupffer cells induce signaling pathways that inhibit the expression and function of hepatobiliary transport mediators, resulting in cholestasis.[26-28] Intrahepatic accumulation of bile acids and other toxins and a persistent inflammatory state perpetuate ongoing hepatocyte injury and promote fibrosis, leading to end-stage cirrhosis.[26,27,29-34]

Parenteral Nutrition

Factors related to the composition and route of PN administration have been implicated in the development of liver dysfunction in patients with IF, including catheter-related bloodstream infections, continuous PN infusion, macronutrient and micronutrient imbalances, and inappropriate use of amino acid solutions and lipid emulsions.[13,15]

Catheter-related bloodstream infections are a common complication associated with the administration of PN via central venous catheters and contribute to the development of IFALD.[11,13,35,36] The frequency of catheter-related bloodstream infections in children receiving HPN ranges from 0.34 to 3.94 episodes per catheter year.[11,12,37-41] Multiple studies have shown that repeated episodes of catheter-related sepsis in infants receiving PN are associated with the development of cholestatic liver disease and liver fibrosis.[35,42-44] Central venous catheter complications can be reduced by catheter selection, meticulous maintenance of the catheter, use of taurolidine or ethanol locks, and involvement of specialized HPN centers with a multidisciplinary nutrition team.[5,12,45,46]

Imbalances of PN solution components can also lead to metabolic abnormalities contributing to the development of IFALD. Excessive or inadequate amino acid provision and a deficiency of conditionally essential substrates such as taurine, carnitine, and glutamine have been associated with IFALD, though a definitive causal relationship has not been established.[10,11,13] An excess of total energy, delivered either as glucose or fat, promotes hepatic steatosis.[11,13] In addition, excessive glucose intake and continuous PN infusion are associated with hyperinsulinism and subsequent steatosis.[10,11,13] Finally, infusion of lipid emulsions at rates exceeding the capacity of the liver to clear phospholipids and fatty acids and/or the capacity of endothelial lipoprotein lipase to hydrolyze the circulating artificial chylomicrons can increase lipid peroxidation and lead to reticuloendothelial system overload.[1,10,13,47]

Steatosis caused by metabolic complications is the predominant liver injury in adults receiving long-term PN.[19,48] In contrast, the primary pattern of liver injury in infants and children receiving long-term PN is fibrosis secondary to cholestasis and persistent portal inflammation.[10,49] This suggests that modern PN solutions are not usually the primary cause of liver disease in pediatric patients with IFALD. This might be partially attributable to refinements in the composition and delivery of PN, including the use of well-adapted amino acid solutions, the avoidance of excess glucose intake, the adoption of cyclical PN infusion, and the development of mixed-oil lipid emulsions with a balanced ω-6:ω-3 fatty-acid ratio and provision of medium-chain triglycerides (MCT), which offer metabolic benefits.[10,50]

Intravenous Lipid Supply and Cholestatic Liver Disease

A possible role for lipid emulsions in the pathogenesis of cholestatic liver disease was first identified in studies that showed a correlation between the use of soybean oil lipid emulsions and the development of cholestatic liver disease in patients receiving HPN.[51,52] Several mechanisms for lipid-mediated liver injury have been proposed, including increased oxidative stress, phytosterol accumulation, and activation of the reticuloendothelial system.[10,15]

Compared with the latest generation of lipid emulsions containing fish oil, soybean oil lipid emulsions contain high concentrations of ω-6 PUFAs such as linoleic acid and relatively low concentrations of α-tocopherol, an isoform

of vitamin E that exhibits strong antioxidant effects.[1,53] Peroxidation of PUFAs such as linoleic acid can lead to hepatocyte damage, while low plasma concentrations of α-tocopherol reduces antioxidant defense, further increasing oxidative stress.[10,15,54,55] In addition, linoleic acid is converted to arachidonic acid, a precursor of inflammatory prostaglandins, leukotrienes, and thromboxanes.[2,15] Excessive intake of linoleic acid may promote a persistent inflammatory state that contributes to progressive hepatocyte damage and/or portal inflammation, leading to cholestasis and fibrosis.[10,15,56]

Lipid emulsions based purely on vegetable oils also contain higher concentrations of phytosterols such as stigmasterol, β-sitosterol, and campesterol, compared with other lipid sources (eg, those containing fish oil).[57] There is evidence that phytosterols may contribute to the development of IFALD,[58-68] though the role of phytosterols in the development of IFALD remains controversial. Phytosterols have been observed to accumulate in the liver and plasma in children receiving a soybean oil emulsion,[58] elevated serum phytosterol concentrations have been shown to correlate with the development of cholestatic liver disease in infants and children requiring long-term PN,[64,65,67] and liver concentrations of phytosterols have been shown to correlate with liver fibrosis in PN-dependent children with IF.[68] However, no studies have demonstrated a direct relationship between decreased phytosterol levels and improvements in liver function or cholestasis. Animal studies have suggested that phytosterols inhibit transcription of bile transport proteins via antagonism of the farnesoid X receptor.[59-63,66,69] The addition of stigmasterol to a fish-oil emulsion resulted in activation of hepatic macrophages in mice, suggesting that phytosterols might act synergistically with lipopolysaccharides and other mediators to promote inflammation and hepatocellular injury.[66]

The rate of lipid infusion can also contribute to liver injury. Chronic administration of lipid emulsions or their infusion at rates exceeding the rate of lipoprotein lipase hydrolysis and oxidation (3–3.5 g/kg/d) can cause overload and activation of the reticuloendothelial system, leading to hematologic disorders, liver dysfunction, and cholestasis.[1,15,47]

Lipid Emulsions' Role in the Treatment and Prevention of Cholestatic Liver Disease

There have been efforts to prevent or reverse cholestasis by modifying lipid administration in patients requiring long-term PN. Modifications include lipid minimization,[70-72] temporarily discontinuing lipids,[52] and using lipid emulsions containing lipid sources other than soybean oil (eg, pure fish oil or composite lipid emulsions with or without fish oil).[73-88]

Reversal of Intestinal Failure Associated Liver Disease

Reversal of cholestasis has been documented following changes in lipid management in children with IF receiving long-term PN (Table 2).[52,72-76] Plasma bilirubin concentrations were normalized in 17 of 24 episodes of cholestasis in 10 children following temporary discontinuation of soybean oil lipid emulsion.[52] However, prolonged discontinuation of lipids may be associated with growth retardation and EFA deficiency. A retrospective analysis of 31 children with irreversible IF referred for intestinal transplantation showed that significant improvements in plasma bilirubin levels and platelet counts occurred following changes in global management.[72] The changes included reducing soybean oil intake by introducing combined soybean oil/MCT emulsions, performing cyclical PN infusion, adding α-tocopherol to PN solutions, managing bacterial overgrowth with tapering and lengthening procedures, and promoting oral feeding.

Lipid emulsions containing fish oil offer several advantages compared with those containing only soybean oil, including high concentrations of the ω-3 PUFAs DHA and EPA and the antioxidant α-tocopherol, reduced ω-6 PUFA content, and a reduced phytosterol load.[1,2,9,10,15] Moreover, some mixed-oil/composite lipid emulsions contain MCTs that are metabolically beneficial, as they are oxidized rapidly with low carnitine dependency.[50] Initial evidence concerning a reversal of cholestasis with fish oil was in 2 PN-dependent infants with end-stage liver disease who experienced normalization of direct bilirubin levels after substitution of a pure fish oil (1 g/kg/d) for a conventional soybean oil emulsion (3 g/kg/d).[73] Similar findings were reported in an open-label trial evaluating a pure fish oil emulsion in 42 infants with short bowel syndrome who developed cholestasis while receiving a soybean oil emulsion.[75] Serum bilirubin levels normalized in 50% of infants who were switched to pure fish oil emulsion (1 g/kg/d) compared with 5.6% of those in a historical cohort of 49 infants given a soybean oil emulsion (1–4 g/kg/d). A higher response rate was seen in an observational study in 57 infants with cholestasis who received a pure fish oil emulsion, with 82.5% achieving resolution after a median treatment duration of 35 days.[80] Zhang et al[85] evaluated 32 children with IF who were switched from a 50:50 soybean oil/MCT emulsion (mean dose, 1.3 g/kg/d) to a fish oil emulsion (mean dose, 1.2 g/kg/d) after any 3 of 7 measures of liver function increased to $\geq$2 times the normal value. This resulted in significant improvements in measures of liver function as well as reductions in inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and white blood cells. A retrospective cohort study in children with short bowel syndrome and advanced liver disease showed that adding a pure fish oil emulsion (target dose, 1 g/kg/d)

Table 2. Studies Evaluating the Effect of Modifying Lipid Administration on Reversal of Cholestasis in Infants and Children.

