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Intravenous Lipid Emulsions

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Intravenous Lipid Emulsions

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Intravenous Lipid Emulsions

Volume Editors

Philip C. Calder Southampton

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Preface

Intravenous (parenteral) nutrition can be lifesaving and is an essential intervention for those without a functional gastrointestinal tract. Lipids have been in clinical use as components of intravenous nutrition for over 50 years. They were introduced as a source of energy and essential fatty acids, undoubtedly two important roles. Initially, a number of plant seed oils were explored as sources of lipids for use in intravenous nutrition. Soybean oil was favoured over other candidate oils and, since the 1960s, emulsions of soybean oil with egg lecithin have been the most widely used. A better understanding of the metabolic and functional roles of the fatty acid components of intravenous lipid emulsions has led to a re-consideration of what lipid emulsions should bring to intravenous nutrition beyond the basic nutritional attributes of energy and essential fatty acids. There is a view that pure soybean oil may not present an optimal fatty acid composition, being very rich in one fatty acid, i.e. the essential omega-6 fatty acid linoleic acid. Hence, progressively more complex lipid formulations have been introduced that typically combine soybean oil with one or more other oils. These formulations include mixtures of soybean oil with the so-called 'medium-chain triglycerides' or MCTs, which are usually derived from coconut oil or palm kernel oil, mixtures of soybean oil with olive oil, mixtures of soybean oil, MCTs and fish oil, and mixtures of soybean oil, MCTs, olive oil and fish oil. A pure fish oil emulsion is also available, as are the so-called 'structured lipids', in which the fatty acids from soybean oil and MCTs have been randomly inter-esterified. These emulsions are all considered safe and well tolerated, although they may be cleared from the circulation at different rates. The most exciting characteristics of this range of lipid emulsions for intravenous use is that they offer the opportunity to deliver high amounts of specific fatty acids and that they are likely to possess different functional properties; in particular, they can influence inflammatory processes, immune responses and hepatic metabolism. The uptake of the different new lipid emulsions into routine clinical care has been varied according to patient type and geography, but these emulsions have been subject to considerable research. Relevant applications include children and adults who require intravenous nutrition because of short bowel syndrome, premature infants, those destined to undergo elective surgery, post-surgical patients, and the critically ill. These varied patient groups may benefit in different ways from the

new lipid emulsions, for example, some could benefit from a better balanced supply of fatty acids for maintenance of organ function and others could benefit from the ability of some fatty acids, such as the long-chain omega-3 fatty acids found in fish oil, to modulate inflammation and immune responses. The new lipid emulsions may also offer the opportunity to deliver high amounts of specific functional fatty acids in acute settings such as after severe head injury or myocardial infarction. This book brings together expert authors to provide state-of-the-art reviews of different nutritional, technological, and clinical aspects of the lipid emulsions designed for intravenous nutrition. It is our belief that the articles herein will provide the reader with a broad range of relevant and up-to-date information on the covered topics. In our view, these articles will appeal equally to basic scientists, clinical researchers and clinical practitioners and will serve to provide significant advances in the knowledge and understanding of this field. Of course, this is a moving field, with new studies being published regularly; nevertheless, these articles will remain a valuable resource to understand the background on newly emergent research in this exciting field.

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Introduction to Fatty Acids and Lipids

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Abstract

The purpose of this article is to describe the structure, function and metabolism of fatty acids and lipids that are of particular importance in the context of parenteral nutrition. Lipids are a heterogeneous group of molecules that share the common property of hydrophobicity. Lipids range in structure from simple short hydrocarbon chains to more complex molecules, including triacylglycerols, phospholipids and sterols and their esters. Lipids within each class may differ structurally. Fatty acids are common components of complex lipids, and these differ according to chain length and the presence, number and position of double bonds in the hydrocarbon chain. Structural variation among complex lipids and among fatty acids gives rise to functional differences that result in different impacts upon metabolism and upon cell and tissue responses. Fatty acids and complex lipids exhibit a variety of structural variations that influence their metabolism and their functional effects.

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Introduction

Lipids are a heterogeneous group of molecules that share the common properties of being predominately hydrophobic and soluble in organic solvents. Lipids range in structure from simple short hydrocarbon chains to more complex molecules, including triacylglycerols (TAGs), phospholipids (PLs) and sterols and their esters. Lipids within each class may differ in the number of carbon atoms and double bonds; the branching of the hydrocarbon chain; the position and orientation of double bonds; the addition of polar groups such as choline, inositol, and ethanolamine; and glycosylation. The purpose of this article is to describe the structure, function and metabolism of fatty acids and lipids that are of particular importance in the context of parenteral nutrition.

cis 12-octadecenoic acid) and a commonly used shorthand notation in which the number of carbons and the number of double bonds are written as 18:2 and the position of the first double bond is indicated relative to the methyl carbon as 18:2*n*-6.

The range of fatty acids that are commonly encountered in the human diet and are therefore predominant in human tissues is summarised in table 1. Many of these fatty acids are relevant to parenteral nutrition. All of the unsaturated fatty acids shown in table 1 have double bonds in the *cis* configuration. *Trans* fatty acids also exist; changing the orientation of the double bonds from *cis* to *trans* changes the biophysical properties of a fatty acid and influences its biological properties.

Fatty Acid Biosynthesis

Biosynthesis of Saturated Fatty Acids

Saturated fatty acids are synthesised by the sequential addition of C₂ to an acyl chain. The full details of this pathway may be found elsewhere [1]. The process is catalysed by the cytosolic multienzyme complex known as fatty acid synthase. The initial condensation reaction results in the addition of C₂ from an acetyl group bound to a condensing enzyme to the malonyl-acyl carrier protein (ACP) complex to form acetoacetyl-ACP and CO₂ derived from the malonyl group. Acetoacetyl-ACP is reduced to butyryl-ACP, and the 4-carbon butyryl group is translocated from ACP to a condensing enzyme, thus forming a fatty acid chain-condensing enzyme complex for the next cycle of addition of 2 carbons. Palmitic acid (16:0) is generally considered to be the main product of fatty acid synthesis (i.e., the fatty acid that is finally released from the growing acyl chain) (fig. 2). However, enzymes that act to release fatty acids of shorter chain length than palmitic acid exist in some tissues. For example, in the mammary gland of some species, there are enzymes that are responsible for the release of the medium-chain saturated fatty acids that are characteristic of the milks of those species. In eukaryotes, longer-chain fatty acids are formed from palmitic acid by elongation reactions catalysed by elongases [2]. In fatty acid elongation reactions, elongases act as the condensing enzyme that transfers 2 carbons from malonyl-CoA to a fatty acyl-CoA. This step is followed by reduction and dehydration reactions to form a saturated hydrocarbon chain. Seven elongases, which differ in their selectivity for fatty acids with different chain lengths and levels of unsaturation, have been identified [2]. Elongases 1, 3, 6, and 7 preferentially catalyse the extension of saturated fatty acids and MUFAs, and the others (elongases 2, 4 and 5) act on PUFAs (fig. 2). For example, elongation of palmitic acid to stearic acid (18:0) is catalysed by elongase 6. Elongases 1, 3, and 7 catalyse the elongation of 18:0 to 24:0, while only elongases 1 and 3 act on 24:0. Further chain elongation of 26:0 involves elongase 4 (which primarily catalyses reactions involving PUFAs) (fig. 2) [2].

Table 1. Fatty acid naming, shorthand notation and common sources

Systematic name	Trivial name	Short-hand notation	Sources
Ethanoic	Acetic	2:0	Fermentation of fibre in colon
Propanoic	Propionic	3:0	Fermentation of fibre in colon
Butanoic	Butyric	4:0	Fermentation of fibre in colon; milk
Hexanoic	Caproic	6:0	Milk
Octanoic	Caprylic	8:0	Milk
Decanoic	Capric	10:0	Milk; coconut oil; palm kernel oil
Dodecanoic	Lauric	12:0	Milk; coconut oil; palm kernel oil
Tetradecanoic	Myristic	14:0	Milk; coconut oil; palm kernel oil
Hexadecanoic	Palmitic	16:0	Milk; eggs; animal fats; meat; cocoa butter; palm oil (other vegetable oils contain lesser amounts); fish oils
Octadecanoic	Stearic	18:0	Milk; eggs; animal fats; meat; cocoa butter
<i>cis</i> 9-Hexadecenoic	Palmitoleic	16:1 n -7	Desaturation of palmitic acid; fatty fish; fish oils
<i>cis</i> 9-Octadecenoic	Oleic	18:1 n -9	Desaturation of stearic acid; milk; eggs; animal fats; meat; cocoa butter; most vegetable oils, and especially olive oil
<i>cis</i> 9, <i>cis</i> 12-Octadecadienoic	Linoleic	18:2 n -6	Cannot be synthesised in mammals; some milks; eggs; animal fats; meat; most vegetable oils, and especially corn, sunflower, safflower and soybean oils; green leaves
All <i>cis</i> 9, 12, 15-Octadecatrienoic	α -Linolenic	18:3 n -3	Cannot be synthesised in mammals; green leaves; some vegetable oils, and especially rapeseed (canola), soybean and linseed oils
All <i>cis</i> 6, 9, 12-Octadecatrienoic	γ -Linolenic	18:3 n -6	Synthesised from linoleic acid; borage and evening primrose oils
All <i>cis</i> 11, 14, 17-Eicosatrienoic	Mead	20:3 n -9	Synthesised from oleic acid; indicator of essential fatty acid deficiency
All <i>cis</i> 8, 11, 14-Eicosatrienoic	Dihomo- γ -linolenic	20:3 n -6	Synthesised from γ -linolenic acid
All <i>cis</i> 5, 8, 11, 14-Eicosatetraenoic	Arachidonic	20:4 n -6	Synthesised from linoleic acid via γ -linolenic and dihomogamma-linolenic acids; meat
All <i>cis</i> 5, 8, 11, 14, 17-Eicosapentaenoic	Eicosapentaenoic	20:5 n -3	Synthesised from α -linolenic acid; fatty fish; fish oils
All <i>cis</i> 7, 10, 13, 16, 19-Docosapentaenoic	Docosapentaenoic	22:5 n -3	Synthesised from α -linolenic acid via eicosapentaenoic acid; fatty fish; fish oils
All <i>cis</i> 4, 7, 10, 13, 16, 19-Docosahexaenoic	Docosahexaenoic	22:6 n -3	Synthesised from α -linolenic acid via eicosapentaenoic acid; fatty fish; fish oils

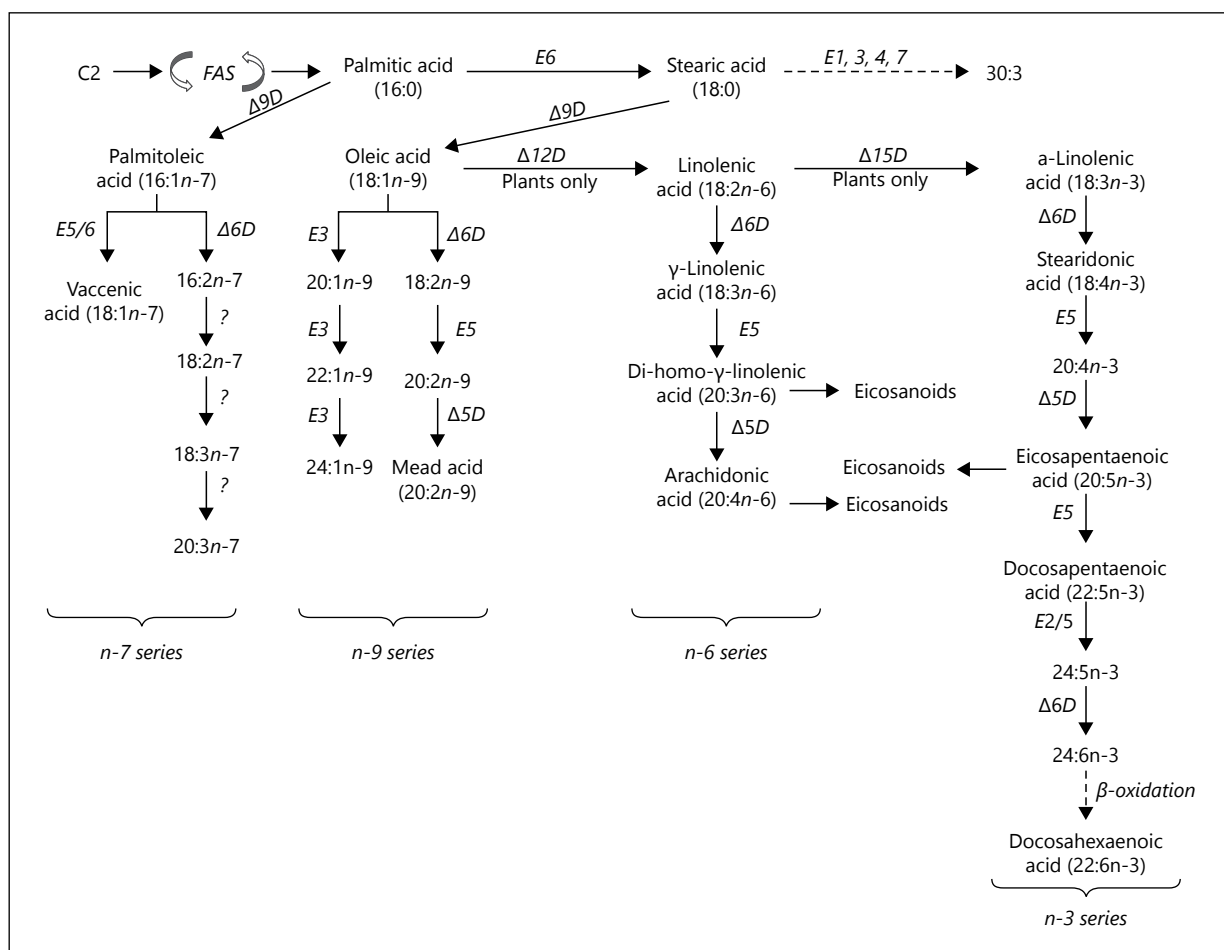


Fig. 2. The biosynthesis of saturated, monounsaturated and polyunsaturated fatty acids. C2 = Acetyl CoA; E 1–7 = elongases 1–7; FAS = fatty acid synthase; Δ5D, Δ6D, Δ9D, Δ12D, Δ15D, Δ5, Δ6, Δ9, Δ12 and Δ15 = desaturases.

Biosynthesis of Monounsaturated Fatty Acids

In mammals, fatty acid desaturation occurs primarily in the endoplasmic reticulum. The pathway used is highly conserved and has been identified in bacteria, yeasts, algae, higher plants, protozoa and animals. The enzymes that catalyse fatty acid desaturation are known as desaturases. The primary saturated fatty acid substrates for desaturation are palmitoyl-CoA (16:0) and stearoyl-CoA (18:0). The predominant reaction is insertion of a double bond between carbons 9 and 10 to form palmitoleoyl-CoA (16:1n-7) and oleoyl acid (18:1n-9). This reaction is catalysed by Δ9-desaturase (also known as stearoyl-CoA desaturase) (fig. 2).

Biosynthesis of Polyunsaturated Fatty Acids

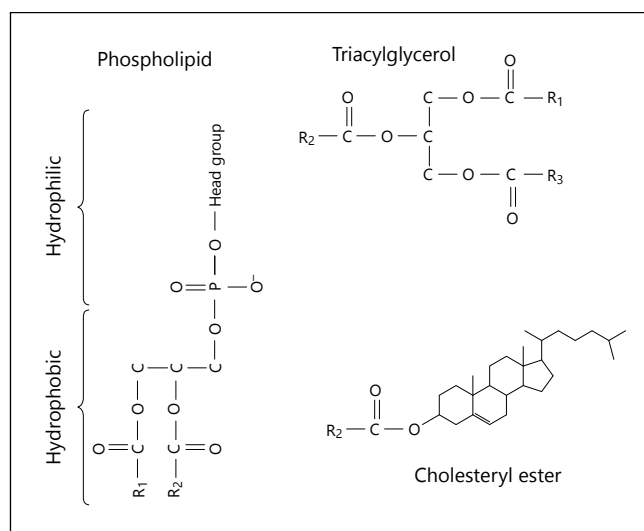
All eukaryotes and some bacteria can produce PUFAs. However, there are important differences in the specificity of the desaturases expressed in plant and animal tissues, which have implications for dietary fatty acid requirements. Plant desaturases normally introduce a new double bond between an existing double bond and the terminal methyl group (see fig. 1). The insertion of a double bond between carbons 12 and 13 of oleic acid (18:1 n -9) by the action of Δ 12-desaturase produces linoleic acid (18:2 n -6) (fig. 2). Linoleic acid can be further desaturated by insertion of a double bond between carbons 15 and 16 by Δ 15-desaturase to yield α -linolenic acid (18:3 n -3) (fig. 2). Linoleic and α -linolenic acids are the simplest members of the n -6 and n -3 families of fatty acids, respectively.

Mammals lack Δ 12- and Δ 15-desaturases, which introduce double bonds at carbon atoms beyond carbon 9 in the acyl chain. Thus, mammals cannot synthesise linoleic and α -linolenic acids. Since these fatty acids, or their metabolites, are required by mammalian cells, they are termed essential fatty acids and have to be consumed in the diet. However, to some extent, mammalian cells are able to convert linoleic and α -linolenic acids to longer-chain, more unsaturated PUFAs by further desaturation and elongation. Desaturation occurs at carbon atoms between carbon number 9 and the carboxylic acid group. Linoleic and α -linolenic acids are converted to longer-chain metabolites by the same pathway (fig. 2) [3]. The initial reaction is the insertion of a double bond at carbon 6, which is catalysed by Δ 6-desaturase. The carbon chain is then lengthened by elongase 5 to form 20-carbon fatty acids, and a further double bond is then inserted at carbon 5 by Δ 5-desaturase. The primary products of these reactions are arachidonic acid (20:4 n -6) and eicosapentaenoic acid (20:5 n -3) (fig. 2). Two carbons are then added by either elongase 5 or elongase 2, depending upon the tissue, and 2 carbons are further added by elongase 2. A further double bond is inserted at carbon 6 by Δ 6-desaturase to yield 24:5 n -6 and 24:6 n -3. These fatty acids are translocated from the endoplasmic reticulum to peroxisomes, where removal of 2 carbons by one cycle of fatty acid β -oxidation yields docosapentaenoic acid (22:5 n -6) and docosahexaenoic acid (22:6 n -3) (fig. 2) [3]. In mammals, the pathway of desaturation and elongation occurs mainly in the liver.

Since linoleic, α -linolenic and oleic acids are substrates for the rate-limiting enzyme Δ 6-desaturase, there is competition among the n -6, n -3 and n -9 families of fatty acids for the desaturation-elongation pathway. α -Linolenic acid is the preferred substrate for Δ 6-desaturase, followed by linoleic acid and then oleic acid [4]. However, because linoleic acid is much more prevalent than α -linolenic acid in most human diets, or approximately 6- to 11-fold more [5], the metabolism of n -6 fatty acids is quantitatively more important.

In the absence of dietary linoleic and α -linolenic acids, the metabolism of oleic acid is enhanced, resulting in the accumulation of mead acid (20:3 n -9) (fig. 2), which is normally only found in tissues in trace amounts. The appearance and accumulation of mead acid are taken to indicate dietary essential fatty acid deficiency.

Fig. 3. The structure of complex lipids. R = Fatty acid. For phospholipids, the head group may be any of the following: choline, ethanolamine, serine, glycerol or inositol.



The activities of $\Delta 6$ - and $\Delta 5$ -desaturases are regulated by nutritional status, by hormones and by feedback inhibition by end products. For example, high-fat diets and insulin down-regulate the activities of these enzymes [6, 7]. The conversion of α -linolenic acid to longer-chain PUFAs is very low in men [8]. However, there is evidence that women and female rats of reproductive age have higher docosahexaenoic acid levels than males do, irrespective of diet [9]. This difference is due to a greater capacity for conversion of α -linolenic acid in females and has been associated with higher levels of the mRNAs that encode $\Delta 6$ - and $\Delta 5$ -desaturases. Although sex hormones are involved, the precise mechanism of regulation is not known. Furthermore, polymorphisms in the FADS1 and FADS2 genes, which encode $\Delta 5$ - and $\Delta 6$ -desaturases, respectively, have been associated with differences in n -6 and n -3 PUFA status and with atopic and cardiovascular disease risk [10].

Structure and Synthesis of Complex Lipids

Structure of Triacylglycerols and Phospholipids

The three main classes of complex lipids in the diet and in mammalian blood and tissues are TAGs, PLs and cholesterol. TAGs and PLs share some structural features, in that the core of these molecules is glycerol, to which fatty acids and other groups are attached, mainly through ester bonds (fig. 3). Each of the carbons in the glycerol backbone of TAGs is bound to a fatty acid via an ester bond. The fatty acids at the *sn*-1 and *sn*-3 carbons are usually saturated, while the fatty acid esterified at the *sn*-2 carbon is more variable and is often unsaturated (fig. 3).

The fatty acid esterified at the *sn*-1 carbon of PLs is typically saturated and is predominately palmitic acid or stearic acid, while the fatty acid esterified at the *sn*-2 carbon is more variable. The *sn*-3 carbon is linked to phosphate via a phosphoester bond, to which a polar 'head' group is attached (fig. 3). The common head groups are choline, ethanolamine, serine, glycerol and inositol, which give rise to different classes of PLs: phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine, phosphatidylglycerol and phosphatidylinositol, respectively. Other lipids with similar structures to PLs are sphingolipids and ceramides. Each PL class contains a number of molecular species that are defined by the combination of fatty acids at the *sn*-1 and *sn*-2 carbons. An example is *sn*-1 palmitoyl (16:0), *sn*-2 linoleoyl (18:2*n*-6)PC, which can be abbreviated to PC16:0/18:2. Further diversity of molecular species is produced by differences in the nature of the bond that links the fatty acid at the *sn*-1 carbon to the glycerol backbone. This fatty acid may be an ester, alkyl or alkenyl (plasmalogen) bond. The precise composition of PL classes and molecular species differs between cells and tissues. PC is the predominant PL in most cell membranes, which contain smaller and more variable amounts of other PL classes.

Biosynthesis of Triacylglycerols and Phospholipids

There are two distinct pathways for the synthesis of TAGs, one of which occurs only in enterocytes, while the other is found in a wide range of tissues, including the liver, skeletal muscle and adipose tissue. TAG biosynthesis in enterocytes involves the step-wise esterification of fatty acids to carbons 1 and 3 of monoacylglycerol (in which the fatty acyl chain is esterified at carbon 2), derived from digested lipids. In other tissues, TAG biosynthesis involves the synthesis of phosphatidate from glycerol-3-phosphate by sequential esterification of fatty acids at carbons 1 and 2, followed by dephosphorylation and esterification of a third fatty acid at carbon 3.

The Kennedy pathway is the principal mechanism of PC and PE biosynthesis in mammals [11]. For example, PC is activated in the rate-limiting reaction by the addition of cytidine diphosphate to form cytidine diphosphate-choline. Choline is then transferred to phosphatidate to form PC [11]. The fatty acid composition of newly synthesised PC and PE may then undergo further modification by acyl-remodelling reactions that exchange fatty acids at either the *sn*-1 or the *sn*-2 position, known as the Lands pathway [12]. PC can also be synthesised by N-methylation of PE [13], particularly in the liver, where approximately 50% of PC molecular species that contain PUFAs are derived from PE N-methylation [14].

Structure and Biosynthesis of Cholesterol

Cholesterol, a member of the sterol family of lipids, is characterised by a planar structure comprising four fused rings and a hydrocarbon side chain on ring D (fig. 3) [1]. The hydroxyl group on ring A orientates cholesterol in cell membranes and can be esterified to fatty acids to form cholesteryl esters (CEs). Cholesterol is a substrate for the formation of sex hormones, including testosterone and oestrogen, and for the syn-

thesis of vitamin D in skin. The initial reaction in cholesterol biosynthesis involves the formation of acetoacetyl-CoA, which is converted to hydroxymethylglutaryl-CoA (HMG-CoA) by HMG-CoA reductase in a rate-limiting reaction. HMG-CoA reductase is the target of statins, a class of cholesterol-lowering drugs used in the treatment of hypercholesterolaemia and cardiovascular disease. HMG-CoA is converted to cholesterol via a series of condensation and isomerisation reactions [1]. The formation of CEs occurs in the blood and involves the transfer of a fatty acid from the *sn*-2 position of PC to cholesterol. This reaction is catalysed by lecithin:cholesterol acyl transferase. The pattern of fatty acids that are esterified to cholesterol is determined by the specificity of lecithin:cholesterol acyl transferase, which differs between animal species [15].

Lipid Digestion, Absorption, and Transport in the Bloodstream and Delivery to Tissues

Digestion and Absorption of Dietary Lipids

TAGs are the main form of dietary lipid and must be hydrolysed to their constituent fatty acids before they can be absorbed across enterocyte membranes. Pancreatic lipase is quantitatively the most important enzyme involved in TAG hydrolysis in adults [16]. Lipid droplets are emulsified by the action of bile salts to form large molecular aggregates described as ‘mixed micelles’. Pancreatic lipase catalyses the hydrolysis of fatty acids from the *sn*-1 and *sn*-3 positions of TAGs to yield 2-monoacylglycerols and free fatty acids [16]. These products of TAG digestion are assimilated by enterocytes. Dietary PLs and CEs are hydrolysed by phospholipases and cholesterol esterases, respectively.

In humans, lipid absorption occurs primarily in the jejunum. Short- and medium-chain fatty acids are absorbed by enterocytes and released directly into the portal bloodstream [16]. Long-chain fatty acids are re-esterified into TAGs and PLs in enterocytes. These TAGs and PLs are then packaged within the enterocyte into lipoproteins, termed chylomicrons, that are secreted into the lymphatic circulation and that then enter the bloodstream via a thoracic lymphatic duct, thus bypassing the liver.

Transport of Fatty Acids in the Bloodstream and Delivery to Tissues

Lipids are characteristically hydrophobic, which represents a challenge for transporting them around the body in the blood, which is aqueous. Two physiological strategies have evolved to solve this problem: the transport of fatty acids non-covalently bound to albumin, known as non-esterified fatty acids (NEFAs), and the transport of complex lipids in lipoproteins [16] (fig. 4). The bulk of circulating NEFAs is derived from the hydrolysis of TAG stores within adipose tissue by hormone-sensitive lipase (HSL). The remaining NEFAs are derived from fatty acids that are released by

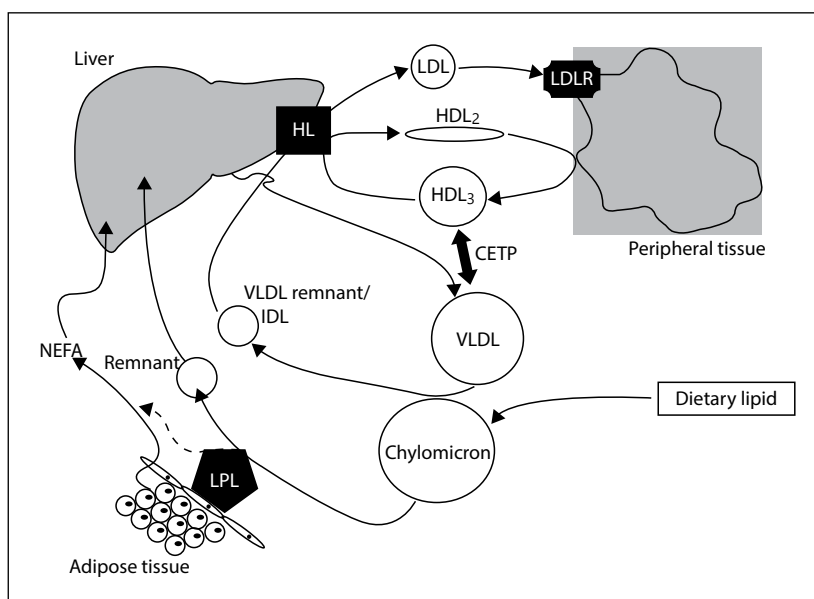


Fig. 4. An overview of lipoprotein metabolism. CETP = Cholesteryl ester transfer protein; HDL = high-density lipoprotein; HP = hepatic lipase; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDLR = LDL receptor; LPL = lipoprotein lipase; NEFA = non-esterified fatty acid; VLDL = very-low-density lipoprotein.

lipoprotein lipase (LPL)-mediated hydrolysis of the TAGs carried in lipoproteins but that are not entrapped by tissues and thus spill over into the circulation [17]. Plasma NEFAs are destined to be used mainly as energy sources or are esterified into TAGs and PLs by the liver and secreted in very-low-density lipoprotein (VLDL) (see below).

Lipoproteins are large complexes of lipid and protein. There are four major classes of lipoprotein, which differ in their ratio of lipid to protein; in their proportions of TAGs, CEs, cholesterol and PLs; and in their function and metabolism. The protein moieties of lipoproteins are termed apolipoproteins. These proteins, along with the hydrophilic head groups of PLs, facilitate the interaction of lipoprotein particles with the aqueous phase of the blood, maintain these particles' structural integrity, and mediate the interaction between lipoproteins and enzymes and cell surface receptors, thus directing lipoprotein metabolism.

Chylomicrons transport lipids of dietary origin (fig. 4), the principal components being a large core of TAGs encapsulated by a PL monolayer and specific apolipoproteins, including apoB48 [16]. Chylomicrons in the bloodstream bind to LPL on the endothelial surfaces of blood capillaries, primarily in adipose tissue but also in muscle and other organs [16]. LPL catalyses the hydrolysis of chylomicron TAGs, releasing fatty acids that are assimilated by tissues by the action of fatty acid-binding proteins and transporters [16]. The remaining particles, which con-

tain fewer TAGs and are enriched in CEs, are termed chylomicron remnants. These are removed from the plasma by a receptor-mediated process in the liver. LPL is regulated by diet and hormones such as insulin so that following a meal, LPL activity increases specifically in adipose tissue to facilitate the storage of fatty acids [16].

VLDL particles, like chylomicrons, contain predominantly TAGs and apoB100. VLDL particles transport TAGs of endogenous origin [16], which are synthesised in the liver, primarily from the circulating NEFA pool and from *de novo* synthesis from glucose [16]. The catabolism of VLDL is very similar to that of chylomicrons and results in VLDL remnants or intermediate-density lipoproteins, which in humans, are further processed by the liver to yield LDL (fig. 4).

LDL particles are the major carriers of plasma cholesterol in humans, although this is not so in all mammals, including the rat. ApoB100 acts as a ligand for the cell surface receptors that are responsible for LDL uptake and metabolism by the cell.

HDL particles transport cholesterol from peripheral cells and tissues to the liver (fig. 4), a process generally referred to as reverse cholesterol transport. This process enables the removal of unesterified cholesterol from cell membranes and plasma lipoproteins and its transport to the liver, where it is degraded or used for bile acid synthesis [16]. There is also a reciprocal exchange of CEs and TAGs between VLDL and HDL, which is facilitated by cholesteryl ester transfer protein.

The Roles of Fatty Acids

Fatty acids have many diverse functions in cells; their principal roles are as energy sources and as membrane constituents. Through these different actions, fatty acids are able to influence cellular functions (fig. 5) and to thus affect physiological responses.

Fatty Acids as Fuels

Fatty acids are stored as TAGs in adipose tissue and, to some extent, in skeletal and cardiac muscle. The release of fatty acids from TAGs in adipose tissue is catalysed by HSL, which is positively regulated by adrenaline, noradrenaline, and glucagon and is inhibited by insulin [16]. Thus, following a meal, the action of insulin drives the deposition of dietary fatty acids in adipose tissue by up-regulating LPL and suppressing HSL. Insulin also increases glucose uptake into adipose tissue, which provides, via glycolysis, the glycerol-3-phosphate that is required for TAG synthesis. In contrast, an increase in the adrenaline or noradrenaline concentration during exercise or a stress response or in glucagon during fasting enhances HSL activity and increases the release of NEFAs from adipose tissue.

The fatty acids released by TAG hydrolysis are used primarily for the production of energy in the fatty acid β -oxidation pathway in mitochondria and peroxisomes. The rate of fatty acid β -oxidation is controlled by the intracellular fatty acid concen-

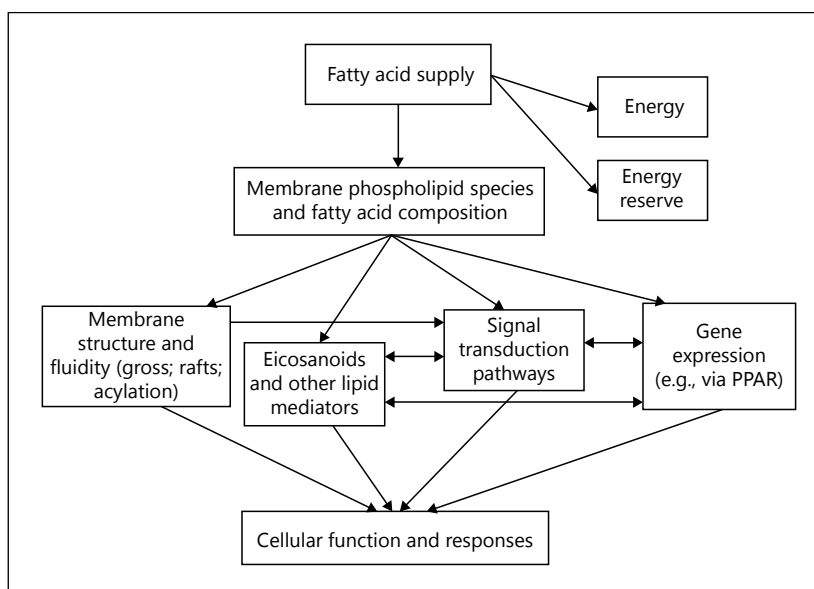


Fig. 5. A summary of the roles of fatty acids in cell function. PPAR = Peroxisome proliferator-activated receptor.

tration, which in turn is determined by the plasma NEFA concentration [16]. Short- and medium-chain fatty acids can readily penetrate mitochondria, while long-chain acyl-CoA requires the coordinated action of isoforms of carnitine palmitoyl transferase on the mitochondrial outer and inner membranes, which represents the rate-limiting step of fatty acid β -oxidation [1]. Fatty acid β -oxidation involves the progressive removal of two-carbon units as acetyl-CoA, which is normally oxidised in the Krebs cycle. Compared with mitochondrial β -oxidation, peroxisomal β -oxidation has a much broader substrate specificity and is especially active towards very long-chain fatty acids [1]. The rate-limiting reaction of peroxisomal fatty acid β -oxidation is catalysed by acyl-CoA oxidase rather than carnitine palmitoyltransferase-1, which is rate limiting for mitochondrial fatty acid oxidation.

Fatty Acids as Membrane Components

Fatty acids have important roles in membrane structure and function that influence cell activity (fig. 5). The fatty acid composition of the lipid bilayer influences the fluidity of the membrane, which in turn can modify the activities and interactions between integral proteins. In addition, membrane lipids, and particularly PLs, can be substrates for the production of lipid second messengers in signal transduction pathways.

The overall fatty acid composition of membrane lipids is characteristic of the individual cell and membrane types [18]. Under normal conditions, the membrane bi-

layer is in a 'fluid' state, meaning that membrane proteins and lipids can migrate within the plane of the membrane. The fluidity of a membrane is strongly influenced by the fatty acid composition of its constituent lipids [18, 19], so changes in the fatty acid composition of cell membranes can modify protein activities and, consequently, cell function [18, 20–23].

Fatty Acids and Signal Transduction

Eicosanoids are a group of bioactive mediators that are oxygenated derivatives of the 20-carbon PUFAs dihomo- γ -linolenic, arachidonic and eicosapentaenoic acids. Eicosanoids include prostaglandins (PGs) and thromboxanes (TXs) (collectively termed prostanoids) and leukotrienes (LTs), lipoxins, hydroperoxyeicosatetraenoic acids and hydroxyeicosatetraenoic acids. Usually, the main precursor for eicosanoid synthesis is arachidonic acid. Eicosanoids produced from arachidonic acid tend to have greater biological activities than those derived from dihomo- γ -linolenic or eicosapentaenoic acid. Release of the precursor PUFA from membrane PC is catalysed by phospholipase A2, while release from membrane phosphatidylinositol-4,5-bisphosphate is catalysed by phospholipase C and a diacylglycerol (DAG) lipase. The pathways of eicosanoid synthesis begin with cyclooxygenase (COX), which ultimately yields the PGs and TXs, or with 5-, 12- or 15-lipoxygenase (LOX), which yields the LTs, hydroperoxyeicosatetraenoic acids, hydroxyeicosatetraenoic acids and lipoxins. The amount and nature of the eicosanoids that are synthesised are determined by the availability of arachidonic acid and other substrates; by the relative activities of phospholipase A2, phospholipase C, COX and LOX; by the cell stimulus; and by the cell type. The arachidonic acid-derived eicosanoids have important roles in inflammation and in the regulation of immune responses, platelet aggregation and smooth muscle contraction.

Dihomo- γ -linolenic and eicosapentaenoic acids compete with arachidonic acid for metabolism and therefore decrease the production of COX and LOX products from arachidonic acid. Dihomo- γ -linolenic and eicosapentaenoic acid-derived eicosanoids tend to be less potent than those generated from arachidonic acid. Eicosapentaenoic acid and docosahexaenoic acid give rise to mediators, termed resolvins and protectins, that appear to be important in the resolution of inflammation and the control of immune responses [24].

The hydrolysis of membrane PLs by phospholipases C and D generates second messengers, including DAG and phosphatidic acid, which in turn activate enzymes such as protein kinase C. The combination of fatty acids at the *sn*-1 and *sn*-2 positions of DAG and phosphatidic acid modifies the activation of protein kinase C [25].

Fatty Acids and Gene Expression

In addition to their effects on cell signalling processes, fatty acids can modify transcription directly via the family of transcription factors known as peroxisome proliferator-activated receptors (PPARs). Fatty acids bind to PPAR/retinoic-X-recep-

tor heterodimers that in turn bind to PPAR response elements in gene promoters, including those of enzymes involved in fatty acid β -oxidation [26, 27]. Members of the PPAR transcription factor family have distinct tissue distributions and functions. For example, PPAR α is highly expressed in the liver and promotes fatty acid β -oxidation, while PPAR γ 2 is involved in regulating adipocyte differentiation and the metabolic responses of adipocytes [28].

Concluding Remarks

Lipids are ubiquitous in the human diet and in human blood, cells and tissues and are a heterogeneous group of molecules that share the common property of hydrophobicity. Lipids range in structure from simple short hydrocarbon chains to more complex molecules, including TAGs, PLs and sterol esters, and are transported in the bloodstream as complexes with proteins, termed lipoproteins. The proteins serve to stabilise the lipoprotein structure and to direct its metabolism. The bulk of excess dietary lipid is stored as TAGs in adipose tissue. Complex lipids have roles in lipid transport, in cell membrane structure and in cell signalling. The fatty acid components of complex lipids have diverse biological functions that are determined by their structural characteristics, such as chain length and the presence, number and position of double bonds within the hydrocarbon chain. Fatty acids are important substrates for energy generation and present an important alternative to glucose in this regard. As constituents of PLs and other complex lipids, fatty acids are important cell membrane components that act to influence membrane fluidity and the function of membrane proteins through effects on the membrane environment. Several fatty acids seem to play direct roles in cell signalling, thus influencing gene expression, and a number of PUFAs serve as substrates for the biosynthesis of biologically active lipid mediators, including PGs, TXs, LTs and resolvins. Through these many actions, the mix of complex lipids and their constituent fatty acids in the environment of cells and tissues modifies the responsiveness and functionality of those cells and tissues. This phenomenon is well described for metabolic responses and for inflammatory, immune, platelet, cardiac and neurological function. Therefore, modifying the lipid environment may lead to alterations of metabolic responses and of cell and tissue function, opening the way for such modifications of the lipid environment to be used for therapeutic purposes. Lipid emulsions that are commercially available for use in intravenous nutrition include a range of oils from soybean oil alone; mixtures of soybean oil and so-called medium-chain triglycerides (derived from coconut oil or palm kernel oil) or of soybean oil and olive oil; and more complex mixtures of soybean, medium-chain triglyceride, olive and fish oils [29]. These different oil mixtures present quite a variety of fatty acid compositions, varying greatly in the proportions of medium-chain saturated, long-chain saturated, monounsaturated, *n*-6

polyunsaturated, and *n*-3 polyunsaturated fatty acids [29]. Given that these different fatty acid classes have different biological roles and functions, it is likely that the different lipid emulsions available will have variable effects on cell and tissue function when they are used [30]. This variability could in turn influence clinical outcome.