Author	Population	N	Design	Intervention	Results
Colomb et al 2000[52]	PN-dependent children with cholestasis	10	Retrospective cohort study	Discontinuation of SO ILE	Plasma bilirubin concentrations normalized in 17 of 24 episodes of cholestasis; platelet counts returned to normal values in 11 of 12 episodes of cholestasis with thrombocytopenia
Gura et al 2006[73]	Infants with IFALD	2	Case report	Pure FO ILE (1 g/kg/d)	Reversal of cholestasis observed by day 60, following switch from SO ILE to pure FO ILE
Gura et al 2008[74]	Infants with SBS and cholestasis	18	Retrospective cohort study	Pure FO ILE (1 g/kg/d) vs historical cohort receiving SO ILE (median, 1.8 g/kg/d; n = 21)	Faster median time to reversal of cholestasis observed in infants switched to a pure FO ILE vs historical controls (9.4 vs 44.1 weeks, respectively)
Puder et al 2009[75]	Infants with SBS and cholestasis	42	Open-label trial	Pure FO ILE (1 g/kg/d) vs historical cohort receiving SO-based ILE (1–4 g/kg/d; n = 49)	Serum bilirubin normalized in 50% of infants switched to a pure FO ILE vs 5.6% of those in historical cohort receiving a SO-based ILE
Diamond et al 2009[76]	Children with SBS and advanced liver disease	12	Retrospective cohort study	Addition of pure FO ILE (target dose, 1 g/kg/d) to SO-based ILE (target dose, 1 g/kg/d)	Resolution of hyperbilirubinemia in 9 of 12 patients, 5 of whom experienced resolution after discontinuation of SO-based ILE
Le et al 2010[78]	PN-dependent infants with cholestasis	10	Prospective cohort study	Pure FO ILE (1 g/kg/d)	Significant improvement in lipid profiles (HDL, LDL, VLDL, TG, cholesterol), DB, and TB; 6 of 10 infants experienced resolution of cholestasis after a median of 14 weeks (range, 7–41 weeks)
Muhammed et al 2012[79]	Children with cholestatic jaundice	8	Retrospective cohort study	SMOF (median dose, 2 g/kg/d) vs historical cohort receiving SO ILE (median dose 3.5 g/kg/d; n = 9)	SMOF associated with significant improvement in bilirubin levels compared with control cohort (median change, −99 vs +79 μmol/L, respectively; $P = .02$); total resolution of jaundice observed in 5 of 8 children in the SMOF group vs 2 of 9 children in control cohort, respectively.
Premkumar et al 2012[80]	Infants <6 months of age with PNALD	57	Prospective observational study	Pure FO ILE (1 g/kg/d)	Resolution of cholestasis observed in 82.5%; median time to resolution of cholestasis, 35 days (range, 7–129 d)

(*continued*)

Table 2. (continued)

Author	Population	N	Design	Intervention	Results
Calkins et al 2014[81]	Infants and children (age, 2 weeks to 18 years) with IFALD	10	Prospective cohort study	Pure FO ILE (mean dose, 1.5 g/kg/d) vs historical cohort receiving SO ILE (mean dose, 2.7 g/kg/d; n = 20)	Kaplan–Meier estimates showed resolution of cholestasis by week 17 in 75% of patients receiving pure FO ILE compared with 6% of historical cohort receiving SO ILE ($P < .0001$)
Pichler et al 2014[83]	Hospitalized children (age 0–16 years) expected to require prolonged PN	127[a]	Retrospective cohort study	SMOF (mean, 2.2 g/kg/d) vs SO/MCT (mean, 2.3 g/kg/d)	Significant reductions in ALT and ALP with SMOF and SO/MCT; SMOF also associated with significant reductions in γ-GT and CRP and a lower incidence of persistent hyperbilirubinemia (14% vs 38%, respectively; $P = .001$)
Ganousse-Mazeron et al 2015[72]	Children with IF referred for intestinal transplant evaluation	118	Retrospective cohort study	Global modifications, including reduced dose of SO-based ILE, cyclical PN infusion, α-tocopherol supplementation, aggressive SIBO management, and promotion of oral feeding	Significant improvements in bilirubin, platelets, and *z*-scores for body weight and height during the first 12 months of follow-up in 31 patients who were not transplanted
Calkins et al 2018[86]	Infants with IFALD	14	Prospective observational study	Pure FO ILE (1 g/kg/d)	Cholestasis resolved in 79% of infants after a median of 13 weeks; phytosterol concentrations decreased by 80% and 96% at 3 and 6 months, respectively; positive correlation between early changes in stigmasterol and subsequent change in DB
Zhang et al 2018[85]	Children with IFALD	32	Prospective cohort study	Switch from SO/MCT (mean dose, 1.3 g/kg/d) to pure FO ILE (mean dose, 1.2 g/kg/d)	Significant improvements in measures of liver function (ALT, AST, γ-GT, TB, and DB); significant reductions in inflammatory markers (CRP, TNF-α, and WBC)
Wang et al 2019[88]	Children with IFALD	48	Prospective cohort study	Patients switched from SO ILE to FO ILE for 6 months, then resumed treatment with SO ILE	After 6 months of PN with FO ILE, resolution of cholestasis was observed in 71% (95% CI, 54%–82%); among patients who resumed SO ILE (n = 27), cholestasis recurred in 26% (95% CI, 8%–47%) during a median duration of follow-up of 16 months (range, 3–51 months)

ALP, alkaline phosphatase; ALT, alanine amino transferase; AST, aspartate amino transferase; CRP, C-reactive protein; DB, direct bilirubin; FO, fish oil; HDL, high-density lipoprotein; IF, intestinal failure; IFALD, intestinal failure associated liver disease; ILE, intravenous lipid emulsion; LDL, low-density lipoprotein; MCT, medium-chain triglyceride; N, number of patients; PN, parenteral nutrition; PNALD, PN associated liver disease; SBS, short bowel syndrome; SIBO, small intestinal bacterial overgrowth; SMOF, soybean oil/medium-chain triglycerides/olive oil/fish oil (SMOFlipid); SO, soybean oil; TB, total bilirubin; TG, triglycerides; TNF-α, tumor necrosis factor-α; VLDL, very low-density lipoprotein; WBC, white blood-cell count; γ-GT, γ-glutamyl transferase.

[a]Includes 74 children with abnormal liver function tests during prior exposure to an SO ILE.

to a soybean oil emulsion (target dose, 1 g/kg/d) and reducing total lipid intake resulted in complete resolution of hyperbilirubinemia in 9 of 12 children.[76] Furthermore, PN-dependent children with IFALD who were switched from a soybean oil emulsion to a fish oil emulsion for 6 months before resuming treatment with soybean oil, showed that fish oil treated cholestasis, whereas returning to a soybean oil emulsion resulted in redevelopment of cholestasis in one-quarter of patients.[88]

According to the current ESPGHAN/ESPEN/ESPR/CSPEN pediatric PN guidelines, long-term administration of a pure fish oil emulsion as the sole source of lipids is not recommended, but current evidence suggests that short-term administration is an effective rescue therapy in pediatric patients with IFALD.[1] A study evaluating plasma fatty-acid profiles in PN-dependent infants (n = 10), who received a pure fish oil emulsion (1 g/kg/d) for at least 1 month, showed none of the patients had biochemical evidence of EFA deficiency (triene:tetraene ratio > 0.2).[89] However, blood levels of the essential ω-6 fatty acid linoleic acid declined markedly from baseline at 6 weeks, supporting concerns that use of pure fish oil as the sole source of lipids over longer periods might result in insufficient intake of linoleic acid.[10]

Composite lipid emulsions containing fish oil may offer hepatoprotective benefits and provide an adequate supply of rapidly oxidizable MCTs as well as an ω-6:ω-3 PUFA ratio that meets current recommendations.[65,77,79,83,87] Rapid and marked reductions in serum bilirubin occurred in children with cholestatic jaundice after switching from a soybean oil emulsion to a composite lipid emulsion containing a mixture of 30% soybean oil, 30% MCTs, 25% olive oil, and 15% fish oil (SMOF).[79] At 6 months, serum bilirubin declined by 99 μmol/L in children switched to SMOF and increased by 79 μmol/L in a historical cohort of children given a soybean oil lipid emulsion ($P = .02$). In a retrospective cohort study of pediatric patients (n = 127) requiring long-term PN, patients were given either SMOF or a 50:50 mixture of soybean oil/MCT, 74 of whom were switched from a pure soybean oil lipid emulsion after increases in total bilirubin (to >50 μmol/L) or alanine aminotransferase (ALT), alkaline phosphatase (ALP), or γ-glutamyl transferase (γ-GT) to >1.5 times the upper limit of normal.[83] Both SMOF and soybean oil/MCT resulted in significant reductions in ALT and ALP; however, SMOF was also associated with significant reductions in γ-GT and CRP, as well as a lower incidence of persistent hyperbilirubinemia compared with soybean oil/MCT (14% vs 38%, respectively; $P = .001$).

Administration of a composite lipid emulsion containing fish oil should be considered as first-line treatment for infants and children with existing cholestasis (consensus statement 37, Table 1). If elevated levels of conjugated or direct bilirubin (>2 mg/dL) persist, short-term rescue therapy with a pure fish oil emulsion should be considered (consensus statement 37, Table 1). Continued administration of a pure fish oil emulsion as the sole source of lipids after resolution of cholestasis is not recommended (consensus statement 37, Table 1).[1]

Prevention of Intestinal Failure Associated Liver Disease

Pediatric patients at risk for developing IFALD should be identified early to prevent cholestasis, by promoting oral feeding, if possible, and limiting the risk of sepsis and small intestinal bacterial overgrowth.[1] Because long-term use of a pure soybean oil emulsion is a risk factor for cholestasis, both lipid restriction and the use of alternative lipid sources are potential preventative strategies.[1,90] Studies evaluating the effect of lipid emulsions on the prevention of cholestasis in infants and children are shown in Table 3.[70,71,77,84,87]

Restricting lipid intake (soybean oil emulsion, target 1 g/kg/d) in infants requiring long-term PN has resulted in a lower incidence of liver disease compared with a historical cohort given 2-3 g/kg/d (22% vs 43%, respectively; $P = .002$).[71] However, the effect of restricted lipid intake on EFA status was not assessed, and dextrose provision was increased to maintain adequate energy provision, but the long-term metabolic and nutrition consequences of this were not addressed. A similar strategy was assessed in a randomized controlled trial comparing a reduced dose of soybean oil emulsion (1 g/kg/d) with a standard dose of 3 g/kg/d in 28 infants receiving >50% of energy from PN.[70] The rate of increase in conjugated bilirubin was significantly lower in those on the lower-than-standard dose (mean change, 0 vs 1.3 mg/dL, respectively; $P = .04$). However, lipid restriction resulted in lower weight-for-age z-scores compared with standard dosing (−0.06 vs 0, respectively; $P = .02$).

The effect of a composite lipid emulsion containing fish oil on hepatobiliary function in children at risk for IFALD has been evaluated in 2 randomized controlled trials[77,84] and 1 prospective cohort study.[87] A randomized trial in 28 children receiving HPN showed a reduction in total bilirubin levels in patients receiving SMOF but not those given a soybean oil lipid emulsion (mean change from baseline, −1.5 vs 2.3 μmol/L, respectively; $P < .01$).[77] In addition, the SMOF group had significant increases in plasma concentrations of DHA and EPA and in serum concentrations of α-tocopherol compared with those given soybean oil. Another randomized trial compared SMOF with soybean oil emulsion in infants with hepatic dysfunction receiving >40% of energy from PN.[84] At 4 weeks, conjugated bilirubin was significantly lower in the SMOF group compared with the soybean oil group (mean difference, −59 μmol/L; $P = .03$). Patients receiving SMOF also had a higher likelihood of experiencing a decrease in serum conjugated bilirubin compared with those receiving soybean oil (hazard

Table 3. Studies Evaluating the Effect of Lipid Emulsions on the Prevention of Cholestasis in Infants and Children.

Author	Population	N	Design	Intervention	Results
Goulet et al 2010[77]	Children receiving HPN	28	Randomized controlled study	SMOF (target 2g/kg/d) vs SO ILE (target 2 g/kg/d)	Significant improvement in plasma bilirubin concentration in SMOF group vs SO ILE (mean change, −1.5 vs 2.3 μmol/L, respectively; $P < .01$); higher plasma concentrations of DHA, EPA, and α-tocopherol in SMOF group vs SO ILE, respectively
Rollins et al 2013[70]	Infants receiving >50% of energy from PN	28	Randomized controlled study	Reduced vs standard dose of SO ILE (1 vs 3 g/kg/d)	Significantly lower rate of increase in conjugated bilirubin in infants receiving reduced vs standard dose SO ILE (mean change, 0 mg/dL vs 1.3 mg/dL, respectively; $P = .04$); lower weight z-score with reduced vs standard dose SO ILE (−0.6 vs 0, respectively; $P = .02$)
Sanchez et al 2013[71]	Surgical infants requiring long-term PN	82	Retrospective cohort study	Restriction of lipid intake (SO-based ILE goal, 1 g/kg/d vs historical cohort receiving 2–3 g/kg/d)	Significant reduction in the incidence of liver disease compared with control cohort receiving standard SO ILE dose (22% vs 43%, respectively; $P = .002$)
Diamond et al 2017[84]	Infants with hepatic dysfunction receiving >40% of energy from PN	24	Randomized controlled study	SMOF vs SO ILE (lipids dosed according to PN dosing nomogram)	Significantly lower conjugated bilirubin in SMOF group vs SO ILE (mean difference, −59 μmol/L, $P = .03$); SMOF associated with higher likelihood of achieving a decrease in serum conjugated bilirubin to 0 μmol/L than SO ILE (HR 10.6; 95% CI, 1.3–86.9; $P = .006$)
Lam et al 2018[87]	Hospitalized children requiring long-term PN	20	Prospective cohort study	SMOF (median, 2.2 g/kg/d) vs historical cohort receiving SO ILE (median, 2.1 g/kg/d)	Significantly lower trajectory of conjugated bilirubin in children receiving SMOF vs historical controls ($P < .0001$)[a]

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HPN, home parenteral nutrition; HR, hazard ratio; ILE, intravenous lipid emulsion; N, number of patients; PN, parenteral nutrition; SMOF, soybean oil/medium-chain triglycerides/olive oil/fish oil (SMOFlipid); SO, soybean oil.
[a]Based on a generalized estimating equation model.

ratio, 10.6; 95% CI, 1.3–86.9; $P = .006$). A prospective cohort of hospitalized children (n = 20) was evaluated for biochemical measures of liver injury during PN (>4 weeks) when receiving SMOF (median dose, 2.2 g/kg/d) compared with an age- and diagnosis-matched historical cohort (n = 20) given a soybean oil emulsion (median dose, 2.1 g/kg/d).[87] Analysis of longitudinal measures of liver function using a generalized estimating equation model showed that median values for conjugated bilirubin were significantly lower for children given SMOF ($P < .001$).[87]

Studies in PN-dependent infants and children at risk for IFALD indicate that composite lipid emulsions containing fish oil can reduce the risk of cholestasis and improve biochemical measures of hepatobiliary function compared with soybean oil emulsions.[77,84,87] While restriction of soybean oil emulsion intake has also been shown to reduce the

risk of cholestasis, prolonged restriction of lipid intake can lead to EFA deficiency with subsequent adverse effects on growth and neurodevelopment.[1] Fatty-acid profiles in the red blood cells (RBCs) of children with IF (n = 31) given HPN with SMOF for 6–38 months showed significantly higher DHA and EPA levels and significantly lower levels of linoleic acid and arachidonic acid compared with fatty-acid profiles measured after 4 weeks of treatment with SMOF in a previous randomized controlled trial.[77,91] Total bilirubin levels (mean ± SD, 12.2 ± 8.5 μmol/L) and *z*-scores for body weight and height (0.1 ± 1.8 and −0.1 ± 1.4, respectively) remained within the normal range during long-term PN with SMOF.[91] Long-term administration of SMOF did not cause liver disease or impair growth without evidence of EFA deficiency (triene:tetraene ratio > 0.2). These results should be confirmed soon in patients receiving SMOF over a longer term and in comparison with a control group. Open questions remaining are the EFA safety of long-term administration of pure fish oil emulsions (ie, administration for periods longer than required for rescue treatment) and the optimal analytical measures to be used for assessing the EFA profile in plasma or in RBCs.

However, there is insufficient evidence to establish a direct correlation between improvements in biochemical measures of cholestasis and improvements in histologic measures of hepatic fibrosis or extrahepatic outcomes such as growth and cognition.[15,36,92] Additional evidence from well-designed studies with long-term follow-up is required.