References

- Gurr MI, Frayn KN, Harwood JL: Lipid Biochemistry. Oxford, Blackwell Science, 2002.
- Guillou H, Zadavec D, Martin PG, Jacobsson A: The key roles of elongases and desaturases in mammalian fatty acid metabolism: Insights from transgenic mice. *Prog Lipid Res* 2010;49:186–199.
- Sprecher H, Chen Q, Yin FQ: Regulation of the biosynthesis of 22:5n-6 and 22:6n-3: a complex intracellular process. *Lipids* 1999;34(suppl):S153–S156.
- British Nutrition Foundation: Unsaturated Fatty Acids: Nutritional and Physiological Significance: the Report of the British Nutrition Foundation's Task Force. London, Chapman & Hall, 1992.
- Burdge GC, Calder PC: Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod Nutr Dev* 2005;45:581–597.
- Cho HP, Nakamura M, Clarke SD: Cloning, expression, and fatty acid regulation of the human delta-5 desaturase. *J Biol Chem* 1999;274:37335–37339.
- Cho HP, Nakamura MT, Clarke SD: Cloning, expression, and nutritional regulation of the mammalian Delta-6 desaturase. *J Biol Chem* 1999;274:471–477.
- Burdge G: Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. *Curr Opin Clin Nutr Metab Care* 2004;7:137–144.
- Burdge GC, Calder PC: Dietary alpha-linolenic acid and health-related outcomes: a metabolic perspective. *Nutr Res Rev* 2006;19:26–52.
- Lattka E, Illig T, Koletzko B, Heinrich J: Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. *Curr Opin Lipidol* 2010;21:64–69.
- Gibellini F, Smith TK: The Kennedy pathway – De novo synthesis of phosphatidylethanolamine and phosphatidylcholine. *IUBMB Life* 2010;62:414–428.
- Shindou H, Hishikawa D, Harayama T, Yuki K, Shimizu T: Recent progress on acyl CoA: lysophospholipid acyltransferase research. *J Lipid Res* 2009;50(suppl):S46–S51.
- Li Z, Vance DE: Phosphatidylcholine and choline homeostasis. *J Lipid Res* 2008;49:1187–1194.
- Burdge GC, Hunt AN, Postle AD: Mechanisms of hepatic phosphatidylcholine synthesis in adult rat: effects of pregnancy. *Biochem J* 1994;303:941–947.
- Subbaiah PV, Liu M: Comparative studies on the substrate specificity of lecithin:cholesterol acyltransferase towards the molecular species of phosphatidylcholine in the plasma of 14 vertebrates. *J Lipid Res* 1996;37:113–122.
- Frayn KN: Metabolic Regulation: a Human Perspective. Chichester, Wiley-Blackwell, 2010.
- Evans K, Burdge GC, Wootton SA, Clark ML, Frayn KN: Regulation of dietary fatty acid entrapment in subcutaneous adipose tissue and skeletal muscle. *Diabetes* 2002;51:2684–2690.
- Stubbs CD, Smith AD: The modification of mammalian membrane polyunsaturated fatty acid composition in relation to membrane fluidity and function. *Biochim Biophys Acta* 1984;779:89–137.
- Calder PC, Yaqoob P, Harvey DJ, Watts A, News-holme EA: Incorporation of fatty acids by concanavalin A-stimulated lymphocytes and the effect on fatty acid composition and membrane fluidity. *Biochem J* 1994;300:509–518.
- Brenner RR: Effect of unsaturated acids on membrane structure and enzyme kinetics. *Prog Lipid Res* 1984;23:69–96.
- Murphy MG: Dietary fatty acids and membrane protein function. *J Nutr Biochem* 1990;1:68–79.
- Murphy MG, Byczko Z: Effects of membrane polyunsaturated fatty acids on adenosine receptor function in intact N1E-115 neuroblastoma cells. *Biochem Cell Biol* 1990;68:392–395.
- Mitchell DC, Niu SL, Litman BJ: Enhancement of G protein-coupled signaling by DHA phospholipids. *Lipids* 2003;38:437–443.
- Bannenberg G, Serhan CN: Specialized pro-resolving lipid mediators in the inflammatory response: An update. *Biochim Biophys Acta* 2010;1801:1260–1273.
- Bell MV, Sargent JR: Effects of the fatty acid composition of phosphatidylserine and diacylglycerol on the in vitro activity of protein kinase C from rat spleen: influences of (n-3) and (n-6) polyunsaturated fatty acids. *Comp Biochem Physiol B* 1987;86:227–232.

- 26 Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S, Staels B, Auwerx J: PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J* 1996; 15:5336–5348.
- 27 Schoonjans K, Staels B, Auwerx J: The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation. *Biochim Biophys Acta* 1996;1302:93–109.
- 28 Spiegelman BM, Flier JS: Adipogenesis and obesity: rounding out the big picture. *Cell* 1996;87:377–389.
- 29 Calder PC, Jensen GL, Koletzko BV, Singer P, Wanten GJ: Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- 30 Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.

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Fatty Acids, Lipid Emulsions and the Immune and Inflammatory Systems

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Abstract

Fatty acids modulate the responses of cells of the immune system. Inflammatory and immune responses in patients receiving parenteral nutrition may be modulated by the type of lipid used, which may influence clinical outcomes. Lipid emulsions based solely upon soybean oil may not be optimal because of the role of n-6 fatty acids in promoting inflammation and suppressing immune responses. Lipid emulsions with soybean oil in various combinations with medium-chain triglycerides (MCTs), olive oil and fish oil are available. Some early studies have suggested better immune function with MCT-soybean oil than with soybean oil alone, but the differences were small, and more recent studies suggested little difference between soybean oil, MCT-soybean oil and soybean oil-olive oil regarding markers of inflammation and immunity. The inclusion of fish oil in combination with one or more other oils (i.e. soybean, MCT, olive) in the parenteral regimen administered to patients following major gastrointestinal surgery reduces the post-surgery rise in inflammatory markers and the fall in cell-mediated immune markers. These changes are associated with improvements in clinical outcomes. Whether similar effects of intravenous fish oil occur in critically ill patients is not clear at present because of the small number, small size and variable findings of existing studies. The lipid component of parenteral nutrition may modify inflammatory and immune processes in ways that influence patient outcome. The inclusion of fish oil in parenteral nutrition for post-surgical patients is associated with benefits. The situation regarding critically ill patients is not clear.

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Introduction

Patients indicated to receive parenteral nutrition may show alterations in immunity, including the inflammatory component, beyond the expected range of change. This excessive response may relate to the nature and severity of any physical insult that the

patient has received (e.g. surgery, injury, burns, irradiation); to co-morbidities, including undernutrition and frailty; and to genotype, amongst other factors. An excessive inflammatory response and/or a suppressed acquired immune response can increase risk of adverse outcomes like organ failure and sepsis, which in turn increase the risk of mortality. It is possible that the artificial nutrition regimen can create an environment that favours excessive inflammation and immunosuppression, thus contributing to a poor outcome. It is also possible that the artificial nutrition regimen can create an environment that enables better control of inflammatory processes and makes immunosuppression less likely to occur. There is a large literature describing the effects of many different types of fatty acids, including various saturated, mono-unsaturated, n-6 polyunsaturated and n-3 polyunsaturated fatty acids, on a range of inflammatory and immune cell functions and responses [1–7]. Therefore, it is now believed that the lipid component of artificial nutrition may exert functional effects upon inflammatory and immune responses and, in this way, may be a factor involved in determining patient outcome. The aim of this chapter is to provide an overview of the effects of the different lipid emulsions currently used in parenteral nutrition on inflammatory and immune markers in patients receiving those emulsions in clinical trial settings. Parts of this chapter are based upon and updated from previous reviews on this topic [8–12].

Immunity and Inflammation: An Overview

The role of the immune system is to identify antigens derived from threatening organisms and to seek out and eliminate the sources of those antigens. Thus, the immune system is usually thought of in the context of protection against bacteria, viruses, fungi and parasites. However, it also plays roles in the identification and elimination of tumour cells and in the host's response to physical insults such as injury, surgery, burns and irradiation. The immune system is highly complex, involving many different specialised cell types dispersed throughout the body and moving between body compartments as part of routine immune surveillance or in response to specific stimuli. The cells of the immune system interact with one another and with other cell types (e.g. epithelial cells, endothelial cells, platelets, hepatocytes and adipocytes) in order to elicit and regulate local and systemic responses to infection, injury or insult. Many chemical mediators are produced during the course of an immune response; some of these are directly damaging to infectious organisms, and others play a regulatory role in promoting the activity of particular cell types, while others serve to terminate the response when the source of the initial immune stimulation has been eliminated. The immune response is often classified into two general arms, termed innate (or natural) and acquired (or specific). The innate immune response can be activated via recognition of certain general structural features of pathogens; these features may be shared by numerous pathogens. For example, lipopolysaccharide, a component of the cell

wall of Gram-negative bacteria that is also known as endotoxin, is recognised by Toll-like receptor 4 on the surface of innate immune cells. In contrast, the acquired immune response is specific for a single antigen, which must be presented by an antigen-presenting cell to an antigen-specific T cell. Due to these features, the innate response is induced quickly and is not improved by prior exposure to the triggering pathogen, while the acquired response is induced slowly but is enhanced by prior exposure to the antigen. However, the two arms of the immune system do not operate in isolation from one another: during an immune response, they interact because innate immune cells can present antigen, thus inducing the acquired response, while the acquired immune response produces chemicals that activate innate immune cells or make their processes more efficient.

Inflammation is part of a normal innate immune response. Obviously, immune responses, including the inflammatory component, are protective and hence are beneficial to health. However, inappropriate, overzealous or unregulated responses can be harmful to the host; this is particularly so for the inflammatory component since it involves the generation of chemicals that cause tissue damage. Systemic inflammatory response syndrome is the name given to an uncontrolled inflammatory response to insult (e.g. surgery, injury, trauma, burns) involving excessive production of inflammatory cytokines, and particularly tumour necrosis factor, interleukin (IL)-1 β , IL-6 and IL-8 [13]. Sepsis is the presence of systematic inflammatory response syndrome in response to or in combination with an infection [13]. In addition to hyperinflammation, patients with sepsis may also display immunosuppression, sometimes called compensatory anti-inflammatory response syndrome [14]. This state is characterised by decreased monocyte expression of human leukocyte antigens, the proteins involved in antigen presentation to T cells; an impaired ability of monocytes to stimulate T cells; impaired T lymphocyte proliferation; and an altered pattern of production of cytokines by T lymphocytes, with low levels of key cytokines involved in host defence against bacteria and viruses but high levels of the regulatory cytokines associated with inhibition of host defence against bacteria and viruses being produced (see [1, 14] for references).

Fatty Acids, Immunity and Inflammation: An Overview

The lipids within parenteral nutrition regimens are oils of plant or fish origin that present fatty acids that are mainly esterified into triglycerides emulsified by a phospholipid monolayer. The different plant and fish oils used have different fatty acid compositions, and it is these compositions that cause different lipid emulsions to have different physiological properties. There is evidence from cell culture studies that different lipid emulsions [15], different triglycerides [16] and different free fatty acids [17] have different effects on the function of immune cells. Thus, it is possible that intravenous provision of different lipids could influence host immunity and inflam-

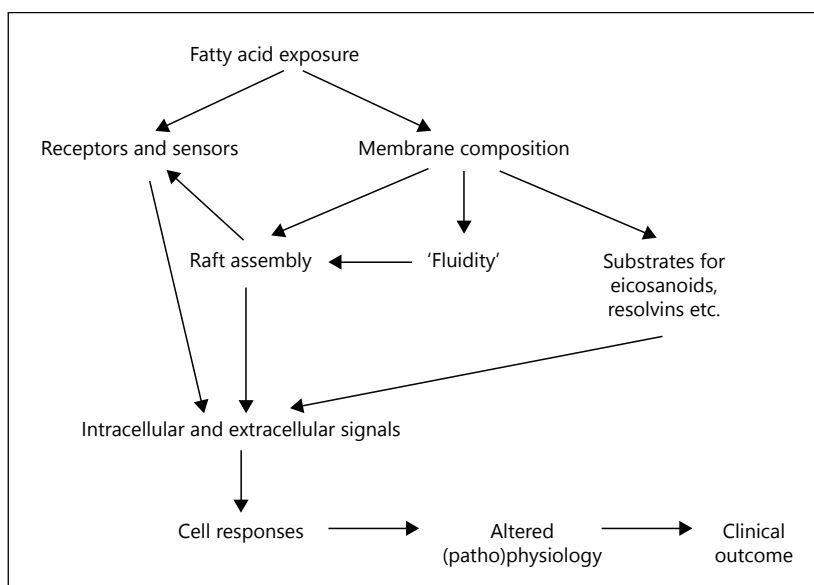


Fig. 1. General overview of the mechanisms by which fatty acids can influence the function of cells involved in inflammation and immune responses. Modified from [3] with permission from Elsevier.

matory responses, in turn influencing outcomes like infection risk and organ failure. The literature on the effects of different fatty acids on immunity and inflammation and on the underlying mechanisms is vast and is beyond the scope of this chapter. Extensive reviews of the topic may be found elsewhere [1–7]. Figure 1 depicts the general mechanisms by which different fatty acids can modify the functions of cells involved in inflammation and immunity.

Parenteral Soybean Oil, Immunity and Inflammation

Eicosanoids produced from the n-6 fatty acid arachidonic acid are involved in the inflammatory response and are regulators of inflammation and innate and acquired immunity [18, 19]. Although a simplification, these mediators are generally considered to promote inflammation and to suppress cell-mediated immunity. Arachidonic acid is synthesised from the essential n-6 fatty acid linoleic acid. Soybean oil is rich in linoleic acid, which accounts for about 50% of the fatty acids present. Therefore, there is a view that intravenous provision of lipid based solely on soybean oil may not be optimal for patient outcome. Indeed, a meta-analysis of total parenteral nutrition has suggested that compared with no lipid, the inclusion of lipids might be detrimental as far as complications are concerned [20], at least in very ill patients; most of the studies included in the meta-analysis used soybean oil-based lipid emulsions. Furthermore,

a study in patients following major gastrointestinal surgery identified that the amount of n-6 fatty acid (i.e. linoleic acid) infused was one of two predictors of the length of hospital stay (increased by 1.6 days/100 g n-6 fatty acid infused) [21]. A number of in vitro experiments have shown that soybean oil-based lipid emulsions can exert immunosuppressive effects (see [8] for references), which would clearly be detrimental in patients at risk of infection and sepsis. However, clinical trials with soybean oil-based lipid emulsions have provided conflicting evidence [22–28], with some showing selective immunosuppressive effects (table 1), perhaps linked to poorer patient outcomes (table 1). However, other studies have not shown such effects on the immune system (table 1) or on clinical outcomes (table 1). Despite the inconsistencies in the outcomes of such studies, the view that the use of lipid emulsions based entirely on soybean oil may not be optimal (or may even be harmful) has led to the development of alternative lipid emulsions for parenteral applications.

Parenteral Medium-Chain Triglycerides, Immunity and Inflammation

MCTs were introduced into parenteral nutrition regimens in the 1980s as 50:50 (by volume) mixtures with soybean oil; these MCTs are usually derived from coconut oil or palm kernel oil. The main fatty acids found in the MCTs used are medium-chain saturated fatty acids like caprylic and capric acids. Studies have directly compared the effects of soybean oil and a 50:50 mixture of MCTs and soybean oil on immune function [24, 25]. In critically ill patients, there was no difference in the numbers of various immune cells in the bloodstream, but the ratio of CD4⁺ to CD8⁺ cells was maintained in the MCT-soybean oil group, whereas it declined in the soybean oil group [24]; this finding may be indicative of better maintenance of cell-mediated immune function in the former group. Lymphocyte proliferation and IL-2 production did not differ between post-gastrointestinal surgery patients given either soybean oil or MCT-soybean oil [25]. However, natural killer cell activity was higher in the MCT-soybean oil group, again suggestive of better immune function with MCT-soybean oil than with pure soybean oil [25].

Parenteral Olive Oil, Immunity and Inflammation

Oleic acid, a major constituent of olive oil, has relatively little impact on immune function. ClinOleic® (Baxter Healthcare) is a lipid emulsion formed as an 80:20 (by volume) mix of olive oil and soybean oil. ClinOleic® does not affect lymphocyte proliferation in vitro, while soybean oil-based emulsions are suppressive [29]. Trials of ClinOleic® in home parenteral nutrition and in burn, trauma and critically ill patients have been conducted; where immune and inflammatory outcomes were reported, these were not different from in the comparator group, which received either soybean

Table 1. Some reported immuno-inflammatory and clinical outcomes of studies using lipid emulsions based entirely on soybean oil. Modified from [8, 10]

Patient characteristics	Parenteral nutrition used	Duration	Immuno-inflammatory and clinical outcomes measured	Effects observed	Reference
Undernourished patients undergoing surgery for gastric or oesophageal cancer	No lipid vs. soybean oil	Daily for 2 weeks before and then for 1 week after surgery	Numbers of blood granulocytes, lymphocytes, T cells and B cells	Number of granulocytes increased at week 3 in soybean oil group; total lymphocytes decreased (approx. 50%) at week 3 in the no-lipid group	22
			Serum IgG and IgM concentrations	None	
			Leukocyte chemotaxis	None	
			Granulocyte adherence to nylon	Decreased (approx. 30%) at week 3 in the no-lipid group	
			Granulocyte phagocytosis	None	
Malnourished patients undergoing surgery for gastrointestinal cancer	Soybean oil	For 7 days before surgery	Natural killer cell activity of PBMNCs	Decreased (approx. 50%) at day 7	23
			T-cell proliferation in response to mitogen	None	
			T-cell IL-2 production in response to mitogen	None	
			Cytotoxicity of IL-2-activated PBMNCs	Decreased (approx. 50%)	
Malnourished, seriously ill patients	No lipid vs. soybean oil	10 days	Numbers of T cells, helper T cells and suppressor T cells in the blood	Helper: suppressor cells decreased (approx. 20%) in the soybean oil group	24
			Number of natural killer cells in the blood	Absolute number and percentage of natural killer cells decreased (approx. 5–10%) in the no-lipid group	
Malnourished patients undergoing surgery for gastrointestinal cancer	No lipid vs. soybean oil	For 7 days before surgery	Natural killer cell activity of PBMNCs	None	25
			T-cell proliferation in response to mitogen	None	
			T-cell IL-2 production in response to mitogen	Decreased (approx. 10%) in the no-lipid group; increased (approx. 35%) in the soybean oil group	
			Cytotoxicity of IL-2-activated PBMNCs	Decreased (approx. 35%) in the soybean oil group	
Patients with trauma	No lipid vs. soybean oil	10 days	Natural killer cell activity of PBMNCs	Lower (approx. 65%) in the soybean oil group	26
			Period on mechanical ventilation	Greater in the soybean oil group (27 vs. 15 days)	
			Number of infections	Greater in the soybean oil group (72 vs. 39)	
			Length of intensive care unit stay	Greater in the soybean oil group (29 vs. 18 days)	
			Length of hospital stay	Greater in the soybean oil group (39 vs. 27 days)	

Table 1. Continued

Patient characteristics	Parenteral nutrition used	Duration	Immuno-inflammatory and clinical outcomes measured	Effects observed	Reference
Patients undergoing bone marrow transplantation	Low-dose soybean oil vs. standard soybean oil	From 3 days before transplantation until oral energy intake exceeded 42 kJ/kg for two successive days	Time to first blood infection	None	27
			Types of bacteria cultured from the blood	None	
			Types of fungi cultured from the blood	None	
			Urinary tract infections	None	
			Lung infections	None	
Patients undergoing gastrointestinal or oesophageal surgery	No lipid vs. soybean oil	From 7 days before until 14 days after surgery	Serum C-reactive protein concentration	None	28
			Serum IL-6 concentration	None in unstressed patients, but IL-6 higher at 2 h and 1 day post-surgery in stressed patients in the soybean oil group	
			T-cell proliferation in response to mitogens	None in unstressed patients, but T-cell proliferation lower at day 7 post-surgery in stressed patients in the soybean oil group	

Ig = Immunoglobulin; IL = interleukin; PBMNCs = peripheral blood mononuclear cells.

oil or a MCT-soybean oil mix [30–34], as summarised in table 2. Thus, compared with these more traditional lipid emulsions, ClinOleic® does not appear to modify immune or inflammatory responses.

Parenteral Fish Oil, Immunity and Inflammation

Fish oil contains about 30% of its fatty acids as the long-chain n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids possess many anti-inflammatory properties and may promote cell-mediated immunity, although the literature is not consistent about this [1–7]. Many of the mechanisms of action of EPA and DHA involve antagonism of the action of the n-6 fatty acid arachidonic acid. In addition, both EPA and DHA give rise to mediators that act to resolve inflammation [35]. Thus, fish oil is an attractive option for inclusion in parenteral regimens. Currently, three fish oil-containing lipid emulsions are commercially available for use in parenteral nutrition. Lipoplus® (known in some countries as Lipidem®; B Braun) is a 50:40:10 (by volume) mixture of MCTs, soybean oil and fish oil. SMOFLipid® (Fresenius Kabi) is a 30:30:25:15 (by volume) mixture of MCTs, soybean oil, olive oil and fish oil. Omegaven® (Fresenius Kabi) is 100% fish oil and is available as a supplement to be diluted with another lipid emulsion of choice.

Table 2. Some reported immuno-inflammatory and clinical outcomes of studies using ClinOleic®

Patient characteristic	Comparator for ClinOleic®	Duration	Immuno-inflammatory and clinical outcomes measured*	Reference
Home parenteral nutrition	None	3 months	Inflammatory and immune markers (C-reactive protein, several cytokines, neopterin) Oxidative stress marker (malondialdehyde) Adverse effects	30
Intradialytic	Soybean oil	5 weeks	Inflammatory markers (C-reactive protein, several cytokines) Antioxidant enzymes and oxidative stress marker (malondialdehyde) Adverse effects	31
Critically ill (mainly post-surgery ICU)	Soybean oil	>5 days	Inflammatory markers (leukocyte count, C-reactive protein, fibrinogen, albumin) Number and types of infections Length of ICU stay Length of hospital stay Mortality Adverse effects	32
Severely burned	MCT-Soybean oil	5–7 days	Inflammatory markers (C-reactive protein, several cytokines) Organ dysfunction Ventilation requirement Number of infections Length of ICU stay Length of hospital stay Mortality Adverse effects	33
Medical-surgical ICU	Soybean oil	Mean 13 days	Inflammatory markers (C-reactive protein, several cytokines) Immune markers (monocyte and granulocyte phagocytosis and oxidative burst) Number of infections Length of ICU stay Length of hospital stay Mortality	34

ICU = Intensive care unit; MCT = medium-chain triglyceride.
 * No study reported any difference between ClinOleic and the comparator for any of the outcomes listed.
 Modified from [10].

Intravenous infusion of a lipid emulsion containing fish oil into patients for 5 days following gastrointestinal surgery resulted in altered fatty acid composition of leukocytes; the EPA content was increased 2.5-fold [36]. This change would be expected to impact the profile of eicosanoids and other lipid mediators produced from arachidonic acid and EPA. Table 3 describes studies using intravenous fish oil in different patient groups that reported on aspects of immune function or inflammation [36–46]; where those studies also reported on clinical outcomes, this information is also in-

Table 3. Some reported immuno-inflammatory and clinical outcomes of studies using fish oil containing lipid emulsions

Patient characteristic	Fish oil-containing emulsion	Comparator for fish oil-containing emulsion	Duration	Immuno-inflammatory and clinical outcomes measured	Effects of fish oil	Reference
Gastro-intestinal surgery	50:30:20 Soybean/MCT/fish	50:50 Soybean/MCT	Days 1–6 post-surgery	Ratio of LTB ₄ to LTB ₅ produced by leukocytes	Lower at days 6 and 10	37
				Serum TNF concentration	Lower at day 6	
				Serum IL-1 β , IL-6 and IL-10 concentrations	None	
				Infections	None	
				ICU stay	Shorter (0.9 vs. 2 days; NS)	
				Hospital stay	None	
Gastro-intestinal surgery	40:50:10 Soybean/MCT/fish (Lipoplus [®])	Soybean	Days 1–6 post-surgery	Ratio of LTB ₄ to LTB ₅ produced by leukocytes	Lower at day 6	38
Gastro-intestinal surgery	30:30:25:15 Soybean/MCT/olive/fish (SMOF Lipid [®])	Soybean	Days 1–6 post-surgery	Ratio of LTB ₄ to LTB ₅ produced by leukocytes	Lower at day 6	39
				Hospital stay	Shorter (13.4 vs. 20.4 days)	
Gastro-intestinal surgery	Omegaven [®]	Soybean	Day 1 before surgery; then days 1–5 postsurgery	Blood leukocyte count	None	40
				Serum C-reactive protein and TNF concentrations	None	
				Serum IL-6 concentration	Lower at days 0, 1 and 3	
				TNF production in whole blood stimulated with Endotoxin	Lower at day 5	
				Granulocyte phagocytosis and respiratory burst	None	
				Monocyte human leukocyte antigen DR expression	Higher at days 3 and 5	
				Infections	None	
				ICU stay	Shorter (4.1 vs. 9.1 days; NS)	
				Hospital stay	Shorter (17.8 vs. 23.5 days; NS)	
				Mortality	None	
Gastro-intestinal surgery	83:17 Soybean/Omegaven [®]	Lipid free; Soybean	Days 1–6 post-surgery	Numbers of lymphocytes and T, CD4, CD8, B, and natural killer cells	None	41
				Lymphocyte proliferation in response to mitogen	None	
				T-cell IL-2 production in response to mitogen	Increased	
				T-cell interferon- γ production in response to mitogen	Post-surgery decline prevented	

Table 3. Continued

Patient characteristic	Fish oil-containing emulsion	Comparator for fish oil-containing emulsion	Duration	Immuno-inflammatory and clinical outcomes measured	Effects of fish oil	Reference
Septic ICU	Omegaven®	Soybean	10 days	Neutrophil production of LTB ₄ and LTB ₅	LTB ₅ production increased	42
				Neutrophil function (respiratory burst)	Improved	
				Requirement for mechanical ventilation	Shorter but NS	
				Mortality at 10 days	None	
Septic ICU	Omegaven®	Soybean	5 days	Production of inflammatory cytokines (TNF, IL-1 β , IL-6, IL-8) by mononuclear cells stimulated with endotoxin	All lower	43
				Requirement for mechanical ventilation	None	
				Mortality at 14 days	None	
Severe acute pancreatitis	80:20 Soybean/Omegaven®	Soybean	5 days	Blood leukocyte count	None	44
				Serum C-reactive protein concentration	Lower	
				Serum IL-6 concentration	None	
				Gas exchange	Improved at day 5	
				Infections	Fewer but NS	
				Days of renal replacement therapy	Fewer (18 vs. 26 days)	
				Length of ICU stay	Shorter (21 vs. 27 days; NS)	
				Length of hospital stay	Shorter (65 vs. 71 days; NS)	
Septic ICU	40:50:10 Soybean/MCT/fish (Lipoplus®)	50:50 Soybean/MCT	5 days	Blood leukocyte numbers	None	45
				C-reactive protein concentration	None	
				TNF, IL-1 β , IL-6 and IL-10 concentrations	Greater decrease in IL-6; smaller decrease in IL-10	
				Production of TNF, IL-1 β , IL-6, IL-10 and prostaglandin E ₂ by mononuclear cells stimulated with endotoxin	None	
				Gas exchange	Improved at day 6	
				Duration of mechanical ventilation	None	
				Length of ICU stay	None	
				Length of hospital stay	Shorter (28 vs. 82 days)	
				Mortality at 5 and 28 days	None	

Table 3. Continued

Patient characteristic	Fish oil-containing emulsion	Comparator for fish oil-containing emulsion	Duration	Immuno-inflammatory and clinical outcomes measured	Effects of fish oil	Reference
Medical ICU	83:17 (Soybean/MCT)/Omegaven®	50:50 Soybean/MCT	7 days	Serum IL-6 concentration	None	46
				Monocyte human leukocyte antigen DR expression	None	
				Infections	None	
				Duration of mechanical ventilation	None	
				Length of ICU stay	None	
				Mortality at 28 days	None	

ICU = Intensive care unit; IL = interleukin; LT = leukotriene; MCT = medium-chain triglyceride; NS = not significant; TNF = tumour necrosis factor.

cluded. Studies in patients who had undergone gastrointestinal surgery have convincingly demonstrated that inclusion of fish oil in the parenteral nutrition regimen decreases the generation of inflammatory eicosanoids [36–39] and cytokines [37, 40] and may help to counter the surgery-induced decline in antigen-presenting cell activity [40] and in the production of cytokines by T lymphocytes [41]. Furthermore, studies that have examined the hard end point of the length of hospital stay in post-surgery patients have suggested a real clinical benefit from fish oil infusion in these patients (see [12] for references). Whether the improvement in patient outcome is causally related to the fish oil-induced reduction in inflammation and enhancement in cell-mediated immunity is not clear.

Studies of parenteral fish oil in critically ill patients [42–46] have been less consistent in their findings (table 3). Mayer et al. [42, 43] reported a range of anti-inflammatory effects of intravenous Omegaven® in septic patients intolerant of enteral nutrition. Patients with severe acute pancreatitis showed some clinical improvements with parenteral fish oil [44]. Although there was no effect on inflammatory markers, the number of infections or the lengths of ICU and hospital stays, there was better gas exchange and a reduced requirement for continuous renal replacement therapy in those patients receiving fish oil [44]. Barbosa et al. [45] compared MCT-soybean oil with Lipoplus® given over 5 days in septic patients. The decrease in the plasma IL-6 concentration over time was greater in the Lipoplus® group, but there were no differences between groups for other inflammatory markers, and there was better gas exchange at day 6 in that group. The length of ICU stay did not differ between groups, but the length of hospital stay was shorter with Lipoplus® (table 3). In contrast to the generally positive findings from these studies [42–45], no differences were found be-

tween MCT-soybean oil and MCT-soybean oil-Omegaven[®] given over 7 days in medical patients in the ICU for several outcomes, including immune markers, inflammatory markers, ventilation requirement, the number of infections, the length of ICU stay and mortality [46]. Thus, overall, it is difficult to make a firm conclusion about the influence of fish oil on inflammatory processes and on immune function in critically ill patients; data on inflammation are not consistent, and immune function has not been explored much. Similarly, the impact of fish oil on clinical end points such as infections, the length of ICU and hospital stays and mortality is not clear in critically ill patients since there are too few studies, and those that are available have reported contradictory findings. Further studies of intravenous fish oil are required in critical illness; such studies need to be properly designed and adequately powered and should explore effects on inflammation and immunity as well as clinical outcomes.

Summary and Conclusions

Because of the effects of triglycerides and fatty acids on the responses of cells of the immune system, it is anticipated that inflammatory and immune responses in patients receiving parenteral nutrition may be modulated by the type of lipid used and that this may influence clinical outcomes. For some time, there has been concern that lipid emulsions based solely upon soybean oil, which is rich in the n-6 fatty acid linoleic acid, may not be optimal because of the role of n-6 fatty acids in promoting inflammation and suppressing immune responses. There is some clinical evidence to support this concern, but this evidence is not overwhelming. Nevertheless, lipid emulsions with soybean oil in various combinations with MCTs, olive oil and fish oil are available. Some early studies have suggested better immune function with MCT-soybean oil than with soybean oil alone, but the differences were small, and more recent studies have suggested little difference between soybean oil, MCT-soybean oil and ClinOleic[®] as far as markers of inflammation and immunity are concerned. The inclusion of fish oil in combination with one or more other oils (i.e. soybean, MCT, olive) in the parenteral regimen received by patients following major gastrointestinal surgery reduces the post-surgery rise in inflammatory markers and fall in cell-mediated immune markers. These changes are associated with improvements in clinical outcomes in that patient group. Whether similar effects of intravenous fish oil occur in more ill patients (e.g. critically ill) is not clear at present because few studies have been performed, and those that have are typically small in size and report different findings. However, the potential for benefit from intravenous fish oil in critically ill patients is good [47], and the lack of reported adverse effects, coupled with the positive findings seen in some small randomised controlled trials [44, 45] and in a large uncontrolled open-label study [48], strongly support performing more studies in these patients.

References

- Calder PC: The 2008 ESPEN Sir David Cuthbertson Lecture: fatty acids and inflammation – from the membrane to the nucleus and from the laboratory bench to the clinic. *Clin Nutr* 2010;29:5–12.
- Kim W, Khan NA, McMurray DN, Prior IA, Wang N, Chapkin RS: Regulatory activity of polyunsaturated fatty acids in T-cell signaling. *Prog Lipid Res* 2010;49:250–261.
- Calder PC: Fatty acids and inflammation: the cutting edge between food and pharma. *Eur J Pharmacol* 2011;668(suppl 1):S50–S58.
- Calder PC: Long-chain fatty acids and inflammation. *Proc Nutr Soc* 2012;71:284–289.
- Shaikh SR, Jolly CA, Chapkin RS: n-3 Polyunsaturated fatty acids exert immunomodulatory effects on lymphocytes by targeting plasma membrane molecular organization. *Mol Aspects Med* 2012;33:46–54.
- Calder PC: n-3 fatty acids, inflammation and immunity: new mechanisms to explain old actions. *Proc Nutr Soc* 2013;72:326–336.
- Calder PC: Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* 2013;75:645–662.
- Calder PC: Use of fish oil in parenteral nutrition: rationale and reality. *Proc Nutr Soc* 2006;65:264–277.
- Calder PC: Immunonutrition in surgical and critically ill patients. *Br J Nutr* 2007;98:S133–S139.
- Calder PC: Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults. *Proc Nutr Soc* 2009;68:252–260.
- Calder PC: Rationale and use of n-3 fatty acids in artificial nutrition. *Proc Nutr Soc* 2010;69:565–573.
- Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.
- Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
- Ward NS, Casserly B, Ayala A: The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. *Clin Chest Med* 2008;29:617–625.
- Wanten G: An update on parenteral lipids and immune function: only smoke, or is there any fire? *Curr Opin Clin Nutr Metab Care* 2006;9:79–83.
- Calder PC, Yaqoob P, Newsholme EA: Triacylglycerol metabolism by lymphocytes and the effect of triacylglycerols on lymphocyte proliferation. *Biochem J* 1994;298:605–611.
- Calder PC, Yaqoob P, Harvey DJ, Watts A, Newsholme EA: The incorporation of fatty acids by lymphocytes and the effect on fatty acid composition and membrane fluidity. *Biochem J* 1994;300:509–518.
- Lewis RA, Austen KF, Soberman RJ: Leukotrienes and other products of the 5-lipoxygenase pathway: biochemistry and relation to pathobiology in human diseases. *N Engl J Med* 1990;323:645–655.
- Tilley SL, Coffman TM, Koller BH: Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest* 2001;108:15–23.
- Heyland DK, MacDonald S, Keefe L, Drover JW: Total parenteral nutrition in the critically ill patient: a meta analysis. *JAMA* 1998;280:2013–2019.
- Koch T, Heller AR: Auswirkungen einer parenteralen Ernährung mit n-3-Fettsäuren auf das Therapieergebnis – Eine multizentrische Analyse bei 661 Patienten. *Aktuelle Ernährungsmedizin* 2005;30:15–22.
- Dionigi P, Dionigi R, Prati U, Pavesi F, Jemos V, Nazari S: Effect of Intralipid® on some immunological parameters and leukocyte functions in patients with esophageal and gastric cancer. *Clin Nutr* 1985;4:229–234.
- Monson JRT, Sedman PC, Ramsden CW, Brennan TG, Guillou PJ: Total parenteral nutrition adversely influences tumour-directed cellular cytotoxic responses in patients with gastrointestinal cancer. *Eur J Surg Oncol* 1988;14:435–443.
- Gogos CA, Kalfarentzos FE, Zoumbos NC: Effect of different types of total parenteral nutrition on T-lymphocyte subpopulations and NK cells. *Am J Clin Nutr* 1990;51:119–122.
- Sedman PC, Somers SS, Ramsden CW, Brennan TG, Guillou PJ: Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. *Br J Surg* 1991;78:1396–1399.
- Battistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K: A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* 1997;43:52–58.
- Lenzen P, Bruemmer BA, Bowden RA, Gooley T, Aker SN, Mattson D: Intravenous lipid dose and incidence of bacteremia and fungemia in patients undergoing bone marrow transplantation. *Am J Clin Nutr* 1998;67:927–933.
- Furukawa K, Yamamori H, Takagi K, Hayashi N, Suzuki R, Nakajima N, Tashiro T: Influences of soybean oil emulsion on stress response and cell mediated immune function in moderately or severely stressed patients. *Nutrition* 2002;18:235–240.
- Granato D, Blum S, Rossle C, Le Boucher J, Malnoë A, Dutot G: Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro. *JPEN J Parenter Enteral Nutr* 2000;24:113–118.

- 30 Reimund JM, Rahmi G, Escalin G, Pinna G, Finck G, Muller CD, Duclos B, Baumann R: Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;21:445–454.
- 31 Cano NJ, Saingra Y, Dupuy AM, Lorec-Penet AM, Portugal H, Lairon D, Cristol JP, Come A, Le Brun A, Atlan P, Leverve XM: Intradialytic parenteral nutrition: comparison of olive oil versus soybean oil-based lipid emulsions. *Br J Nutr* 2006;95:152–159.
- 32 Mateu-de Antonio J, Grau S, Luque S, Marín-Casino M, Albert I, Ribes E: Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr* 2008;99:846–854.
- 33 Garcia-de-Lorenzo A, Denia R, Atlan P, Martinez-Ratero S, Le Brun A, Evard D, Bereziat G: Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion v. medium/long chain triacylglycerols. *Br J Nutr* 2005;94:221–230.
- 34 Umpierrez GE, Spiegelman R, Zhao V, Smiley DD, Pinzon I, Griffith DP, Peng L, Morris T, Luo M, Garcia H, Thomas C, Newton CA, Ziegler TR: A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. *Crit Care Med* 2012;40:1792–1798.
- 35 Serhan CN, Chiang N, van Dyke TE: Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008;8:349–361.
- 36 Morlion BJ, Torwesten E, Lessire A, Sturm G, Peskar BM, Fürst P, Puchstein C: The effect of parenteral fish oil on leukocyte membrane fatty acid composition and leukotriene-synthesizing capacity in post-operative trauma. *Metabolism* 1996;45:1208–1213.
- 37 Wachtler P, König W, Senkal M, Kemen M, Köller M: Influence of a total parenteral nutrition enriched with w-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma* 1997;42:191–198.
- 38 Koller M, Senkal M, Kemen M, König W, Zumtobel V, Muhr G: Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. *Clin Nutr* 2003;22:59–64.
- 39 Grimm H, Mertes N, Goeters C, Schlotzer E, Mayer K, Grimminger F, Fürst P: Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006;45:55–60.
- 40 Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H: Immunomodulation by perioperative administration of n-3 fatty acids. *Br J Nutr* 2002;87:S89–S94.
- 41 Schauder P, Rohu U, Schafer G, Korff G, Schenk HD: Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. *Br J Nutr* 2002;87:S103–S110.
- 42 Mayer K, Fegbeutel C, Hattar K, Sibelius U, Krämer HJ, Heuer KU, Temmesfeld-Wollbrück B, Gokorsch S, Grimminger F, Seeger W: Omega-3 vs omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. *Intens Care Med* 2003;29:1472–1481.
- 43 Mayer K, Gokorsch S, Fegbeutel C, Hattar K, Rousseau S, Walrath D, Seeger W, Grimminger F: Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. *Am J Respir Crit Care Med* 2003;167:1321–1328.
- 44 Wang X, Li W, Li N, Li J: Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *JPEN J Parenter Enteral Nutr* 2008;32:236–241.
- 45 Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC: Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care* 2010;14:R5.
- 46 Friessecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P: Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. *Intens Care Med* 2008;34:1411–1420.
- 47 Calder PC: Fishing for improved outcomes in the critically ill. *Crit Care Med* 2014;42:1306–1307.
- 48 Heller AR, Rossler S, Litz RJ, Stehr SN, Heller SC, Koch R, Koch T: Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;4:972–979.

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Importance of Fatty Acids in the Perinatal Period

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Abstract

Long-chain polyunsaturated fatty acids (LC-PUFAs) influence a variety of cellular and physiological processes during the perinatal period by serving as membrane components, precursors of eicosanoids and docosanoids, and nuclear receptor activators. These processes include the growth of neural cells and signal transduction, the growth and differentiation of adipocytes, and the function of regulatory T cells. LC-PUFA levels depend on these fatty acids' dietary availability and their endogenous synthesis from essential fatty acids, which is known to differ among subjects according to fatty acid desaturase genotype. Intrauterine placental mechanisms support the preferential transfer of LC-PUFAs from the mother to the foetus. After birth, breast milk provides arachidonic acid and docosahexaenoic acid, although not in amounts that can prevent lower percentages in infant plasma than in umbilical cord blood plasma. The available epidemiological data suggest associations of perinatal LC-PUFAs with later body weight, the risk of allergic diseases and cognitive performance. Randomised clinical trials that compare different maternal or infant intakes of n-3 LC-PUFAs or combinations of n-3 and n-6 fatty acids so far have not led to firm conclusions about the optimal LC-PUFA status of pregnant women or infants, but there are good indications of beneficial effects of a higher pre- or postnatal docosahexaenoic acid status on visual function and asthma risk.

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Indications of the relevance of fatty acids during the perinatal period

Dietary fat is a major contributor to total energy intake. It has long been recognised that the nature of the fatty acid classes and the individual fatty acids present in the diet are both important for human health [1]. It is now known that there are long-term consequences of early life events, termed 'the developmental origins of long-term health and disease', that are based on the programming effects of early life exposures, including diet [2]. Early nutrition programming is the concept that differences in nutritional experiences at critical periods in early life, both pre- and postnatal, can pro-

gramme an individual's development, metabolism and health for the future [3]. This concept has been well established in animal studies, and there is also a large amount of data from retrospective observational studies suggesting that similar effects occur in humans. In this context, maternal, foetal and infant fatty acid status has received considerable attention during the last few decades.

Fatty acids are major components of lipids and are generally grouped into saturated fatty acids without double bonds (e.g. palmitic acid; 16:0), monounsaturated fatty acids with a single double bond (e.g. oleic acid; 18:1n-9), and polyunsaturated fatty acids with two or more double bonds. The polyunsaturated fatty acids are of special importance, as they cannot be synthesised *de novo* by the human organism. The essential fatty acid linoleic acid (LA; 18:2n-6), with 18 carbon atoms and two double bonds at positions 6 and 9 from the methyl end of the carbon chain, is the parent substance of the n-6 polyunsaturated fatty acid family. The n-6 family includes the LA derivatives dihomo- γ -linolenic acid (20 carbon atoms, 3 double bonds, 20:3n-6) and arachidonic acid (AA; 20:4n-6). The fatty acids of the n-3 series are derived from the essential fatty acid α -linolenic acid (ALA; 18:3n-3), with the 3 double bonds at positions 3, 6 and 9 from the methyl end. Among the derivatives of ALA are eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), whose functional properties and beneficial effects on health are widely studied. It is important to note that humans can synthesise the derivatives of the n-3 and n-6 series from their essential fatty acid precursors via desaturases and elongases, but interconversion between families is not possible [4]. Although endogenous conversion of essential fatty acids to their long-chain polyunsaturated fatty acid (LC-PUFA) derivatives is low for n-6 and n-3 fatty acids, conversion within the n-6 series seems to be due to the quantitatively higher availability of LA compared with ALA. Therefore, dietary intake is assumed to be the major determinant of n-3 LC-PUFA status [5]. This assumption is supported by findings that polymorphisms in the desaturase gene cluster clearly influence levels of n-6 LC-PUFAs, while the relevance for n-3 LC-PUFA levels is weaker [6]. In most food stuffs, n-3 LC-PUFAs are of relatively low abundance, and only fatty sea fish (e.g. herring, mackerel, salmon) are rich dietary sources of n-3 LC-PUFAs, although some enriched foods and dietary supplements are available [7]. n-3 LC-PUFAs in enriched food products and supplements can be derived from fish oil or algal oil [7]. Specific interest in n-3 LC-PUFAs is supported by the observed shift towards a higher dietary intake of n-6 fatty acids at the expense of n-3 fatty acids during the 20th century, which has been proposed to be related to the increases in obesity and the incidence of allergic manifestations within the same time period [8].

Genetic and dietary influences on fatty acid status occur in humans of all ages and thus also determine fatty acid status during the perinatal period. From a physiological perspective, indications of the importance of individual fatty acids for infant development come from the observation that certain fatty acids are enriched in the foetus by trans-placental transfer during pregnancy and from comparisons between breastfed

infants and infants who were fed formulas not providing certain fatty acids. These pre- and postnatal observations point towards the importance of LC-PUFAs.

Pregnant women show high concentrations of lipids in their bloodstream, while lipid concentrations in cord blood are comparatively low, thus establishing a maternal-to-foetal gradient that promotes the transfer of fatty acids across the placenta and to the foetus. Studies of the phospholipid fatty acid profile of circulating lipids in maternal blood and cord blood have revealed pronounced differences. While the percentages of saturated fatty acids are similar, parent essential fatty acids contribute significantly less to total fatty acids among cord phospholipids than among maternal phospholipids [9]. This phenomenon is compensated for by higher percentages of LC-PUFAs in cord blood compared with maternal blood [9]. Although there is placental uptake of lipoproteins, non-esterified fatty acids occur as intermediates either before uptake or during placental metabolism, before fatty acid transfer across the placenta and into the foetal circulation is completed [10]. This process provides a mechanistic basis for the preferential placental transfer of AA and DHA relative to other fatty acids.

Further evidence for the importance of DHA during pregnancy comes from the observation that although the concentrations of all fatty acids in the maternal circulation are increased in pregnant women, the percentages of DHA decrease, which indicates a high requirement for DHA by the growing foetus [11]. While measured concentrations indicate a high foetal requirement for LC-PUFAs, they do not demonstrate higher transfer of LC-PUFAs than of other fatty acids from the mother to the foetus, although this is the most plausible explanation. Such investigations require dynamic measurements that follow the flux of fatty acids. One technique for doing this that can be used in pregnant women and in infants involves the use of stable isotope tracers.

In pregnant women, using stable isotopes, it has been demonstrated that there is preferential placental uptake of DHA from the maternal circulation relative to the uptake of palmitic, oleic and linoleic acids [12, 13]. This phenomenon was established by comparing maternal plasma tracer concentrations with placental and foetal tracer concentrations 4 and 12 h after tracer intake. Application of the 12 h schedule enabled the demonstration of preferential transfer of DHA into the foetal circulation by comparing the maternal/foetal ratio found for DHA with the significantly lower ratios found for the other studied fatty acids. The distribution of the tracer fatty acids 4 h after intake only indicated preferential uptake of DHA by the placenta. Thus, placental transfer mechanisms seem to be complex processes that cannot completely be explained by diffusion processes. The selective LC-PUFA transfer not only highlights the relevance of the placenta for achieving an optimal foetal fatty acid supply but also strongly indicates the importance of DHA, and probably other LC-PUFAs, for foetal development.

While the importance of an adequate fatty acid supply for foetal development has been widely recognised, the mechanisms relevant for the differences in placental up-

take and transfer intensity between fatty acids have not been fully elucidated so far. In the placenta, two lipases have been identified as important for the release of fatty acids from circulating maternal lipoproteins: lipoprotein lipase and endothelial lipase. Lipoprotein lipase hydrolyses triacylglycerols, whereas endothelial lipase is a phospholipase with little triacylglycerol lipase activity [14]. At the end of pregnancy, endothelial lipase is the dominantly expressed lipase. It has been speculated that the different substrate preferences of the lipases contribute to the different fatty acid transfer intensities.

Several membrane-bound proteins involved in fatty acid transfer are expressed in the trophoblast: fatty acid translocase (FAT/CD36), fatty acid transport proteins (FATP-1 to FATP-6), plasma-membrane fatty acid-binding protein (FABPpm) and placental FABPpm (p-FABPpm) [10]. Only p-FABPpm is specific for placental tissue, and it has been speculated that p-FABPpm is relevant for the preferential uptake of DHA and other LC-PUFAs. This phenomenon has been suggested by in vitro studies, in which blocking p-FABPpm abolished the uptake preference for DHA in immortalised trophoblast cells [15]. This protein has not been sequenced so far, and further evidence about the function of p-FABPpm in primary trophoblasts is needed [16]. In the cytosol, fatty acids are bound to cytosolic fatty acid-binding proteins (FABPs), and further metabolism or alteration, e.g. esterification into triacylglycerols and incorporation into lipid droplets, may depend on the specific FABP [17]. Cytosolic FABPs are also likely to deliver fatty acids as activators of nuclear transcription factors, such as the peroxisome proliferator-activated receptors (PPARs) [10].

Although placental fatty acid transfer is not fully understood, evidence collected to describe the complexity of transfer supports the assumption that perinatal fatty acid status is of relevance for short-term and long-term infant development.

After birth, the placental transfer of fatty acids is replaced by intake of dietary fatty acids from breast milk or formula. This change is associated with a decrease in the percentages of AA and DHA among circulating phospholipids in the infant, while LA and ALA levels increase [18]. Although breast milk provides some DHA and AA, this decrease in neonatal LC-PUFA status is still observed in breastfed infants. Nevertheless, the mean values of 0.3% (range: 0.06–1.4%) DHA and 0.5% (range: 0.24–1.0%) AA seen in breast milk in 65 studies from different countries [19] indicates the establishment of higher plasma concentrations in breastfed infants than in infants receiving formula without LC-PUFAs [20]. Aiming to achieve similar plasma LC-PUFA concentrations to those seen in breastfed infants (and the related biological benefits), most infant formulas on the market today are enriched with AA and DHA from various sources [7], while the majority of the fat in the formulas is plant oil, providing the essential fatty acids. As in adults, some LC-PUFAs can be produced by endogenous synthesis from essential fatty acids in term and preterm infants, but this does not compensate for the absence of a dietary supply [21].

Since relationships between maternal or infant dietary LC-PUFA intake and fatty acid status are reasonably well established, the focus of research has shifted towards

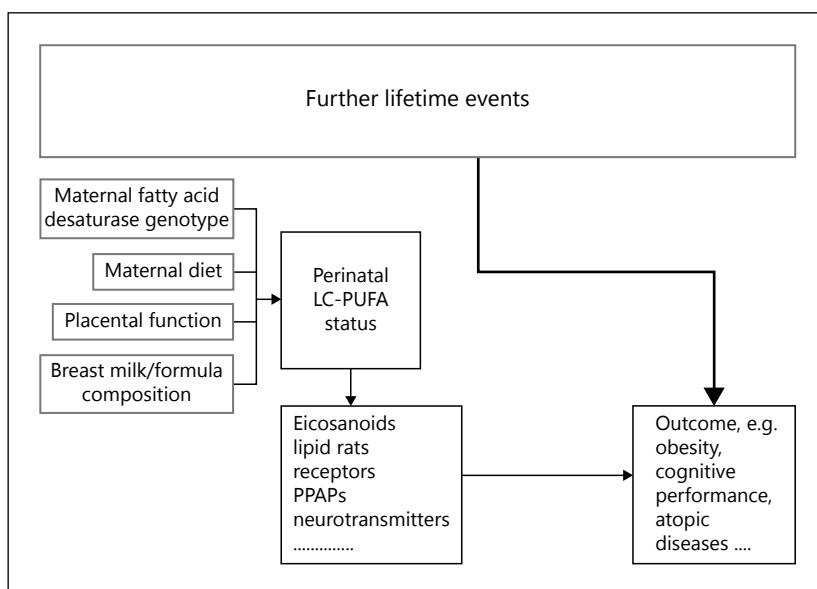


Fig. 1. Schematic presentation of the identified perinatal factors that influence long-chain polyunsaturated fatty acid (LC-PUFA) status during the perinatal period and of how these may contribute, beyond the whole variety of lifetime experiences, to the long-term outcome.

establishing the relationship between perinatal fatty acid status and both infant development and short-term and long-term health and disease risk. Three major fields of interest in this context are cognitive function, atopic diseases, and the risk of developing obesity and related diseases (fig. 1).

Body Composition and the Risk of Obesity

Maternal prepregnancy obesity and high weight gain during pregnancy have implications for the risk of later obesity in the offspring, which is in turn associated with an increased incidence of metabolic diseases, and most prominently type 2 diabetes [22]. The importance of the composition of dietary and body fat in the perinatal period, and thus maternal, foetal, and infant fatty acid status, for longer-term body fat accumulation in the offspring (i.e. the obesity risk) is less clear, although potential mediating mechanisms have been described. In vitro and animal studies of LC-PUFAs have shown the effects of different fatty acids on adipocytes. Incubation of preadipocytes with AA increased the growth and differentiation of adipocytes [23]. The adipogenic effect of AA can partially be blocked by cyclooxygenase inhibitors, and the effect is induced by analogues of prostacyclin (PGI₂). This finding suggests that the underlying mechanism involves cyclooxygenase-mediated conversion of AA to the eico-

sanoid PGI₂, which then interacts with the cell surface PGI₂ receptor, IP. Only AA, and not saturated, monounsaturated or other polyunsaturated fatty acids, triggers cAMP production and, through the IP/PGI₂ system, activates the protein kinase A pathway to induce adipocyte differentiation and growth. In contrast, EPA and DHA, which are not converted to PGI₂, are less potent than AA in inducing adipocyte differentiation [24] and may even suppress lipid storage in adipocytes [25]. Furthermore, it has been shown that long-chain fatty acids generally and directly, without further metabolism, act as transcriptional regulators of PPARs [26]. Interestingly, AA and some of its metabolites generated through cyclooxygenase and lipoxygenase activities are also activators/ligands of PPARs. This concept suggests a higher importance of AA than of saturated and monounsaturated fatty acids and n-3 LC-PUFAs in the early and later phases of adipogenesis [26].

Feeding female mice with a high-fat diet rich in LA (LA diet, with an LA-to-ALA ratio of 59/1) or an isocaloric diet with an LA-to-ALA ratio of 2/1 before mating and during the gestation/suckling period led to higher body weight, fat mass, epididymal fat pad weight and adipocyte size in the offspring of the 59/1 group than in those of the 2/1 group [27]. The pups of the mothers fed with the 59/1 diet were 50% heavier at weaning than those of the mothers fed with the 2/1 diet. During this period of life, adipose tissue was being extensively formed, and the difference in body weight was maintained until adulthood. Thus, the replacement of LA by ALA prevents enhanced adipogenesis, which is in agreement with the adipogenic effect of n-6 PUFAs observed *in vitro*. The importance of LA-derived AA and AA-derived PGI₂ was confirmed by comparing this observation in wild-type mice with the results of a corresponding experiment in PGI₂ receptor-knock-out mice [27]. In contrast to the wild-type mice, the PGI₂ receptor-null mice did not have pups with a higher body weight or fat mass whether the mothers were fed with the high-LA diet or the lower-LA or standard diet. This finding shows that the PGI₂ signalling is the mandatory effector responsible for the enhanced fat mass observed in pups after their mothers are administered an LA-enriched diet [27].

The conclusion from the mouse study agrees with the observation that addition of AA can increase PGI₂ in adipocyte cell cultures and correspondingly enhance the differentiation of preadipocytes into adipocytes [23], although the effect may be conditional upon further factors [28]. The increase in PGI₂ in response to high AA levels was confirmed in the adipose tissue of guinea pigs, which were supplemented with AA during postnatal days 5–21 [29]. Nevertheless, this increase was not associated with a higher fat mass in the supplemented group, although the higher levels of PGI₂ were maintained until day 105. This finding might be due to a species difference, as the intensive growth of fat depots occurs earlier in guinea pigs than in mice, suggesting the existence of critical early time windows for the adipogenic effect of AA.

Feeding a herring- or beef-based diet to C57BL/6 mice during gestation and lactation was clearly reflected in the fatty acid composition of breast milk and in the fatty

acid profile of different offspring tissues, with increased levels of n-3 LC-PUFAs in the herring-fed animals [30]. After weaning, half of the pups in each group were changed to a different diet. At age 9 weeks, the offspring of the herring-fed dams had less body fat than the offspring of beef-fed dams did, independent of the postnatal diet. Thus, only the n-3 LC-PUFAs provided by the maternal diet reduced body fat in the offspring. Nevertheless, the postnatal diet had a significant influence on insulin sensitivity, plasma lipids and the amount of brown adipose tissue. The n-3 LC-PUFA-rich diet was more beneficial than the n-6-rich diet. In another experiment, the male offspring of C57BL/6 mice were fed with a diet containing vegetable oils only or 80% vegetable oils plus 20% fish oil (as a source of n-3 LC-PUFAs) from days 2 to 42 of life and with an n-6 fatty acid-rich diet without LC-PUFAs until day 98 [31]. Although body weights were not different between groups, the results showed that n-3 LC-PUFAs in the diet reduced fat accumulation by ~30% and decreased the number of hypertrophic adipocytes at day 98 and also led to a healthier blood lipid profile. These findings show that moderate alterations of fat quality during early postnatal life can affect later metabolic health.

Wielinga et al. [32] compared feeding either an AA/DHA or an EPA/DHA mixture to ApoE*3Leiden-transgenic mice from postnatal weeks 4 to 12, followed by a high-fat and high-carbohydrate diet without these LC-PUFAs until age 20 weeks. The AA/DHA-fed mice gained less body weight compared with controls, which received a chow diet throughout the study, until weeks 12 and 20, while EPA/DHA had no significant effect on weight in comparison with the control diet. A similar trend was seen for fat mass at 20 weeks, and at this age, both supplementations tended to reduce adipocyte cell size and plasma cholesterol and triglyceride levels. These findings confirm the potential of LC-PUFAs to influence body weight and lipid metabolism beyond the period of supplementation, thus indicating metabolic programming by the early diet. Furthermore, the findings show the complexity of the influence of LC-PUFAs on the development of body composition, as certain combinations of AA and DHA may be more effective than an increase in n-3 LC-PUFAs alone.

Although the animal studies have mainly confirmed the beneficial effects of n-3 LC-PUFAs, there are indications that n-6 LC-PUFAs might also have an inhibitory effect on adipocyte and adipose tissue development. Thus, findings in humans are not fully predictable from in vitro and animal studies. Information about the importance of perinatal LC-PUFAs in humans comes from observational studies, and some randomised trials have been performed using n-3 LC-PUFA supplementation. Several clinical studies have tested the effect of various doses of n-3 LC-PUFA supplementation during pregnancy (0.2–2.9 g/day) on offspring anthropometry and/or on measures of adiposity [33]. With the exception of one relatively small study [34], which found lower infant weight with DHA supplementation at age 21 months, no relevant effects were observed. A German intervention study combined 1,200 mg/day n-3 LC-PUFA supplementation from week 15 of gestation to 16 weeks post-delivery with a

dietary recommendation to reduce AA intake [35]. Maternal red-blood-cell fatty acids confirmed that supplementation and a 20% lower AA intake in the intervention group were effective, as shown by higher DHA and EPA and lower AA percentages [36]. Nevertheless, the major reason for the n-6-to-n-3 LC-PUFA ratio of 1.5 in red blood cells in the intervention group (compared with 2.8 in the control group), determined at gestation week 32, was the increased n-3 LC-PUFA level. The offspring followed up until the age of 1 year showed no effect of the supplementation on weight or body composition. Thus, this study suggests that pre- and postnatal increases in n-3 LC-PUFAs do not affect the weight gain of infants. This agrees with the conclusion of recent reviews and meta-analyses that there is not enough evidence available from randomised clinical trials showing that n-3 LC-PUFA supplementation during pregnancy can decrease the obesity risk of offspring [37].

The effect of the early postnatal LC-PUFA status on infant growth can be studied in clinical trials by randomly allocating infants to feeding with formula with or without LC-PUFAs. In a meta-analysis based on individual patient data, Rosenfeld et al. found no indication of a relationship of LC-PUFA intake with weight until the age of 18 months [38], and a long-term follow-up of intervention studies for up to 9 years did not reveal differences in growth or markers of cardiovascular risk between infants receiving formulas with and without LC-PUFAs [39].

The data provided by observational studies, which have related markers of n-3 and n-6 LC-PUFA status to later adiposity, are more diverse. In a US population, n-3 LC-PUFAs, as estimated from dietary intake and plasma phosphatidylcholine, were inversely associated with measures of adiposity at age 3 years, while n-6 LC-PUFAs showed no clear effect [40]. Conversely, in a UK-based cohort, n-6 LC-PUFA status, as estimated from plasma samples at 34 weeks of gestation, was positively associated with body fat at ages 4 and 6 years, while an influence of n-3 LC-PUFAs was not confirmed [41]. Thus, observational studies agree with respect to an effect of LC-PUFAs on later adiposity, but the details remain to be clarified. It may well be that the situation is affected by the generally higher n-6-to-n-3 ratio in the US, which determines the importance of one series of fatty acids for growth. Additionally, the finding that there are effects in observational studies, but not in interventions, and especially not in interventions after birth, points to the possible importance of early periods of gestation, which are difficult to study by intervention. Intervention studies usually only start during pregnancy and do not include the long-term habitual diet, which also strongly influences LC-PUFA status.

Taken together, the relevance of perinatal fatty acid status for long-term anthropometric development and obesity risk is biologically plausible, but it is too early to consider this relevance as confirmed in humans or to derive dietary recommendations from the available findings. As the mechanisms and observed relationships are complex, it remains an open question whether decreasing n-6 LC-PUFAs or increasing n-3 LC-PUFAs is of more relevance, and the long-term effects may even differ at different offspring ages [42].

Neurological and Cognitive Development

There is good evidence from basic research and from animal experiments for the importance of LC-PUFAs for neurological development. The focus of research is very much on DHA, but AA also has important roles [43]. The LC-PUFA percentages among membrane phospholipids are a major determinant of membrane fluidity, which is a critical factor for all membrane functions, including those of receptors, ion channels, and membrane-bound enzymes, and which can influence neuronal functions [44]. However, the importance of n-3 and n-6 LC-PUFAs goes beyond their influence on membrane properties. n-3 LC-PUFA status influences the levels of neurotransmitters such as dopamine and serotonin [45]. Furthermore, the interaction of n-3 LC-PUFAs with ligand-activated transcription factors (e.g. retinoid X receptors, PPARs, cAMP response-element binding protein) and the associated effects on gene expression seem important for synaptic plasticity and transmission [44]. DHA supplementation supported neurite growth and synaptic protein expression in cultured neurons from embryonic mice [46]. This finding agrees with the enhancement of neurite growth in hippocampal neurons by DHA, which is assumed to promote learning [47].

The important role that DHA plays in brain structure and in numerous functions, and thus its potential to influence neurocognitive development and performance, is supported by animal studies, mainly in rodents, that showed a dependence of behaviour and learning ability on LC-PUFA status [48]. Besides the available information on the functional effects of LC-PUFAs, the high relative contribution of AA and especially DHA to the totality of fatty acids in the brain and retina strongly suggests their importance [43]. The importance of the perinatal period has been suggested, as it coincides with the most intensive period of brain growth (a brain growth spurt), including in the last trimester of pregnancy and in the first 18 months of postnatal life, during which the amount of DHA in the brain has been estimated to increase about 30-fold [43]. Thus, during this period, neuronal development is particularly vulnerable to the suboptimal availability of nutrients, including LC-PUFAs, which may have long-term consequences [49].

While there is convincing biological evidence that DHA and AA are relevant for neurological and cognitive functions, the results of randomised trials in humans, which looked at prenatal and/or postnatal supplementation with LC-PUFAs, have been mixed [50]. Although reviews and meta-analyses indicate that there are not enough data available or that the performed studies have weaknesses that limit the conclusions to be drawn from the results for the general population, it might nevertheless be the case that improvement of DHA status is beneficial for subgroups [51]. A distinction can be made between studies of maternal supplementation with LC-PUFAs either during pregnancy or lactation and studies of direct supplementation of infants.

There is much evidence to support the concept that DHA and AA supplementation of infant formulas introduces beneficial effects on neurological and cognitive function

in infants. This finding led to the introduction of infant formulas with AA and DHA, replicating concentrations typically found in breast milk in Western European countries [52]. A huge number of studies that compared neurological or cognitive outcomes between infants receiving formula with and without LC-PUFAs, often including a breastfed reference group, have been performed. Qawasmi et al. examined published results of randomised controlled trials that compared visual function at the ages of 2, 4 and 12 months [53]. Studies in which feeding with LC-PUFA-supplemented or control formulas was initiated within the first month of postnatal life were considered in the meta-analysis. The authors evaluated results obtained by determining visually evoked potentials and by behavioural methods, such as observation of preferential looking, in term and preterm infants. At all of the studied ages, there seemed to be a beneficial effect of LC-PUFAs when evoked potential measurements were applied, while behaviour-based methods showed a significant benefit only at age 2 months. Further exploratory analyses could not identify a dose-response relationship or a greater likelihood of demonstrable positive effects in preterm infants. Although several questions remain open, this is strong evidence that infants benefit from LC-PUFA supplementation, at least during the first year of life. In contrast to other meta-analyses, which did not find overall beneficial effects for LC-PUFAs [54, 55], here, term and preterm studies were jointly evaluated, which increased the statistical power.

More questions emerge once cognitive functions are considered. Following the same inclusion criteria as above, Qawasmi also combined the results of 12 studies on a total of 1,802 infants that applied the Bayley scales of infant development and did not identify a significant benefit of LC-PUFA supplementation [56]. Although the Bayley developmental scales were widely used in these investigations, it might be that this test procedure is not sensitive enough. This possibility is suggested by the observations that the likelihood of observing positive effects of LC-PUFAs varies with the version of the Bayley scales used [57] and that the application of other tests has shown positive effects [58]. It may well be that the test procedures that include problem solving, and thus more advanced cognitive functions, are more relevant [59]. As it is not known which cognitive domains are most affected or most sensitive to perinatal LC-PUFA status, it is not possible to identify the most informative test procedure or even the most suitable time schedule for studies. This schedule may relate to the timing of LC-PUFA supplementation and, even more, to the timing of outcome measurements. While any effect of the early postnatal LC-PUFA status may be attenuated by events later in life, it may also be that effects only become relevant and measurable at a later age.

Randomised studies that supplement mothers during pregnancy may have different effects, as fatty acid status is affected at an early stage of offspring development. n-3 LC-PUFA supplementation during pregnancy affects foetal LC-PUFA status, as shown by increased DHA in the maternal circulation and cord blood after fish oil supplementation during pregnancy [60]. Supplementation during lactation influences the fatty acid composition of breast milk and infant plasma [61]. However, as with

postnatal interventions, clearly significant positive effects of earlier supplementation on neurodevelopment could not be found in meta-analyses, although some trials found significant improvements [50]. It might be that the mechanisms that support the enrichment of LC-PUFAs by trans-placental transfer suffice in establishing adequate availability of LC-PUFAs during pregnancy in well-nourished populations. In fact, the greatest number of studies has been performed in high-income countries; corresponding studies in less-well-off populations may yield a different picture.

Although potentially subject to confounding, observational studies are important in this context, as they take into account the long-term status of the mother, while interventions are limited to certain time windows. In the ALSPAC cohort, Hibbeln et al. showed a positive effect of higher maternal seafood intake (more than 340 g/week) on the outcome of intelligence tests at the age of 8 years [62]. High fish intake significantly reduced the risk of suboptimal test results, even after considering 28 potential confounding factors. This study was enabled by collecting data from more than 5,000 children. The authors considered dietary n-3 LC-PUFAs as the most probable mediating factors, but as fish provides further valuable nutrients, the study was not fully conclusive [63]. Analysis of the maternal red-blood-cell DHA in this cohort revealed that there is in fact a positive relationship between DHA status and test scores, but only 0.3% of the variance in the test scores could additionally be explained by maternal DHA [64]. Thus, a further reason for the ambiguous results might be that the effects are small and, as such, only detectable in studies including very high numbers of subjects. It is worth noting that this study also indicated the relevance of AA and some other fatty acids, which might further complicate the situation. Furthermore, the influence of the fatty acid desaturase genotype of the mother and infant may complicate the interpretation of the randomised trials, as a significant interaction of the fatty acid desaturase genotype with the relationship between infant feeding and later measures of intelligence has been shown [65], which has not been considered so far in intervention studies.

Allergic Disease Risk

There are convincing indications that the immune status at birth may predispose an individual to the development of allergic disease [66]. Predictive factors for later allergy development relate to cord blood cytokines, regulatory T cell and TLR function [66]. It has been well described that LC-PUFA status, and specifically the ratio of AA to EPA, can influence these factors [67]. The major link between LC-PUFAs and the regulation of immune function is established via eicosanoids, or biologically active lipid mediators produced from LC-PUFAs [68]. Typically precursor fatty acids are released from phospholipids by A₂ phospholipases and are subjected to conversion by cyclooxygenase (prostaglandins and thromboxanes), lipoxygenase (leukotrienes) and cytochrome P450 (hydroxylated fatty acids). The potent series 2 prostaglandins and

series 4 leukotrienes are derived from AA, while series 3 prostaglandins and series 5 leukotrienes are produced from EPA. Eicosanoid production is dependent on precursor availability; thus, increased n-3 LC-PUFA incorporation into cell membrane phospholipids at the expense of AA changes the eicosanoid pattern. This phenomenon is important because the EPA-derived eicosanoids are usually much less biologically active. This event influences the behaviour of the cells of the immune system and changes the patterns of activation and of the cytokines and other immune factors produced. Additionally, inflammation-resolving resolvins and protectins are derived from EPA and DHA [69], which may explain much of the anti-inflammatory effects of n-3 LC-PUFAs.

Furthermore, n-3 fatty acids negatively influence the potential of NF- κ B to upregulate inflammatory cytokines. The activation of NF- κ B involves the phosphorylation of an inhibitory subunit, which can be limited by EPA [68]. DHA has been shown to induce PPAR- γ , which interferes with the activation of NF- κ B and thus decreases the production of pro-inflammatory cytokines. Further anti-inflammatory effects of n-3 LC-PUFAs could be mediated by limiting the aggregation of signalling molecules and TLR-4 in lipid rafts and by the activity of the membrane receptor GPR120, which acts in an anti-inflammatory manner [70]. Lipid rafts, or membrane areas with a higher content of cholesterol, sphingolipids and phospholipids with saturated fatty acid moieties, are important for the interaction of cells with external signals [68]. It has been shown that EPA can interfere with lipid raft formation, and it is assumed that other n-3 LC-PUFAs do so as well. This might be a mechanism to limit the pro-inflammatory response of immune cells to stimuli. Thus, there are a number of interaction points of n-3 LC-PUFAs with immune responses, and as a consequence, a significant influence of fatty acid status on inflammation and the expression of Th1- and Th2-type cytokines can be expected. Combined with the importance of the early-life immune status for the later-in-life risk of allergic diseases, including hay fever and asthma, this concept suggests the importance of perinatal fatty acid status for the programming of the long-term risk of immune-related disease.

The clinical relevance of the outlined mechanisms for disease risk has been investigated in observational and some intervention studies. Kremmyda et al. categorised the observational studies of fish intake available in 2011 into studies that focussed on maternal diet and studies looking at infant diet [71]. While the included studies that looked at maternal intake all found at least some beneficial effect of fish intake on allergic disease in offspring, the picture was more mixed for studies of infant diet. Only 9 of the included 14 studies observed a positive effect of higher fish intake by infants and children on atopic outcomes. This finding agrees with the assumption that there is a very early programming effect. Although fish is the major source of n-3 LC-PUFAs, the observation of fish intake implied that the other nutrients provided by fish are not of relevance for the outcome, and there is a risk that confounding factors were not considered adequately. These limitations can be overcome by randomised intervention studies of n-3 LC-PUFAs. While randomised interventions in infants and

children have not convincingly demonstrated a beneficial effect of fish oil supplementation on allergic disease, there are good indications that maternal supplementation during pregnancy programmes the immune system in a way that decreases the risk of atopic diseases. Klemens et al. performed a systematic review of randomised intervention studies looking at the role of n-3 LC-PUFA supplementation during pregnancy or lactation with respect to infant and childhood allergies, asthma, atopic diseases and inflammatory markers [72]. The review considered 4 major studies with n-3 LC-PUFA supplementation during pregnancy, comparing a total of about 800 mothers receiving n-3 doses of 0.6–3.7 g/day with controls receiving a placebo oil. One study looked only at inflammatory markers in cord blood [73], but the other trials looked at clinical outcomes at age 1 year or performed a follow-up investigation at age 16 years [74]. Additionally, the review included a randomised intervention during the first 4 months of lactation, comparing 1.5 g n-3 LC-PUFAs with olive oil in 147 women and following up the children at age 30 months [75]. The 3 studies that looked at food allergy could not identify a significant benefit of n-3 supplementation. Together, the two pregnancy intervention trials [76, 77], which included skin prick tests at age 12 months, identified a reduction of the risk of positive tests (odds ratio 0.33, 95% CI 0.19–0.70). An influence of the intervention on the frequency of eczema or atopic dermatitis could not be identified in the 3 studies that reported these results. This finding does not seem to depend on the timing of the intervention, as exclusion of the lactation supplementation study did not change the result. In contrast, asthma risk could only be identified as significantly decreased by combining the pregnancy studies assessing this outcome (odds ratio 0.35, 95% CI 0.15–0.79), and inclusion of supplementation during lactation led to a statistically significant decrease in risk [74–76]. As different measurement procedures were applied, results for IL-13 measurements could not be combined for evaluation, but both studies looking at IL-13 found a decreasing effect of n-3 LC-PUFAs. Thus, there are good indications that the established effects of fatty acid status on the immune system at the biochemical and cellular levels have clinical correlates. This finding suggests a programming effect of fatty acids on the immune system. However, although one of the studies [74] followed its subjects until the age of 16 years, the relevance of perinatal fatty acid status compared with other, later-occurring events still has to be proven.

Conclusion

Perinatal LC-PUFA status is accessible to modification by diet and the intake of supplements. An impact of LC-PUFAs on the biochemical and physiological mechanisms behind the risk of major diseases makes perinatal LC-PUFA status (and its modification) a promising field of research, with clinical and public health consequences. Although the effects of LC-PUFAs may be comparatively small, on the population level, there is the potential for long-term improvement of quality of life. The relevance of

fatty acid status is not limited to obesity, allergies and cognitive performance, as discussed here. Among the further discussed associations are that the risk of extreme preterm deliveries is decreased by improved DHA status [78] and that the incidence of behavioural difficulties in children may depend on cord-blood LC-PUFAs [79].

Although it seems difficult to quantify the clinical effects of perinatal LC-PUFA status, it is one of the modifiable factors influencing long-term health, disease and quality of life.

References

- 1 Willett WC: Dietary fats and coronary heart disease. *J Intern Med* 2012;272:13–24.
- 2 Bateson P, Barker D, Clutton-Brock T, et al: Developmental plasticity and human health. *Nature* 2004;430:419–421.
- 3 Koletzko B, Symonds ME, Olsen SF, Early Nutrition Programming Project, Early Nutrition Academy: Programming research: where are we and where do we go from here? *Am J Clin Nutr* 2011;94:2036S–2043S.
- 4 Schmitz G, Ecker J: The opposing effects of n-3 and n-6 fatty acids. *Prog Lipid Res* 2008;47:147–155.
- 5 Plourde M, Cunnane SC: Extremely limited synthesis of long chain polyunsaturates in adults: Implications for their dietary essentiality and use as supplements. *Appl Physiol Nutr Metab* 2007;32:619–634.
- 6 Schaeffer L, Gohlke H, Müller M, et al: Common genetic variants of the fads1 fads2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. *Hum Mol Genet* 2006;15:1745–1756.
- 7 Ganesan B, Brotherson C, McMahon DJ: Fortification of foods with omega-3 polyunsaturated fatty acids. *Crit Rev Food Sci Nutr* 2014;54:98–114.
- 8 Simopoulos AP: The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med* (Maywood) 2008;233:674–688.
- 9 Berghaus TM, Demmelmair H, Koletzko B: Fatty acid composition of lipid classes in maternal and cord plasma at birth. *Eur J Pediatr* 1998;157:763–768.
- 10 Gil-Sánchez A, Koletzko B, Larqué E: Current understanding of placental fatty acid transport. *Curr Opin Clin Nutr Metab Care* 2012;15:265–272.
- 11 Al MD, van Houwelingen AC, Kester AD, et al: Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. *Br J Nutr* 1995;74:55–68.
- 12 Gil-Sánchez A, Larqué E, Demmelmair H, et al: Maternal-fetal in vivo transfer of [13c]docosahexaenoic and other fatty acids across the human placenta 12 h after maternal oral intake. *Am J Clin Nutr* 2010;92:115–122.
- 13 Larqué E, Demmelmair H, Berger B, et al: In vivo investigation of the placental transfer of (13)c-labeled fatty acids in humans. *J Lipid Res* 2003;44:49–55.
- 14 Gauster M, Hiden U, Blaschitz A, et al: Dysregulation of placental endothelial lipase and lipoprotein lipase in intrauterine growth-restricted pregnancies. *J Clin Endocrinol Metab* 2007;92:2256–2263.
- 15 Campbell FM, Clohessy AM, Gordon MJ, et al: Uptake of long chain fatty acids by human placental choriocarcinoma (bewo) cells: Role of plasma membrane fatty acid-binding protein. *J Lipid Res* 1997;38:2558–2568.
- 16 Larqué E, Demmelmair H, Gil-Sánchez A, et al: Placental transfer of fatty acids and fetal implications. *Am J Clin Nutr* 2011;94:1908S–1913S.
- 17 Scifres CM, Chen B, Nelson DM, et al: Fatty acid binding protein 4 regulates intracellular lipid accumulation in human trophoblasts. *J Clin Endocrinol Metab* 2011;96:E1083–E1091.
- 18 Szitanyi P, Koletzko B, Mydlilova A, et al: Metabolism of 13C-labelled linoleic acid in newborn infants during the first week of life. *Pediatr Res* 1999;45:669–673.
- 19 Brenna JT, Varamini B, Jensen RG, et al: Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. *Am J Clin Nutr* 2007;85:1457–1464.
- 20 Fleddermann M, Demmelmair H, Grote V, et al: Infant formula composition affects energetic efficiency for growth: The BeMIM study, a randomized controlled trial. *Clin Nutr* 2013;33:588–595.
- 21 Sauerwald UC, Fink MM, Demmelmair H, et al: Effect of different levels of docosahexaenoic acid supply on fatty acid status and linoleic and alpha-linolenic acid conversion in preterm infants. *J Pediatr Gastroenterol Nutr* 2012;54:353–363.