Monitoring

Tolerance of lipid administration is generally assessed by monitoring biochemical parameters.[1] Markers of liver integrity and function and triglyceride concentrations should be routinely monitored in pediatric patients receiving lipid emulsions.[1] Current ESPGHAN/ESPEN/ESPR/CSPEN guidelines indicate that assessment of serum triglyceride levels may be considered 1–2 days after starting or adjusting lipid infusions, with subsequent assessments performed weekly to monthly depending on the patient's history and clinical status.[1] For older children, serum triglyceride concentrations of 3.4–4.5 mmol/L (300–400 mg/dL) may be acceptable based on the fact that lipoprotein lipase is saturated at ≈4.5 mmol/L (400 mg/dL).[1] Hypertriglyceridemia can be caused by lipogenesis owing to excessive glucose intake, and in these cases glucose intake should be reduced before reducing lipid intake.[1]

Consensus recommendations for monitoring tolerance of lipid administration in pediatric patients are shown in Table 1. Liver function tests (total, direct, and conjugated bilirubin; ALT; aspartate aminotransferase; ALP; and γ-GT) should be monitored weekly in hospitalized patients and at least every 3 months in patients receiving HPN. Fatty-acid profiles, optimally in RBCs, should be obtained if there is a specific clinical question (eg, the effect of lipid emulsion administration on EFA status in patients receiving pure fish oil as the sole lipid source).

Conclusions

The development of liver disease is recognized as a limiting factor in the management of infants and children with IF who require long-term PN.[9,10] While the etiology of IFALD is multifactorial, the composition of lipid emulsions is implicated as a potential contributor.[10,15] Lipid emulsions should be an integral part of pediatric PN.[1] Evidence from clinical evaluations indicates that lipid emulsions containing fish oil offer advantages over conventional pure soybean oil emulsions, including decreased ω-6 and increased ω-3 PUFA content, high concentrations of α-tocopherol, and lower phytosterol content.[1,2,9,15] Studies in infants and children receiving long-term PN have shown that multicomponent lipid emulsions containing fish oil reduce the risk of cholestasis and improve biochemical measures of liver function.[77,84,87] Pure fish oil lipid emulsions have been shown to be a valuable short-term rescue therapy in pediatric patients with IFALD.[73-75,78,80,81,85] There is some evidence that lipid emulsions containing fish oil may slow the progression of IFALD.[84] Randomized controlled trials with long-term follow-up are necessary to explore the strength of the evidence and the effect of lipid-based strategies on histological outcomes and clinical outcomes such as growth and cognitive development.

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Statement of Authorship

O. J. Goulet, W. Cai, and J.-M. Seo contributed to the conception and design of the research; O. J. Goulet contributed to acquisition, analysis, and interpretation of the data; O. J. Goulet drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Pharmacoeconomics of Parenteral Nutrition with ω-3 Fatty Acids in Hospitalized Adults

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Abstract

The inclusion of ω-3 fatty acids as part of parenteral nutrition is associated with clinical benefits such as a reduced likelihood of infectious complications and shorter hospital and intensive care unit (ICU) stays. As healthcare resources are limited, pharmacoeconomic analyses have been performed, typically modeling studies, using cost and outcomes data to investigate the cost-effectiveness of parenteral nutrition regimens including ω-3 fatty acids from fish oil compared with standard parenteral nutrition without such ω-3 fatty acids. This review covers pharmacoeconomic studies encompassing Italian, French, German, and UK hospitals for ICU and non-ICU hospitalized patients, and for ICU patients in China. The results show that the use of parenteral nutrition including ω-3 fatty acids more than offsets any additional acquisition costs in all national scenarios investigated to date, indicating that parenteral nutrition including ω-3 fatty acids is a clinically and economically beneficial strategy compared with standard parenteral nutrition. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S68–S73)

Keywords

China; cost-effectiveness; Europe; fish oil; infections; intensive care; lipids; omega-3; parenteral nutrition; pharmacoeconomics

Introduction

Pharmacoeconomic evaluations are a way to assess the efficiency of interventions such as a particular pharmaceutical product or treatment strategy, providing information allowing the optimal allocation of limited healthcare system resources. To assess efficiency, pharmacoeconomic studies simultaneously consider both inputs (ie, "costs") and outcomes (ie, clinical "benefits") resulting from an intervention.[1] Evaluation methods include cost-benefit, cost-effectiveness, cost-minimization, and cost-utility analyses.[1,2] Cost and outcomes are used to inform a decision on whether to adopt a particular pharmaceutical product or treatment strategy compared with an alternative (control or comparator).[3-5] Often, a new intervention

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may have a better health effect than the comparator but is more costly, and in these cases there needs to be a judgment by the decision maker on whether or not (and how much) they are willing to pay for this improvement in healthcare.[3] One such intervention that has received much attention within the field of parenteral nutrition is whether to use fish oil (henceforward referred to as ω-3 fatty acids). Thus, this review will cover pharmacoeconomic evidence regarding the use of parenteral nutrition with ω-3 fatty acids (intervention) vs standard parenteral nutrition (ie, containing lipids such as soybean oil, olive oil, and medium-chain triglycerides, but without ω-3 fatty acids), using modeling studies and collecting data from a variety of sources to apply these pharmacoeconomic analyses to a range of scenarios.

This review is based on presentations given at the international summit "Lipids in Parenteral Nutrition" on November 2–4, 2018 (Miami, FL, USA).

Modeling and Meta-Analyses

A thorough pharmacoeconomic analysis usually requires the use of modeling. This is because it is rare that a single trial contains all the evidence that should be considered when making evidence-based decisions, so otherwise any other evidence on treatment effects, outcomes, and resources is effectively ignored.[6] In contrast, modeling studies can collect data from a wide range of sources (including meta-analyses, observational studies, etc) and perform syntheses using an economic model.[7] Models are used very widely in a range of scientific disciplines and are a way of representing the complexity of the real world in a simpler and more understandable form.[8,9] Furthermore, modeling is particularly useful within the field of parenteral nutrition, as large-scale clinical trials are uncommon and collection of economic data is not generally performed as part of these studies.

When performing a modeling study, the reliability of any outcomes depends on the quality of data used. As such, the hierarchy of evidence used in modeling is as relevant as in any other field of evidence-based medicine. Thus, meta-analyses have proven to be valuable tools, as they are the highest level of the evidence-based medicine hierarchy,[10] though others still believe that individual randomized controlled trials remain the "gold standard." Furthermore, many meta-analyses have been conducted showing that parenteral nutrition including ω-3 fatty acids is associated with clinical benefits.[11-19] Results from these meta-analyses have been discussed in more detail in another review in this supplement.[20]

The 2012 meta-analysis by Pradelli et al[13] has formed the basis for clinical outcomes data for all published ω-3 parenteral nutrition pharmacoeconomic studies,[21-23] as it formed the largest and most comprehensive dataset until being updated in 2019.[19] Pradelli et al, 2012, included 23 randomized controlled trials and 1502 patients, covering intensive care unit (ICU) populations (13 studies, 762 patients) as well as non-ICU/major abdominal surgery patients (10 studies, 740 patients).[13] This meta-analysis found that the use of ω-3 fatty acids was associated with ≈40% fewer infections (relative risk [RR] 0.61; 95% confidence interval [CI], 0.45–0.84; $P = .002$), ≈3 days' shorter hospital stay (−3.29 mean days' difference; 95% CI, −5.13 to −1.45; $P = .0005$), and ≈2 days' shorter ICU stay (−1.92 mean days' difference; 95% CI, −3.27 to −0.58; $P = .005$).[13] The 2019 meta-analysis update used essentially the same method but a total of 49 randomized controlled trials with 3641 patients were included, with the addition of trial sequential analysis.[19] Very similar results were obtained compared with the 2012 meta-analysis, though with greater precision owing to the larger sample sizes. Thus, the use of ω-3 fatty acids was found to reduce the risk of infection and sepsis by 40% and 56%, respectively, and the length of both ICU and hospital stay by ≈2 days.[19]

The following sections review the pharmacoeconomic analyses published using the clinical data provided by the 2012 meta-analysis, investigating the cost-effectiveness of parenteral nutrition regimens including ω-3 fatty acids compared with standard parenteral nutrition, for Italian, French, German, and UK hospitals for ICU and non-ICU patients,[21] and for ICU patients in China.[22,23]

Cost-Effectiveness of Parenteral Nutrition Including ω-3 Fatty Acids

European Perspective

To find out whether potential clinical benefits were economically justifiable, a pharmacoeconomic evaluation was performed to investigate the cost-effectiveness of parenteral nutrition with lipid emulsions with or without ω-3 fatty acids in a variety of clinical settings (ie, ICU or surgical/non-ICU) and in 4 national scenarios (Italy, France, Germany, and the UK).[21] The perspective of the analysis was from the point of view of a healthcare provider of these 4 countries, with a time horizon limited to patients' hospital stay. The method used a model based on a patient-level, probabilistic, discrete-event simulation (DES) technique. In this, the experience of individuals is modeled over time in terms of the events that occur and the consequences of those events. Thus, 2 alternative treatment arms were simulated, representing parenteral nutrition (1) with ω-3 fatty acids from fish oil, or (2) without ω-3 fatty acids (standard parenteral nutrition, such as soybean oil, medium-chain triglycerides/long-chain triglycerides, or olive oil/soybean oil emulsions). Two patient populations were considered: (1) medical and surgical patients with an ICU stay, and (2) surgical patients without an ICU stay. The main clinical

Table 1. Results of a Cost-Effectiveness Analysis for Italy.

	ICU Patients			Non-ICU Patients		
	ST + ω-3	ST	Difference	ST + ω-3	ST	Difference
Total cost, €	19,825	24,504	−4679	13,595	14,619	−1025
ICU cost, €	7475	10,166	−2691	N/A	N/A	N/A
Ward (pre-ICU) cost, €	4318	4318	0	N/A	N/A	N/A
Ward cost, €	6336	8531	−2195	12,171	13,399	−1228
Infection cost, €	90	119	−28	131	261	−130
Treatment cost, €	1605	1370	235	1292	959	333
ICER, €/LOS day		Dominant			Dominant	

Note: Death rates per 10,000 patients are 2509 (ICU patients) and 511 (non-ICU patients), regardless of treatment in all of the base–case scenarios. Results are mean costs (€) per patient (Pradelli et al, 2014).[21]
ICER, incremental cost-effectiveness ratio (ST + omega-3 vs ST); ICU, intensive care unit; LOS, length of stay; N/A, not applicable; ST, standard parenteral nutrition, defined as any parenteral nutrition not containing fish oil; ST + omega-3, any parenteral nutrition containing fish oil.
Reproduced with permission from Pradelli et al. Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: a discrete event simulation model. *Clin Nutr*. 2014;33(5):785-792.

outcomes simulated by the model were death rate in the ICU, infection rate in the ICU, death rate in the ward, and length of hospital stay (LOS) divided into LOS pre-ICU, LOS in the ICU, and LOS in the ward (post-ICU for ICU patients). Probability distributions for these outcomes were estimated for ICU patients by using publicly available data representative of the ICU population,[24] but as no comparable source was available for non-ICU patients international clinical trial data were used for this population.[25-30] No discount rate was applied to outcomes and costs owing to the short time frame of the simulation. Country-specific cost data (ie, cost per day of ICU and ward stay, cost of nosocomial infections, and local acquisition costs for parenteral nutrition products) were obtained from Italian, French, German, and UK healthcare systems. The reliability of the results was tested by using probabilistic and deterministic sensitivity analyses.[21]

The results showed that parenteral nutrition containing ω-3 fatty acids was more effective than standard parenteral nutrition containing lipids without ω-3 fatty acids, both in ICU and in non-ICU patients, in all 4 countries, reducing infection rates and overall LOS, and resulting in a lower total cost per patient.[21] Thus, the base–case model outcomes were that ω-3 fatty-acid enriched lipid emulsions prevented 23.8% and 49.7% of ICU and non-ICU patient infections, respectively, and reduced overall LOS by 4.6 days (ICU patients) and 1.6 days (non-ICU patients). Thus, the model reflects the results from the meta-analysis very well, providing further confidence in the model results. Results for Italy showed a total mean cost saving of €4679 per ICU patient and €1025 per non-ICU patient when using parenteral nutrition containing ω-3 fatty acids compared with the use of standard lipid emulsions (equating to US $4212 and US $923, respectively, calculated at exchange rates on August 15, 2019). Extension of the model to also include France, Germany, and the UK, revealed overall cost savings of about ≈€4000–€4900 per ICU patient and €600–€1800 per non-ICU patient for this treatment strategy (equating to US $3601–US $4411, and US $540–US $1620, respectively, calculated at exchange rates on August 15, 2019). These findings indicate that the extra acquisition cost of parenteral nutrition containing ω-3 fatty acids is more than offset by savings arising from reductions in the cost of ICU and hospital stay, and to a lesser extent by lower costs resulting from fewer nosocomial infections. Thus, parenteral nutrition containing ω-3 fatty acids is said to "dominate" standard parenteral nutrition for Italy (Table 1) and the other 3 countries (results not shown).[21]

The model results were shown to be robust according to the sensitivity analyses performed for each national scenario.[21] In addition, the deterministic sensitivity analyses also showed that the most influential cost parameters were reduction in length of stay in both ICU and non-ICU patients. Because of the robustness of these results, these findings are likely to be applicable in healthcare settings and systems similar to those in these 4 European countries. Thus, the results of this study strongly suggest that parenteral nutrition containing ω-3 fatty acids is a clinically and economically attractive strategy compared with standard parenteral nutrition in Italian, French, German, and UK hospitals, for both patients and healthcare providers.[21]

Chinese Perspective: Omegaven Validation Study

The same cost-effectiveness pharmacoeconomic techniques used in the European study[21] were utilized and validated in a Chinese ICU setting, this time comparing parenteral nutrition including ω-3 fatty acids (specifically Omegaven 10% fish-oil emulsion, Fresenius Kabi, Bad Homberg, Germany) with standard lipid emulsions that did not contain fish oil.[22] The perspective of the analysis was

from the point of view of patients and their families in China, with a time horizon limited to patients' time in hospital. The method used a model based on a patient-level, probabilistic DES. Importantly, part of this study involved the validation of the model predictions by a formal comparison of predicted data from the model with real-life data not used in the modeling exercise.

Methods used by Wu et al[22] were similar to those in the previous European pharmacoeconomics study.[21] In brief, a similar DES model was used, and the events considered were transfers between ICU and ward, new nosocomial infection, discharge from the hospital, and death.[22] However, only ICU patients were considered in this analysis. Two treatment arms were simulated: parenteral nutrition (1) with ω-3 fatty acids from fish oil, or (2) without fish oil (standard parenteral nutrition, control population). No discounting was applied to outcomes and costs owing to of the short time frame of the simulation. The DES model used was based on efficacy data from an international meta-analysis,[13] and clinical and economic input parameters were derived from a Chinese observational study conducted in a large hospital based in Shanghai.[31] Cost inputs were based on regression analyses of cost data from the same Chinese hospital dataset. The reliability of the results was tested by using probabilistic and deterministic sensitivity analyses. The model's predictive accuracy for clinical outcomes in the Omegaven cohort was also validated externally by comparison with actual data obtained from this subset of patients in the Shanghai hospital database not used in the modeling.[22] One potential drawback of this study was that it only considered direct costs to the patients and their family, which may be of particular importance given the study perspective. Thus, we do not know the effect of any indirect medical or non-medical expenses or benefits. However, it seems likely that the faster recovery and shorter hospital stay for the Omegaven group might result in lower indirect costs (eg, earlier return to work resulting in reduced income losses).

The model predicted (and observed data confirmed) that Omegaven would "dominate" standard lipid emulsions, with better clinical outcomes and lower overall healthcare costs (mean savings ≈10,000 Chinese yuan renminbi [¥], equating to US $1421 or €1274 calculated at exchange rates on August 15, 2019), mainly because of faster recovery and shorter hospital stay (by ≈6.5 days).[22] The external validation process also confirmed the reliability of the model's predictions as all external observations were reasonably close to the mean of model predictions and were well within the 95% CI of the values predicted by the probabilistic sensitivity analysis. If anything, the model results were somewhat conservative, as the model slightly underestimated the stay reduction compared with the stay reduction observed in the ICU patient population admitted. Thus, the results of this study showed that the use of Omegaven for Chinese ICU patients can shorten recovery as well as more than offset any extra acquisition costs, resulting in net savings for the overall hospital stay.[22]

Chinese Perspective: SMOFlipid

The same cost-effectiveness pharmacoeconomic techniques used in the European study[21] were again used in a Chinese ICU setting, but this time comparing parenteral nutrition including standard lipid emulsions (without fish oil) with those containing ω-3 fatty acids (specifically SMOFlipid [Fresenius Kabi, Bad Homberg, Germany], a multi-component intravenous lipid emulsion containing 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil [henceforward referred to as SMOF]).[23] In this case, the perspective was that of the hospital, and this study also incorporated an update to the meta-analysis of Pradelli et al,[13] leading to the inclusion of data from 5 additional recent clinical trials.[23] To perform the pharmacoeconomic analysis, a DES model was again produced based on these updated efficacy data and China-specific clinical and economic input parameters.[32,33] Two treatment arms were simulated: parenteral nutrition including (1) an ω-3 fatty-acid enriched lipid emulsion (SMOF), and (2) standard lipid emulsions (ie, that did not contain fish oil, control population). Again, no discounting was applied, and the robustness of the findings was tested by using probabilistic and deterministic sensitivity analyses.[23]