- 22 Poston L: Gestational weight gain: Influences on the long-term health of the child. *Curr Opin Clin Nutr Metab Care* 2012;15:252–257.
- 23 Négrel R, Gaillard D, Ailhaud G: Prostacyclin as a potent effector of adipose-cell differentiation. *Biochem J* 1989;257:399–405.
- 24 Ailhaud G, Massiera F, Weill P, et al: Temporal changes in dietary fats: Role of n-6 polyunsaturated fatty acids in excessive adipose tissue development and relationship to obesity. *Prog Lipid Res* 2006;45:203–236.
- 25 Barber E, Sinclair AJ, Cameron-Smith D: Comparative actions of omega-3 fatty acids on in-vitro lipid droplet formation. *Prostaglandins Leukot Essent Fatty Acids* 2013;89:359–366.
- 26 Hihi AK, Michalik L, Wahli W: PPARs: Transcriptional effectors of fatty acids and their derivatives. *Cell Mol Life Sci* 2002;59:790–798.
- 27 Massiera F, Saint-Marc P, Seydoux J, et al: Arachidonic acid and prostacyclin signaling promote adipose tissue development: A human health concern? *J Lipid Res* 2003;44:271–279.
- 28 Madsen L, Pedersen LM, Liaset B, et al: cAMP-dependent signaling regulates the adipogenic effect of n-6 polyunsaturated fatty acids. *J Biol Chem* 2008;283:7196–7205.
- 29 Aprikian O, Reynaud D, Pace-Asciak C, et al: Neonatal dietary supplementation of arachidonic acid increases prostaglandin levels in adipose tissue but does not promote fat mass development in guinea pigs. *Am J Physiol Regul Integr Comp Physiol* 2007;293:R2006–R2012.
- 30 Hussain A, Nookaew I, Khoomrung S, et al: A maternal diet of fatty fish reduces body fat of offspring compared with a maternal diet of beef and a post-weaning diet of fish improves insulin sensitivity and lipid profile in adult C57BL/6 male mice. *Acta Physiol (Oxf)* 2013;209:220–234.
- 31 Oosting A, Kegler D, Boehm G, et al: N-3 long-chain polyunsaturated fatty acids prevent excessive fat deposition in adulthood in a mouse model of postnatal nutritional programming. *Pediatr Res* 2010;68:494–499.
- 32 Wielinga PY, Harthoorn LF, Verschuren L, et al: Arachidonic acid/docosahexaenoic acid-supplemented diet in early life reduces body weight gain, plasma lipids, and adiposity in later life in ApoE*3Leiden mice. *Mol Nutr Food Res* 2012;56:1081–1089.
- 33 Rodríguez G, Iglesia I, Bel-Serrat S, et al: Effect of n-3 long chain polyunsaturated fatty acids during the perinatal period on later body composition. *Br J Nutr* 2012;107 (Suppl 2):S117–S128.
- 34 Lucia Bergmann R, Bergmann KE, Haschke-Becher E, et al: Does maternal docosahexaenoic acid supplementation during pregnancy and lactation lower bmi in late infancy? *J Perinat Med* 2007;35:295–300.
- 35 Hauner H, Much D, Vollhardt C, et al: Effect of reducing the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on infant adipose tissue growth within the first year of life: An open-label randomized controlled trial. *Am J Clin Nutr* 2012;95:383–394.
- 36 Much D, Brunner S, Vollhardt C, et al: Effect of dietary intervention to reduce the n-6/n-3 fatty acid ratio on maternal and fetal fatty acid profile and its relation to offspring growth and body composition at 1 year of age. *Eur J Clin Nutr* 2013;67:282–288.
- 37 Hauner H, Brunner S, Amann-Gassner U: The role of dietary fatty acids for early human adipose tissue growth. *Am J Clin Nutr* 2013;98:549S–555S.
- 38 Rosenfeld E, Beyerlein A, Hadders-Algra M, et al: IPD meta-analysis shows no effect of LC-PUFA supplementation on infant growth at 18 months. *Acta Paediatr* 2009;98:91–97.
- 39 de Jong C, Boehm G, Kikkert HK, et al: The Groningen LCPUFA study: No effect of short-term postnatal long-chain polyunsaturated fatty acids in healthy term infants on cardiovascular and anthropometric development at 9 years. *Pediatr Res* 2011;70:411–416.
- 40 Donahue SM, Rifas-Shiman SL, Olsen SF, et al: Associations of maternal prenatal dietary intake of n-3 and n-6 fatty acids with maternal and umbilical cord blood levels. *Prostaglandins Leukot Essent Fatty Acids* 2009;80:289–296.
- 41 Moon RJ, Harvey NC, Robinson SM, et al: Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood. *J Clin Endocrinol Metab* 2013;98:299–307.
- 42 Standl M, Thiering E, Demmelmair H, et al: Age-dependent effects of cord blood long-chain PUFA composition on BMI during the first 10 years of life. *Br J Nutr* 2014 Feb 13;1–8. [Epub ahead of print] PubMed PMID: 24521544.
- 43 Lauritzen L, Hansen HS, Jørgensen MH, et al: The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res* 2001;40:1–94.
- 44 Luchtman DW, Song C: Cognitive enhancement by omega-3 fatty acids from childhood to old age: Findings from animal and clinical studies. *Neuropharmacology* 2013;64:550–565.
- 45 Chalon S: Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot Essent Fatty Acids* 2006;75:259–269.
- 46 Cao D, Kevala K, Kim J, et al: Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J Neurochem* 2009;111:510–521.
- 47 Calderon F, Kim HY: Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J Neurochem* 2004;90:979–988.

- 48 Brenna JT: Animal studies of the functional consequences of suboptimal polyunsaturated fatty acid status during pregnancy, lactation and early post-natal life. *Matern Child Nutr* 2011;7 (Suppl 2):59–79.
- 49 Nyaradi A, Li J, Hickling S, et al: The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Front Hum Neurosci* 2013;7:97.
- 50 Gould JF, Smithers LG, Makrides M: The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: A systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2013;97:531–544.
- 51 Makrides M: DHA supplementation during the perinatal period and neurodevelopment: Do some babies benefit more than others? *Prostaglandins Leukot Essent Fatty Acids* 2013;88:87–90.
- 52 Koletzko B, Lien E, Agostoni C, et al: The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: Review of current knowledge and consensus recommendations. *J Perinat Med* 2008;36:5–14.
- 53 Qawasmi A, Landeros-Weisenberger A, Bloch MH: Meta-analysis of LCPUFA supplementation of infant formula and visual acuity. *Pediatrics* 2013;131:e262–e272.
- 54 Schulzke SM, Patole SK, Simmer K: Long-chain polyunsaturated fatty acid supplementation in pre-term infants. *Cochrane Database Syst Rev* 2011; DOI: 10.1002/14651858.CD000375.pub4.
- 55 Simmer K, Patole SK, Rao SC: Long-chain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev* 2011, DOI: 10.1002/14651858.CD000376.pub3.
- 56 Qawasmi A, Landeros-Weisenberger A, Leckman JF, et al: Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. *Pediatrics* 2012;129:1141–1149.
- 57 Makrides M, Collins CT, Gibson RA: Impact of fatty acid status on growth and neurobehavioural development in humans. *Matern Child Nutr* 2011; 7(Suppl 2):80–88.
- 58 Carlson SE: Early determinants of development: A lipid perspective. *Am J Clin Nutr* 2009;89:1523S–1529S.
- 59 Drover J, Hoffman DR, Castañeda YS, et al: Three randomized controlled trials of early long-chain polyunsaturated fatty acid supplementation on means-end problem solving in 9-month-olds. *Child Dev* 2009;80:1376–1384.
- 60 Krauss-Etschmann S, Shadid R, Campoy C, et al: Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: A European randomized multicenter trial. *Am J Clin Nutr* 2007;85:1392–1400.
- 61 Gibson RA, Neumann MA, Makrides M: Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. *Eur J Clin Nutr* 1997;51:578–584.
- 62 Hibbeln JR, Davis JM, Steer C, et al: Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort study. *Lancet* 2007;369:578–585.
- 63 Bath SC, Steer CD, Golding J, et al: Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: Results from the Avon longitudinal study of parents and children (ALSPAC). *Lancet* 2013;382:331–337.
- 64 Steer CD, Lattka E, Koletzko B, et al: Maternal fatty acids in pregnancy, FADS polymorphisms, and child intelligence quotient at 8 y of age. *Am J Clin Nutr* 2013;98:1575–1582.
- 65 Steer CD, Davey Smith GD, Emmett PM, et al: FADS2 polymorphisms modify the effect of breastfeeding on child IQ. *PLoS ONE* 2010;5:e11570.
- 66 Lehmann I, Herberth G: Cord blood immune status: Predicting health or allergy? *Allergy* 2012;67:445–448.
- 67 Prescott SL, Dunstan JA: Prenatal fatty acid status and immune development: The pathways and the evidence. *Lipids* 2007;42:801–810.
- 68 Calder PC: N-3 fatty acids, inflammation and immunity: New mechanisms to explain old actions. *Proc Nutr Soc* 2013;72:326–336.
- 69 Serhan CN, Chiang N, Van Dyke TE: Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008;8:349–361.
- 70 Oh DY, Talukdar S, Bae EJ, et al: GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 2010;142:687–698.
- 71 Kremmyda LS, Vlachava M, Noakes PS, et al: Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: A systematic review. *Clin Rev Allergy Immunol* 2011;41:36–66.
- 72 Klemens CM, Berman DR, Mozurkewich EL: The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: A systematic review. *BJOG* 2011;118:916–925.
- 73 Krauss-Etschmann S, Hartl D, Rzehak P, et al: Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. *J Allergy Clin Immunol* 2008;121:464–470.

- 74 Olsen SF, Østerdal ML, Salvig JD, et al: Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr* 2008;88:167–175.
- 75 Lauritzen L, Kjaer TM, Fruekilde MB, et al: Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. *Lipids* 2005;40:669–676.
- 76 Dunstan JA, Mori TA, Barden A, et al: Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: A randomized, controlled trial. *J Allergy Clin Immunol* 2003;112:1178–1184.
- 77 Furuholm C, Warstedt K, Larsson J, et al: Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr* 2009; 98:1461–1467.
- 78 Imhoff-Kunsch B, Briggs V, Goldenberg T, et al: Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: A systematic review. *Paediatr Perinat Epidemiol* 2012;26 (Suppl 1):91–107.
- 79 Kohlboeck G, Glaser C, Tiesler C, et al: Effect of fatty acid status in cord blood serum on children's behavioral difficulties at 10 y of age: Results from the lisap-lus study. *Am J Clin Nutr* 2011;94:1592–1599.

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Commercial Lipid Emulsions and All-in-One Mixtures for Intravenous Infusion – Composition and Physicochemical Properties

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Abstract

In the 20th century, the potential clinical application of lipid emulsions (LEs) for intravenous application was extensively studied, and this goal was eventually accomplished. The first safe LE for clinical use that was based on soybean oil was introduced in 1961. In the 1980s, LEs based on mixtures of soybean oil and medium-chain triglycerides (MCTs) were introduced. More recently, LEs combining various oils (soybean, MCT, fish and olive oils) have become available for safe clinical use in both acute care and long-term settings. This article focuses on the following essential aspects of the current formulations: (1) the basic physicochemical properties; (2) the relevant pharmacopoeial standards; and (3) important clinical issues to ensure their safe use in patients. LEs with a variety of chemical compositions are commercially available. They adhere to standards laid down in relevant pharmacopoeias, and they are safe to use. Different compositions may result in different functional properties.

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Introduction

Lipid emulsions (LEs) serve three primary purposes in the clinical setting. First, they provide essential fatty acids, which is likely to be especially important in patients requiring long-term total parenteral nutrition; indeed, LEs were introduced as weekly or biweekly nutritional supplements for use in such patients. Second, because fatty acids are good substrates for energy generation, LEs form part of a balanced parenteral nutrition regimen, reducing the need for calories from glucose. Third, LEs are used as a delivery vehicle for poorly soluble drugs, such as diazepam, propofol and clevidipine. Although the latter application is not the focus of this review, it should,

nonetheless, be recognised that LEs have additional and important uses in medicine. As to the current status of commercial LEs for nutrition support, the reader is directed to a recent, comprehensive review [1].

Basic Physicochemical Properties of Lipid Emulsions

LEs are principally two-phase systems consisting of an aqueous, or water, phase, and an oleaginous, or oil, phase, that are brought together (made miscible or mixable) with the aid of a surfactant, or emulsifier. The two phases of an emulsion do not normally mix, or are 'immiscible', because the polar and non-polar forces between them are so great that a high degree of interfacial tension is created. Consequently, a surfactant, or emulsifier, is required to lower the surface tension between the phases in order to form a single, seemingly soluble (or miscible) homogenous dispersion of the two, otherwise immiscible, liquids. Hence, the surfactant is the 'backbone' that stabilises the emulsion and keeps the oil phase from physically separating from the water phase. Even in emulsions that are 'reasonably' stable, the effect is only temporary because the truly 'stable' or 'state of equilibrium' between all polar and non-polar liquids is separate phases of oil and water. However, for practical purposes and depending upon the application, a reasonable shelf life can be obtained for commercial emulsions. For example, homogenised whole milk (approximately 3.4% milk fat in water) can be stabilised for up to 2 weeks at 4°C, whereas in other cases, such as LEs, stability can be enhanced for up to 2 years at 25°C.

Today, biodegradable emulsions are most commonly applied and are water-based; in these cases, the oil phase, or 'internal' phase, is dispersed as droplets throughout the water, or external, phase, forming the so-called oil-in-water (o/w) emulsion. This type of emulsion is a critically important requirement for all LEs, whereby the 'external' phase must be aqueous in order to be miscible with blood. On the other hand, if the external phase is oleaginous, as a water-in-oil emulsion, the emulsion is no longer miscible with blood and can produce a potentially fatal capillary fat embolism. This clinical risk is always present, even in the case of injectable o/w emulsions, because if the emulsion formulation is not stable or becomes unstable prior to use, the internal oil phase will begin to separate relatively quickly from the external aqueous phase, thereby forming large-diameter fat globules via a process known as coalescence.

To be effective, the emulsifier must therefore reduce the interfacial tension between phases, and it does so in two ways: (1) by coating each homogenised submicron oil droplet, thus creating a molecular film between the oil droplets and the water phase and (2) by establishing electrostatic repulsion between the droplets. Egg lecithin, or egg phospholipids, is universally used as the main emulsifier for LEs, and it is ampho-teric (i.e., possesses hydrophilic head groups that extend into the aqueous phase, exerting a net negative charge, with hydrophobic tails that embed into the droplets of the oil phase). At a pH range between 6 and 9, the hydrophilic head is optimally ion-

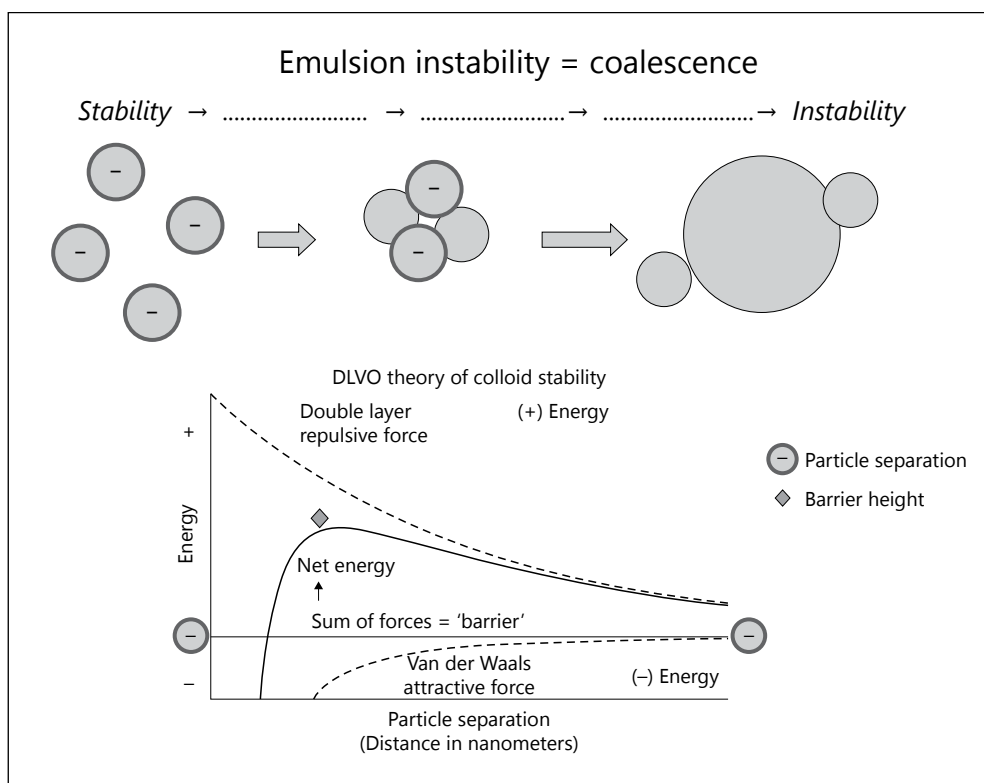


Fig. 1. Colloid or emulsion stability.

ised and produces a negative electrical charge, which is described by the zeta potential. If all oil droplets in the emulsion are evenly coated and therefore possess the same electrical charge, they will repel one another (i.e., 'opposite charges attract, and like charges repel') and remain dispersed in the water phase. Therefore, the emulsion is stable. If the droplets become less negatively charged (e.g., by addition of oppositely charged cations), the emulsion becomes less stable. If the charge sufficiently drops, the attractive forces between the oil droplets will supersede the repulsive forces, causing the submicron oil droplets to fuse, forming large-diameter fat globules. These unstable emulsions are no longer safe and may produce significant clinical harm.

Figure 1 depicts the essential principle behind the DLVO Theory of Colloid Stability that governs the stability of ionically stabilised dispersions such as LEs. In essence, the repulsive forces caused by the emulsifier must be greater than the Van der Waals attractive forces between the non-polar oil droplets, thus creating an effective inter-particle (inter-droplet) potential energy barrier between neighbouring oil droplets. The height of the energy barrier is a function of the difference between these opposing forces, and the stability of LEs is optimised when the electrostatically charged droplets have a zeta potential of -40 to -50 mV.

Relevant Pharmacopoeial Standards for Lipid Emulsions

Pharmacopoeias around the world function variably to serve as liaisons between government regulatory authorities and the pharmaceutical industry. Generally, pharmacopoeias write official specifications for drugs, raw materials, dosage forms, and methods of analyses that can be used to achieve a particular pharmaceutical standard. In this way, the industry is compelled to meet certain pharmacopoeial standards for the approval of a drug and/or dosage form for use in humans. In America, for example, the US Pharmacopoeia, or USP, writes the specifications (as monographs) and the associated methods of analysis (as chapters) for all drugs, which are then enforced at the discretion of the Food and Drug Administration. Similarly, for example, the European Pharmacopoeia (Pharm Eur) also creates official pharmacopoeial articles, e.g., monographs for drugs, raw materials, etc., that also influence regulatory oversight. In addition, individual countries have national pharmacopoeias (e.g., British Pharmacopoeia, German Pharmacopoeia, etc.) that are often, but not always, in harmony with the Pharm Eur. In addition, the USP and Pharm Eur seek harmonisation whenever possible, but achieving this goal can take years to accomplish for various reasons.

In the USP, there are two key pharmacopoeial articles that uniquely apply to the quality and safety of LEs. The first is USP Chapter <729>, entitled ‘Globule Size Distribution in Lipid Injectable Emulsions’, which was adopted in 2007. This article identified two physical methods and the associated globule-size limits that must be met by all lipid-injectable emulsion products in the US to ensure pharmaceutical equivalence between manufacturers. LEs have been commercially available and in clinical use in Europe since 1961. Pharm Eur briefly adopted a globule size limit in 1978, as did the British Pharmacopoeia in 1980, but both were subsequently abandoned [2]. LEs have been routinely used in the US since 1976, but before USP <729> came into effect, no standing official pharmacopoeial standard existed. USP <729> applies to 10–30% of the o/w LEs intended for nutritional and drug purposes. Method I of USP <729> is a qualitative standard that specifies that the *intensity-weighted* mean droplet diameter, determined by light-scattering techniques, e.g., photon correlation spectroscopy or PCS, must be less than 500 nm. Method II of USP <729> is a stability-indicating method that is based on a single-particle optical sensing technique, which uses the method of light extinction, and that specifies that the volume-weighted percentage of fat residing in globules larger than 5 micrometres (or PFAT5) must not exceed 0.05%. The PFAT5 parameter tracks the growth of potentially embolic fat globules and therefore has significant patient safety implications (fig. 2). The second USP article is the corresponding monograph entitled ‘Lipid Injectable Emulsion’, which includes suitable raw materials, chemical limits and a specific reference to USP Chapter <729>.

Two key pharmacopoeial articles by Pharm Eur can be uniquely applied to the quality of certain raw materials used in LEs. This is especially significant with respect

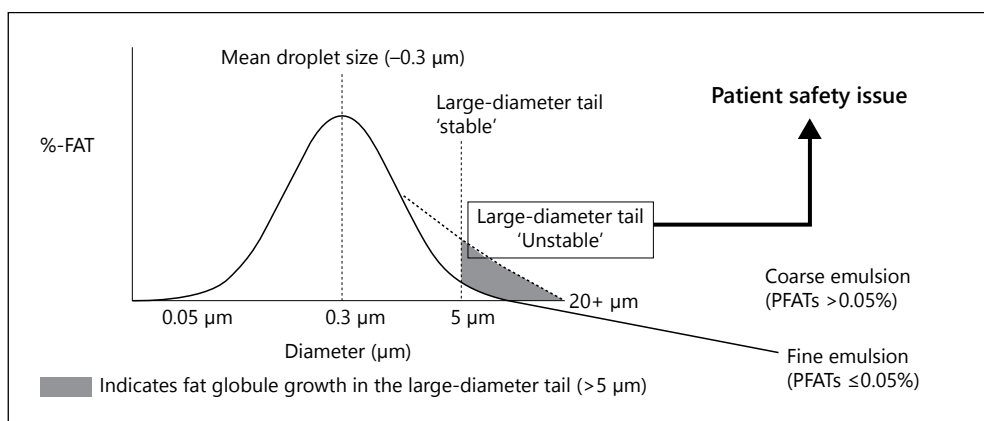


Fig. 2. Globule size distribution, stability and patient safety.

to the use of omega-3 fatty acid-containing triglycerides (TGs), given their potential importance as active pharmaceutical ingredients in the therapeutic management of several inflammatory diseases. Ironically, however, Pharm Eur created two monographs for omega-3 fatty acids-containing TGs. In 1999, Pharm Eur Monograph No. 1352, entitled 'Omega-3 Acid Triglycerides', was adopted. The specified omega-3 fatty acid requirements included that the *minimum* sum of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), expressed as TGs, be 45.0% and that the *minimum* total omega-3 fatty acids, expressed as TGs, be 60.0%. Then, in 2005, Pharm Eur adopted Monograph No. 1912, entitled 'Fish Oil, Rich in Omega-3 Acids'. The omega-3 fatty acid requirements were then approximately one-half the amounts specified in Pharm Eur 1352. That is, EPA, expressed as TGs, must have a minimum concentration of 13.0%, and DHA must have a minimum concentration of 9.0% (therefore, the minimum sum of EPA + DHA = 22%). The total omega-3 acids, expressed as TGs, must have a minimum concentration of 28.0%. Consequently, both oils are used in commercial LEs by different companies. Therefore, if the omega-3 fatty acids are included for therapeutic purposes, the clinician cannot rely simply on the 'fish oil' concentration in the oil phase of a given emulsion but rather must know the pharmacopoeial quality of the fish oil omega-3 fatty acid-containing TGs to ensure that the desired dose of EPA and DHA is administered [3].

Important Clinical Issues

The administration of LE to acutely ill patients must be undertaken with great care to ensure they are safely applied. To achieve this, it is important to consider 3 key factors: (1) the composition of the emulsion formulation; (2) the quality and stabil-

ity of the LE; and, (3) the desired dose and infusion rate for the selected patient population. The 3 factors will be addressed separately, as each may affect clinical outcome.

Composition of the Lipid Emulsion

The composition of the LE is a critical factor. For example, the types of oil(s) that are used and the concentrations that make up the internal oil phase are important clinical considerations. The current TG oils that are available for use in commercially available LEs include plant oils (soybean, coconut or palm kernel (both as sources of MCTs), and olive) and fish oils. Of the single-oil emulsion compositions, only soybean and fish oil are commercially available as such; all others, such as soybean-MCT, soybean-olive, soybean-MCT-fish or soybean-MCT-olive-fish, are physical mixtures. There are also experimental formulations under study that include fish-MCT oil mixtures, but these are not yet commercially available. With clinical experience, the use of soybean oil-only emulsions has lost favour (outside of North America), and such emulsions have been replaced by oil-mixtures designed to reduce the pro-inflammatory omega-6 fatty acid load, particularly during the high metabolic stress states that are typically found in acutely ill patients. Approximately 50% of the fatty acid profile of soybean oil is contributed by the omega-6 fatty acid linoleic acid (18:2n-6), and about 10% consists of the saturated long-chain fatty acid palmitic acid (16:0). Alternative compositions containing oil mixtures have reduced the soybean oil content from the conventional 100% soybean o/w emulsions to between 20 and 50% of the oil phase, depending upon the formulation. Reducing the amount of soybean oil and its components, which may be converted into pro-inflammatory mediators, by substitution with oils/fatty acids with no or fewer pro-inflammatory effects is desirable. This can be achieved with MCTs that contain mainly two medium-chain saturated fatty acids (8:0 and 10:0) or olive oil, which contains a high amount of the monounsaturated fatty acid oleic acid (18:1n-9). Alternatively, the clinician may opt to use fish oil to provide two omega-3 polyunsaturated fatty acids (20:5n-3 and 22:6n-3), which can be converted into metabolites with anti-inflammatory properties. This may be especially important for certain acute-care conditions, such as in critically ill adults with profound metabolic stress and a heightened systemic inflammatory response syndrome [4, 5] or in critically ill infants with intestinal failure-associated cholestatic liver disease that is associated with the use of soybean oil LE [6–8].

A second example of the clinical importance of the emulsion composition is the concentration of the surfactant, or emulsifier, in the formulation. Historically, soybean oil emulsions have contained the same amount of egg phospholipids (PLs; 12 g/l), irrespective of the final oil concentration (i.e., 10%_{w/v} or 20%_{w/v} o/w emulsions). So clearly, the amount of PLs was higher than necessary in the 10%_{w/v} o/w formulations, creating a PL:TG ratio of 0.12 versus 0.06 as is found in the 20% emulsion. In a study, 20 pre-term infants were given 20%_{w/v} Intralipid emulsions at doses up to 4 g/kg/day for 2 weeks, and they then received 10%_{w/v} Intralipid emulsions at 2 g/kg/day. The in-

infants then demonstrated various alterations in their plasma lipid profiles [9]. Plasma TGs, total cholesterol and PLs significantly increased during the 10 versus 20% Intra-lipid infusions; and excess PL liposomes acquired free cholesterol, albumin and apoprotein E, producing abnormal Lipoprotein X-like particles that delayed the actions of lipoprotein lipase. Therefore, PL:TG ratios of 0.06 were recommended for use in this patient population. Of note, a current fish oil emulsion that has been used in infants and children with intestinal failure associated cholestatic liver disease [10] has a PL:TG ratio of 0.12, but no adverse effects in tolerance have been reported at the recommended dose of 1 g/kg/day.

Quality and Stability of Lipid Emulsions

LEs are thermodynamically unstable formulations, and as such, their shelf-lives are much shorter (18–24 months) when compared to other pharmaceutical dosage forms, such as solutions, tablets, and capsules (36–60 months). Consequently, the quality of the final emulsion is critical for its safe use in the clinical setting, whether the emulsion is administered from its original container, via a syringe in its undiluted form or as part of a parenteral nutrition admixture containing amino acids, glucose, electrolytes, vitamins and trace minerals (i.e., all-in-one mixtures). However, of course, the quality of the emulsion begins with the manufacturer, whose goal is to produce a high-quality, or ‘fine’, emulsion that minimises the presence of the large-diameter fat globules that would be seen in a ‘coarse’ emulsion. It is this feature that determines emulsion stability and the subsequent safety under the clinical conditions of use, and it is the core requirement in USP <729> under Method II, known as the PFAT5 criterion. For example, when comparing the physical stability between ‘fine’ (PFAT5 $\leq 0.05\%$) versus ‘coarse’ (PFAT5 $> 0.05\%$) LEs in a simulated neonatal syringe-based infusion, the stability of the coarse emulsions significantly deteriorated during the 24-hour infusion period, reaching a PFAT5 level as high as 0.44%, or nearly ten times the upper limit defined in USP <729> [11]. In critically ill premature infants receiving a fine ($n = 50$) versus coarse ($n = 72$) injectable LE, the incidence of hypertriglyceridemia was significantly higher ($p = 0.004$) for the coarse (19/72) versus the fine LE (3/50). Moreover, in an adjusted logistic regression model for the odds of hypertriglyceridemia, which assessed 8 patient factors, the coarse emulsion was the only significant variable ($p = 0.01$) [12]. This was an important clinical finding recognising that lipid intolerance (serum TG ≥ 1.69 mmol/l) has been shown to be associated with liver dysfunction and foetal growth retardation [13]. In addition, such coarse emulsions have produced less stable all-in-one mixtures [14, 15].

Desired Dose and Infusion Rate in the Selected Patient Population

The ‘dose’ of LE depends on the composition of the oil phase, which influences its metabolic fate, the rate of infusion and, subsequently, the intended clinical response. The oil phase of all LEs is comprised of TGs containing fatty acids of varying hydro-

carbon chain lengths and degrees of saturation. Commercial MCT oil primarily consists of two saturated medium-chain fatty acids, caprylic acid (8:0) and capric acid (10:0), in an approximate 3:1 ratio. Saturated long-chain fatty acids, such as palmitic acid (16:0), can be found in plant oils, including soybean and olive oils, and in fish oil. Long-chain monounsaturated fatty acids primarily come from olive oil (oleic acid, 18:1n-9), but they also make up approximately 25% of the fatty acid profile of soybean oil. Long-chain polyunsaturated fatty acids from plants (soybean oil) include linoleic acid (18:2n-6) and α -linolenic acid (18:2n-3), while very-long chain, highly polyunsaturated fatty acids are found in fish oil (arachidonic acid, 20:4n-6; EPA, 20:5n-3; and DHA, 22:6n-3). Longer hydrocarbon chain lengths (C8 $\rightarrow$ C22), result in slower clearance from plasma upon infusion. For long-chain TG infusions (mostly based on soybean o/w emulsions), the maximum utilisation rate for safe infusion is approximately 0.11 g/kg/h [16]. For MCT-based infusions (i.e., 6–12 carbons), the plasma clearance is faster, while it is slowest for very long-chain TG infusions (>18 carbons). Mixing oils of varying chain lengths, especially with MCTs, can favourably influence the plasma clearance of LCT infusions. Hence, great care must be undertaken to ensure the effective plasma clearance of an injectable LE and that it does not induce fat overload and its attendant complications.

Summary

The introduction of a reasonably safe LE was a major milestone accomplished in the 20th century. Today, we know much more about the stability of these complex dosage forms, and there are pharmacopoeial standards that now exist to ensure pharmaceutical equivalence amongst manufacturers and various oil compositions. This has led to the development of safer products for clinical use. We are also learning much more about the biological impact of fatty acids in human disease, the linkage between lipid source, eicosanoid metabolism and the systemic inflammatory response as well as how these factors may influence clinical outcomes [17].

References

- 1 Vanek VW, Seidner DL, Allen P, Bistran B, Collier S, Gura K, Miles J, Valentine C, Kochevar M: ASPEN Position Paper: Clinical role for alternative intravenous fat emulsions. *JPEN J Parenter Enteral Nutr* 2012;27:150–192.
- 2 Driscoll DF: Lipid injectable emulsions: Pharmacopoeial and safety issues. *Pharm Res* 2006;23:1959–1969.
- 3 Driscoll DF, Ling PR, Bistran BR: Pharmacopoeial compliance of fish oil-containing parenteral lipid emulsion mixtures: Globule size distribution and fatty acid analyses. *Int J Pharm* 2009;379:125–130.
- 4 Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, Koch T: Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;34:972–979.

- 5 Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW: Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF 541): data from a prospective, randomized, multicenter trial. *Crit Care Med* 2007;35:700–706.
- 6 Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrrian BR, Puder M: Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: Implications for future management. *Pediatrics* 2006;118:e197–e201.
- 7 Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Revillon Y, Jan D, De Potter S, Gorski-Colin AM, Lamor M, Herreman K, Corriol O, Landais P, Ricour C, Goulet O: Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. *J Pediatr Gastroenterol Nutr* 2007;44:347–353.
- 8 Koletzko B, Goulet O: Fish oil containing intravenous lipid emulsions in parenteral nutrition-associated cholestatic liver disease. *Curr Opin Clin Nutr Metab Care* 2010;13:321–326.
- 9 Haumont D, Richelle M, Deckelbaum RJ, Coussaert E, Carpentier YA: Effect of liposomal content of lipid emulsions on plasma concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992;121:759–763.
- 10 Cowan E, Nandivada P, Puder M: Fish oil-based lipid emulsion in the treatment of parenteral nutrition-associated liver disease. *Curr Opin Pediatr* 2013;25:193–200.
- 11 Driscoll DF, Ling PR, Bistrrian BR: Physical stability of 20% lipid injectable emulsions via simulated syringe infusion: Effects of glass vs. plastic product packaging. *JPEN J Parenter Enteral Nutr* 2007;31:148–153.
- 12 Martin CR, Dumas GJ, Shoaie C, Zheng Z, MacKinnon B, Al-Aweel I, Bistrrian BR, Pursely DM, Driscoll DF: Incidence of hypertriglyceridemia in critically ill neonates receiving lipid injectable emulsions in glass versus plastic containers: A retrospective analysis. *J Pediatr* 2008;152:232–236.
- 13 Toce SS, Keenan WJ: Lipid intolerance in newborns is associated with liver dysfunction but not infection. *Arch Pediatr Adolesc Med* 1995;149:1249–1253.
- 14 Driscoll DF, Silvestri AP, Bistrrian BR, Mikrut BA: Stability of total nutrient admixtures with lipid injectable emulsions in glass versus plastic packaging. *Am J Health Syst Pharm* 2007;64:396–403.
- 15 Driscoll DF, Thoma A, Franke R, Klütsch K, Nehre J, Bistrrian BR: Lipid globule size in total nutrient admixtures prepared in 3-chamber plastic bags. *Am J Health-Syst Pharm* 2009;66:649–656.
- 16 Klein S, Miles JM: Metabolic effects of long-chain and medium-chain triglycerides in humans. *JPEN J Parenter Enteral Nutr* 1994;18:396–397.
- 17 Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.

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In vivo Handling and Metabolism of Lipid Emulsions

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Abstract

While a number of pathways for the catabolism and tissue delivery of intravenous lipid emulsions are shared by chylomicrons, there are also important differences. The introduction of medium-chain triglycerides (MCTs) and n-3 fatty acid-containing fish oils into lipid emulsions has marked effects on their clearance from the bloodstream and the delivery of fatty acids to organs, and it involves pathways different from those required for n-6 fatty acid-rich soybean oil-based particles. 1) Multiple pathways are responsible for the blood clearance and tissue uptake of MCT- and fish oil-containing emulsions. 2) Both human and animal model-based studies were needed to define these 'classical' and 'novel' pathways, which are respectively similar to and different from those involved in chylomicron clearance. 3) n-3 fatty acid-rich triglycerides and MCTs provide new opportunities for lipid emulsions to act as metabolic and immune modulators.

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Intravenous Lipid Emulsions: An Overview

Lipid emulsion particles for intravenous (iv) use have been developed based on the model of the intestinally derived chylomicron. Both types of particles are large (although chylomicrons are larger than iv lipid emulsion particles), with a core rich in triglycerides (TGs) (and with tocopherols in some emulsions) and with a surface rich in phospholipids (PLs) (with some free cholesterol and plant sterols); in iv lipid emulsions, the surface PL is usually egg lecithin. In contrast to chylomicrons, emulsion particles contain no apolipoproteins. In addition, emulsions are manufactured with an amount of PL that exceeds what is strictly needed for particle emulsification, with the excess forming separate PL-rich liposome-like particles. A large amount of such liposome-like particles, as were present in 10% lipid emulsions in the past, was shown to impede the hydrolysis and clearance of exogenous TGs, particularly in

subjects with low lipoprotein lipase (LPL) activity, such as preterm neonates [1, 2]. This finding led to a reduction in the PL/TG ratios used in more recently developed emulsions.

Metabolism of Intravenous Lipid Emulsions

After their administration into the blood circulation, TG-rich and PL-rich particles rapidly acquire apolipoproteins (namely apoC-II and apoE) by transfer from high-density lipoprotein particles as well as from endogenous TG-rich lipoproteins [3]. Another (less rapid) process is the transfer of exogenous TGs from emulsion particles to circulating low-density lipoprotein and high-density lipoprotein in exchange for cholesteryl esters, a process mediated by the cholesteryl ester transfer protein [4, 5].

Acquisition of apoC-II enables TG-rich particles to activate emulsion-bound LPL, an enzyme found attached to the endothelium of capillary vessels or free in the circulation. LPL hydrolyses part of the TG-rich particle and releases non-esterified fatty acids (NEFAs) and monoglycerides; these are largely taken up by the adjacent tissue, and a proportion of NEFAs remains in the circulation, largely bound to albumin [6]. Of note, a proportion of surface-bound tocopherols is also released and is taken up by adjacent tissues [7, 8]. TG hydrolysis by LPL substantially reduces particle size and leads to the formation of remnants that contain some cholesteryl esters. Direct uptake of the remnant particles takes place not only in the liver but also in extra-hepatic tissues and plays an important role in the delivery of some fatty acids (namely n-3 polyunsaturated fatty acids (PUFAs)) as well as tocopherols and other lipid-soluble vitamins. This process, which is facilitated by the presence of ligands such as apoE and LPL, involves receptor-mediated and non-receptor-mediated pathways [9].

Introduction of Non-Soybean Oil Triglycerides into Lipid Emulsions

In humans, apart from (substantial) interindividual variability and the influence of metabolic and inflammatory conditions, the fatty acid composition of exogenous TGs affects the above-mentioned clearance pathways. Emulsions made of soybean oil TGs have been used for many decades, and while their plasma clearance is efficient, their high content of n-6 PUFAs may increase inflammatory reactions and peroxidative damage. This situation has led to the development of emulsions with reduced n-6 PUFA content [10, 11]. Medium-chain TGs (MCTs) are particularly good substrates for LPL-mediated hydrolysis [12]; studies using a TG clamp technique showed that inclusion of MCTs in TG mixtures accelerates lipolysis and leads to the rapid formation of small remnants that are efficiently taken up by tissues.

In contrast, fish oil (FO)-based TGs, rich in long-chain n-3 PUFAs, are a poor substrate for LPL; when present in proportions exceeding 20% TGs, they may delay plas-

ma clearance [13]. A pure FO emulsion has been on the European market for >15 years, with interesting results, including reduced inflammatory reactions in surgical patients [14] and restored liver function in neonates and children on long-term parenteral nutrition [15]. However, TG clearance is slow with such an emulsion, and the infusion rate must be adapted to avoid an excessive increase in the plasma TG concentration, which may cause side effects [16]. Of note, the inclusion of MCTs appears to compensate for the slow hydrolysis of FO-based TGs, and the concomitant presence of both n-3 PUFA-rich TGs and MCTs may facilitate tissue uptake of remnant particles [17].

Other preparations have been developed with structured TGs containing both long-chain and medium-chain fatty acids on the same glycerol backbone. While specific molecules ('MLM') with medium-chain fatty acids in the sn-1 and sn-3 positions and a long-chain fatty acid in the sn-2 position of the glycerol show rapid and efficient hydrolysis, molecules with long-chain fatty acids in the sn-1 and sn-3 positions and a medium-chain fatty acid in position 2 are poor substrates for LPL [18]. Emulsions proposed for clinical use contain structured TG molecules obtained by random inter-esterification and contain a mixture of MLM, LML, LLM, MML, etc., i.e., molecules with different metabolic properties. These preparations do not appear to have advantages in comparison with long-chain TG (LCT)/MCT mixtures [19].

Clinical Aspects of Intravenous Lipid Emulsions in Humans

The presence of n-3 PUFAs in iv lipid emulsions appears to shorten the length of the hospital stay of surgical and intensive care unit patients, with a tendency towards reduced mortality [20–22]. This phenomenon is probably due to a reduction in inflammatory reactions [23], as shown in surgical patients receiving n-3 PUFAs perioperatively [24] and, to some extent, in intensive care unit patients [23]. An important reduction in the inflammatory reaction was also reported in healthy subjects injected with endotoxin as a model of a septic episode [25].

As indicated above, the intravascular metabolism of lipid emulsions may vary between individuals. Lipids should not be infused into subjects with plasma TGs >3–4 mmol/l (or 250–350 mg/dl) [26]. Caution is required in those subjects with high basal TG concentrations (e.g., >2–3 mmol/l or 170–250 mg/dl); lipids should be infused at a slow rate (<0.1 g TGs/kg body weight/h), and TG levels should be monitored (2–4 times/day) during lipid infusion over the first 24 h. Patients with acute renal or hepatic failure should also be carefully evaluated prior to and monitored during slow lipid infusion. Even greater caution should be applied for those patients with severe sepsis, particularly when at risk of developing shock. In contrast, patients having undergone uncomplicated surgery or trauma generally show good plasma TG clearance and efficient oxidative fat metabolism after stabilisation of hemodynamic parameters. In these subjects, lipids may be infused at a rate of 0.1 g TGs/kg body weight/h for

soybean oil, at 0.2 g TGs/kg body weight/h for MCT-containing preparations, or at <0.05 g TGs/kg body weight/h for pure FO emulsions.

Recently, an emulsion that contains a mixture of FO (20%) and MCTs (80%) as well as added alpha-tocopherol was developed [27]. This preparation, largely devoid of plant n-6 PUFAs, aims to rapidly enrich the membranes of cells in key tissues with n-3 PUFAs. The emulsion is very efficiently cleared from the plasma, which allows for bolus injections (e.g., 50 ml within 5 min). The administration of such injections in healthy volunteers confirmed the safety and tolerance observed in animal studies and led to an enrichment of eicosapentaenoate in white blood cell and platelet PLs that was maximal at 1 h post-injection [27]. Of interest, the plasma NEFA concentration remained within an acceptable range.

Animal Models for Studying Metabolism of Intravenous Lipid Emulsions

Animal models have been used to better understand the metabolism of iv lipid emulsions. Different models have allowed studies that would be more difficult to carry out in either healthy or sick humans to be performed. As an example, pigs have been widely used to understand lipid emulsion metabolism in neonates. Our own group has utilised dogs to understand how iv lipid emulsions of different compositions affect the fatty acyl content of organs [18]. Our group also used rat models to demonstrate that structured LCT/MCT emulsions offered no advantages in terms of emulsion clearance [19]. Rat models have been used to improve understanding of the effects of the metabolism and effects of lipid emulsions in diabetic rats [28]. Bach et al. reviewed the utility of animal models for understanding the metabolism of different lipid emulsions with varied TG concentrations [29]. Using in vitro model systems, after NMR studies, we proposed that one reason that MCT-containing emulsions were cleared faster from the plasma than were traditional soybean oil-based emulsions was the four-times greater solubility of MCTs compared with LCTs at the PL/water interface [12].

The classical pathways that deliver LCT-based lipid emulsions to tissues include (a) receptor-mediated endocytosis; (b) non-receptor-mediated endocytosis; and (c) extracellular lipolysis of emulsion TGs by lipase, followed by cellular uptake of the released fatty acids. These pathways are similar to what occurs with chylomicrons. However, particles that are enriched with n-3 fatty acids appear to be cleared by whole particle uptake compared with n-6 PUFA-rich emulsions. Additionally, clearance of n-6 PUFA-rich emulsions (e.g., Intralipid) depends upon intravascular hydrolysis by LPL and apoE-mediated uptake pathways for efficient clearance from the plasma. In contrast, LPL- and apoE-mediated pathways appear to contribute little to the uptake of chylomicron-sized n-3 PUFA-based lipid emulsions (e.g., Omegaven) [9]. Using mouse models as well as tissue culture techniques, it was shown that n-3 PUFA-based emulsion particles utilise heparan sulphate proteoglycans for anchoring to and foster-

ing uptake by cells. In terms of blood clearance, it appears that lipid-lipid interactions between emulsions and cells, as well as CD36, contribute to n-3, but not n-6, emulsion uptake and clearance [30]. Understanding the mechanisms of emulsion clearance, as affected by different TG contents and particle sizes, could not have been carried out without using different animal models.

Conclusions

In summary, iv lipid emulsions are more than 'artificial' chylomicrons. While sharing a number of structural and metabolic properties, the abilities of these emulsions to deliver a variety of TGs with markedly different fatty acid compositions provide opportunities that extend beyond classical nutritional support, in which emulsions are considered to be a rich source of calories and essential fatty acids. Decreasing the content of n-6 fatty acids by the inclusion of other TGs and adding n-3 fatty acids to the types of emulsions now available will allow for the use of emulsions as important metabolic and immune modulators under a wide spectrum of adverse conditions throughout the life course.

References

- 1 Haumont D, Richelle M, Deckelbaum RJ, Coussaert E, Carpentier YA: Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992;121:759–763.
- 2 Haumont D, Deckelbaum RJ, Richelle M, Dahlan W, Coussaert E, Bihain BE, Carpentier YA: Plasma lipid and plasma lipoprotein concentrations in low birth weight infants given parenteral nutrition with twenty or ten percent lipid emulsion. *J Pediatr* 1989;115:787–793.
- 3 Schwiigelshohn B, Presley JF, Gorecki M, Vogel T, Carpentier YA, Maxfield FR, Deckelbaum RJ: Effects of apoprotein E on intracellular metabolism of model triglyceride-rich particles are distinct from effects on cell particle uptake. *J Biol Chem* 1995;270:1761–1769.
- 4 Granot E, Deckelbaum RJ, Eisenberg S, Oschry Y, Bengtsson-Olivecrona G: Core modification of human low-density lipoprotein by artificial triacylglycerol emulsion. *Biochim Biophys Acta* 1985;833:308–315.
- 5 Richelle M, Deckelbaum RJ, Vanweyenberg V, Carpentier YA: Lipoprotein metabolism during and after a 6-h infusion of MCT/LCT vs LCT emulsion in man. *Clin Nutr* 1997;16:119–123.
- 6 Peterson J, Bihain BE, Bengtsson-Olivecrona G, Deckelbaum RJ, Carpentier YA, Olivecrona T: Fatty acid control of lipoprotein lipase: a link between energy metabolism and lipid transport. *Proc Natl Acad Sci USA* 1990;87:909–913.
- 7 Traber MG, Carpentier YA, Kayden HJ, Richelle M, Galeano NF, Deckelbaum RJ: Alterations in plasma alpha- and gamma-tocopherol concentrations in response to intravenous infusion of lipid emulsions in humans. *Metabolism* 1993;42:701–709.
- 8 Hacquebard M, Vandenbranden M, Malaisse WJ, Ruyschaert JM, Deckelbaum RJ, Carpentier YA: Vitamin E transfer from lipid emulsions to plasma lipoproteins: mediation by multiple mechanisms. *Lipids* 2008;43:663–671.
- 9 Qi K, Seo T, Al-Haideri M, Worgall TS, Vogel T, Carpentier YA, Deckelbaum RJ: Omega-3 triglycerides modify blood clearance and tissue targeting pathways of lipid emulsions. *Biochemistry* 2002;41:3119–3127.
- 10 Carpentier YA: Are present fat emulsions appropriate?; in Wilmore DW, Carpentier YA (eds): *Metabolic Support of the Critically Ill Patient*. Berlin, New York, Springer-Verlag, 1993, pp 157–174.

- 11 Vanek VW, Seidner DL, Allen P, Bistran B, Collier S, Gura K, Miles JM, Valentine CJ, Kochevar M; Novel Nutrient Task Force, Intravenous Fat Emulsions Workgroup: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors: A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutria Clin Pract* 2012;27:150–192.
- 12 Hamilton JA, Vural JM, Carpentier YA, Deckelbaum RJ: Incorporation of medium chain triacylglycerols into phospholipid bilayers: effect of long chain triacylglycerols, cholesterol, and cholesteryl esters. *J Lipid Res* 1996;37:773–782.
- 13 Oliveira FL, Rumsey SC, Schlotzer E, Hansen I, Carpentier YA, Deckelbaum RJ: Triglyceride hydrolysis of soy oil vs fish oil emulsions. *JPEN J Parenter Enteral Nutr* 1997;21:224–229.
- 14 Li NN, Zhou Y, Qin XP, Chen Y, He D, Feng JY, Wu XT: Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomized controlled trials. *Clin Nutr* 2014;33:226–239.
- 15 Gabe SM: Lipids and liver dysfunction in patients receiving parenteral nutrition. *Curr Opin Clin Nutr Metab Care* 2013;16:150–155.
- 16 Holland DJ, Erne D, Kostner K, Leano R, Haluska BA, Marwick TH, Sharman JE: Acute elevation of triglycerides increases left ventricular contractility and alters ventricular-vascular interaction. *Am J Physiol Heart Circ Physiol* 2011;301:123–128.
- 17 Simoons CM, Deckelbaum RJ, Massault JJ, Carpentier YA: Inclusion of 10% fish oil in mixed medium-chain triacylglycerol-long-chain triacylglycerol emulsions increases plasma triacylglycerol clearance and induces rapid eicosapentaenoic acid (20:5n-3) incorporation into blood cell phospholipids. *Am J Clin Nutr* 2008;88:282–288.
- 18 Simoons CM, Deckelbaum RJ, Carpentier YA: Metabolism of defined structured triglyceride particles compared to mixtures of medium and long chain triglycerides intravenously infused in dogs. *Clin Nutr* 2004;23:665–672.
- 19 Hultin M, Müllertz A, Zundel MA, Olivecrona G, Hansen TT, Deckelbaum RJ, Carpentier YA, Olivecrona T: Metabolism of emulsions containing medium- and long-chain triglycerides or interesterified triglycerides. *J Lipid Res* 1994;35:1850–1860.
- 20 Pradelli L, Mayer K, Muscaritoli M, Heller AR: N-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care* 2012;16:R184.
- 21 Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK: Alternative lipid emulsions in the critically ill: a systematic review of the evidence. *Intensive Care Med* 2013;39:1683–1694.
- 22 Calder PC, Jensen GL, Koletzko BV, Singer P, Wanten GJA: Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- 23 Calder PC: Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* 2012;75:645–662.
- 24 Berger MM, Delodder F, Liaudet L, Tozzi P, Schlaepfer J, Chioloro RL, Tappy L: Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: A randomized controlled trial. *Am J Clin Nutr* 2013; 97:246–254.
- 25 Pittet YK, Berger MM, Pluess TT, Voirol P, Revelly JP, Tappy L, Chioloro RL: Blunting the response to endotoxin in healthy subjects: Effects of various doses of intravenous fish oil. *Intensive Care Med* 2010; 36:289–295.
- 26 Carpentier YA: Indications for different populations in different clinical settings. An ASPEN/FDA Workshop on lipid emulsions. *JPEN J Parenter Enteral Nutr* 2014; in press.
- 27 Carpentier YA, Hacquebard M, Portois L, Dupond IE, Deckelbaum RJ, Malaisse WJ: Rapid cellular enrichment of eicosapentaenoate after a single intravenous injection of a novel medium-chain triacylglycerol: fish-oil emulsion in humans. *Am J Clin Nutr* 2010;9:875–882.
- 28 Yeh S, Chao C, Lin M, Chen W: Effects of parenteral infusion with medium-chain triglycerides and safflower oil emulsions on hepatic lipids, plasma amino acids and inflammatory mediators in septic rats. *Clin Nutr* 2000;19:115–120.
- 29 Bach AC, Storck D, Meraihi Z: Medium-chain triglyceride-based fat emulsions: an alternative energy supply in stress and sepsis. *JPEN J Parenter Enteral Nutr* 1988;12:82S–88S.
- 30 Densuoonontorn N, Carpentier YA, Racine R, Murray FM, Seo T, Ramakrishnan R, Deckelbaum RJ: CD36 and proteoglycan-mediated pathways for (n-3) fatty acid enriched triglyceride-rich particle blood clearance in mouse models in vivo and in peritoneal macrophages in vitro. *J Nutr* 2008;138:257–261.

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Parenteral Lipids: Safety Aspects and Toxicity

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Abstract

Lipid emulsions (LEs) used in modern parenteral nutrition formulations are indispensable sources of calories and (essential) fatty acids ((E)FAs). Several generations of LEs based on various FA sources have been developed, and issues related to their safe use deserve attention. The relevant issues concern LE composition, stability and sterility, while other problems are related to the lipid infusion rate, including hypertriglyceridemia and lipid overload syndrome. The FA structure of LEs translates into effects on inflammatory processes and immune cell function and affects the functions of organs, such as the liver and lungs. In addition, disturbed balances of (anti)oxidants and the presence of other bioactive agents in LEs, such as phytosterols, are mechanisms that may underlie the potential adverse effects. Lipid emulsions (LEs) are key components of parenteral nutrition (PN) that bypass the need for (essential) fatty acids ((E)FAs) and provide sufficient energy to decrease the need for the infusion of large amounts of dextrose, thus preventing its associated complications. The oldest available LEs are based on soybean oil (SO-LE) and meet these requirements. (Pre)clinical evidence suggests that various, next-generation LEs based on alternative oil sources are safe and effective; particularly, those based on fish oil (FO-LEs) have less pro-inflammatory characteristics that may convey beneficial effects on the immune system and organ functions. With the exception of decreased liver damage with the use of FO-LEs instead of SO-LEs, the clinical relevance of many of these data needs further validation.

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Introduction

Attempts to administer lipids to humans for therapeutic purposes remained unsuccessful until 1961, when Wretling introduced a non-toxic LE for clinical use (Intralipid); this LE is based on SO-LE. This development fuelled the adoption of the concept of lipid-based total parenteral nutrition (TPN) in Europe, which prevented the complications from high-dose dextrose infusions that were seen with the use of lipid-free hyperalimentation in the US [1]. Later, concerns regarding the high content of ω -6 FAs in SO-LEs, which may be converted into pro-inflammatory mediators,

sparked the development of next-generation LEs. This chapter covers relevant issues for the safe use of LEs because it has become clear over the years that infusion of modern LEs can still cause some problems.

Physicochemical Stability

LEs consist of a lipid source (soybean or other oils) and an emulsifier (egg yolk-derived phospholipids) that envelopes the fat globules and keeps them soluble within the water phase of a TPN admixture. Consequently, hypersensitivity to LE has been described in patients with allergies to egg-yolk and soybean oil [2, 3]. The size of LE droplets (200–600 nm) should remain well below the diameter of capillaries to avoid vascular occlusion. Because LE stability is key for their safe use, pharmaceutical standards demand that the proportion of droplets >5 µm should not exceed 0.05% [4]. The stability of LEs in TPN admixtures is threatened by adding components that lower the pH or impose ionic stress, for example, divalent (calcium, magnesium) or trivalent (iron) cations [5]. Of note, medium-chain triglycerides (MCTs) improve the stability of LEs by displacing long-chain triglycerides at the droplet surface and reducing stress on the emulsifier due to the shorter hydrocarbon chain [4].

Hypertriglyceridemia and Fat Overload Syndrome

Plasma clearance of LEs is mediated by lipoprotein lipase (LPL), and adverse events are likely if lipid administration exceeds the LPL clearance capacity. Infusion of LEs at 0.8–1.5 g/kg/day is considered safe, but the infusion rate should not exceed 2.6 g/kg/day (0.11 g/kg/h) to avoid hypertriglyceridemia and its associated complications, such as pancreatitis or development of fat overload syndrome [6]. The latter is characterised by headaches, fever, jaundice, abdominal pain due to hepatosplenomegaly, respiratory distress and pancytopenia. FO-LEs reduce the risk of lipid overload by accelerating lipolysis and triglyceride clearance, and a paper on paediatric cases where pure FO-LE was given rapidly (>0.17 g/kg/h) by accident reported an absence of fat overload symptoms in these patients [7]. Although experts agree that the safest way to administer parenteral LEs to metabolically stressed (trauma, ICU) patients and avoid fat overload is by continuous infusion at the lowest possible rate, considerable differences remain between (inter)national guidelines regarding the use and infusion rate of LEs in critically ill patients [8, 9]. Free phospholipids are more abundantly present in 10% LEs when compared with 20% LEs, and because these interfere with LPL activity, 10% LEs are cleared more slowly than 20% LEs [5]. A part of these phospholipids is present as liposome-resembling particles that accumulate as an abnormal lipoprotein X and may cause hypercholesterolemia; this can be prevented by administering LEs at higher concentrations and at low speed [10].

Liver Function

The use of LEs has been implicated in the development of liver disease, both in the context of intestinal failure (intestinal failure-associated liver disease (IFALD)) and its treatment by PN. This entity will be coined here as IFALD, which is characterised by decreased bile flow independent of an obstruction in patients on PN with consecutive cholestatic liver disease [11]. Additional risk factors include liver immaturity associated with early premature birth, inflammation, oxidative stress, early (catheter) infection, and contaminants in PN. The incidence of IFALD is higher in infants and young children, and it is more likely associated with jaundice and elevated transaminases, whereas PN-associated liver disorders in adults mostly present as cholestasis, hepatosteatosis, or cholelithiasis. IFALD may progress to cirrhosis and end-stage liver disease, whereas sludge formation can cause biliary obstruction or gallstones [11]. There is currently no consensus definition for IFALD. A French landmark study in adult home parenteral nutrition (HPN) patients has shown that chronic cholestasis predicts serious liver problems and can be defined as a value of at least 1.5-fold above the upper limit of the normal on two of three liver function measures for cholestasis that persists for ≥ 6 months [12]. This study also associated the development of cholestasis to lipid infusions at a rate greater than 1 g/kg/day. Minor abnormalities of liver function tests occur in $>50\%$ of adult HPN patients, but these abnormalities are usually confined to raised markers of cholestasis without jaundice. IFALD has become less common due to guidelines that advise limiting lipid administration to <1 g/kg/day [13]. Accordingly, a Danish study on 202 HPN patients showed that only 2 of the 51 patients who died did so because of IFALD [14].

The mechanism behind IFALD is unknown but most likely includes macrophage activation by excess ω -6 polyunsaturated fatty acids (PUFAs) in SO-LEs, leading to the production of pro-inflammatory cytokines and the accumulation of hepatotoxic phytosterols (PYs) [11, 14–17]. A common therapeutic strategy for suspected IFALD is to temporarily disrupt lipid administration and then reintroduce lipids at a lower dose or by using another LE after normalisation of liver function tests. Irreversible cholestasis is a strong indication of combined liver and small bowel transplantation. Much of the recent progress in treating IFALD is based on therapeutic strategies that reduce the dose of SO-LE and/or use pure FO-LE or blended LE containing ω -3, ω -6, and ω -9 FA [11].

Beneficial effects of LEs on liver dysfunction have been consistently shown after reducing the dose of SO-LEs or after switching from SO-LEs to pure FO-LEs in infants with IFALD, and these effects have been attributed, in part, to the anti-inflammatory effects of metabolites of ω -3 PUFA. Starting with a report on the use of pure FO-LEs (Omegaven) in an adolescent with (essential) fatty acid deficiency ((E)FAD) due to a soy allergy precluding the use of SO-LE and in whom, in addition to the reversal of (E)FAD, decreases in disturbed liver markers were observed, several studies have

compared the effects of FO-LE monotherapy after discontinuation of SO-LE therapy at a dose of 1 g/kg/day [3, 18, 19]. This amount was substantially higher than the manufacturer's recommended dose (0.2 g/kg/day), but most patients showed clinical improvement within 1 month with resolution of cholestasis after 1 to 2 months. Even so, early treatment might be more effective because some failures were seen in critically ill patients and in those with severe cholestasis or cirrhosis. A second strategy, where patients received equal doses of SO-LE and FO-LE to treat pre-existing IFALD and prevent (E)FAD, was also effective [20].

The third approach used a blended LE containing SO, MCT, OO, and FO (SMOFlipid), with a lower amount of FO than the pure FO-LE regimens. One double-blind, randomized controlled trial in children on HPN, whereby the patients were randomized to SMOFlipid or SO-LE that was administered 4 to 5 times per week at a goal dose of 2 g/kg/day, showed changes in total bilirubin between the start of study and the final values, which were lower in the SMOFlipid group [21]. In spite of these seemingly clear and positive data, recent reviews of studies conducted in children with IFALD concluded that high-quality data that support the use of FO-LEs in this group are lacking [17, 22].

The potential adverse effects of FO-LE therapy and/or the reduction of SO-LEs include the development of (E)FAD. An evaluation of patients receiving FO-LE as a sole fat source at 1 g/kg/day identified normal triene/tetraene ratios, but 50% of patients had linoleic acid concentrations below normal [23].

The reduction of SO-LE intake in neonates with IFALD to 1 g/kg/day at 2 times per week resulted in a decline in bilirubin levels when compared to controls receiving 3 g/kg/day, and mild (E)FAD that was reversed with additional lipid infusions developed in 26% of the infants. Therefore, monitoring of (E)FAs with this regimen seems to have occurred [24].

PYs, which are present in SO-LEs but not FO-LEs, are the plant equivalents of the animal sterol cholesterol. PYs have long been considered a cause of IFALD [15, 16]. PYs are absorbed in small amounts by the gut and are metabolised slowly by the liver. Neonates with IFALD have higher plasma concentrations of PYs compared with those without IFALD, and the duration of PN is associated with the PY concentration and elevated transaminases. PYs may lead to IFALD by antagonising nuclear receptors involved in hepatoprotection from cholestasis. Parenteral administration of PYs in a piglet model markedly reduced bile acid excretion [25].

Pulmonary Dysfunction

Animal and human studies suggest that parenteral SO-LEs induce intravascular inflammation of the lungs with phagocyte activation, granuloma formation and the development of pulmonary hypertension [26]. Compromised pulmonary gas exchange may result from the accumulation of lipids in the microcirculation by

lipid peroxides, lipid-derived eicosanoids and diminished bioavailability of the vascular relaxant nitric oxide. Accordingly, the administration of long-chain triglycerides and/or MCTs to patients with adult respiratory distress syndrome resulted in the deterioration of oxygenation, pulmonary compliance and vascular resistance, with increased levels of inflammatory mediators in bronchoalveolar fluid [27]. Continuous lipid infusion might decrease the risk of pulmonary complications due to the increased oxidation of fat compared with intermittent infusion [28].

Oxidative Stress and Bioactive Emulsion Components Other Than Lipids

Oxidative stress, which is a disturbed (anti)oxidant balance, can cause damage to tissues, cells or biomolecules. LEs may cause oxidative stress because PUFAs, which depend on protection by anti-oxidants such as tocopherol and are influenced by storage conditions (light exposure, temperature), can be peroxidised to harmful hydroperoxides when an oxygen molecule is incorporated and breaks down any double bonds. Peroxides are harmful because they trigger chain reactions that inactivate enzymes and other key components of cell function. Patients with intestinal failure mainly rely on the composition of their PN formulation to maintain their (anti)oxidant balance. Oleic acid in olive oil is a MUFA and therefore is very resistant to peroxidation. A study on 41 HPN patients, 31 of whom used an olive oil-based LE, found no evidence of oxidative damage when compared with healthy controls, despite their lower anti-oxidant (plasma glutathione) defences and higher oxidant (leukocyte oxygen radical production) concentrations [29].

Blood Clotting/Bleeding

While LEs, which depend on the vitamin K content of the vegetable oil source, may counteract the effect of warfarin on prothrombin time, these effects do not seem to have clinical relevance [30]. Conversely, the supposed anti-platelet effects of FO therapy do not seem to increase bleeding risk [31].

Infections

LEs in TPN have long been considered a risk factor for the development of infectious complications. Lipids directly support microbial growth, and depending on their FA structure (carbon chain length, number and position of double bonds), lipids can modulate immune-system functions following the incorporation of FAs into cell membranes by exerting distinct effects on receptor functions, on the production of

bioactive lipid mediators, on the regulation of gene expression and on the modulation of apoptotic pathways [32, 33]. In particular, SO-LEs, which have a high ratio of ω -6 to ω -3 PUFAs (7:1), are considered dangerous in situations of overproduction of pro-inflammatory mediators, such as sepsis and trauma [34]. These concerns are supported by early studies that suggested an increased risk for infectious complications in mildly malnourished surgical patients [35]. Studies in critically ill patients have also reported increased complication rates in patients receiving SO-based TPN, whereas fewer infections, a decreased length of stay in the hospital and the ICU, and a shorter duration of mechanical ventilation were observed in trauma patients in the ICU receiving PN without SO-LE compared to those receiving PN with SO-LE [36, 37]. During the past decades, several generations of novel LEs that are based on (physical mixtures of) different oil sources such as palm kernel oil (rich in MCTs), olive oil (rich in the monounsaturated FA oleic acid) and fish oil (rich in the PUFAs eicosapentaenoic acid and docosahexaenoic acid) have been introduced into the clinical arena and promise to modulate inflammatory responses in a favourable manner and to improve the outcomes of patients with immune-mediated conditions [32]. However, the overall data regarding the effects of SO-LEs and structurally different LEs on immune responses have been very disparate, and a meta-analysis reported the absence of evidence for any lipid effect on a wide range of immune cell functions [38]. The use of hypercaloric feeding in early clinical studies and different experimental approaches (in vitro, ex vivo, in vivo) in animal and human studies that were sometimes performed with the use of supra-physiological lipid concentrations most likely contribute to this inconsistency. A recent retrospective analysis on the use of SO-LEs in ICU patients receiving premixed PN with ($n = 2,646$) or without SO-based lipids ($n = 2,023$) found no differences in the risk of bacterial infections or bloodstream infections [39].

Some authors have tried to overcome the limitations of earlier meta-analyses by focusing on head-to-head comparisons of LEs (mainly between SO-LEs and FO-LEs) and by including more delineated populations, such as surgical patients [40, 41]. Chen et al. found a good tolerance to and safety of FO-LEs in several studies; overall, this group described 611 patients who underwent major abdominal surgery with a dose ranging from 0.07 to 0.225 g/kg/day, with clear effects on FA profiles and on the synthesis of bioactive lipid mediators [40]. Improvements in clinical outcomes were observed with the use of FO-LEs in these patients in terms of decreased postoperative infection rates and shorter hospital and ICU lengths of stay; however, no effects on postoperative mortality were found. Essentially similar findings were reported in another recent meta-analysis of 892 surgical patients [41].

A recent position paper from an expert group in the US [8] tried to describe the clinical roles of various LEs and came to the overall conclusion that at this point, the available literature suggests that alternative, oil-based LEs may have fewer pro-inflammatory effects, be less likely to be associated with immune suppression, and have stronger antioxidant effects than SO-LEs and may therefore be potentially superior to

SO-LEs. However, the authors also concluded that the evidence for the clinical use of these alternative LEs is still unclear, particularly with regards to the specific indications, due to the heterogeneity and lack of adequate clinical data [8].

Conclusion

LEs are key components of PN that bypass the need for (E)FAs and provide sufficient calories. The oldest available LEs are based on soybean oil (SO-LEs) and meet these requirements. Next-generation LEs based on alternative oil sources seem safe and effective, and in particular, those based on fish oil (FO-LE) have fewer pro-inflammatory characteristics that may convey beneficial effects on the immune system and organ functions. With the exception of decreased liver damage with the use of FO-LEs instead of SO-LEs, the clinical relevance of these data needs further validation.

References

- 1 Vinnars B, Hammarqvist F: 25th Arvid Wretling's Lecture-Silver anniversary, 25 years with ESPEN, the history of nutrition. *Clin Nutr* 2004;23:955–962.
- 2 Lunn M, Fausnight T: Hypersensitivity to total parenteral nutrition fat-emulsion component in an egg-allergic child. *Pediatrics* 2011;128:1025–1028.
- 3 Gura KM, Parsons SK, Bechard LJ, et al: Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. *Clin Nutr* 2005;24:839–847.
- 4 Driscoll DF: Lipid injectable emulsions: 2006. *Nutr Clin Pract* 2006;21:381–386.
- 5 Mirtallo JM, Dasta JF, Kleinschmidt KC, et al: State of the art review: Intravenous fat emulsions: current applications, safety profile, and clinical implications. *Ann Pharmacother* 2010;44:688–700.
- 6 Safe practices for parenteral nutrition formulations. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition. *JPEN J Parenter Enteral Nutr* 1998;22:49–66.
- 7 Gura KM, Puder M: Rapid infusion of fish oil-based emulsions in infants does not appear to be associated with fat overload syndrome. *Nutr Clin Pract* 2010;25:399–402.
- 8 Vanek VW, Seidner DL, Bistran B, et al: A.S.P.E.N. position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract* 2012;27:150–192.
- 9 Singer P, Berger MM, Van den Berghe G, et al: ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr* 2009;28:387–400.
- 10 Kalfarentzos F, Kokkinis K, Leukaditi K, et al: Comparison between two fat emulsions: Intralipid 30 cent vs Intralipid 10 cent in critically ill patients. *Clin Nutr* 1998;17:31–34.
- 11 Tillman EM: Review and clinical update on parenteral nutrition-associated liver disease. *Nutr Clin Pract* 2013;28:30–39.
- 12 Cavicchi M, Beau P, Crenn P, et al: Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;132:525–532.
- 13 Staun M, Pironi L, Bozzetti F, et al: ESPEN Guidelines on Parenteral Nutrition: home parenteral nutrition (HPN) in adult patients. *Clin Nutr* 2009;28:467–479.
- 14 Ugur A, Marashdeh B, Gottschalck I, et al: Home parenteral nutrition in Denmark in the period from 1996 to 2001. *Scand J Gastroenterol* 2006;41:401–407.
- 15 Clayton PT, Bowron A, Mills KA, et al: Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993;105:1806–1813.
- 16 Llop JM, Virgili N, Moreno-Villares JM, et al: Phytosterolemia in parenteral nutrition patients: implications for liver disease development. *Nutrition* 2008;24:1145–1152.
- 17 Goulet O, Joly F, Corriol O, et al: Some new insights in intestinal failure-associated liver disease. *Curr Opin Organ Transplant* 2009;14:256–261.

- 18 Puder M, Valim C, Meisel JA, et al: Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009;250:395–402.
- 19 Gura KM, Lee S, Valim C, et al: Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008;121:678–686.
- 20 Diamond IR, Sterescu A, Pencharz PB, et al: Changing the paradigm: omegaven for the treatment of liver failure in pediatric short bowel syndrome. *J Pediatr Gastroenterol Nutr* 2009;48:209–215.
- 21 Goulet O, Antebi H, Wolf C, et al: A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2010;34:485–495.
- 22 Seida JC, Mager DR, Hartling L, et al: Parenteral ω -3 fatty acid lipid emulsions for children with intestinal failure and other conditions: a systematic review. *JPEN J Parenter Enteral Nutr* 2013;37:44–55.
- 23 de Meijer VE, Le HD, Meisel JA, et al: Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr* 2010;50:212–218.
- 24 Cober MP, Killu G, Brattain A, et al: Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease. *J Pediatr* 2012;160:421–427.
- 25 Iyer KR, Spitz L, Clayton P: New insight into mechanisms of parenteral nutrition-associated cholestasis: role of plant sterols. *J Pediatr Surg* 1998;33:1–6.
- 26 Aksnes J, Borsum K, Rollag H, et al: Intravascular lung macrophages play an essential role in lipid entrapment and the inflammatory tissue reaction seen after long-term lipid-based parenteral nutrition in pigs. An ultrastructural study. *APMIS* 1996;104:429–436.
- 27 Lekka ME, Liokatis S, Nathanail C, et al: The impact of intravenous fat emulsion administration in acute lung injury. *Am J Respir Crit Care Med* 2004;169:638–644.
- 28 Abbott WC, Grakauskas AM, Bistran BR, et al: Metabolic and respiratory effects of continuous and discontinuous lipid infusions. Occurrence in excess of resting energy expenditure. *Arch Surg* 1984;119:1367–1371.
- 29 Schepens MA, Roelofs HM, Peters WH, et al: No evidence for oxidative stress in patients on home parenteral nutrition. *Clin Nutr* 2006;25:939–948.
- 30 Lennon C, Davidson KW, Sadowski JA, et al: The vitamin K concentration of intravenous lipid emulsions. *JPEN J Parenter Enteral Nutr* 1993;17:142–144.
- 31 Brown WV, Bays H, Harris W, et al: Using omega-3 fatty acids in the practice of clinical lipidology. *J Clin Lipidol* 2011;5:424–433.
- 32 Kim CH, Lewis DE, Kumar A: Bacterial and fungal growth in intravenous fat emulsions. *Am J Hosp Pharm* 1983;40:2159–2161.
- 33 Miles EA, Calder PC: Fatty acids, lipid emulsions and the immune and inflammatory systems; in Calder PC, Waitzberg DL, Koletzko B (eds): *Intravenous Lipid Emulsions*. World Rev Nutr Diet. Basel, Karger, 2015, vol 112, pp 17–30.
- 34 Furukawa K, Yamamori H, Takagi K, et al: Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition* 2002;18:235–240.
- 35 Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. *N Engl J Med* 1991;325:525–532.
- 36 Heyland DK, MacDonald S, Keefe L, et al: Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* 1998;280:2013–2019.
- 37 Batistella FD, Widergren JT, Andersen JT, et al: A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* 1997;43:52–58.
- 38 Wirtitsch M, Wessner B, Spittler A, et al: Effect of different lipid emulsions on the immunological function in humans: a systematic review with meta analysis. *Clin Nutr* 2007;26:302–313.
- 39 Pontes-Arruda A, Liu FX, Turpin RS, et al: Bloodstream infections in patients receiving manufactured parenteral nutrition with vs without lipids: is the use of lipids really deleterious? *JPEN J Parenter Enteral Nutr* 2012;36:421–430.
- 40 Chen B, Zhou Y, Yang P, et al: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 41 Wei C, Hua J, Bin C, et al: Impact of lipid emulsion containing fish oil on outcomes of surgical patients: systematic review of randomized controlled trials from Europe and Asia. *Nutrition* 2010;26:474–481.

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Intravenous Lipids in Preterm Infants: Impact on Laboratory and Clinical Outcomes and Long-Term Consequences

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Abstract

Postnatal growth failure is still one of the most commonly observed morbidities in preterm infants. Intolerance of enteral nutrition is a common problem in these infants and in neonates with surgical conditions. Therefore, adequate parenteral nutrition is crucial to support organ development, including that of the brain. Short-term studies on the early introduction of parenteral lipids have demonstrated that early lipid administration seems safe and well tolerated and prevents essential fatty acid deficiency. Further well-designed and adequately powered studies are necessary to determine the optimal dose of lipid infusion and the long-term effects on morbidity, growth, and neurodevelopment. Administration of a pure soybean oil emulsion might result in excess formation of proinflammatory eicosanoids and peroxidation, and their use reduces the availability of the long-chain polyunsaturated fatty acids necessary for central nervous system development and immune function. Alternatives to the use of pure soybean oils include emulsions with partial replacement of soybean oil with medium-chain triglycerides, olive oil, and/or fish oil. These newer lipid emulsions offer many theoretical advantages. Future large-scale randomized controlled trials in premature infants should demonstrate whether these newer lipid emulsions are truly safe and result in improved short- and long-term outcomes. It seems safe to start lipid emulsions from birth onward at a rate of 2 g lipids/kg/day (based on short-term results only). Mixed lipid emulsions, including those containing fish oil, seem to reduce nosocomial infections in preterm infants and might reduce bile acid accumulation. Liver damage may be reduced by decreasing or removing lipids from parenteral nutrition or may be reduced by using fish oil-containing lipid emulsions containing high levels of vitamin E.

Introduction

Nutrition is an essential part of the acute care of preterm infants, especially in very-low-birth-weight (VLBW) infants. Because of the clinical problems that VLBW infants experience, especially during the first several days of life, nutritional needs are frequently not given the highest priority. As a result, postnatal growth failure is one of the most commonly observed morbidities in VLBW infants. Intolerance to enteral nutrition is a common problem in VLBW infants and in neonates with surgical conditions, such as intestinal atresias, gastroschisis, necrotizing enterocolitis, and short-bowel syndrome. Therefore, adequate parenteral nutrition is crucial to support organ development, including that of the brain.

During the first few postnatal days, fluid intake in preterm infants is limited, making parenteral lipid emulsions an attractive energy source because of their high energy density (8–9 kcal/g, or more than twice than that of protein and glucose). Lipids are crucial not only for providing energy but also for both supplying the essential n-6 and n-3 fatty acids necessary for central nervous system development and providing fat-soluble vitamins.

This review will emphasize the importance of lipid administration to preterm infants for the prevention of essential fatty acid (EFA) deficiency and normal (neuro) development. Tolerance of early lipid introduction will be reviewed as well. Furthermore, different lipid emulsions with (partial) replacement of soybean oil by medium-chain triacylglycerols (MCTs), olive oil, and/or fish oil will be compared.

Essential and Long-Chain Polyunsaturated Fatty Acids

In the absence of an exogenous lipid supply, combined with the very limited endogenous EFA pool in preterm infants, EFA deficiency can develop as early as on the second day of life and may lead to scaly dermatitis, increased susceptibility to infection, and poor growth. Furthermore, an inadequate exogenous supply of EFAs and/or their derivative long-chain polyunsaturated fatty acids (LCPUFAs) during the critical periods of rapid brain and retinal growth may lead to long-term impairment in neurodevelopment and visual function [1]. EFA deficiency can be prevented with administration of as little as 0.5–1 g parenteral lipids/kg/day.

The LCPUFAs docosahexaenoic acid (DHA) and arachidonic acid (AA) are considered the most important derivatives of the EFAs α -linolenic acid and linoleic acid (LA), respectively. To a certain degree, premature infants are capable of *de novo* synthesis of the LCPUFAs DHA and AA from the precursors α -linolenic acid and LA, respectively [2]. However, the synthesis rates are insufficient to maintain adequate plasma and erythrocyte concentrations of these LCPUFAs, indicating that DHA and AA can be considered conditionally as EFAs for preterm and term infants and should also be administered [2]. Data from multiple studies in term infants have established

that an exogenous supply of DHA of at least 0.2–0.3% of total fatty acid intake enhances visual acuity and mental and psychomotor development [2]. For preterm infants, an even larger supply might be necessary because they lack a physiologic supply of preformed DHA after early termination of the materno-fetal transfer of these fatty acids and because of insufficient endogenous synthesis rates of DHA [2].

Early Lipid Administration

During the first days of life, VLBW infants are dependent on parenteral nutrition. Since the 1960s, safe commercial parenteral lipid emulsions have been widely used. These emulsions were developed for use in adults but are also used in children and infants. Parenteral lipid emulsions are composed of triacylglycerols and phospholipids; the latter serve as emulsifiers. In vivo, the triacylglycerols are partly hydrolyzed, and free fatty acids are released. The rate of hydrolysis varies according to the type of triacylglycerol (e.g., the length of the fatty acid, the degree of unsaturation). For example, MCTs are hydrolyzed more quickly than long-chain triacylglycerols.