The model predicted that a strategy of parenteral nutrition with SMOF would "dominate," as it was more effective and less expensive than parenteral nutrition with standard lipid emulsions for Chinese ICU patients.[23] In brief, for parenteral nutrition with SMOF vs standard lipid emulsions, results showed a reduced overall LOS (19.48 vs 21.35 days, respectively), reduced length of ICU stay (5.03 vs 6.18 days, respectively), and prevention of 35.6% of nosocomial infections, leading to a lower total cost per patient (¥47,189 [US $6937] vs ¥54,783 [US $8053], respectively). Any extra costs for parenteral nutrition with SMOF were more than offset by savings in the cost of hospital and ICU stay and antibiotic costs, leading to an average cost saving of ¥7594 (US $1116) per patient. The robustness of these findings was also confirmed by sensitivity analyses. Thus, in the Chinese ICU setting, giving patients parenteral nutrition with SMOF may be an effective way of reducing the length of hospital and ICU stays and infectious complications and also decreasing overall treatment costs. As such, this represents a "win–win" situation for patients, hospital administration, and health insurance companies.[23]

Summary and Future Perspectives

So far, in all national scenarios investigated, the use of parenteral nutrition including fish oil has more than offset any additional acquisition costs, indicating that this an

economically and financially beneficial strategy. The studies in this review have covered different perspectives, demonstrating cost-effectiveness for different stakeholders (ie, healthcare provider, patient and family, or hospital). However, none of these studies have assessed cost-effectiveness from a third-party payer perspective, which is helpful for insurance providers to decide whether to adopt the intervention for their formulary. Although the third-party payer perspective is generally extremely relevant within pharmacoeconomic studies, it has presumably been omitted in all of the studies reviewed here because it is less relevant than other perspectives, owing to the acquisition dynamics of parenteral nutrition products (ie, these tend to be accounted for out of hospital budgets—or by patients and their families in China—rather than reimbursed by the third-party payer).

Further work is also needed to update and extend the pharmacoeconomic analyses. To this end, the 2019 meta-analysis by Pradelli et al,[34] which is the largest and most comprehensive conducted to date, has been used as the basis for a pharmacoeconomic study published recently as a conference abstract.[34] This cost–consequence analysis using a DES technique showed average cost savings in the UK, Germany, France, Italy, and Spain, ranging from €1766 to €2528 for ω-3 fatty-acid enriched parenteral nutrition vs standard parenteral nutrition (equating to US $1590–US $2276, respectively, calculated at exchange rates on August 15, 2019).[34] Thus, ω-3 fatty-acid enriched parenteral nutrition seems likely to be a cost-effective alternative to standard parenteral nutrition in the majority of patients. However, the studies conducted thus far have only covered adult hospitalized patients in China, Italy, France, Germany, and the UK, and so it would be beneficial to perform further pharmacoeconomic studies encompassing other countries and clinical settings.

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Statement of Authorship

L. Pradelli, M. Muscaritoli, S. Klek, and R. G. Martindale, equally contributed to the conception and design of the research; L. Pradelli, M. Muscaritoli, S. Klek, and R. G. Martindale, contributed to the acquisition, analysis, and interpretation of the data; R. Clark drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Review

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Use of Intravenous Lipid Emulsions With Parenteral Nutrition: Practical Handling Aspects

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Abstract

A number of topics important to the handling of intravenous lipid emulsions (ILEs) were discussed at the international summit. ILE handling includes the preparation and the administration steps in the typical use of parenteral nutrition (PN). The discussion and consensus statements addressed several issues, including standardization of the PN process, use of commercially available multi-chamber PN or compounded PN bags, the supervision by a pharmacist with expertise, limiting ILE repackaging, and infusion duration. (*JPEN J Parenter Enteral Nutr.* 2020;44(suppl S1):S74–S81)

Keywords

compounding, filtration; intravenous administration; lipid emulsions; multi-chamber; parenteral nutrition; preparation; repackaging; safety; standardization

Introduction

This manuscript is based upon presentations given at a meeting (Lipids in Parenteral Nutrition–International Summit, November 2–4, 2018, Miami, FL, USA). Statements from the consensus document that are most relevant to this article are shown in Table 1. The full consensus document is also available as part of this supplement.[1] These consensus statements provide practical advice regarding the handling and use of lipid emulsions in parenteral nutrition (PN), and as such complement formal nutrition society guidelines on this subject.

PN remains a valuable therapeutic intervention in adults and children across care settings, whether used for the short-term or long-term. Of the many vital components of a PN regimen, the intravenous lipid emulsion (ILE) with its

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Table 1. Consensus Statements From the Lipids in Parenteral Nutrition–International Summit (November 2–4, 2018, Miami, FL) Relevant to This Article.[1]

Statement Number	Consensus Statement	Expert Voting Results
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 using all-in-one admixtures, the preferable maximum infusion duration is 24 hours	100% agreement (14 agree, 0 do not agree, 0 do not wish to answer)
43	If using repackaged 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)

ILE, intravenous lipid emulsion; PN, parenteral nutrition.

various ingredients, is available for providing a dense source of energy as well as essential and conditionally essential fatty acids. As with all therapeutic interventions, the benefits of ILE outweigh the potential risks, as long as these risks are taken into account. All commercially available ILEs are thermodynamically complex oil-in-water mixtures. This combination is acceptable thanks to the use of an appropriate emulsifier. Emulsification allows the oil and water phases to exist together at a lower surface tension, to create commercial products with a homogeneous dispersion of sub-micron fat droplets in water. The ILE products therefore contain thousands of fat droplets per mL, with a mean diameter of ≈0.25–0.5 μm that are each kept separate from one another, providing a stable shelf life of 18–24 months.[2,3] Despite sharing these general characteristics, ILE products differ from each other in terms of the oil source(s), lipid concentration, fatty-acid composition, and other ingredients such as vitamin E and phytosterols. The ILE product may or may not be administered separately from all the other intravenous nutrients. Separate ILE administration may occur using the multi-bottle system, or more commonly in the 2-in-1 system (2 macronutrients [amino acids, glucose] and all micronutrients in a single bag; ILE separate). The 3-in-1 system (ie, all-in-1 or total nutrient admixture [TNA]) has all 3 macronutrients and the micronutrients in a single bag. These are the types of PN formulation *delivery* systems. There are also different types of PN *preparations* depending on how they are made and whether the proportions of macronutrients are standardized or customized to a patient's needs. The PN admixture may be compounded by a pharmacy—either customized to individual patients or standardized for patient subsets. Alternatively, the PN admixture can be prepared from commercially available multi-chamber bags (MCBs; 2-chamber or 3-chamber), with the latter containing ILE with the other 2 macronutrients. The choices of delivery system and type of preparation will vary by the institution, region, or country.

Fat droplets tend to join together over time, making ILE products thermodynamically unstable. Regardless of whether the PN admixture is compounded or commercially available (ie, MCB), when the ILE is included as part of the PN admixture its thermodynamic stability is further reduced.[2] Reflecting the properties of the ILE, a TNA is also an oil-in-water emulsion susceptible to instability. Compounding of ILEs with other PN components accelerates the rate of their physicochemical destabilization.[2] Although some physical changes might not be visible initially, these can occur over time, such as aggregation, creaming, and coalescence with fewer lipid globules but of increasing size.[4] This knowledge contributes to the limited duration of stability and the assigned beyond-use date. TNA emulsion stability is particularly compromised by the addition of ingredients that decrease pH or that increase cation load.[4] The qualitative and quantitative limits of numerous combinations of additives for relatively stable admixtures are provided by the manufacturers of specific MCBs, can be found in the literature for selected compounded PN, or must be tested according to accepted pharmacopeial methods. Although there is no comprehensive stability data for all possible combinations for emulsion compatibilities, there are generalities to minimize risks that are incorporated by the pharmacist to standardize the PN process. Thus,

pharmacists play a key role in nutrition support teams because of their expert knowledge of practical handling aspects of PN admixtures.