In the last few decades, research in this field has focused on determining the amount and composition of parenteral amino acid and lipid solutions that can be administered safely to improve outcomes in these VLBW infants. While protein synthesis is the main determinant of growth, the energy generated by glucose and lipid oxidation finances the cost of this energy-demanding process. The optimal glucose and lipid intakes to maximize protein accretion and growth have not yet been determined. The ESPGHAN Committee on Nutrition recommends the use of parenteral lipid emulsions within the first few days of life in preterm infants [3]. Despite these recommendations, initiation of parenteral lipid emulsions is postponed beyond the first few days in many NICUs due to concerns regarding impaired lipid tolerance, impairment of oxygenation, and increased oxidative stress, which are associated with major neonatal morbidities like bronchopulmonary dysplasia [4] and periventricular leukomalacia [5]. However, meta-analyses [6, 7] and a recent randomized clinical trial [8] have not shown any association between early lipid initiation and an increased risk of bronchopulmonary dysplasia or other pulmonary morbidities, including long-duration respiratory support, long-duration supplemental oxygen, pneumothorax, pulmonary hemorrhage, and pulmonary interstitial emphysema. Early lipid administration was also not associated with an increased risk of necrotizing enterocolitis, retinopathy of prematurity, patent ductus arteriosus, sepsis, intraventricular hemorrhage, or significant jaundice. In a recent study, VLBW infants were randomized to receive lipids from birth onward or no lipids during the first 2 days. In the early lipid group, lipids were started at 2 g/kg/day and were increased to 3 g/kg/day the following day. Early lipid administration improved nitrogen balance, thus creating conditions for anabolism and growth [8, 9]. However, the in-hospital growth velocity was not different between groups. In addition, meta-analyses comparing lipid administration within

the first days of life with later introduction did not show beneficial effects on growth during hospital admission [6, 7]. A few-days difference in lipid introduction is probably too small an interval to result in persistent differences in growth.

Parenteral lipid emulsions provide the EFAs necessary for central nervous development. During intrauterine development, more than 80% of brain DHA accumulates between 26 and 40 weeks gestation. As a consequence, all infants born preterm have low concentrations of brain DHA and are very vulnerable to suboptimal nutrition. Neurodevelopmental outcomes are often hampered in preterm infants. Providing these vulnerable infants with adequate amounts of EFAs and LCPUFAs from birth onward might therefore improve neurodevelopment. So far, randomized controlled trials (RCTs) with long-term follow-up of early lipid administration are lacking. Cohort studies have suggested advantages for neurodevelopment and growth and a reduction of early morbidity with the early introduction of lipids and/or a higher energy intake [10–12].

Considering the good tolerance and many theoretical advantages of early lipid administration for protein synthesis and anabolism, amino acid tolerance [8, 9], and the prevention of EFA deficiency, we recommend initiation of lipids within hours after birth. Long-term follow-up studies should demonstrate whether the use of lipid emulsions from birth onward will have long-lasting (positive) effects on growth and neurodevelopment.

Monitoring during Lipid Administration

Clinically, tolerance of lipid administration is generally monitored by biochemical parameters. However, a specific indicator of lipid intolerance is lacking. Plasma clearance of infused lipid emulsions can be monitored by the assessment of plasma triacylglycerol concentrations, although it is unclear at what concentrations adverse effects may occur. Preterm infants might be at a higher risk of hypertriacylglycerolemia than term infants due to their relatively limited muscle and fat mass and, therefore, the decreased hydrolytic capacity of the enzyme lipoprotein lipase [3]. The ESPGHAN committee suggests checking plasma triacylglycerol concentrations with each increase of 1.0 g parenteral lipids/(kg·day) and weekly after the maximal dose is achieved. They recommend reducing the dosage of parenteral lipid emulsions if the serum triacylglycerol concentration exceeds 250 mg/dl (2.85 mmol/l) [3], while ASPEN recommends discontinuing parenteral lipid administration if the plasma triacylglycerol concentration exceeds 200 mg/dl (2.26 mmol/l) [13]. Both these recommendations and the common practice of frequent monitoring of the triacylglycerol concentration are based on very limited scientific evidence, and there are no scientifically based guidelines on critical values and subsequent alterations in the infusion rate [14]. In a recent study on early lipid administration to VLBW infants [8], early lipid administration did not result in a higher incidence of hypertriacylglycerolemia (triacylglyc-

erol concentration >3 mmol/l). Moreover, the occurrence of hypertriacylglycerolemia was not associated with a higher prevalence of neonatal morbidities such as necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, and intraventricular hemorrhage. Future studies, and preferably studies that do not adjust lipid dosage based on triacylglycerol concentrations, should demonstrate which triacylglycerol concentration in VLBW infants can be regarded as safe, both in the short term and in the long term. Until that time, we recommend measurement of the triacylglycerol concentration within approximately 1–2 days after initiation or adjustment of lipid infusion and lowering, but not stopping, the dosage if plasma concentrations are above 3.0 mmol/l (265 mg/dl). We recommend stopping intravenous lipid administration temporarily at triacylglycerol concentrations higher than 5.0 mmol/l (>440 mg/dl).

Others suggest analyzing the free fatty acid:albumin ratio. The free fatty acid:albumin ratio is an important marker for identifying infants at risk, and especially infants ≤ 28 weeks gestational age, for displacement of bilirubin from albumin by free fatty acids. Free bilirubin can cause kernicterus. However, significant displacement of bilirubin does not occur until the free fatty acid:albumin molar concentration ratios are greater than five, while infusion rates of up to 3.25 g/(kg·day) do not result in ratios over four [15]. Therefore, it is unlikely that lipid infusion at rates of 3–3.5 g/(kg·day) results in an increased incidence of hyperbilirubinemia or kernicterus.

Search for the Optimal Composition of Lipid Emulsions

Pure soybean oil-based emulsions, available since the 1960s, are the most often used lipid emulsions worldwide. However, these emulsions have been linked to increased pulmonary vascular resistance, impaired pulmonary gas exchange, hyperbilirubinemia, parenteral nutrition-associated liver disease (PNALD), enhanced oxidative stress, and adverse immunologic effects such as increased rates of infection and sepsis [16–18]. Additionally, the high LA content of pure soybean oil emulsions can induce low blood concentrations of their bioactive LCPUFA metabolites, and especially eicosapentaenoic acid (EPA) and DHA [16, 17]. EPA is important for immune function, while DHA plays a crucial role in neurodevelopment. In newer lipid emulsions, soybean oil is partly or completely replaced with MCTs, olive oil, and/or fish oil (table 1). A meta-analysis comparing purely soybean oil emulsions with multicomponent emulsions in preterm infants did not demonstrate a difference in laboratory values, growth or outcome until discharge home [19]. However, a weak favorable association of non-purely soybean-based emulsions with the incidence of sepsis (RR: 0.75; 95% CI: 0.56, 1.00) was found. In a recent RCT in VLBW infants [20], administration of a multicomponent emulsion containing soybean oil, MCTs, olive oil, and fish oil compared with administration of a pure soybean oil emulsion from birth onward prevented a decrease in the concentrations of DHA and EPA, and these effects remained on day 14, when

Table 1. Composition of commercially available parenteral lipid emulsions

	Lipid emulsion (Manufacturer)									
	Intralipid (Fresenius Kabi)	Lipoven* (Fresenius Kabi)	Liposyn III (Hospira)	Lipofundin MCT/LCT (B. Braun)	Structolipid (Fresenius Kabi)	Lipoven-MCT (Fresenius Kabi)	ClinOleic (Baxter)	Omegaven (Fresenius Kabi)	Lipoplus# (B. Braun)	SMOFlipid (Fresenius Kabi)
<i>Oil source, %</i>										
Soybean	100	100	100	50	64	50	20		40	30
Coconut (MCTs)				50	36	50			50	30
Olive							80			25
Fish								100	10	15
<i>Composition of major fatty acids, wt %</i>										
Linoleic acid (18:2n-6)	53	53	53	29	35	27	19	4	24	19
Arachidonic acid (20:4n-6)	–	–	–	0.2	–	–	0.5	2	–	0.5
α-Linolenic acid (18:3n-3)	8	8	8	4	5	4	2	2	3	2
Eicosapentaenoic acid (20:5n-3)	–	–	–	–	–	–	–	19	3	3
Docosahexaenoic acid (22:6n-3)	–	–	–	–	–	–	0.5	12	2	2
Data provided by manufacturers.										
* Lipoven is also known as Lipovenoes.										
# Lipoplus is also known as Lipidem.										

the majority of infants were already on full enteral feeding (containing less preformed DHA and EPA). Weight gain during the first weeks of life, bronchopulmonary dysplasia, hypertriacylglycerolemia, hyperglycemia, and death before discharge were not significantly different between lipid emulsions. Adding these results to the previously mentioned meta-analyses improved the power, suggesting that nosocomial infections are more frequent in infants receiving pure soybean emulsions than in those who receive other lipid emulsions. Future large-scale RCTs in preterm infants are warranted to show whether these multicomponent lipid emulsions result in improved long-term outcomes.

Lipids and Parenteral Nutrition-Associated Liver Disease

As stated before, during their first days of life, preterm infants are dependent on parenteral nutrition. However, parenteral nutrition is associated with the development of PNALD, which ultimately can lead to fatal liver failure.

While the etiology of PNALD is still unknown, the risk factors associated with PNALD are multifactorial and include immature hepatic function; a lack of enteral feeding, resulting in fewer cholekinetic triggers; infection; sepsis; toxin exposure; and nutrient deficiencies [21].

Accumulating evidence suggests that lipid emulsions may be an important contributor to the pathogenesis of PNALD. Studies in infants have shown that increased lipid loads trigger increased serum bilirubin concentrations [22]. Other studies have suggested that the phytosterols present in soybean oil are associated with the onset of cholestasis [23] and that these compounds directly reduce the expression of bile acid transporters in cultured hepatocytes [23, 24]. Several small non-randomized trials have suggested that switching from soybean oil-based to fish oil-based emulsions may be effective in the treatment of PNALD. The beneficial effects of the substitution of soybean oil with fish oil emulsions are likely related to improved bile flow (possibly due to lower phytosterol content), decreased steatosis, and a shift in the eicosanoid profile toward a less inflammatory state [25, 26]. Animal and in vitro studies [27] have suggested that soybean oil emulsions suppress both bile acid production and hepatocyte export via nuclear receptor-dependent regulation of hepatobiliary bile acid transporters and enzymes, leading to intrahepatic bile acid accumulation (fig. 1). Reports of the beneficial effects of fish oil-based emulsions in infants and children with PNALD are limited to cohort studies, case reports and case series (n = 216) [28]. The use of fish oil decreased concentrations of bilirubin and liver enzymes and resulted in a reversal of cholestasis in most of these infants and children with PNALD. However, the effects might have been confounded by the fact that along with the replacement of soybean oil with fish oil-based lipids, the total daily amount of lipids was also reduced (to 1 g/(kg·day)). Reduction of the lipid load itself has been shown to reverse cholestasis [22, 29]. Furthermore, pure soybean oil emulsions contain a much lower α -tocopherol concentration than fish oil emulsions do: the α -tocopherol content of a pure soybean oil emulsion is 87 $\mu\text{mol/l}$, while a pure fish oil emulsion and a multicomponent emulsion contain 505 and 500 $\mu\text{mol/l}$ α -tocopherol, respectively. α -Tocopherol is added to fish oil emulsions to counteract the possible peroxidation of the higher number of double bonds in the LCPUFAs, while no α -tocopherol is added to pure soybean oil emulsions by the manufacturers. Increased serum α -tocopherol concentrations might be associated with the preservation of liver function, beneficial effects on immune function and clinical outcomes [30, 31]. Therefore, the low amount of α -tocopherol provided by these lipid emulsions might also explain some of the harmful effects of soybean oil emulsions related to the development of PNALD. Studies with equal α -tocopherol doses in different solutions or with different doses in similar solutions are thus needed to elucidate this concept further.

Summary

Studies so far have provided evidence for the beneficial effects of parenteral lipid administration from birth onward on anabolism, tolerance, and prevention of EFA deficiency in preterm infants. Withholding adequate amounts of nutrition, even for a

References

- Driscoll DF, Bistran BR, Demmelmair H, Koletzko B: Pharmaceutical and clinical aspects of parenteral lipid emulsions in neonatology. *Clin Nutr* 2008;27:497–503.
- Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, Willatts P, Uauy R; World Association of Perinatal Medicine Dietary Guidelines Working Group: The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med* 2008;36:5–14.
- Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R: 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41(suppl 2):S1–S87.
- Cooke RW: Factors associated with chronic lung disease in preterm infants. *Arch Dis Child* 1991;66(7 Spec No):776–779.
- Saugstad OD: The oxygen radical disease in neonatology. *Indian J Pediatr* 1989;56:585–593.
- Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB: Parenteral lipid administration to very-low-birth-weight infants—early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;96:255–268.
- Simmer K, Rao SC: Early introduction of lipids to parenterally-fed preterm infants. *Cochrane Database Syst Rev* 2005;(2):CD005256.
- Vlaardingerbroek H, Vermeulen MJ, Rook D, van den Akker CH, Dorst K, Wattimena JL, Vermes A, Schierbeek H, van Goudoever JB: Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. *J Pediatr* 2013;163:638–644.e1–e5.
- Vlaardingerbroek H, Roelants JA, Rook D, et al: Adaptive regulation of amino acid metabolism on early parenteral lipid and high-dose amino acid administration in VLBW infants – a randomized, controlled trial. *Clin Nutr* 2014; in press.
- Ehrenkranz RA, Das A, Wrage LA, Poindexter BB, Higgins RD, Stoll BJ, Oh W; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network: Early nutrition mediates the influence of severity of illness on extremely LBW infants. *Pediatr Res* 2011;69:522–529.
- dit Trolle SE, Kermorvant-Duchemin E, Huon C, Bremond-Gignac D, Lapillonne A: Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. *Early Hum Dev* 2012;88(suppl 1):S25–S29.
- Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, Nye J, Vohr BR: First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* 2009;123:1337–1343.
- ASPEN Board of Directors and the Clinical Guidelines Task Force: Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPN J Parenter Enteral Nutr* 2002;26(1 suppl):1SA–138SA.
- Neu J: Is it time to stop starving premature infants? *J Perinatol* 2009;29:399–400.
- Hammerman C, Aramburo MJ: Decreased lipid intake reduces morbidity in sick premature neonates. *J Pediatr* 1988;113:1083–1088.
- Calder PC, Jensen GL, Koletzko BV, Singer P, Wanten GJ: Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- Krohn K, Koletzko B: Parenteral lipid emulsions in paediatrics. *Curr Opin Clin Nutr Metab Care* 2006;9:319–323.
- Koletzko B, Goulet O: Fish oil containing intravenous lipid emulsions in parenteral nutrition-associated cholestatic liver disease. *Curr Opin Clin Nutr Metab Care* 2010;13:321–326.
- Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB: Parenteral lipid administration to very-low-birth-weight infants—early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. *Am J Clin Nutr* 2012;96:255–268.
- Vlaardingerbroek H, Vermeulen MJ, Carnielli V, Vaz FM, Van den Akker CH, Van Goudoever JB: Growth and fatty acid profiles of VLBW infants receiving a multicomponent lipid emulsion from birth onwards. *J Pediatr Gastroenterol Nutr* 2014;58:417–427.
- Carter BA, Shulman RJ: Mechanisms of disease: update on the molecular etiology and fundamentals of parenteral nutrition associated cholestasis. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:277–287.
- Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C: Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *JPN J Parenter Enteral Nutr* 2000;24:345–350.

- 23 Clayton PT, Bowron A, Mills KA, Massoud A, Casteels M, Milla PJ: Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993;105:1806–1813.
- 24 Carter BA, Taylor OA, Prendergast DR, Zimmerman TL, Von Furstenberg R, Moore DD, Karpen SJ: Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. *Pediatr Res* 2007;62:301–306.
- 25 Diamond IR, Sterescu A, Pencharz PB, Wales PW: The rationale for the use of parenteral omega-3 lipids in children with short bowel syndrome and liver disease. *Pediatr Surg Int* 2008;24:773–778.
- 26 de Meijer VE, Gura KM, Le HD, Meisel JA, Puder M: Fish oil-based lipid emulsions prevent and reverse parenteral nutrition-associated liver disease: the Boston experience. *JPEN J Parenter Enteral Nutr* 2009;33:541–547.
- 27 Vlaardingerbroek H, Ng K, Stoll B, et al: New generation lipid emulsions prevent PNALD in chronic parenterally-fed preterm pigs. *J Lipid Res* 2014;55:466–477.
- 28 Park KT, Nespor C, Kerner J Jr: The use of Omega-ven in treating parenteral nutrition-associated liver disease. *J Perinatol* 2011;31(suppl 1):S57–S60.
- 29 Cober MP, Teitelbaum DH: Prevention of parenteral nutrition-associated liver disease: lipid minimization. *Curr Opin Organ Transplant* 2010;15:330–333.
- 30 Antebi H, Mansoor O, Ferrier C, Tetegan M, Morvan C, Rangaraj J, Alcindor LG: Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr* 2004;28:142–148.
- 31 Grimm H, Mertes N, Goeters C, Schlotzer E, Mayer K, Grimminger F, Furst P: Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006;45:55–60.
- 32 Vlaardingerbroek H: Content Matters – Quantity and Quality of Parenteral Nutrition for Preterm Infants; thesis. Erasmus Universiteit Rotterdam, Rotterdam, 2013.

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Intravenous Lipid Emulsions in Term Infants: Impact on Laboratory and Clinical Outcomes and Long-Term Consequences

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Abstract

Parenteral nutrition (PN) in term newborns and older infants is often required for nutritional support for temporary or permanent intestinal failure from any reason. Lipid emulsions (LEs) are an essential source of high-density energy, essential fatty acids, and fat-soluble vitamins. Depending on the fatty acid type, LEs may also have significant immunomodulatory effects. All LEs, starting with soybean oil-based LE and subsequently with medium-chain triglycerides-, olive oil- and fish oil-based LEs, have been investigated in newborns and infants. Laboratory data (mainly liver enzymes, plasma lipid profiles and some metabolic markers) have been investigated for some LEs. The outcome of intestinal failure-associated liver disease after switching to new fish oil-based LEs has been sporadically reported. Long-term outcome data have only looked at the relationship between PN and mortality/morbidity, especially liver disease, and a few studies have looked at growth. There are no controlled studies in this age group that investigated the relationship between different types of LEs and long-term outcomes. In spite of their contribution to understanding the use and indications of various LEs as well as their advantages and adverse effects, most studies in newborns and infants have been observational or retrospective, and the investigated population has been heterogeneous, either in terms of the degree of maturation, age or diagnoses. High-quality studies, preferably randomized and controlled, in this particular population are needed, especially with the widespread use of PN and the emergence of new LEs.

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Introduction

The main indication for parenteral nutrition (PN) in the pediatric population is the inability to tolerate adequate oral or enteral feedings to sustain nutritional requirements.

Lipid emulsions (LEs) are an essential component of PN solutions and are a source of high-density energy, essential fatty acids (EFAs), and fat-soluble vitamins. In addition to their nutritional role, the fatty acid (FA) profile of lipids provided by the parenteral route influences the FA composition of plasma lipoproteins and cell membranes, making them important bioactive compounds.

The first LEs for neonates and older infants were soybean oil-based emulsions. Subsequent LEs were developed as combinations of soybean oil (rich in the ω -6 FA linoleic acid) with other oil sources, including coconut oil (rich in medium-chain triglycerides, MCTs), olive oil (rich in the ω -9 monounsaturated FA oleic acid) and fish oil (rich in ω -3 FAs). This article reviews the available data from studies on LEs in newborns and infants but not premature infants, who are discussed elsewhere. This task was sometimes difficult, as many studies included a mixed population of preterm and full-term infants and older children. The review focuses on studies that have contributed to improve the knowledge on the use of PN and LEs in several areas of infant nutrition and care.

The Effect of Lipid Emulsions on Substrate Utilization and Protein Sparing

The major goal of PN in neonates and older infants is to provide adequate energy and nutrients and to preserve normal growth and body composition, ideally similar to that of a healthy, breastfed infant. Many authors have investigated the role of the source of infused calories (glucose, fat, or amino acids) and the ideal proportion of carbohydrate, fat, and protein in the PN that provides the optimal nitrogen-sparing effect. The administration of LEs has the potential to eliminate many of the problems associated with high-glucose infusion, such as high osmolarity, hyperglycemia, and hypercapnia. Studies in both adults and infants have indicated that combined infusion of glucose and lipids might confer a metabolic advantage over a glucose infusion alone, as it lowers the metabolic rate and increases the efficiency of energy utilization.

Bresson et al. [1] showed a significant difference in the pattern of energy-substrate utilization according to PN regime. Seven newborn infants were studied during isocaloric and isonitrogenous PN infusions with different sources of calories (glucose only or a mixture of 50% energy as glucose and 50% as fat). Protein turnover (11.3 ± 0.7 vs. 9.8 ± 0.4 g/kg/day; $p < 0.05$), protein breakdown (8.4 ± 0.6 vs. 7.1 ± 0.4 g/kg/day; $p < 0.05$), and amino acid oxidation rates (2.7 ± 0.4 vs. 1.4 ± 0.5 g/kg/day; $p < 0.05$) were higher for the glucose than the glucose-lipid treatment, whereas protein synthesis rates did not differ significantly, suggesting that the nature of the energy substrates delivered to parenterally fed infants might affect protein metabolism [1].

Provision of non-protein energy as a mixture of glucose and fat, with 18% (group A), 29% (group B), and 40% fat (group C), showed that glucose oxidation increased with increasing total glucose intake ($p < 0.05$). Maximal glucose oxidation occurred

in group A (11.2 g/kg/day), while maximal fat oxidation was observed in group C (2 g/kg/day), suggesting better fat utilization with higher fat delivery [2].

Earlier studies mainly investigated the effects of pure soybean oil-based LEs on nitrogen economy. The long-chain triglycerides (LCTs) from soybean oil have, however, been reported to be metabolized slowly, particularly by infants suffering from sepsis and by patients in intensive care units. MCTs have been suggested as an alternative energy source, as they offer the advantage of being more rapidly utilized and are not stored in adipose tissue to any appreciable extent. The effects of MCTs on intravenous fat utilization during PN in stable surgical newborn infants showed that, compared to LCT-based LEs, the net fat oxidation and metabolic rate were not increased. There were no significant differences between the MCT/LCT admixture and LCT groups with regard to various indices of liver function or serum triglycerides [3].

Protein retention significantly correlates with protein intake, total energy intake, and energy storage. Therefore, greater protein retention can be obtained by increasing either protein or energy intake. The majority of data indicate that both nutrients (glucose or lipids at a wide variety of ratios) induce similar nitrogen retention in intravenously fed full-term infants when the delivered energy is maintained in the range of 70–90 kcal/kg/day and when protein intake is at 2.5–3 g/kg/day. Newer LEs may perform better in terms of energy utilization and protein sparing, as illustrated by the studies with MCT-based LEs, but other types of newer LEs have not been studied in this respect in infants.

The Effect of Lipid Emulsions on Laboratory and Clinical Outcomes

The biochemical parameters, safety, and short-term clinical outcomes were the earliest and most frequently reported outcomes. Several hazardous effects of LE infusion in newborn infants have been reported. However, serious adverse reactions are comparatively rare. A decrease in pulmonary diffusing capacity has been reported in adults and pulmonary fat embolism in infants. Hyperlipidemia following LE infusion may displace bilirubin from albumin-binding sites and may increase the risk of kernicterus in jaundiced newborns. Further potential hazards are related to the unknown fate of phytosterols, which may accumulate with long-term infusions, altered prostaglandin synthesis rate and turnover, deposition of lipid material in macrophages and alteration in immune function [4]. These complications are not always related to the serum levels of triglycerides, as none of these complications have been correlated with the newborn's capacity to utilize exogenous fat.

Plasma Lipids

The effects of LEs on plasma triglycerides have been among the most studied biochemical outcomes. Compared to 10% LEs, 20% LCT-based LEs induced a lesser de-

gree of hyperlipidemia in infants but resulted in comparable biochemistry values and weight gain [5].

During the 1980s, studies in adults suggested that the addition of MCTs to intravenous LEs might have additional benefits over the administration of LCTs alone in terms of increased clearance capacity and fat oxidation. Studies that compared MCT/LCT LEs with LCTs in a mixed population of newborns (preterm and full-term) showed that plasma triglycerides were not different between the two groups. Even though both emulsions showed similar tolerance, infants who received MCT/LCT had significantly lower mean total plasma cholesterol levels than those who received LCTs [6].

Plasma-free FAs and serum triglyceride levels after 5 days of PN in 78 neonates (gestational age of 26–41 weeks) supplemented with either 100% LCT- or olive oil-based LEs were not elevated compared to baseline and were within the normal range, suggesting adequate plasma clearance of lipid for infants receiving either of the two emulsions [7]. Other studies in children have reported a significant treatment effect for total cholesterol, which was lower in the olive-oil group than in the soybean-oil or MCT/LCT groups [8].

Enteral supplementation with fish-oil decreased plasma triglycerides and VLDL and increased the plasma HDL concentration in adults [9]. Ten PN-dependent children who received exclusively fish oil-based LE for a median duration of 14 weeks showed 24% increase in their HDL concentration. Compared to baseline, the levels of serum LDL, VLDL, total cholesterol, and triglyceride were significantly decreased by 22%, 41%, 17%, and 46%, respectively, suggesting that parenteral fish oil may be the preferred lipid source of children who have dyslipidemia while on PN [10].

In summary, the use of PN with conventional soybean oil-based LEs has been associated with an unfavorable atherogenic change in lipid profiles that includes hypertriglyceridemia, but also hypercholesterolemia, lower levels of HDL, and elevated LDL. Alternative LEs may generate more favorable lipid profiles but require further investigation.

Hepatic Complications

Abnormalities in liver function have been reported in patients receiving PN both with and without fat [11, 12]. Oshita et al. investigated the effects of a fat-free PN in rat pups [13]. After 4 days of isocaloric PN, aspartate transaminase, alanine transaminase, total and direct bilirubin, and gamma-glutamyl transpeptidase were significantly higher in the 0% fat group compared with the group receiving total PN containing 20 or 40% fat from a soybean oil emulsion. The relationship between cholestasis and LEs has been described in both adults and children [14, 15]. The mechanism is speculative, but suggestions include excess ω -6 polyunsaturated FA and the associated accumulation of hepatic phospholipids and/or phytosterols, excessive peroxidation and production of pro-inflammatory cytokines. Most studies in children have evaluated a mixed population of preterm and full-term infants with different conditions. These

studies suggest that lipid dosage and type are both implicated in the pathogenesis of intestinal failure-associated liver disease (IFALD). It is not surprising, therefore, that manipulation of lipid dosages or switching between different lipids types have been among the most frequent strategies used when faced with developing liver dysfunction in children on PN.

Lipid restriction has been evaluated in several studies in different age groups with conflicting results. In the only prospective randomized controlled trial (RCT), 28 post-surgical full-term and premature infants received PN for an average of 5.4 weeks. The elevations of direct bilirubin ($p = 0.04$) and total bile acids ($p = 0.02$) were smaller, and the markers of cholestasis rose at a slower rate when LCT LE was restricted (1.0 g/kg/day) compared with the standard infusion rate (3 g/kg/day) [16]. Additional outcomes, including liver enzymes, alkaline phosphatase, and EFA levels, were not different between the restricted and standard groups. The weight z-score increased more in the standard group, and no patient experienced EFA deficiency.

Lipid restriction is not without risk and is not acceptable as a preventive strategy, especially in the newborn or in low-birth-weight infants. Growth delay, effects on neurodevelopment and the risk of EFA deficiency are serious concerns and have been reported in the setting of lipid minimization strategy. Further evidence is needed regarding the use of any LE at a lipid dose of less than 1 g/kg daily during a prolonged period in infants.

Reduction of the content of LCT-based LEs by switching to different LEs or using a fish oil-based LE as the exclusive lipid supply or in combination have been used as alternative strategies in children with IFALD.

Socha et al. [17] studied the effects of parenteral LEs with LCT or a mixture of LCT/MCT on serum bilirubin and lipid metabolism in 9 cholestatic infants aged 2–8 months of age (mean age 4.2 months). There was a significant decrease in direct bilirubin from 7.9 ± 1.7 to 6.6 ± 1.6 mg/dl ($p < 0.05$) with the LCT infusion, but no significant changes in the direct bilirubin concentration was observed during MCT/LCT infusion (8.0 ± 1.9 vs. 8.0 ± 2.1 mg/dl (baseline vs. 6 h thereafter)). The authors speculated that these effects were the result of polyunsaturated FA deficiency (particularly low docosahexaenoic acid) and lower lipid-soluble vitamins A and E, which were present in the group of children with severe liver disease [17].

Observational or retrospective studies with historical controls have shown the resolution of cholestasis in children, mainly preterm infants, who were switched from conventional LCT LEs (2–3 g/kg/day) to exclusive fish oil-based LE (Omegaven, Fresenius Kabi) (1 g/kg/day) [18]. Other reports on the use of Omegaven to treat pediatric IFALD are limited to small case series or single-patient reports with outcomes similar to those initially reported.

SMOFlipid (Fresenius Kabi) is a mixed LE that contains soybean oil (30%), MCTs (30%), olive oil (25%), and fish oil (15%). The experience with this new LE is currently limited to 5 RCTs [19–23] and 3 prospective cohort studies [24–26] in premature and low-birth-weight infants ($n = 6$), children with heart disease ($n = 1$) and in-

testinal failure on home PN ($n = 1$). In young children, fish oil-based LEs resulted in improvement in some biochemical indicators of liver disease [27].

When evaluating the existing literature regarding both ω -3 LEs and lipid minimization, it is critical to recognize that, except for the study of Rollins et al. [16], all available studies in children with cholestasis were not controlled trials and therefore were subject to confounding and bias. Most notably, it is unclear as to whether the beneficial impact of ω -3 lipids relates solely to a change in lipid source or is also related to decreased lipid dosing, as Omegaven is typically given at a maximum of 1 g/kg/day. Furthermore, it has been pointed out that more than 80% of infants have good chances of being weaned off PN without apparent hepatic sequelae, raising the questions of which strategy should be selected and when and to whom it should be given [28].

Furthermore, the use of fish oil-based LEs as an exclusive lipid supply carries the risk of down regulation of the arachidonic acid pathway, which may result in growth suppression, immunosuppression, anemia and abnormalities in hemostasis. In spite of the low content of linoleic acid that is present in Omegaven (0.1–0.7% linoleic acid), its short-term use was not associated with EFA deficiency [29]. Another theoretical concern regarding fish oil-based LEs is increased hepatic fibrosis, as demonstrated in a rabbit model of IFALD [30]. Soden et al. [31] demonstrated progressive fibrosis with Omegaven use despite biochemical normalization. The impact of alternative LEs to neuro-cognitive development, neuronal maturation, or cellular membrane composition in seriously ill neonates and infants is not known, and future studies will need to address these concerns.

The preliminary results from an RCT designed to assess the safety and efficacy of a fish oil-based LE vs. soybean oil-based LE (both supplied at 1 g/kg/day) in reducing the incidence of cholestasis in neonates (mean gestational age of 36 weeks and mean birth weight 2,410 g) showed a lower than expected incidence of cholestasis, which resulted in early termination of the study due to the inability to assess differences in the incidence of cholestasis [32].

Long-Term Outcomes

Colomb et al. [33] published the follow-up of the largest cohort of children on home PN. The probabilities of survival at 2, 5, and 10 years were 97%, 89%, and 81%, respectively. The probability of survival was significantly influenced by age when PN was started, the underlying disease and the presence of IFALD. The impact of the type or dose of LE was not investigated.

Nutritional status and growth in children on PN have been reported by several studies [34–36]. Poor growth, metabolic bone disease and increased fracture rate were reported by these studies. No associations with PN content or LEs were investigated.

Calkins et al. [37] reported the long-term outcome of two children who received exclusive fish oil-based LEs and achieved biochemical resolution of IFALD/cholesta-

sis. The cases revealed two points: (1) after resolution of cholestasis, liver disease did not re-occur after resuming PN with soybean oil-based LE, and (2) in spite of prolonged use of a fish oil-based LE only, for 10 months, without much enteral support, the described children did not develop EFA deficiency. Normalization of liver enzymes or bilirubin, however, does not necessarily mean resolution of liver fibrosis, and progression to cirrhosis has been described after the 'resolution' of cholestasis [31].

Early reports from studies on fish oil-based LEs used outcomes based on clinical presentation and biochemical markers of cholestasis (AST, ALT, total bilirubin, and direct bilirubin) and were not based on liver biopsy results. Investigators from Boston have now reported 83 biopsy results of 66 children [38]. Of the 83 biopsies, 74 demonstrated fibrosis, and 8 of these also demonstrated cirrhosis. Forty-one of the 74 fibrotic biopsies (55%) were obtained in patients without biochemical evidence of cholestasis. Seventy percent of these patients were treated with fish oil-based LEs during their clinical course.

The most extensive study on home PN outcome to date, which was published in 2012, was a European prospective survey that included 25 studies in children [39]. No relationship between the type of lipids and long-term outcomes such as morbidity, mortality, PN dependence or other outcomes (bone disease, growth and development) in children were found.

Summary

In summary, the innovations and technologies concerning new LEs have much advanced the scientific knowledge, either experimentally (in vitro and animal studies) or clinically. We have new and improved LEs. However, the currently available clinical data on the use of new LEs are either contradictory (in adults) or of poor quality (in children), especially in newborns and older infants. The combined efforts of scientists and industry should target the appropriate populations, and the relevant questions should be asked in well controlled preferably randomized studies designed to achieve the proposed objectives.

References

- 1 Bresson JL, Bader B, Rocchiccioli F, Mariotti A, Ricour C, Sachs C, Rey J: Protein-metabolism kinetics and energy-substrate utilization in infants fed parenteral solutions with different glucose-fat ratios. *Am J Clin Nutr* 1991;54:370–376.
- 2 Salas-Salvadó J, Molina J, Figueras J, Massó J, Martí-Henneberg C, Jimenez R: Effect of the quality of infused energy on substrate utilization in the newborn receiving total parenteral nutrition. *Pediatr Res* 1993;33:112–117.
- 3 Donnell SC, Lloyd DA, Eaton S, Pierro A: The metabolic response to intravenous medium-chain triglycerides in infants after surgery. *J Pediatr* 2002;141:689–694.
- 4 Koletzko B: Lipid supply and metabolism in infancy. *Curr Opin Clin Nutr Metab Care* 1998;1:171–177.
- 5 Coran AG, Drongowski R, Sarahan TM, Wesley JR: Comparison of a new 10% and 20% safflower oil fat emulsion in pediatric parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1981;5:236–239.

- 6 Lima LA, Murphy JF, Stansbie D, Rowlandson P, Gray OP: Neonatal parenteral nutrition with a fat emulsion containing medium chain triglycerides. *Acta Paediatr Scand* 1988;77:332–339.
- 7 Webb AN, Hardy P, Peterkin M, Lee O, Shalley H, Croft KD, Mori TA, Heine RG, Bines JE: Tolerability and safety of olive oil-based lipid emulsion in critically ill neonates: a blinded randomized trial. *Nutrition* 2008;24:1057–1064.
- 8 Sala-Vila A, Barbosa VM, Calder PC: Olive oil in parenteral nutrition. *Curr Opin Clin Nutr Metab Care* 2007;10:165–174.
- 9 Mackness MI, Bhatnagar D, Durrington PN, Prais H, Haynes B, Morgan J, Borthwick L: Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. *Eur J Clin Nutr* 1994;48:859–865.
- 10 Le HD, de Meijer VE, Zurakowski D, Meisel JA, Gura KM, Puder M: Parenteral fish oil as monotherapy improves lipid profiles in children with parenteral nutrition-associated liver disease. *J Parenter Enteral Nutr* 2010;34:477–484.
- 11 Bernstein J, Chang CH, Brough AJ, Heidelberger KP: Conjugated hyperbilirubinemia in infancy associated with parenteral alimentation. *J Pediatr* 1977;90:361–367.
- 12 Postuma R, Trevenen CL: Liver disease in infants receiving total parenteral nutrition. *Pediatrics* 1979;63:110–115.
- 13 Oshita M, Takehara H, Yamaguchi M, Doi K, Ueda N, Naito S, Hiraoka I, Tashiro S: Significance of administration of fat emulsion: hepatic changes in infant rats receiving total parenteral nutrition with and without fat. *Clin Nutr* 2004;23:1060–1068.
- 14 Cavicchi M, Crenn P, Beau P, Degott C, Boutron MC, Messing B: Severe liver complications associated with long-term parenteral nutrition are dependent on lipid parenteral input. *Transplant Proc* 1998;30:2547.
- 15 Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C: Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *J Parenter Enteral Nutr* 2000;24:345–350.
- 16 Rollins MD, Ward RM, Jackson WD, Mulroy CW, Spencer CP, Ying J, Greene T, Book LS: Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: a pilot study. *J Pediatr Surg* 2013;48:1348–1356.
- 17 Socha P, Koletzko B, Demmelmair H, Jankowska I, Stajniak A, Bednarska-Makaruk M, Socha J: Short-term effects of parenteral nutrition of cholestatic infants with lipid emulsions based on medium-chain and long-chain triacylglycerols. *Nutrition* 2007;23:121–126.
- 18 Diamond IR, Pencharz PB, Feldman BM, Ling SC, Moore AM, Wales PW: Novel lipid-based approaches to pediatric intestinal failure-associated liver disease. *Arch Pediatr Adolesc Med* 2012;166:473–478.
- 19 Skouroliaou M, Konstantinou D, Koutri K, Kakavelaki C, Stathopoulou M, Antoniadis M, Xemelidis N, Kona V, Markantonis S: A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr* 2010;64:940–947.
- 20 Tomsits E, Pataki M, Tolgyesi A, Fekete G, Rischak K, Szollar L: Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, doubleblind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2010;51:514–521.
- 21 Goulet O, Antebi H, Wolf C, Talbotec C, Alcindor LG, Corriol O, Lamor M, Colomb-Jung V: A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *J Parenter Enteral Nutr* 2010;34:485–495.
- 22 Larsen BM, Goonewardene LA, Joffe AR, Van Aerde JE, Field CJ, Olstad DL, Clandinin MT: Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. *Clin Nutr* 2012;31:322–329.
- 23 Rayyan M, Devlieger H, Jochum F, Allegaert K: Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized, double-blind study in preterm infants. *J Parenter Enteral Nutr* 2012;36(suppl 1):81S–94S.
- 24 Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP, Arsenault DA, Strijbosch RA, Lopes S, Duggan C, Puder M: Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008;121:e678–e686.
- 25 Puder M, Valim C, Meisel JA, Le HD, de Meijer VE, Robinson EM, Zhou J, Duggan C, Gura KM: Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009;250:395–402.
- 26 Pawlik D, Lauterbach R, Turyk E: Fish-oil emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. *Pediatrics* 2011;127:223–228.