ILE in the PN-Use Process

The PN-use process describes the system within which PN is used, and includes several patient-focused steps from patient assessment and PN prescribing, to order review and preparation, followed by administration, monitoring, and reassessment.[5] Medication errors may occur at each of these steps when communication, competency, and standardization are not in force.[6] Standardization of PN is advantageous, and should address all steps, maximizing safety and quality. The adjacent steps of *preparation* and *administration*, collectively referred to as "handling," include a number of tasks that may lead to potential challenges. Although this may be true generally for PN, the focus here is on the handling of the ILE specifically. In fact, ≈20%–30% of clinically relevant PN-related medication errors involve ILE.[7-10] Preparation tasks include compounding admixtures or activating commercial MCBs with additives, then labeling and dispensing them appropriately.[11] Administration includes verification procedures followed by setting the appropriate rate and duration of infusion with administration through in-line filtration.[12]

In the subsequent sections, data on the handling of ILE during preparation or administration, and any concerns with these findings, will be discussed from a multinational perspective. Recommendations to address and prevent these concerns will be offered, as well as further discussion of standardization.

ILE Preparation

The American Society for Parenteral and Enteral Nutrition (ASPEN) published the results of a national survey on ILE use with a gap analysis.[13] The results indicated that a majority in the United States still provide compounded PN to meet their patients' needs. This includes a 3-in-1 PN system (ie, TNA) in 42% of adults, 27% of pediatric patients, and 8% of neonates, whereas 2-in-1 PN admixtures are used by 42%, 71%, and 89%, respectively. At the time of the survey, only 22% had access to a multi-oil ILE product (ie, SMOFlipid), with the majority using pure soybean oil ILE in the United States. These data differ slightly from a 2011 survey, which reported that 28% used 3-in-1 and 45% used 2-in-1 compounded PN in adult patients.[14] It was of great interest to note that only 5 or fewer PN admixtures were prepared by those institutions caring for 50% of adults, 82% of pediatrics, and 64% of neonates.[14] Of the 16% minority using commercial MCB PN products in the United States, nearly 5% add separate ILEs to their 2-chambered PN.[13] Three-chambered PN commercial products contain 3 macronutrients, each in a separate compartment, with or without electrolytes; vitamins and trace elements are added extemporaneously to the bag when prepared for the patient.

The use of commercial MCBs, particularly 3-chambered products that include an ILE, is much more widespread in Europe than in the United States for both hospitalized patients and in home PN patients.[15-19] For example, a study in Switzerland, France, and Belgium showed that 80% of adults and 20% of children requiring PN were given standardized rather than customized PN formulae, mainly provided as MCBs.[15] Moreover, a national survey of hospitals in Switzerland revealed that 83% of PN bags were administered as commercial MCBs.[16] Similarly, depending on the market availability, the use of MCBs is increasing in both Asia and Latin America.[20-22] The benefits of standardized PN and processes will be covered later in this manuscript. There was considerable discussion about the roles of compounded PN and commercially available MCB products with regional and national differences based on product availability at this summit. The European market has a much larger variety of commercial MCB PN products than is available in the US market, with a broader range of non-protein energy–nitrogen content.

Several concerns exist with the compounding of PN. Firstly, 23% of pharmacist respondents to the US national survey indicated that they work at organizations where no pharmacist is dedicated to review PN orders.[14] Aside from performing the clinical review to double-check the appropriateness of indication and nutrient dosing, the reviewing pharmacist should evaluate the prescribed formulation for compatibility of each ingredient with all other ingredients, and the stability of the final TNA emulsion. Commercial MCB products require less manipulation to activate, and then require a limited number of additives. However, addition of an ILE to a commercial 2-chamber PN product still requires close evaluation by the pharmacist for compatibility and stability.[11] Survey data suggest that many organizations in the United States may be compounding small numbers of PN with limited experience or appreciation of the compatibility and stability limitations, potentially placing patients at risk of receiving incompatible or unstable PN admixtures.[14] Contrary to what is often presumed, the incompatible or unstable PN admixture is rarely obvious to the unaided eye, and instead requires a good working knowledge of pharmaceutics.[4]

The US Pharmacopeia chapter 729 provides pharmaceutical specifications for ILE products,[23] describing emulsion stability methods and criteria (intensity-weighted mean droplet diameter <0.5 μm; volume-weighted percentage of fat globules >5 μm [$PFAT_5$] <0.05%) also applied to final PN admixtures. Among pharmaceutical criteria, ILE products are most stable at pH ≈7–8, whereas the acidity of the glucose component requires its combination with amino acids for its buffering capacity prior to incorporating ILEs in appropriate proportions for each TNA.[4]

However, at a nonacidic pH there are then limits to calcium compatibility, and in turn, electrolytes can destabilize the ILE by reducing the ζ-potential, which otherwise maintains the homogeneous dispersion of sub-micron fat droplets in water.[4] As the concentration of an ILE is diluted in the course of admixing the TNA, stability is further undermined with a reduction in repulsion forces between lipid droplets, increasing the risk of coalescence.[4] This change allows formation of the larger-size fat globules (ie, increases $PFAT_5$).[4] The administration of these unstable formulations has potentially adverse systemic effects.[24] Relative to long-chain triglycerides, medium-chain triglycerides decrease the stress on the emulsifier system in a PN admixture.[24,25] The specific threshold concentration at which this occurs will differ by ILE product and amino acid product, among other factors.[26] Depending on a patient's nutrient needs, there are occasions in which a prescribed TNA is expected by the pharmacist to be unstable as an emulsion and so requires separate ILE infusion. When feasible, TNA is preferred from multiple perspectives—metabolic, infectious risk with less line manipulation, ease of administration, and cost.

It is recommended that a pharmacist review all ordered PN admixtures, whether they will be compounded or further prepared from a commercial MCB product.[11,26,27] It is worth noting that at this meeting it was discussed that preparation of PN should only be performed by or under the direct supervision of an expert pharmacist (see also statement 40). Such issues have been highlighted by increased risk of bloodstream infection when micronutrients are added to MCB PN on the ward instead of in a controlled pharmacy area.[28]

Pharmacists should use clinical guidelines, consensus recommendations, and published data, and realize that formulation limits on macronutrient dosing will vary by amino acid product *and* by ILE product. The 3-macronutrient MCB PN products are an available option with already recognized compatibility and stability limits available from the manufacturer. State boards of pharmacy or other comparable professional regulatory bodies should hold accountable those who prepare PN admixtures, as this takes place in the pharmacy. Although multi-bottle or 2-in-1 PN systems are used when stability concerns exist, TNA (whether commercial MCBs or custom compounded) reduces manipulations and resultant risk of infection and lowers costs compared with multi-bottle PN systems.[29] Among other advantages, commercial MCB products are also associated with fewer errors.[30]

Although the use of an automated compounding device to prepare PN admixtures from multiple component products generally precludes in-process filtration, this practice can be incorporated as indicated during compounding.[31] This could help reduce the particulate load from extrinsic and intrinsic contamination. The automated compounding device and subsequent infusion container and administration set can also contribute to the particle load administered to patients.[31]

Among other issues, an ASPEN survey identified that the majority of organizations in the United States that care for pediatric and neonatal patients repackaged their original ILE products into smaller volumes.[13] This practice is also common in Europe.[32,33] Most commonly, the ILE is drawn up into syringes (56% pediatric, 81% neonate), followed by the draw-down method (31% pediatric, 9% neonate).[13] This is often done to decrease waste, especially if there are product shortages, and to reduce the risk of administering excessive lipid volume from a large commercial container.

The concern with repackaging is focused on the contamination risk reported to be 2.3%–7.9% in controlled studies,[34-37] which followed earlier reports.[38-42] Although seemingly low, this is an undue risk in such vulnerable patients. Despite the absence of smaller commercial ILE containers, current recommendations are to avoid the repackaging of ILEs into syringes, though using the draw-down technique may be preferable.[26,27] The risks for contamination are best weighed against the benefits of the smaller volumes of ILE for infusion.[43] Notably, at this meeting, there was consensus to avoid repackaging, but if necessary it should be performed aseptically (statement 41). This should be done by the pharmacist. To reduce risk from infusing potentially contaminated repackaged ILEs, the duration of infusion is best limited to a maximum of 12 hours, though disagreement remains on this issue in both the United States and Europe (statement 43). In many settings in the United States and in Europe, the practice remains to allow a 24-hour maximum infusion duration if the repackaging is performed under aseptic conditions in the pharmacy.[13] However, it should be noted, from the limited literature on this subject, that even repackaging using an automated compounder in an aseptic environment was still associated with a contamination risk.[37]

ILE Administration

The ASPEN survey on ILE use revealed that most organizations in the United States administer ILEs separate from the rest of the PN admixture (43% adult, 57% pediatric, and 89% neonatal).[13] Otherwise, the ILE is included as part of the PN admixture in 38% of adult, 18% of pediatric, and 6% of neonatal patients.[13] Other organizations make both options available to their patients (19% adult, 25% pediatric, and 6% neonatal).[13] When the ILE is administered separately, most (72% adult and 41% pediatric) do so in a single container infused over a maximum of 12 hours,[13,14] but the remainder infuse the ILE over as much as 24 hours, from a single container (25% adult, 50% pediatric), or using 2 containers each for a maximum of 12 hours (3% adult and 10% pediatric).[13,14] The administration of ILE separately

may lead to multiple manipulations, increasing the risk of catheter-related infection and cost.[12]