- 27 Seida JC, Mager DR, Hartling L, Vandermeer B, Turner JM: Parenteral w-3 fatty acid lipid emulsions for children with intestinal failure and other conditions: a systematic review. *JPEN J Parenter Enteral Nutr* 2013;37:44–55.
- 28 Bishay M, Pichler J, Horn V, Macdonald S, Ellmer M, Eaton S, Hill S, Pierro A: Intestinal failure-associated liver disease in surgical infants requiring long-term parenteral nutrition. *J Pediatr Surg* 2012;47:359–362.
- 29 de Meijer VE, Le HD, Meisel JA, Gura KM, Puder M: Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition dependent patient. *J Pediatr Gastroenterol Nutr* 2010;50:212–218.
- 30 Kohl M, Wedel T, Entenmann A, Stuttmann J, Bendiks M, Loff S, Koster S, Ortfeld S, Bos I: Influence of different intravenous lipid emulsions on hepatobiliary dysfunction in a rabbit model. *J Pediatr Gastroenterol Nutr* 2007;44:237–244.
- 31 Soden JS, Lovell MA, Brown K, Partrick DA, Sokol RJ: Failure of resolution of portal fibrosis during omega-3 fatty acid lipid emulsion therapy in two patients with irreversible intestinal failure. *J Pediatr* 2010;156:327–331.
- 32 Nehra D, Fallon EM, Carlson SJ, Potemkin AK, Hevelone ND, Mitchell PD, Gura KM, Puder M: Provision of a soy-based intravenous lipid emulsion at 1 g/kg/day does not prevent cholestasis in neonates. *JPEN J Parenter Enteral Nutr* 2013;37:498–505.
- 33 Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Révillon Y, Jan D, De Potter S, Gorski-Colin AM, Lamor M, Herreman K, Corriol O, Landais P, Ricour C, Goulet O: Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. *J Pediatr Gastroenterol Nutr* 2007;44:347–353.
- 34 Colomb V, Dabbas M, Goulet O, Talbotec C, Corriol O, Ricour C: Prepubertal growth in children with long-term parenteral nutrition. *Horm Res* 2002;58(suppl 1):2–6.
- 35 Pichler J, Chomtho S, Fewtrell M, Macdonald S, Hill SM: Growth and bone health in pediatric intestinal failure patients receiving long-term parenteral nutrition. *Am J Clin Nutr* 2013;97:1260–1269.
- 36 Diamanti A, Bizzarri C, Basso MS, Gambarara M, Cappa M, Daniele A, Noto C, Castro M: How does long-term parenteral nutrition impact the bone mineral status of children with intestinal failure? *J Bone Miner Metab* 2010;28:351–358.
- 37 Calkins K, Lowe A, Shew SB, Dunn JC, Reyen L, Farmer DG, Devaskar SU, Venick R: Short-term intravenous fish oil and pediatric intestinal failure associated liver disease: 3-year follow-up on liver function and nutrition. *J Pediatr Surg* 2013;48:228–232.
- 38 Fitzgibbons SC, Jones BA, Hull MA, Zurakowski D, Duro D, Duggan C, Boctor D, Sigalet DL, Jaksic T: Relationship between biopsy-proven parenteral nutrition-associated liver fibrosis and bio-chemical cholestasis in children with short bowel syndrome. *J Pediatr Surg* 2010;45:95–99.
- 39 Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M, Bond G, Gupte G, Pertkiewicz M, Steiger E, Forbes A, Van Gossum A, Pinna AD; Home Artificial Nutrition and Chronic Intestinal Failure Working Group of ESPEN: Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. *Clin Nutr* 2012;31:831–845.

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Intestinal Failure-Associated Liver Disease and the Use of Fish Oil-Based Lipid Emulsions

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Abstract

Intestinal failure (IF) is caused by the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for maintenance in adults and growth in children. The advent of parenteral nutrition (PN) resulted in a dramatic improvement in life expectancy of patients suffering IF, but it has its own complications, such as catheter related sepsis. In pediatric patients suffering IF, intraluminal intestinal bacterial overgrowth may cause bacterial translocation and subsequent cholestasis and liver fibrosis. With our current understanding of the genesis of intestinal failure associated liver disease (IFALD), it should be prevented or at least early recognized and treated especially in patients experiencing prematurity and/or sepsis. Targeting harmful cytokine responses can be expected to reduce the severity and frequency of IFALD. In that view, prevention of sepsis, appropriate management of enteral feeding, prevention and treatment of intestinal bacterial overgrowth and the effects of fish oil, as providing omega-3 fatty with anti-inflammatory effects, are promising in avoiding or reversing cholestasis. This chapter aims to review both IF and PN related factors of liver disease with special emphasis on inflammation as cause of liver injury and on the use of fish oil based lipid emulsions as a provision of both alpha-tocopherol (200 g/l of 20% emulsion), as anti-oxidant agent and long-chain PUFAs.

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Introduction

‘Intestinal failure’ (IF) is caused by the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for maintenance in adults and growth in children [1]. The advent of parenteral nutrition (PN) resulted in a dramatic improvement in the life expectancy of patients suffering from IF, especially for situations of IF occurring in the neonatal period [1]. IF is related to a variety of primary digestive diseases and

may be total or partial and permanent or provisional, depending on the cause. PN has improved the outcome after neonatal surgery for congenital abnormalities of the GI tract, including subsequent short bowel syndrome (SBS) or severe motility disorders such as extensive aganglionosis or chronic intestinal pseudo-obstruction [2, 3]. Moreover, PN has made the emergence and diagnosis of rare congenital digestive diseases possible, especially those involving the development of the intestinal mucosa [4].

Due to technical refinements and steady advances in the development of highly sophisticated nutrient solutions consisting of optimal combinations of macronutrients and micronutrients, PN has become a safe feeding technique and continues to play an important role in patient management. However, some complications, such as catheter-related sepsis (CRS) and liver disease (LD), continue at high incidence, particularly in neonates and infants during even a short course of PN [5–7]. Moreover, IF that requires long-term PN may be associated with various complications, including venous thrombosis, growth failure, metabolic disorders, and bone disease. Cholestatic liver disease (CLD) with the risk of fatal outcome from end-stage liver cirrhosis was rapidly identified as one of the limiting factors of long-term IF management and might lead to the so called ‘nutritional failure’, which is considered a major indication for intestinal transplantation (ITx) or combined liver-intestine transplantation [3].

When assessing CLD, factors related to IF itself, those related to septic complications and PN-related factors should always be considered separately. This makes wording very controversial when considering CLD that occurs during PN in children suffering IF that is complicated by sepsis. There is no doubt that CLD is multifactorial. The term ‘IF-associated liver disease’ (IFALD) seems more adapted than the term ‘parenteral nutrition-associated liver disease’ [8, 9]. In the past, PN itself was thought to be the main cause of LD in relation to inappropriate intake of amino acid solutions, deficiency in macro- and micronutrients or overload with potentially toxic components such as aluminium, iron or manganese [10–13]. Extensive literature, including reviews and textbook chapters, has extensively listed the hypothetical factors of the so-called ‘parenteral nutrition-associated liver disease’ [14, 15]. Today, PN mixtures may be considered as very safe if they are delivered appropriately according to guidelines [16]. Interestingly, clinical data on infants with SBS focused on intravenous lipid emulsions (ILEs) as an important factor of CLD [17], and this will be discussed in this chapter. It is important to note that children demonstrate predominant cholestasis and more rapid progression to fibrosis and end-stage LD, while steatosis is the principal lesion in adults. In patients with SBS, liver dysfunction impairs the intestinal adaptation process, which results in an even more prolonged need for PN. A series of paediatric patients with SBS who required isolated liver grafts for SBS with the potential for adaptation, were reported [18, 19].

Thus, both treatment and prevention of IFALD have the possibility to significantly reduce the need for liver transplantation that is either isolated or combined with the intestine and may enhance the outcome of children with SBS. It is crucial to recognise patients who are at risk for developing LD early on [20–23]. In the scope of this

chapter, I will deal with the setting of long-lasting partial or total IF requiring long-term PN. However, some situations, such as prematurity, are not primarily related to IF and/or digestive disease, making analysis and recommendations sometimes difficult for this age group. Indeed, what might be true for infants and children should be nuanced and adapted for premature babies. Most of the data that will be reviewed in this chapter involve infants and children.

Definition and Pathological Expression of Liver Disease

IFALD may appear at any stage of IF management and is defined clinically or biologically. However the diagnostic criteria for IFALD remain debated. The onset of clinical jaundice in a child within a few weeks after starting PN or during the course of long-term PN has been proposed, and this is a late-onset criterion compared to biological changes. Clinical jaundice represents a major disturbance of liver function and occurs after protracted and serious effects on hepatic structure and function have occurred. One of the earliest indications of IFALD is an elevation in alkaline phosphatase or gamma glutamyl transferase within 7–14 days of starting PN. Increased plasma levels of transaminases are commonly observed at the onset of PN, especially in neonates and intensive care unit (ICU) patients, and elevation of these levels to greater than 1.5 times the upper limit of the reference range for at least 2 weeks in the absence of another cause (e.g. drug-induced disease, viral hepatitis, biliary obstruction, metabolic disorder) may be relevant [14, 15]. The hepatic transaminases become elevated to a lesser degree after 2–4 weeks, and thereafter, the liver function tests may stabilise to within the normal range unless an event such as surgery or a catheter infection occurs. The next significant alteration in liver biochemistry is a rise in the conjugated bilirubin concentration. Elevated plasma bilirubin over 50, 70, 100 and 200 $\mu\text{mol/l}$ (equivalent to 3, 4, 6, and 12 mg/dl) is recognised as the criterion for defining IFALD with good sensitivity and specificity. Finally, the most relevant assessment is based on liver biopsy (LB), which is not performed routinely. There is no current recommendation for performing systematic LB, except when small bowel transplantation is discussed. Histopathological expression of LD includes steatosis, cholestasis and fibrosis with various degrees of portal inflammation. In some cases of severe, worsening cholestasis and progressive biliary cirrhosis together with portal hypertension and its complications, LB is no longer necessary.

Hepatic Steatosis

It is the fatty infiltration of hepatocytes as the consequence of excess calories (>8–12 mg/kg per day of glucose) that causes hepatic accumulation of lipids. Excess parenteral carbohydrate calories may be converted to triglycerides by stimulating insulin release or by lipogenesis and the synthesis of acylglycerol from glucose. Hepatic steatosis may appear early after starting total parenteral nutrition (TPN), but it is reversible after calories are reduced [15]. Steatosis may also be related to excess lipid infu-

Table 1. Liver disease-related factors

<i>Patient and intestinal failure-related factors</i>	
Prematurity and low birth weight	
Lack of enteral feeding	
Total parenteral nutrition	
Disruption of entero-hepatic biliary acid cycle	
Proximal stoma, ileal resection	
Intestinal stasis and bacterial overgrowth	
Obstruction, dysmotility, lack of ileo-caecal valve	

<i>Parenteral nutrition-related factors</i>	
Duration of parenteral nutrition	
Recurrent catheter-related sepsis	
Unadapted protein energy delivery	
Excessive or unadapted amino acid intake	
Continuous versus cyclic infusion	
Excessive glucose intake	
Inappropriate use of lipid emulsion	
Phytosterols	
Lipoperoxidation	
Excess omega-6 fatty acids	
Essential fatty acid deficiency	
Potential toxic components of parenteral nutrition	
Iron	
Aluminium	
Chromium	
Manganese	
Deficiencies	
Taurine	
Chlorine	

sion as well as deficiencies of essential fatty acids (FAs), choline, taurine, or glutathione [24, 25]. Photo-oxidation of parenteral vitamins may cause hepatic steatosis, as shown in pigs [26]. Hepatic steatosis is more common in adults and may develop without evidence of inflammation, cholestasis, or hepatocyte necrosis [15].

Cholestasis and Fibrosis

The development of cholestasis is related to a number of factors (table 1) that will be reviewed below. The histopathological changes of IFALD present a spectrum from hepatic steatosis to biliary cirrhosis. Infants are more likely to present with centrilobular cholestasis, portal inflammation, and necrosis with or without steatosis. Infants and children referred for combined liver and ITx provided insights in the expression of IFALD, including portal fibrosis, pericellular fibrosis, and bile ductular proliferation (in most children). Pigmented Kupffer cells and portal bridging are also very common features. Interestingly, cholestasis is not always present. Biliary cirrhosis is a late development that may be associated with death within 6 months [27, 28]. The Metavir classification is generally used for assessing fibrosis [29].

As reversal of cholestasis is increasingly reported, the question regarding the correlation between biological cholestasis and histopathological changes is debatable [30–34]. A retrospective study aimed to determine the frequency of biochemical cholestasis (direct bilirubin ≥ 2 mg/dl) in SBS infants with biopsy-proven LD and to define predictive factors for the occurrence and degree of hepatic fibrosis [34]. Sixty-six infants with exposure to PN (>30 days) [necrotising enterocolitis (NEC) (36.4%), gastroschisis (22.7%), and intestinal atresia (15.1%)] were included as having undergone a LB. The biopsy specimens were graded from 0 to 3 based upon the degree of fibrosis in the pathology report from 83 LB procedures, and the most recent direct bilirubin results, within 10 days before biopsy, were recorded. The median age at biopsy was 6.1 months, with a median duration of PN of 4.7 months. Of the patients, 70.3% had a history of exposure to parenteral omega-3 lipid emulsion. Of the LB specimens, 89% (74/83) demonstrated some degree of fibrosis (fibrosis scale 1–3), including 9.6% (8/83) with evidence of cirrhosis. Importantly, 83% of biopsies without fibrosis and 55% of biopsies with fibrosis were obtained from patients without evidence of biochemical cholestasis ($p = 0.02$). Three (37%) of the 8 patients with cirrhosis, as shown by LB, had no evidence of biochemical cholestasis. These data support that biochemical cholestasis does not reflect the presence or degree of histologically confirmed liver fibrosis.

Incidence and Prevalence of Liver Disease

The real incidence and prevalence of LD are unknown because, as mentioned before, the clinical and biological definitions of ‘LD’ are unclear. Only few studies report large, single-centre cohorts involving infants and children on long-term PN [35–38]. In addition, patients as well as management differ between studies, and LD is assessed using different criteria. The unique consensus does regard the definition of end-stage LD as with cirrhosis and requiring liver transplantation. Using a bilirubin level of 50 $\mu\text{mol/l}$ as a definition, up to 30–67% of infants aged less than 12 months develop IFALD [35, 36]. It has been consistently reported that around 50% of children on PN for 4–12 weeks have cholestasis [35, 36], but there is a much wider variation in the frequency of IFALD in adults, with around 30–50% having a mild disturbance in liver function tests and between 2% [37] and 30% [38] becoming cholestatic after a median of 6 months of PN. These variations in the incidence and subsequent natural history of IFALD reflect differences in case mix, health care systems and the management of PN solutions, but it is reasonable to assume that one-half of children will develop mild LD with the potential to progress if not managed actively.

There are wide variations in the numbers of patients on long-term home parenteral nutrition (HPN) according to country. In Europe, cohort studies reported by Pironi et al. do not count all of the cases but provide important data regarding the

incidence of end-stage LD [39–41]. Moreover, these data do not take into account infants being hospitalised for months or years and developing severe IFALD that is often fatal when liver ITx cannot be performed. A 5-year paediatric study in Italy in 2003 identified 108 children with IF (22 new cases per year) in a population of 8 million children, giving an incidence of 2.5 per million children [42]. In France, the prevalence of paediatric patients (1 month–18 years) enrolled in a certified program of HPN in 2010 was about 160 for 65 million inhabitants, with an annual incidence of 50 new cases per year. A study by Colomb et al. involved 302 children enrolled in a HPN programme; 230 (76%) had a primary digestive disease (PDD) and 72 (24%) had a non-PDD [43]. The median age at HPN onset was 1.5 years, and the median duration of HPN was 1.3 years. At the end of the inclusion period, 54% were weaned from HPN, 26% were still receiving HPN, 16% had died, and 4% had undergone ITx. The survival probabilities at 2, 5, 10, and 15 years were 97, 89, 81, and 72%, respectively. The likelihood and cause of death depended on the underlying diagnosis. Nine percent of children with PDD died: 24% from their primary disease and 48% from LD or sepsis. Children with intractable diarrhoea during infancy had the highest mortality rate (25%) and the highest incidence of LD (48%). Among children with non-PDD, 38% died: 94% from their primary disease and 6% from LD or sepsis. These data involving infants and children on long-term PN suggest that CLD is not as frequent as in the neonatal units.

Pathophysiology of Liver Disease

Patient and Intestinal Failure-Related Factors (fig. 1)

Prematurity

The high incidence of IFALD in premature babies may be related to immaturity of the neonatal liver with a reduced total bile salt pool. Premature infants have both diminished hepatic uptake and synthesis of bile salts and reduced enterohepatic circulation compared with full-term infants or adults [44]. It is likely that other essential components of bile secretion, such as glutathione, may be reduced in the newborn because hepatic glutathione depletion has been shown in young animals on TPN [45]. Sulphation, which is an important step in the solubilisation of toxic bile salts such as lithocholic acid, is deficient in the foetus and neonate [46]. In rats, lithocholic acid has been shown to produce bile duct hyperplasia, gallstone formation, and intrahepatic cholestasis [47]. It is therefore possible that the liver and biliary system of the premature infant is more susceptible to toxic damage from lithocholic acid or other toxic bile salts. Because many infants requiring TPN are likely to be premature with low birth weight, it is difficult to be certain whether these are independent risk factors or associated factors. A study involving 66 SBS infants with exposure to PN (>30 days) aimed to define the predictive factors for

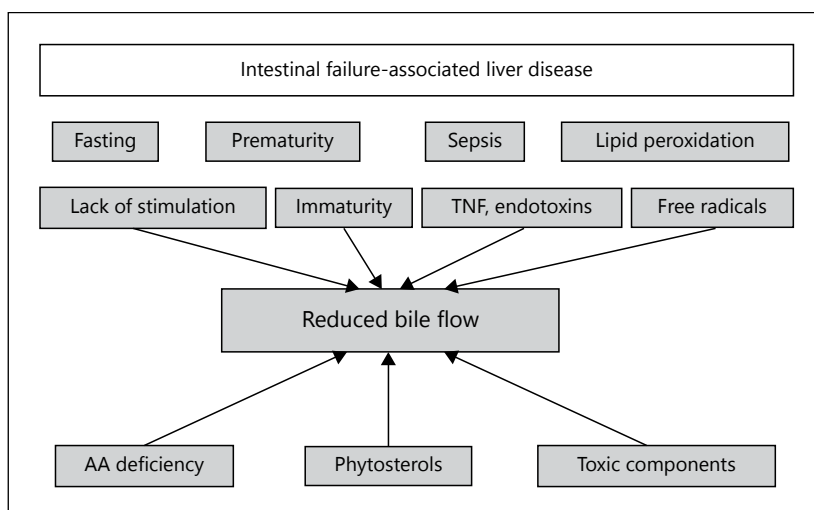


Fig. 1. Factors involved in the genesis of intestinal failure-associated liver disease.

the occurrence and degree of hepatic fibrosis [48]. Univariate analysis identified only gestational age at birth as significantly associated with the degree of liver fibrosis ($p = 0.03$). A multivariate logistic regression model accounting for multiple biopsy procedures in patients revealed that gestational age was a predictor of fibrosis only in patients with a diagnosis other than NEC ($p < 0.01$). However, premature babies were also characterised by additional factors such as lack of enteral feeding, CRS or NEC, which helps to make premature babies at high risk of developing rapidly severe IFALD.

Lack of Enteral Feeding and Impaired Bile Absorption and Recirculation

Loss (ileal resection or jejunostomy) and disease to the distal ileum are mechanisms leading to LD due to their impairing bile acid recirculation. Fasting is an important factor of CLD that appears to develop more frequently in children and adults who are unable to tolerate any enteral feeding. By decreasing the biliary salt pool, this setting may change the lithogenicity of bile. On the other hand, any factor that reduces bile flow is exacerbated by the lack of enteral or oral feeding, which is considered a key factor for the development of CLD [49]. Experimental models have shown that fasting is associated with low levels of gastrointestinal hormones, such as gastrin, motilin, glucose-dependent insulintropic polypeptide, cholecystokinin, secretin, pancreatic polypeptide, glucagon, and VIP [50]. This may lead to intestinal stasis, reduced gall-bladder contractility and the development of biliary sludge and formation of gallstones [51–53]. Intestinal stasis is associated with bacterial overgrowth, bacterial translocation, and sepsis, which may exacerbate cholestasis in infants, as well as the production of lithocholic acid, which is toxic to the liver [54].

Sepsis and Inflammation

Patients with non-hepatic infections may develop cholestasis [55, 56]. As early as 1901, Osler reported that pneumonia can lead to jaundice ('toxaemic jaundice') [57] and noted that *'in this form there is no obstruction in the bile passages, but the jaundice is associated with toxic states of the blood, dependent upon various poisons which either act directly on the blood itself, or in some cases on the liver-cells as well'*.

It is very common to find elevated conjugated bilirubin levels in patients with various infections, with the common infection being by Gram-negative bacteria but also by any microorganisms that cause CRS. In infants, especially in newborns, sepsis can present first with increasing jaundice. Repeated CRS in infants has been shown by several authors as a factor for developing CLD and liver fibrosis [6, 58–60]. Analysis of the pattern of IFALD in 70 neonates after surgery revealed an insidious rise in bilirubin until the onset of sepsis, which heralded a rise to levels of 6–9 mg/dl (100–150 mmol/l). After one or two such episodes, the bilirubin level fell to just above baseline, but jaundice generally persisted after further episodes, regardless of the resolution of infection, if PN feeding continued [51].

In a retrospective study, Hermans et al. clearly showed a link between the incidence of CRS and LD [6]. Medical reports of 30 children on long-term PN were reviewed. Starting at birth, the mean PN duration was 65 months (range, 8–150 months). According to the results of LBs, the patients were split into 2 groups: group A (n = 16) with severe liver fibrosis (i.e. septal fibrosis involving >50% of portal fields or cirrhosis) and group B (n = 14) with normal hepatic architecture or mild fibrosis (<50% of portal fields). The results showed that the duration of PN at the time of LB was shorter in group A (30.5 months; range, 8–96 months) than in group B (105 months; range, 37–150 months; $p < 0.001$). The incidence of sepsis in group A was significantly higher than in group B (3.2 ± 0.3 vs. 1.5 ± 0.2 /year), and the first infection occurred earlier (group A, 1 month [range, 1–2 months]; group B, 4 months [range, 1–19 months]). This study shows that the incidence of sepsis as well as its early onset may contribute to the development of liver fibrosis in children on long-term PN [6].

Short Bowel Syndrome: Liver disorders may occur and have been shown to be more frequent in SBS patients than in any other IF condition [52]. Of 175 neonates with abdominal pathology requiring laparotomy (SBS = 40, without SBS = 135), the patients with SBS suffered significantly more morbidity than the group without SBS in all categories of investigation (surgical complications, septic events, CRS, PN weaning delay, LD, and duration of hospitalisation). The case fatality rate was 37.5% in patients with SBS vs. 13.3% in patients without SBS ($p = 0.001$). Most of the deaths were caused by liver failure or sepsis and occurred within 1 year from the date of surgery. Therefore, LD must be treated or better prevented by carefully avoiding CRS [6, 51, 58–60] and small intestinal bacterial overgrowth (SIBO) [53, 61–63].

It is generally accepted that continuous tube feeding (CTF) offers the advantages of optimal digestion and absorption rate [64]. However, continuous infusion by missing a fasting period changes the intestinal motility pattern. Phase III of the migrating

motor complex, the hallmark of the fasting motility period, thus reflects enteric neuromuscular function [65]. Significant dysmotility impairing intestinal bacterial clearance with subsequent SIBO with Gram-negative bacilli is the consequence of small bowel dysmotility [66]. In some patients with dysmotile intestinal loops and LD, aggressive CTF is attempted to mimic 'hyperphagia' and rapidly end PN that is considered to be the cause of liver disorders. This practice leads to loss of the self-regulation of intakes and may be deleterious to the small intestine. In addition to abdominal discomfort and intestinal distension, CTF leads to bacterial overgrowth with subsequent mucosal injury, increased intestinal permeability and worsened LD. As experienced at our institution, many reported cholestatic SBS patients are referred following such management with CTF. On this basis, children should preferably be tube-fed by bolus in order to mimic normal feeding with discontinuous gastric feeling/emptying and a fasting period [67]. For children with SBS, careful follow-up combined with further refinement of diagnostic and hepato-protective strategies may be warranted (see below in the section 'Prevention of IFALD').

Factors Involved in Liver Injury: Factors that link infection to cholestasis are either cytokines (mainly TNF- α , IL-1 β , IL-6) or microbial TLR2 or TLR4 agonists [68, 69]. Liver targets primarily include hepatocytes but also extend to Kupffer cells, cholangiocytes, endothelial cells, and stellate cells. There are no direct studies on bile flow in humans given endotoxin, but there is sufficient indirect evidence to link endotoxin and endotoxin-induced cytokines to cholestasis [70, 71]. During severe sepsis, including septic shock, hyperbilirubinaemia is usually a central clinical finding and is often out of proportion with the typically mild elevations of serum transaminase [72]. Interestingly, TNF- α administered to humans has been shown to induce significant hyperbilirubinaemia, further supporting a link between cytokines and cholestasis [73, 74].

Conjugated hyperbilirubinaemia is the most typical clinical finding during sepsis because it is always included in standard laboratory analyses. However, serum bile acids are also elevated in sepsis and are most likely related to the altered expression of bile acid transporters that is seen in animal models [75, 76]. Hepatobiliary transport systems are essential for the uptake and excretion of a variety of compounds, including bile acids. Disruption and dysregulation of this excretory pathway result in cholestasis, leading to the intrahepatic accumulation of bile acids and other toxic compounds with the progression of liver pathology [77, 78]. Cholestasis induced by inflammation is a common complication in patients with extrahepatic infections or inflammatory processes and are generally referred to as sepsis-associated cholestasis. Microbial products, including endotoxin, induce signalling pathways within hepatocytes either directly or through the activation of proinflammatory cytokines, which leads to rapid and profound reductions in bile flow [68, 69]. The expression and function of key hepatobiliary transporters are suppressed in response to inflammatory signalling [70–73]. These proinflammatory signalling cascades lead to repressed expression and activity of a large number of nuclear transcriptional regulators, many of

which are essential for the maintenance of hepatobiliary transporter gene expression. Molecular crosstalk between bile acid-activated nuclear receptors and proinflammatory nuclear mediators may provide a new means for understanding the adaptive processes within the liver.

SIBO with subsequent translocation and sepsis, CRS and any other conditions that produce a systemic inflammatory response, such as NEC, are closely associated with IFALD. Endotoxin inhibits the transcription of bile acid transporters that are located on the canalicular membrane and affects the post-transcriptional levels of the Bsep and Ntcp proteins [79]. Bile acid toxicity, inflammation mediated by cytokines from activated hepatic macrophages such as Kupffer cells and bacterial toxins, and increased oxidative damage perpetuate hepatocyte injury and promote fibrosis, leading to end-stage liver cirrhosis. Susceptibility genes that have not been identified to date might influence such liver injury [80–83].

Parenteral Nutrition-Related Factors

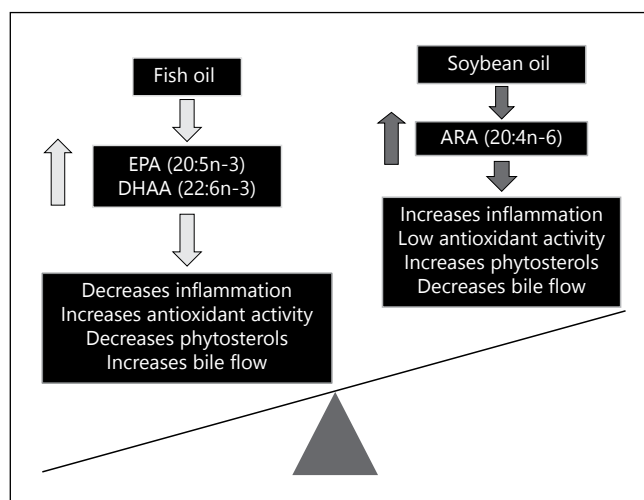
Unadapted amino acid provision and the relative lack of some conditionally essential substrates, such as taurine, carnitine and/or glutamine, as well as an excess of methionine or amino acid intake imbalance have been considered to play a role in the onset of LD [84–86]. Excess manganese or chromium is also thought to worsen IFALD [11, 12]. Additional factors, such as excessive glucose intake and continuous PN infusion with a subsequent insulin/glucagon imbalance, contribute to steatosis and liver injury [87–89]. Intravenous fat intake is a critical component of PN and has been thought to also cause liver injury.

Intravenous Lipid Supply and Cholestatic Liver Disease

A Link between Intravenous Lipid Infusion and CLD (fig. 2)

Cavicchi et al. pointed to a possible link between the occurrence of cholestasis and the intravenous fat emulsion supply in adults on long-term PN [38]. The risk of developing cholestasis over time was shown to be significantly higher in patients receiving more than 1 g of lipid/kg per day, generally as a soybean oil-based lipid emulsion (SOBLE) [38]. Clinical observations of children on long-term PN showed a positive correlation between the dosage of SOBLE and the development of cholestasis. Occurrences of cholestatic episodes were observed after a dosage increase and after a reduction of the elevated serum bilirubin levels after stopping lipid infusion or reducing the dosage [17]. In most cases, the plasma bilirubin levels decreased rapidly within the first month of stopping the infusion or reducing the lipids and reached normal concentrations again after 3.2 ± 2.0 months [17]. These data suggested that the parenteral supply of SOBLE might be one of the risk factors for CLD, and different hypotheses were raised regarding the underlying reasons, including oxidative stress, high n-6 polyunsaturated fatty acid (PUFA) intake, and accumulation of phytosterols.

Fig. 2. Balance between soybean oil-based lipid emulsion (Intralipid®) and the composite emulsion (soybean, MCT, olive, fish; SMOFlipid®) regarding composition and effects.



Oxidative Stress: Due to their high content of PUFAs, mostly n-6 FAs, and their limited content of alpha-tocopherol (α -toc), long-term use of soybean oil-based emulsions may lead to a reduction of α -toc in plasma lipoproteins and to a depletion of antioxidant defences [90–96]. The α -toc isoform is the most biologically active form and is found at its highest concentration in human plasma and tissues. The biological activities of the β , γ - and δ -isoforms of vitamin E are 0.5, 0.25 and 0.01, respectively, compared to α -toc [97] (fig. 2). Because SOBLE (Intralipid®) contains γ -tocopherol, which has fewer antioxidative effects than α -toc [97], a little-known recommendation is to add 0.5 mg of α -toc for each 1 g of long-chain PUFAS to the soybean oil-based emulsions [98]. However, no randomised control trial has evaluated the effects of adding antioxidants such as α -toc on outcome in children with CLD. Interestingly, N-acetyl-cysteine has been proposed as an antioxidant agent for preventing CLD [99].

n-6 PUFA Intake: SOBLE supplies large amounts of the n-6 PUFA linoleic acid, which can be converted to arachidonic acid, a precursor of potent proinflammatory mediators [100]. As mentioned before, repeated or prolonged inflammation is a pathogenic component of CLD that contributes to progressive hepatocyte damage, cholestasis and fibrosis [52, 53, 101]. Reducing the supply of n-6 PUFAs and replacing them with long-chain n-3 PUFAs, as found in fish oil, which primarily contains eicosapentaenoic acid, C20:5n-3, and docosahexaenoic acid, C22:6n-3, were shown to attenuate the levels of proinflammatory mediators, which might be beneficial to patients with CLD and enhanced inflammation [102] (see below). The association of cholestasis with thrombocytopenia has been described in patients on PN [103]. The link between LD and reticulo-endothelial system overload is now better understood [70–73].

Accumulation of Phytosterols: ILEs based on vegetable oils contain significant amounts of phytosterols, such as the plant sterols beta-sitosterol, campesterol and

stigmasterol [104]. Marked accumulation of these phytosterols was found in blood samples of children with CLD [105], but it remained controversial whether these elevated levels were the cause or consequence of cholestasis [106]. Experiments in neonatal piglets showed that daily injections of phytosterols given without any other components of PN reduced bile flow and increased serum bile acid levels [107]. In a hepatocyte cell line, stigmasterol was shown to act as an antagonist of the bile acid nuclear receptor, farnesoid X receptor (NR1H4) [108].

Fish Oil-Containing Lipid Emulsions and Reversal of Cholestasis

Switch to Pure Fish Oil-based Lipid Emulsion: Reversal of cholestasis by using pure fish oil (Omegaven®; Fresenius Kabi, Bad Homburg, Germany) was first reported in two SBS infants with end-stage LD [109]. The same group reported its experience with the use of this emulsion in 42 PN-dependent infants with protracted IF and CLD with serum bilirubin concentrations of at least 2 mg/dl. They compared these patients with a non-randomised, historical control group of 59 PN-dependant infants with short bowel syndrome who were treated between 1999 and 2006 [110]. The fish oil group received a lower intravenous lipid dosage (goal 1 g/kg per day, actual achieved intake not reported) than the historical controls (1–4 g/kg per day, mean intake not reported). Mortality tended to be lower in the fish oil group (3/42 vs. 12/49), and the combined risk of death and undergoing transplantation at any time (during or after cessation of PN) was significantly lower (4/42 vs. 17/49, $p = 0.005$). Among patients who survived and were not transplanted while on PN, 19 of 38 (50%) reached bilirubin levels ≤ 2 mg/dl in the fish oil cohort, and 2 of 36 (5.6%) reached these levels in the historical control group. The median time to reverse cholestasis in the fish oil cohort was 11.7 weeks (IQR 7.7, 13. weeks). It is difficult to consider that cholestasis reversal is related only to the choice of lipid emulsion. Because the trial was not randomised but used a control with patients who had been treated during previous years, other aspects of treatment that were important to outcome might also have changed over time. The lower daily lipid dosage for the fish oil group (up to 1 g/kg) compared with the control group (1–4 g/kg) might also have contributed to the reversal, given that Colomb et al. observed a fall of serum bilirubin from a mean of 9.6 mg/dl to levels below 2 mg/dl within an average 2–3 months after stopping or reducing the dosage of soybean emulsion [17]. This time interval is comparable to the time needed for patients receiving the fish oil emulsion to reach bilirubin levels < 2 mg/dl; however, this group had a lower mean starting value of just above 5 mg/dl. Other authors reported anecdotal cases of the improvement of CLD from the use of fish oil-based lipid emulsions [111–113].

Addition of Pure Fish Oil-based Lipid Emulsion: Diamond et al. reported a retrospective review of their experience with 12 PN-dependent children with SBS and severe CLD [114]. The patients received a daily dose of 1.5 g/kg of soybean emulsion and 0.5 g/kg of the 100% fish oil emulsion for the first week (Omegaven®; Fresenius Kabi, Bad Homburg, Germany), and thereafter, they received 1 g/kg each of the 2

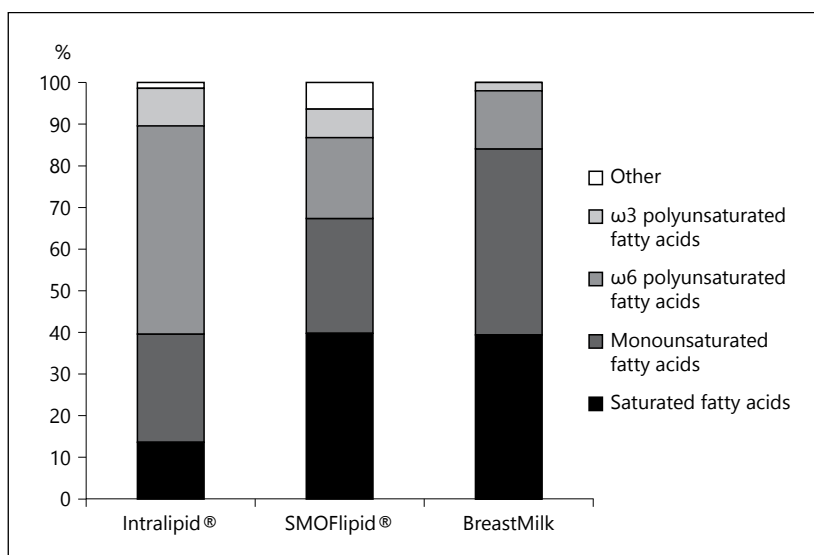


Fig. 3. Fatty acid composition of soybean oil-based lipid emulsion (Intralipid®), the composite emulsion (soybean, MCT, olive, fish; SMOFlipid®) and human breast milk.

emulsions, which provided a lower total dosage than the usual previous dosage of soybean oil emulsion of 2–3 g/kg. Patients with a serum bilirubin level >5.9 mg/dl (mean baseline value 8 mg/dl) or a serum-conjugated bilirubin level >2.9 mg/dl were included. Nine of the 12 patients showed complete resolution of hyperbilirubinaemia within a median of 24 weeks (range 7–37 weeks). Four patients achieved complete resolution of hyperbilirubinaemia while receiving both parenteral lipid emulsions, whereas 5 patients experienced resolution of hyperbilirubinaemia after the soybean oil emulsion was discontinued. Three patients failed to reverse the LD and received a liver-intestine transplant. While these observations again do not allow final conclusions on causality, they raise the questions as to whether emulsions with all of the triglycerides comprising fish oil are necessary to achieve a benefit or whether a mixture of different oil sources might also be effective.

Use of a Mixed-Lipid Emulsion Containing Fish Oil: An emulsion containing a balanced proportion of four types of oils has been developed. SMOFlipid® is a physical mixture of 30% soybean oil, 30% MCT, 25% olive oil and 15% fish oil. It contains high amounts (200 mg/l) of α-toc, as calculated according to the number of double bonds [98]. This new ILE was designed to decrease the amount of n-6 FA and to increase the amount of n-3 FA, thereby reducing the ratio of n-6/n-3 FA to approximately 2.5:1, which is in accordance with the current recommendations and is closer to the FA composition of human milk than SOBLE (fig. 3) [115–118]. SMOFlipid® was demonstrated to be safe and well tolerated in healthy volunteers as well as in adult and paediatric patients [119–125]. It preserved liver function and showed increased plasma levels of α-toc in ICU patients [121]. The safety and tolerance of the new ILE was

Table 2. High-risk situations for developing liver disease

Premature and young infants
Necrotising enterocolitis or gastroschisis ± atresia
Protracted bowel rest/intestinal stasis
Bacterial overgrowth/Gram-negative sepsis
Recurrent catheter-related sepsis
Unadapted and/or continuous parenteral nutrition

recently demonstrated in preterm infants over a treatment period of up to 14 days [126, 127]. A very recent study compared fish oil (SMOFlipid®) and olive oil lipids (Clinoleic) in very preterm neonates. SMOFlipid® was safe, well tolerated, and showed a beneficial effect in terms of the reduction of oxidative stress by reducing lipid per-oxidation levels in high-risk, preterm neonates [127].

The long-term efficacy and safety of SMOFlipid® were assessed in infants and children on HPN in comparison to a conventional soybean oil-based emulsion [128]. Total bilirubin decreased in the SMOFlipid® group during the 4-week infusion period, whereas it increased in the soybean oil group. The change was significant between the treatment groups ($p < 0.003$). Similar beneficial effects on liver function tests have been reported in ICU surgical [117] or ICU patients [118] and in children with CLD receiving SMOFlipid® [129, Rafeeq et al. Communication at BSPGHAN 2009].

Prevention of Intestinal Failure-Associated Liver Disease

It is clear that IFALD is a multifactorial disease whose prevention involves many associated aspects of management. Careful evaluation of patients at risk of developing CLD (table 2), monitoring of hepatic function by routinely performing liver function tests and minimisation or avoidance of factors that are responsible for liver injury are key issues for the prevention of IFALD. Classical measures have been proposed, and some have been shown to limit or reverse LD. However, except for the use of some lipid emulsions, there are no or very few randomised clinical trials supporting most of these accepted issues. Some of the measures include:

- The stimulation of the entero-biliary axis by ingestion of long-chain triglycerides or breast milk or by injection of cholecystokinin analogues [130, 131]. Cholecystokinin infusion has been demonstrated to reverse severe cholestasis and prevent IFALD, but a randomised, placebo-controlled trial has demonstrated no benefit in neonates. Furthermore, this treatment carries the risk of inducing acute pancreatitis. A well-conducted trial of choline-supplemented PN in long-term parenterally fed patients has demonstrated a reduction in steatosis and improvement in liver tests [132].