There are 2 major concerns from these findings. First is the risk of incorrect ILE infusion rates, particularly when administered separately from the 2-in-1 PN, which is a commonly reported error.[7,8] The adverse effects from excessive rates of administration (ie, fat overload syndrome), admittedly vary by oil content and fatty-acid profile; mixed-oil ILE products tend to have better clearance when the fish-oil component does not exceed 20%.[44] Second, the prolonged infusion duration of a single ILE container would increase the risk of infection if the ILE was contaminated, recalling that contamination rates identified at the end of infusion may approach 8%.[26] The infusion of the intravenous anesthetic propofol, which is formulated in ILE, is limited to 6–12 hours before the vial and administration set need to be changed, in large part because of this contamination risk.[45,46]

Overload of lipids has been associated with hypertriglyceridemia and liver dysfunction, among other manifestations. However, these adverse effects related to PN therapy have also been described in patients despite receiving a rational dose of ILE. A statement and discussion on limiting hypertriglyceridemia is noted elsewhere in this supplement. ILEs containing fish oil and medium-chain triglycerides may reduce the risk of hypertriglyceridemia by accelerating triglyceride clearance, and have been suggested to deal with hypertriglyceridemia without lowering the administration of energy.[47] Similarly, the use of pure fish oil or ILEs with a fish-oil component have been related to a lower risk of hepatic dysfunction or recovery of the liver abnormalities.[48-50] The current recommendations are to infuse the ILE, when a part of the TNA, over a period not to exceed 24 hours (statement 42). However, for separate infusion of ILE, the duration of infusion from the original manufacturer's container should not exceed 12 hours.[51]

The ILE-use survey also asked about in-line filtration during administration across PN formulation types.[13] Filtration is required by the Federal Drug Administration (FDA) and remains a best practice in the United States to limit the infusion of unwanted substances (eg, unpredictable microprecipitates or particulate matter). The infusion of a 3-in-1 PN often includes a 1.2-μm filter (79% adult and 81% pediatric), though a filter was not used in the remainder of patients.[13] When infusing a 2-in-1 PN, most used a 0.22-μm filter (78% adult, 79% pediatric, and 87% neonatal), or a 1.2-μm filter (15% adult, 19% pediatric, and 12% neonatal).[13] When administered separately, ILE is commonly infused through a 1.2-μm filter (85% adult, 90% pediatric, and 81% neonatal); however, the remaining patients had ILE infused without filtration, which for some was merely a cost-avoidance method.[13] According to surveys performed in Europe and Japan, the use of filters is not widespread in these geographical locations.[31,52-54]

Given the significant risks of infusing particulates, including large lipid globules, there are long-standing recommendations for filtering PN admixtures in the United Kingdom and United States.[31,55] The concerns over lack of in-line filtration of PN or separately infused ILE include risks for morbidity and mortality. For example, 2 fatalities and at least 2 additional cases were reported of respiratory distress during PN administration, with unrecognized precipitate confirmed by visible diffuse microvascular emboli on autopsy, and thus the FDA issued an alert for this hazard.[56] Large fat globules from unstable emulsions are also problematic if infused without the benefit of filtration. With reference to the $PFAT_5$, the most sensitive indicator of emulsion stability over time, a coarse dispersion that includes larger fat globules may occlude fine pulmonary capillaries or may escape the lungs only to deposit in other organ capillaries and has been associated with organ dysfunction and hypertriglyceridemia in animal models.[57-59] The current recommendations to reduce the risk includes filter use during PN administration, with filters placed as close to the patient as possible, particularly for those with the highest susceptibility to detrimental effects (eg, critically ill, immunocompromised, neonates).[33] The interaction between particulates and damaged endothelium may contribute to local effects (eg, phlebitis) or organ effects (eg, microcirculatory dysfunction).[31] A 1.2-μm filter is considered appropriate for ILE-containing infusions, but a 0.22-μm filter could be used for non-ILE-containing PN admixtures.[27] In the United States, the FDA requires ILE products to be administered through a 1.2-μm filter when administered separately, and this recommendation is supported by the Infusion Nurses Society.[60,61] The review of PN orders by the pharmacist for expected compatibility and stability before preparation, and subsequent filtration during administration of the final admixture are important safety steps. Regardless of how exceptional the preparation or compounding process is, some recommend that intravenous infusion of PN requires filtration to reduce the particulate matter infusing into the patient.[31]

As mentioned previously, the use of in-line filters is not widespread outside of the United States.[31,52-54,62] In Europe, the routine use of in-line filters remains controversial.[63] For instance, in-line filters did not significantly influence the incidence of bloodstream infections, phlebitis, morbidity, and mortality.[64-66] Nevertheless, according to most national recommendations in Europe, there is a role for the use of in-line filtration of TNA for patients who require intensive parenteral therapy; the immunocompromised, neonates, and children might have increased susceptibility to the detrimental effects of particulate contamination and therefore can benefit from the use of filters during the administration of PN.[31,33,67-69] In such cases, 0.22-μm filters should be

used for lipid-free admixtures and 1.2-μm filters for lipid-containing admixtures.[31,33,69,70]

Standardization of PN

Standardization of the PN process can have many benefits. Standardization refers to development and implementation of technical and practice standards incorporated into each step in the PN process so that all healthcare providers deliver the same level of safe care.[5,71] This includes all the tasks around the preparation and administration of PN (statement 38). Standardization may include use of standardized PN formulae (MCB or compounded), which would lead to improved safety and efficiency. The use of standard PN in selected patients may lead to advantages in efficiency and economy without compromising clinical appropriateness.[20,72]

Standardization using MCBs has advantages over compounded bags and multi-bottle systems, including shorter length of hospitalization, reduced time and labor, and fewer errors in PN preparation.[29,30] However, standard PN formulations cannot always cover the macronutrient needs of all patients (eg, some patients with renal impairment, critical illness, and those undergoing long-term PN).[72] Of particular note is the use of MCBs after surgery, as surgical patients account for a large proportion of patients requiring PN. PN surgical guidelines state that individualized nutrition is often unnecessary in patients without serious comorbidity.[73] This allows the use of commercially available MCBs containing ILEs for most patients. Recent pediatric guidelines also suggest that standard PN can generally be used over individualized PN in the majority of pediatric and newborn patients.[74] Of course, individually customized PN should be used when the nutrition requirements cannot be met by the available range of standard PN formulations.[74] The limited availability of MCB products in some countries can also determine usage patterns.

An ILE-containing MCB can be customized depending on patients' needs. For example, besides vitamins and trace elements, electrolytes and l-alanyl-l-glutamine where available can be included. Additional electrolytes or other substances should rarely be added to any PN outside of a dedicated aseptic environment in the pharmacy facility or without pharmacist review. Thus, a knowledge of patients' clinical needs combined with pharmaceutical knowledge and experience means that pharmacists should be an essential part of the nutrition support team.

At the summit, consensus was reached that MCB (including those containing ILEs) should be used when possible, depending on local experience and economic considerations (statement 39). In the past, the potential disadvantage of using MCBs was the limited range of formulae available, but there are currently a large variety of standard MCBs on the market, except in some countries such as the United States. MCBs have certain advantages over hospital-compounded PN such as a longer shelf life, manufacturer-guaranteed stability, easy traceability, and clinical advantages mentioned previously.[29] Moreover, standardization with MCBs appears to offer significant cost savings and reduced preparation time over compounding, as well as a reduction in errors related to PN preparation.[29,30]

Data suggest that hospital-compounded PN cannot be completely replaced by MCB owing to the special needs of some patients and/or the necessity of frequent changes in the nutritional mixture composition, at least until stabilization of clinical and metabolic conditions, for example in home PN patients.[19] Still, a certain degree of customization is also achievable with commercial MCBs by, for example, adding macronutrients or micronutrients. In other words, both compounded PN and MCB systems have a valuable role in PN, and whether the 1 system is preferred over the other depends on numerous factors, including local expertise, established processes, availabilities of products, or economic considerations.

Statement of Authorship

J. Boullata, D. Berlana, M. Pietka, S. Klek, and R. Martindale equally contributed to the conception and design of the research; J. Boullata, D. Berlana, M. Pietka, S. Klek, and R. Martindale contributed to the acquisition, analysis, and interpretation of the data; and J. Boullata drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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