- The reduction of intraluminal bacterial overgrowth caused by intestinal stasis due to giving metronidazole and/or performing tapering enteroplasty [133, 134].
- Oral ursodeoxycholic acid (10 to 20 mg/kg/day) or tauro-ursodeoxycholic acid might contribute in decreasing liver injury by improving bile flow and reducing the formation of biliary sludge [135, 136]. Spagnuolo et al. reported biochemical resolution in 7 children on long-term PN who were treated with ursodeoxycholic acid [135], but another study on infants who were given ursodeoxycholic acid prophylactically to prevent liver dysfunction found no benefit [136]. However, in a prospective study of adults on PN, ursodeoxycholic acid was associated with improved liver function tests [137].

PN intake should be adapted by the following:

- limiting glucose intake to reduce hepatic fat accumulation [16, 128, 138–140],
- using the appropriate type and amount of intravenous fat emulsion, which provides essential FAs, reduces glucose load and limits peroxidation, for example, the new generation of fish oil-based lipid emulsions (see below) [16, 17]
- controlling the lipid supply and rate of delivery and/or stopping intravenous fat emulsion as soon as thrombocytopenia, hyperbilirubinaemia and/or jaundice appear [16, 17]
- using paediatric-adapted amino acid solutions, which provide the appropriate amino acids as well as taurine [141–143]
- adapting iron intake and decreasing the aluminium content of the PN solution [144, 145]
- performing cyclic PN, which helps to reduce hyperinsulinism and liver steatosis [146–151].

The term ‘cyclic PN’ refers to the intermittent administration of intravenous fluids with regular breaks from infusion [146–151]. As soon as is permitted by the metabolic and nutritional statuses, cyclic PN should be started. The aim of this treatment is to reduce permanent hyperinsulinaemia with subsequent fat accumulation and LD. For example, the addition of glucagon to PN has been shown to prevent steatosis in parenterally fed rats [152].

Cyclical PN also allows a greater mobilisation of the energetic stocks and physical activity during the day than continuous PN and might change the quality of the weight gain and avoid unnecessary storage of lipid deposits [147–150]. Cyclic PN might lower the risk for the development of LD. Hwang et al. carried out a prospective study in adults on PN who exhibited various degrees of presumed PN-associated LD (<http://ipsapp003.lwwonline.com/content/getfile/2960/86/2/-R138-2156>). Patients who developed hyperbilirubinaemia were randomised to either remain on continuous PN or to be placed on cyclic PN. Patients with initial serum bilirubin less than 20 mg/dl and who remained on continuous PN had a significant rise in serum bilirubin compared with the cyclic PN groups. There was no apparent advantage of cyclic PN in patients with serum bilirubin levels greater than 20 mg/dl. Similar studies in paediatric patients are now available. In infants with gastroschisis, prophylactic cyclic PN is

associated with a decreased incidence and prolonged time to onset of hyperbilirubinaemia [153]. In general, cyclical PN allows for increased enteral and oral nutrition throughout the day. Glucose tolerance should be monitored, and stepwise increases and decreases of glucose infusion rates at onset and at discontinuation of PN infusion, respectively, should be considered to avoid hyper- and hypoglycaemia. Finally, cyclic PN offers the advantage of increasing the mobility of the patient and family, and it is the only way in which PN can be delivered at home.

Small Intestinal Bacterial Overgrowth

SIBO may occur in some patients with SBS caused by NEC, intestinal atresia and/or gastroschisis, and it is likely to occur with ileocecal valve resection due to poor motility of a dilated small bowel segment [21–23]. SIBO is usually associated with anorexia, vomiting, diarrhoea, cramps, abdominal distension, and failure to thrive. SIBO causes increased intestinal permeability, mucosal inflammation, allergic reactions and villous atrophy, which may further exacerbate nutrient malabsorption, deconjugate bile salts and deplete the bile salt pool with subsequent impaired micellar solubilisation, resulting in steatorrhoea and malabsorption of fat-soluble vitamins. SIBO increases the risk of intestinal bacterial translocation and exacerbates the hepatotoxicity related to PN.

Early detection and appropriate treatment of SIBO is necessary to avoid morbidity and mortality following this severe SBS complication. Whenever possible, performing an intestinal tapering and lengthening procedure or resecting a tight anastomosis may be mandatory to remove SIBO. Surgical procedures such as tapering-lengthening or serial transverse enteroplasty aim not only to enhance the bowel length but also aim to mostly reduce the diameter of the dilated intestinal loop and to change its motility pattern [154–157]. A recent review by Thompson and Sudan [158] suggested that surgical bowel lengthening should be considered in any chronically PN-dependent patient when there is substantial bowel dilation, regardless of the remnant bowel length or when the rate of progression of enteral calories is slow and hampered by bacterial overgrowth. These procedures are clearly capable of preventing or reversing CLD [159–162].

Indeed, medical therapy is difficult because the use of prokinetic drugs for enhancing gut motor activity is not indicated in these conditions. The use of antibiotics should be very cautious and based on their effects on the colonic bacterial flora that should be preserved to produce short-chain FAs and trophic factors. An intermittent, antimicrobial therapy based on oral metronidazole, either alone or in association with trimethoprim-sulfamethoxazole, has been thought to be an effective combination. The use of a broad-spectrum antimicrobial therapy must be very limited due to the high risk of emergence of multi-resistant strains of bacteria and the anti-physiological effect on colonic microbiota. The use of probiotics might be helpful in SBS paediatric patients [163]. However, exogenous flora should be added to an already overgrown small bowel bacterial flora very cautiously. In addition, cases of *Lactobacillus* bacter-

aemia during probiotic treatment of paediatric SBS patients have been reported [164–166]. Cases of *S. boulardii* fungaemia have also been reported in SBS patients with a central venous catheter (CVC) [167], and *S. boulardii* treatment is contraindicated in patients with a CVC. However, the use of probiotics for the prevention of NEC in premature babies has been documented but remains controversial [168–171].

Use of Fish Oil-based Lipid Emulsions

There is now a body of evidence suggesting a link between lipid emulsions and CLD (fig. 1, 2). As mentioned before, several lipid emulsion-associated factors are involved in the clinical effects as well as in cholestasis reversal. Fish oil provides a higher ratio of n-3 to n-6 FAs, which might reduce the production of proinflammatory cytokines [100–102, 115], a reduced content of the phytosterols that have been shown to be partly related to LD [105–107], and a higher amount of α -toc, resulting in an increased plasma α -toc concentration that might contribute to decreased lipoperoxidation injury on the liver [93, 97, 98]. These data allow consideration of the use of fish oil for reversing CLD or preventing cholestasis in infants and children with the risk of developing it. However, no adequate data are available from controlled trials of infants and children using the emulsion with only fish oil or demonstrating that the essential FA status may be preserved. The provision of fish oil as the only lipid source over prolonged periods of time provides less essential n-6 FAs than what is currently considered necessary for infants and young children [102]. Rats fed fish oil as the only fat source during the perinatal period showed marked growth retardation and delayed psychomotor development, which was apparently caused by low levels of the n-6 metabolite arachidonic acid [172]. In preterm infants, an enteral supply of fish oil, which is rich in eicosapentaenoic acid, led to reduced blood levels of arachidonic acid with concomitant, compromised growth during the first year of life [173]. Blood FA profiles were reported for 10 patients who were predominantly parenterally fed fish oil-based emulsions with little oral food intake [174]. The blood levels of the essential omega-6 (n-6) FA linoleic acid dropped markedly from a mean of 1,979.2 $\mu\text{mol/l}$ (SD 941.7) at baseline to 1,091.6 $\mu\text{mol/l}$ (480.9) after 6 weeks, along with a drop of the major n-6 metabolite arachidonic acid from 605.2 (381.2) to 455.0 (179.2) $\mu\text{mol/l}$. Because there was no appreciable increase in the mean acid or in the triene/tetraene ratio, the authors concluded that fish oil contains sufficient amounts of essential FAs. These data raise questions, given that both n-3 and n-6 FAs are necessary for growth and development. Therefore, it is considered prudent to carefully evaluate the resultant biological effects and safety in controlled trials prior to adopting the use of emulsions based only on fish oil as standard care [102].

In adult patients, a meta-analysis aimed to evaluate n-3 PUFA-enriched PN regimens in elective surgical and ICU patients [175]. This analysis included 23 studies ($n = 1,502$ patients; $n = 762$ admitted to the ICU) and showed that n-3 PUFA-enriched emulsions are associated with statistically and clinically significant reductions in the infection rate (RR = 0.61; 0.45, 0.84) and the lengths of stay, both in the ICU (–1.92;

–3.27, –0.58) and in the hospital overall (–3.29; –5.13, –1.45). Other beneficial effects included reduced markers of inflammation and improved lung gas exchange, liver function, antioxidant status and FA composition of plasma phospholipids as well as a trend towards less impairment of kidney function.

Conclusion

Improvements in surgical procedures, ICU management, the involvement of nutrition-support teams as well as the type and mode of delivery of PN and enteral feeding may help to decrease the incidence of end-stage IFALD, which is a special concern in young infants [176–180]. Intestinal and liver transplantation have an important role in treating or avoiding end-stage LD, especially in young children, although there is a shortage of suitable donors. The last results of the Intestinal Transplantation Registry clearly show that the need for combined liver-intestine transplantation dropped during the last 5 years (www.intestinaltransplant.org). This probably results from the decreased incidence of end-stage liver cirrhosis since the introduction of fish oil-based lipid emulsions.

Based on our current understanding of the genesis of IFALD, it should be prevented or at least recognised early and treated, especially in patients experiencing prematurity and sepsis. The factors impacting survival before and after transplantation as well as the optimal timing of ITx for children with IF were updated [176–180]. A new approach involving targeting harmful cytokine responses can be expected to reduce the severity and frequency of IFALD. In that view, the prevention of sepsis, appropriate enteral feeding, the treatment of intestinal bacterial overgrowth and the effects of fish oil in reversing cholestasis have to be considered [181, 182]. These new issues regarding fish oil open the door to pharmaco-nutrition by using fish oil-based lipid emulsions as an anti-inflammatory agent [182]. Randomised controlled trials are necessary to support these issues because evidence-based practices for the management of IF and its resultant complications in children remain very limited [183].

References

- 1 Goulet O, Ruemmele F: Causes and management of intestinal failure in children. *Gastroenterology* 2006; 130:S16–S28.
- 2 Goulet O, Baglin-Gobet S, Talbot C, et al: Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. *Eur J Pediatr Surg* 2005;15:95–101.
- 3 D'Antiga L, Goulet O: Intestinal failure in children: the European view. *J Pediatr Gastroenterol Nutr* 2013;56:118–126.
- 4 Goulet OJ, Brousse N, Canioni D, et al: Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases. *J Pediatr Gastroenterol Nutr* 1998;26:151–161.
- 5 Suita S, Yamanouchi T, Masumoto K, et al: Changing profile of parenteral nutrition in pediatric surgery: a 30-year experience at one institute. *Surgery* 2002;131(1 suppl):S275–S282.

- 6 Hermans D, Talbotec C, Lacaille F, et al: Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2007;44:459–463.
- 7 Pichler J, Horn V, Macdonald S, et al: Sepsis and its etiology among hospitalized children less than 1 year of age with intestinal failure on parenteral nutrition. *Transplant Proc* 2010;42:24–25.
- 8 Goulet O, Joly F, Corriol O, et al: Some new insights in intestinal failure-associated liver disease. *Curr Opin Organ Transplant* 2009;14:256–261.
- 9 Nandivada P, Carlson SJ, Chang MI, et al: Treatment of parenteral nutrition-associated liver disease: the role of lipid emulsions. *Adv Nutr* 2013;4:711–717.
- 10 Rabinow BE, Ericson S, Shellgren T: Aluminium in parenteral products; analysis reduction and implications for paediatric TPN. *J Parenter Sci Technol* 1989;43:132–139.
- 11 Moukarzel AA, Song MK, Buchman AL, et al: Excessive chromium intake in children receiving total parenteral nutrition. *Lancet* 1992;339:385–388.
- 12 Fell JME, Reynolds AP, Meadows N, et al: Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996;347:1218–1221.
- 13 Nightingale JM: Hepatobiliary, renal and bone complications of intestinal failure. *Best Pract Res Clin Gastroenterol* 2003;17:907–929.
- 14 Kelly DA: Intestinal failure-associated liver disease: what do we know today? *Gastroenterology* 2006;130(2 suppl 1):S70–S77. Comment in: *Gastroenterology* 2006;130(2 suppl 1):S67–S69.
- 15 Buchman AL, Iyer K, Fryer J: Parenteral nutrition-associated liver disease and the role of isolated intestine and intestine/liver transplantation. *Hepatology* 2006;43:9–19.
- 16 Koletzko B, Goulet O, Hunt J, et al: Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41(suppl 2):S1–S87.
- 17 Colomb V, Jobert-Giraud A, Lacaille F, et al: Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *J Parenter Enteral Nutr* 2000;24:345–350.
- 18 Botha JF, Grant WJ, Torres C, et al: Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome. *Liver Transplantation* 2006;12:1062–1066.
- 19 Dell-Olio D, Beath SV, de Ville de Goyet J, et al: Isolated liver transplant in infants with short bowel syndrome: insights into outcomes and prognostic factors. *J Pediatr Gastroenterol Nutr* 2009;48:334–340.
- 20 Goulet O: Intestinal failure in children. *Transplant Proc* 1998;30:2523–2525.
- 21 Hsieh MH, Pai W, Tseng HI, et al: Parenteral nutrition-associated cholestasis in premature babies: risk factors and predictors. *Pediatr Neonatol* 2009;50:202–207.
- 22 Willis TC, Carter BA, Rogers SP, et al: High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. *J Parenter Enteral Nutr* 2010;34:32–37.
- 23 Kaufman SS, Pehlivanova M, Fennelly EM, et al: Predicting liver failure in parenteral nutrition-dependent short bowel syndrome of infancy. *J Pediatr* 2010;156:580–585.
- 24 Sokol RJ, Taylor SF, Devereaux MW, et al: Hepatic oxidant injury and glutathione depletion during total parenteral nutrition in weanling rats. *Am J Physiol* 1996;270:691–700.
- 25 Shronts EP: Essential nature of choline with implications for total parenteral nutrition. *J Am Diet Assoc* 1997;6:639–646.
- 26 Chessex P, Lavoie JC, Rouleau T, et al: Photooxidation of parenteral multivitamins induces hepatic steatosis in a neonatal guinea pig model of intravenous nutrition. *Paediatr Res* 2002;52:958–963.
- 27 Beath SV, Needham SJ, Kelly DA, et al: Clinical features and prognosis of children assessed for isolated small bowel (ISBTx) or combined small bowel and liver transplantation (CSBLTx). *J Pediatr Surg* 1997;32:459–461.
- 28 Bueno J, Ohwada S, Kocoshis S, et al: Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. *J Pediatr Surg* 1999;34:27–32.
- 29 Bedossa P, Poynard T: An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996;24:289–293.
- 30 Iyer KR, Horslen S, Torres C, et al: Functional liver recovery parallels autologous gut salvage in short bowel syndrome. *J Pediatr Surg* 2004;39:340–344.
- 31 Puder M, Valim C, Meisel JA, et al: Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009;250:395–402.
- 32 Cowles RA, Ventura KA, Martinez M, et al: Reversal of intestinal failure-associated liver disease in infants and children on parenteral nutrition: experience with 93 patients at a referral center for intestinal rehabilitation. *J Pediatr Surg* 2010;45:84–87.
- 33 Fitzgibbons SC, Jones BA, Hull MA, et al: Relationship between biopsy-proven parenteral nutrition-associated liver fibrosis and biochemical cholestasis in children with short bowel syndrome. *J Pediatr Surg* 2010;45:95–99.
- 34 Kubota A, Okada A, Nezu R, et al: Hyperbilirubinemia in neonates associated with total parenteral nutrition. *J Parenter Enteral Nutr* 1988;12:602–606.

- 35 Beath SV, Davies P, Papadopoulou A, et al: Parenteral nutrition related cholestasis in post surgical neonates: multivariate analysis of risk factors. *J Pediatr Surg* 1996;31:604–606.
- 36 Sondheimer JM, Asturias E, Cadnapaphornchai M: Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* 1998;27:31–37.
- 37 Lumen W, Shaffer JL: Prevalence, outcome and associated factors of deranged liver function tests in patients on home parenteral nutrition. *Clin Nutr* 2002;21:337–343.
- 38 Cavicchi M, Beau P, Crenn P, et al: Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;132:525–532. Comment in: *Ann Intern Med* 2000;133:1009–1010.
- 39 Pironi L, Hébuterne X, Van Gossum A, et al: Candidates for intestinal transplantation: a multicenter survey in Europe. *Am J Gastroenterol* 2006;101:1633–1643.
- 40 Pironi L, Forbes A, Joly F, et al: Survival of patients identified as candidates for intestinal transplantation: a 3-year prospective follow-up. *Gastroenterology* 2008;135:61–71.
- 41 Pironi L, Joly F, Forbes A, et al: Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. *Gut* 2011;60:17–25.
- 42 Guarino A, De Marco G: Natural history of intestinal failure, investigated through a national network-based approach. *J Pediatr Gastroenterol Nutr* 2003;37:136–141.
- 43 Colomb V, Dabbas-Tyan M, Taupin P, et al: Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. *J Pediatr Gastroenterol Nutr* 2007;44:347–353.
- 44 Watkins JB, Szczepanik P, Gould JB, et al: Bile salt metabolism in the human premature infant. *Gastroenterology* 1975;69:706–713.
- 45 Heyman MD, Tseng HC, Thaler MM: Total parenteral nutrition (TPN) decreases hepatic glutathione concentration in weaning rats. *Hepatology* 1984;4:16:9.
- 46 Watkins JB: Placental transport bile acid conjugation and sulphation in the fetus. *J Pediatr Gastroenterol Nutr* 1983;2:365–373.
- 47 Miyai K, Price VM, Fisher MM: Bile acid metabolism in mammals. Ultrastructural studies on the intrahepatic cholestasis induced by lithocholate and chenodeoxycholic acids in the rat. *Lab Invest* 1971;24:292–302.
- 48 Sigalet D, Boctor D, Robertson M, et al: Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. *Eur J Pediatr Surg* 2009;19:348–353.
- 49 Jawahwee G, Pierro A, Lloyd TA, et al: Gall bladder contractility in neonates effect of parenteral and enteral feeding. *Arch Dis Child* 1995;72:F200–F202.
- 50 Greenberg G, Wolman S, Christofides N, et al: Effect of total parenteral nutrition on gut hormone release in human. *Gastroenterology* 1981;80:988–993.
- 51 Pichler J, Horn V, Macdonald S, et al: Sepsis and its etiology among hospitalized children less than 1 year of age with intestinal failure on parenteral nutrition. *Transplant Proc* 2010;42:24–25.
- 52 Wales PW, de Silva N, Kim JH, et al: Neonatal short bowel syndrome: a cohort study. *J Pediatr Surg* 2005;40:755–762.
- 53 Kaufman SS, Loseke CA, Lupo JV, et al: Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. *J Pediatr* 1997;131:356–361.
- 54 Pierro A, van Saene HK, Donnell SC, et al: Microbial translocation in neonates and infants receiving long-term parenteral nutrition. *Arch Surg* 1996;131:176–179.
- 55 Chand N, Sanyal AJ: Sepsis-induced cholestasis. *Hepatology* 2007;45:230–241.
- 56 Kusters A, Karpen SJ: The role of inflammation in cholestasis. Clinical and basic aspects. *Semin Liver Dis* 2010;30:186–194.
- 57 Osler W: Principles and Practice of Medicine. New York, D. Appleton and Company, 1901, p 550.
- 58 Beath SV, Booth IW, Murphy MS: Nutritional care in candidates for small bowel transplantation. *Arch Dis Child* 1995;73:348–350.
- 59 Colomb V, Fabeiro M, Dabbas M, et al: Central venous catheter-related infections in children on long-term home parenteral nutrition: incidence and risk factors. *Clin Nutr* 2000;19:355–359.
- 60 Carter BA, Karpen SJ: Intestinal failure-associated liver disease: management and treatment strategies past, present, and future. *Semin Liver Dis* 2007;27:251–258.
- 61 O’Keefe SJ: Bacterial overgrowth and liver complications in short bowel intestinal failure patients. *Gastroenterology* 2006;130(2 suppl 1):S67–S69.
- 62 Quigley EM: Bacteria: a new player in gastrointestinal motility disorders—infections, bacterial overgrowth, and probiotics. *Gastroenterol Clin North Am* 2007;36:735–748.
- 63 Cole CR, Ziegler TR: Small bowel bacterial overgrowth: a negative factor in gut adaptation in pediatric SBS. *Curr Gastroenterol Rep* 2007;9:456–462.
- 64 Olieman JF, Poley MJ, Gischler SJ, et al: Interdisciplinary management of infantile short bowel syndrome: resource consumption, growth, and nutrition. *J Pediatr Surg* 2010;45:490–498.
- 65 Husebye E: The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. *Neurogastroenterol Motil* 1999;11:141–161.

- 66 Willis TC, Carter BA, Rogers SP, et al: High rates of mortality and morbidity occur in infants with parenteral nutrition-associated cholestasis. *JPEN J Parenter Enteral Nutr* 2010;34:32–37.
- 67 Goulet O, Olieman J, Ksiazek J, et al: Neonatal short bowel syndrome as a model of intestinal failure: physiological background for enteral feeding. *Clin Nutr* 2013;32:162–171.
- 68 Bahador M, Cross AS: From therapy to experimental model: a hundred years of endotoxin administration to human subjects. *J Endotoxin Res* 2007;13:251–279.
- 69 Moseley RH: Sepsis and cholestasis. *Clin Liver Dis* 2004;8:83–94.
- 70 Bahador M, Cross AS: From therapy to experimental model: a hundred years of endotoxin administration to human subjects. *J Endotoxin Res* 2007;13:251–279.
- 71 Santos AA, Wilmore DW: The systemic inflammatory response: perspective of human endotoxemia. *Shock* 1996;6(suppl 1):S50–S56.
- 72 Pastor CM, Suter PM: Hepatic hemodynamics and cell functions in human and experimental sepsis. *Anesth Analg* 1999;89:344–352.
- 73 Sherman ML, Spriggs DR, Arthur KA, et al: Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: phase I toxicity and effects on lipid metabolism. *J Clin Oncol* 1988;6:344–350.
- 74 Jones A, Selby PJ, Viner C, et al: Tumour necrosis factor, cholestatic jaundice, and chronic liver disease. *Gut* 1990;31:938–939.
- 75 Copple BL, Jaeschke H, Klaassen CD: Oxidative stress and the pathogenesis of cholestasis. *Semin Liver Dis* 2010;30:193–202.
- 76 Geier A, Wagner M, Dietrich CG, et al: Principles of hepatic organic anion transporter regulation during cholestasis, inflammation and liver regeneration. *Biochim Biophys Acta* 2007;1773:283–308.
- 77 Wagner M, Zollner G, Trauner M: New molecular insights into the mechanisms of cholestasis. *J Hepatol* 2009;51:565–580.
- 78 Soroka CJ, Ballatori N, Boyer JL: Organic solute transporter, OSTot-OSTI3: Its role in bile acid transport and cholestasis. *Semin Liver Dis* 2010;30:176–183.
- 79 Wagner M, Zollner G, Trauner M: Nuclear receptor regulation of the adaptive response of bile acid transporters in cholestasis. *Semin Liver Dis* 2010;30:158–175.
- 80 El Kasmi KC, Anderson AL, Devereaux MW, et al: Toll-like receptor 4-dependent Kupffer cell activation and liver injury in a novel mouse model of parenteral nutrition and intestinal injury. *Hepatology* 2012;55:1518–1528.
- 81 Fouts DE, Torralba M, Nelson KE, et al: Bacterial translocation and changes in the intestinal microbiome in mouse models of liver disease. *J Hepatol* 2012;56:1283–1292.
- 82 Bhogal HK, Sanyal AJ: The molecular pathogenesis of cholestasis in sepsis. *Front Biosci (Elite Ed)* 2013;5:87–96.
- 83 Schnabl B: Linking intestinal homeostasis and liver disease. *Curr Opin Gastroenterol* 2013;29:264–270.
- 84 Cooke RJ, Whittington PF, Kelts D: Effect of taurine supplementation on hepatic function during short-term parenteral nutrition in the premature infant. *J Pediatr Gastroenterol Nutr* 1984;3:234–238.
- 85 Buchman AL, Ament ME, Sohel M, et al: Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a placebo-controlled trial. *JPEN J Parenter Enteral Nutr* 2001;25:260–268.
- 86 Moreno A, Guez C, Ballibriga A: Aluminium in the neonate related to parenteral nutrition. *Acta Paediatrica* 1994;83:25–29.
- 87 Rabinow BE, Ericson S, Shellgren T: Aluminium in parenteral products; analysis reduction and implications for paediatric TPN. *J Parenter Sci Technol* 1989;43:132–139.
- 88 Moukarzel A: Chromium in parenteral nutrition: too little or too much? *Gastroenterology* 2009;137:S18–S28.
- 89 Hardy G: Manganese in parenteral nutrition: who, when, and why should we supplement? *Gastroenterology* 2009;137:S29–S35.
- 90 Van Gossum A, Shariff R, Lemoyne M, et al: Increased lipid peroxidation after lipid infusion as measured by breath pentane output. *Am J Clin Nutr* 1988;48:1394–1399.
- 91 Steephen AC, Traber MG, Ito Y, et al: Vitamin E status of patients receiving long-term parenteral nutrition: is vitamin E supplementation adequate? *JPEN J Parenter Enteral Nutr* 1991;15:647–652.
- 92 Traber MG, Carpentier YA, Kayden HJ, et al: Alterations in plasma alpha- and gammatocopherol concentrations in response to intravenous infusion of lipid emulsions in humans. *Metabolism* 1993;42:701–709.
- 93 Socha P, Koletzko B, Pawlowska J, et al: Treatment of cholestatic children with water-soluble vitamin E (alpha-tocopheryl polyethylene glycol succinate): effects on serum vitamin E, lipid peroxides, and polyunsaturated fatty acids. *J Pediatr Gastroenterol Nutr* 1997;24:189–193.
- 94 Krohn K, Koletzko B: Parenteral lipid emulsions in paediatrics. *Curr Opin Clin Nutr Metab Care* 2006;9:319–323.
- 95 Roma MG, Sanchez Pozzi EJ: Oxidative stress: a radical way to stop making bile. *Ann Hepatol* 2008;7:16–33.

- 96 Steger PJ, Muhlebach SF: Lipid peroxidation of i.v. lipid emulsions in TPN bags: the influence of tocopherols. *Nutrition* 1998;14:179–185.
- 97 Wanten G, Beunk J, Naber A, et al: Tocopherol isoforms in parenteral lipid emulsions and neutrophil activation. *Clin Nutr* 2002;21:417–422.
- 98 Elmadfa I, Bosse W: Vitamin E Bedarf; in Elmadfa I, Bosse W (eds): *Vitamin E: Eigenschaften, Wirkungsweise und Therapeutische Bedeutung*. Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1985.
- 99 Mager DR, Marcon M, Wales P, et al: Use of N-acetyl cysteine for the treatment of parenteral nutrition-induced liver disease in children receiving home parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:220–223.
- 100 Calder PC, Krauss-Etschmann S, de Jong EC, et al: Early nutrition and immunity – progress and perspectives. *Br J Nutr* 2006;96:774–790.
- 101 Szabo G, Mandrekar P, Dolganiuc A: Innate immune response and hepatic inflammation. *Semin Liver Dis* 2007;27:339–350.
- 102 Koletzko B, Goulet O: Fish oil containing intravenous lipid emulsions in parenteral nutrition-associated cholestatic liver disease. *Curr Opin Clin Nutr Metab Care* 2010;13:321–326.
- 103 Goulet O, Girot R, Maier-Redelsperger M, et al: Hematologic disorders following prolonged use of intravenous fat emulsions in children. *JPEN J Parenter Enteral Nutr* 1986;10:284–288.
- 104 Forchielli ML, Bersani G, Tala S, et al: The spectrum of plant and animal sterols in different oil-derived intravenous emulsions. *Lipids* 2010;45:63–71.
- 105 Clayton PT, Bowron A, Mills KA, et al: Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology* 1993;105:1806–1813.
- 106 Bindl L, Lutjohann D, Buderus S, et al: High plasma levels of phytosterols in patients on parenteral nutrition: a marker of liver dysfunction. *J Pediatr Gastroenterol Nutr* 2000;31:313–316.
- 107 Clayton PT, Whitfield P, Iyer K: The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. *Nutrition* 1998;14:158–164.
- 108 Carter BA, Taylor OA, Prendergast DR, et al: Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. *Pediatr Res* 2007;62:301–306.
- 109 Gura KM, Duggan CP, Collier SB, et al: Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. *Pediatrics* 2006;118:e197–e201.
- 110 Puder M, Valim C, Meisel JA, et al: Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009;250:395–402.
- 111 Ekema G, Falchetti D, Boroni G, et al: Reversal of severe parenteral nutrition-associated liver disease in an infant with short bowel syndrome using parenteral fish oil (Omega-3 fatty acids). *J Pediatr Surg* 2008;43:1191–1195.
- 112 Cheung HM, Lam HS, Tam YH, et al: Rescue treatment of infants with intestinal failure and parenteral nutrition-associated cholestasis (PNAC) using a parenteral fish-oil-based lipid. *Clin Nutr* 2009;28:209–212.
- 113 Sigalet D, Boctor D, Robertson M, et al: Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. *Eur J Pediatr Surg* 2009;19:348–353.
- 114 Diamond IR, Sterescu A, Pencharz PB, et al: The rationale for the use of parenteral omega-3 lipids in children with short bowel syndrome and liver disease. *Pediatr Surg Int* 2008;24:773–778.
- 115 Waitzberg DL, Torrinhas RS, Jacintho TM: New parenteral lipid emulsions for clinical use. *JPEN J Parenter Enteral Nutr* 2006;30:351–367.
- 116 Mayer K, Schaefer MB, Seeger W: Fish oil in the critically ill: from experimental to clinical data. *Curr Opin Clin Nutr Metab* 2006;9:140–148.
- 117 Mertes N, Grimm H, Fürst P, et al: Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. *Ann Nutr Metab* 2006;50:253–259.
- 118 Antébi H, Mansoor O, Ferrier C, et al: Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr* 2004;28:142–148.
- 119 Schlotzer E, Kanning U: Elimination and tolerance of a new parenteral lipid emulsion (SMOF) – a double-blind cross-over study in healthy male volunteers. *Ann Nutr Metab* 2004;48:263–268.
- 120 Genton L, Karsegard VL, Dupertuis YM, et al: Tolerance to a lipid emulsion containing a mixture of soybean, olive, coconut and fish oil compared with a standard fat emulsion containing only soybean oil. *Clin Nutr* 2004;23:793.
- 121 Grimm H, Mertes N, Goeters C, et al: Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006;45:55–60.
- 122 Martin JM, Stapleton RD: Omega-3 fatty acids in critical illness. *Nutr Rev* 2010;68:531–541.

- 123 Chen B, Zhou Y, Yang P, et al: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 124 Skouroliaou M, Konstantinou D, Koutri K, et al: A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr* 2010;64:940–947.
- 125 Rayyan M, Allegaert K, Devlieger H: Effect of a new type of lipid emulsion based on soybean oil, MCT, olive oil, and fish oil (SMOF20%) in preterm infants. *Pediatr Crit Care Med* 2007;8(suppl):A318.
- 126 Tomsits E, Pataki M, Tölgyesi A, et al: Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2010;51:514–521.
- 127 Deshpande G, Simmer K, Deshmukh M, et al: Fish oil (SMOFlipid) and olive oil lipid (Clinoleic) in very preterm neonates. *J Pediatr Gastroenterol Nutr* 2014;58:179–184.
- 128 Salas JS, Dozio E, Goulet O, et al: Energy expenditure and substrate utilization in the course of renutrition of malnourished children. *J Parenter Enteral Nutr* 1991;15:288–293.
- 129 Muhammed R, Bremner R, Protheroe S, Johnson T, Holden C, Murphy MS: Resolution of parenteral nutrition-associated jaundice on changing from a soybean oil emulsion to a complex mixed-lipid emulsion. *J Pediatr Gastroenterol Nutr* 2012;54:797–802.
- 130 Teitelbaum DH, Han-Markey T, Schumacher RE: Treatment of parenteral nutrition-associated cholestasis with cholecystokinin-octapeptide. *J Pediatr Surg* 1995;30:1082–1085.
- 131 Teitelbaum DH, Tracy TF Jr, Aouthmany MM, et al: Use of cholecystokinin-octapeptide for the prevention of parenteral nutrition-associated cholestasis. *Pediatrics* 2005;115:1332–1340.
- 132 Buchman AL: The addition of choline to parenteral nutrition. *Gastroenterology* 2009;137:S119–S128.
- 133 Shulman RJ: New developments in total parenteral nutrition for children. *Curr Gastroenterol Rep* 2002;2:253–258.
- 134 Jones BA, Hull MA, Kim HB: Autologous intestinal reconstruction surgery for intestinal failure management. *Curr Opin Organ Transplant* 2010;15:341–345.
- 135 Spagnuolo MI, Iorio R, Vegnente A, et al: Ursodeoxycholic acid for treatment of cholestasis in children on long-term total parenteral nutrition: a pilot study. *Gastroenterology* 1996;111:716–719.
- 136 Heubi JE, Wiechmann DA, Creutzinger V, et al: Tauroursodeoxycholic acid (TUDCA) in the prevention of total parenteral nutritional associated liver disease. *J Pediatr Gastroenterol Nutr* 2003;36:422–423.
- 137 Beau P, Labat-Labourdette J, Ingrand P, et al: Is ursodeoxycholic acid an effective therapy for total parenteral nutrition related liver disease? *J Hepatol* 1994;20:240–244.
- 138 Lienhardt A, Rakotoambinina B, Colomb V, et al: Insulin secretion and sensitivity in children on cyclic total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1998;22:382–386.
- 139 Beghin L, Michaud L, Hankard R, et al: Total energy expenditure and physical activity in children treated with home parenteral nutrition. *Pediatr Res* 2003;53:684–690.
- 140 Shulman RJ, Phillips S: Parenteral nutrition in infants and children. *J Pediatr Gastroenterol Nutr* 2003;36:587–607.
- 141 Coran AG, Drongowski RA: Studies on the toxicity and efficacy of a new amino acid solution in pediatric parenteral nutrition. *J Parenter Enteral Nutr* 1987;11:368–377.
- 142 Forchielli ML, Gura KM, Sandler R, et al: Aminosyn PF or Trophamine: which provides more protection from cholestasis associated with total parenteral nutrition? *J Pediatr Gastroenterol Nutr* 1995;21:374–382.
- 143 Wright K, Ernst KD, Gaylord MS, et al: Increased incidence of parenteral nutrition-associated cholestasis with aminosyn PF compared to trophamine. *J Perinatol* 2003;23:444–450. Comment in: *J Perinatol* 2003;23:437–438.
- 144 Ben Hariz M, Goulet O, Colomb V, et al: Inappropriate iron intake in children on long-term parenteral nutrition: outcome after iron withdrawal. *Clin Nutr* 1997;16:251–255.
- 145 Advenier E, Landry C, Colomb V, et al: Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2003;36:448–453.
- 146 Putet G, Bresson JL, Ricour C: [Exclusive parenteral nutrition in children. Influence of continuous or cyclic intake on the utilization of food]. *Arch Fr Pédiatr* 1984;41:111–115.
- 147 Matuchansky C, Messing B, Jeejeebhoy KN, et al: Cyclical parenteral nutrition. *Lancet* 1992;340:588–592.
- 148 Gramlich LM: Cyclic parenteral nutrition: considerations of carbohydrate and lipid metabolism. *Nutr Clin Pract* 1994;9:49–50.
- 149 Colomb V, Charbit M, Goulet O, et al: Renal function in young patients on long-term cyclic parenteral nutrition. *Transplant Proc* 1996;28:2785.

- 150 MacFie J: Cyclic parenteral nutrition. *Nutrition* 1997;13:46–48.
- 151 Nicol JJ, Hoagland RL, Heitlinger LA: The prevalence of nausea and vomiting in pediatric patients receiving home parenteral nutrition. *Nutr Clin Pract* 1995;10:189–192.
- 152 Li SJ, Nussbaum MS, McFadden DW, et al: Addition of glucagon to total parenteral nutrition (TPN) prevents hepatic steatosis in rats. *Surgery* 1988;104:350–357.
- 153 Jensen AR, Goldin AB, Koopmeiners JS, et al: The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patients with gastroschisis. *J Pediatr Surg* 2009;44:183–189.
- 154 Reinshagen K, Zahn K, Buch C, et al: The impact of longitudinal intestinal lengthening and tailoring (LILT) on liver function in short bowel syndrome. *Eur J Pediatr Surg* 2008;18:249–253.
- 155 Modi BP, Javid PJ, Jaksic T, et al: First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. *J Am Coll Surg* 2007;204:365–367.
- 156 Andres AM, Thompson J, Grant W, et al: Repeat surgical bowel lengthening with the STEP procedure. *Transplantation* 2008;85:1294–1299.
- 157 Fiel MI, Sauter B, Wu HS, et al: Regression of hepatic fibrosis after intestinal transplantation in total parenteral nutrition liver disease. *Clin Gastroenterol Hepatol* 2008;6:926–933.
- 158 Thompson J, Sudan D: Intestinal lengthening for short bowel syndrome. *Adv Surg* 2008;42:49–61.
- 159 Javid PJ, Sanchez SE, Horslen SP, et al: Intestinal lengthening and nutritional outcomes in children with short bowel syndrome. *Am J Surg* 2013;205:576–580.
- 160 Jones BA, Hull MA, Potanos KM, et al: Report of 111 consecutive patients enrolled in the International Serial Transverse Enteroplasty (STEP) Data Registry: a retrospective observational study. *J Am Coll Surg* 2013;216:438–446.
- 161 Frongia G, Kessler M, Weih S, et al: Comparison of LILT and STEP procedures in children with short bowel syndrome – a systematic review of the literature. *J Pediatr Surg* 2013;48:1794–1805.
- 162 Mercer DF, Hobson BD, Gerhardt BK, et al: Serial transverse enteroplasty allows children with short bowel to wean from parenteral nutrition. *J Pediatr* 2014;164:93–98.
- 163 Goulet O, Joly F: Intestinal microbiota in short bowel syndrome. *Gastroenterol Clin Biol* 2010;34(suppl 1):S37–S43.
- 164 Floch MH, Walker WA, Guandalini S, et al: Recommendations for probiotic use – 2008. *J Clin Gastroenterol* 2008;42(suppl 2):S104–S108.
- 165 Wallace B: Clinical use of probiotics in the pediatric population. *Nutr Clin Pract* 2009;24:50–59.
- 166 Kunz AN, Noel JM, Fairchok MP: Two cases of *Lactobacillus* bacteremia during probiotic treatment of short gut syndrome. *J Pediatr Gastroenterol Nutr* 2004;38:457–458.
- 167 Hennequin C, Kauffmann-Lacroix C, Jobert A, et al: Possible role of catheters in *Saccharomyces boulardii* fungemia. *Eur J Clin Microbiol Infect Dis* 2000;19:16–20.
- 168 Mihatsch WA, Braegger CP, Decsi T, et al: Critical systematic review of the level of evidence for routine use of probiotics for reduction of mortality and prevention of necrotizing enterocolitis and sepsis in preterm infants. *Clin Nutr* 2012;31:6–15.
- 169 Hall NJ, Eaton S, Pierro A: Necrotizing enterocolitis: Prevention, treatment, and outcome. *J Pediatr Surg* 2013;48:2359–2367.
- 170 Janvier A, Malo J, Barrington KJ: Cohort study of probiotics in a North American neonatal intensive care unit. *J Pediatr* 2014;164:980–985.
- 171 Ofek Shlomai N, Deshpande G, Rao S, et al: Probiotics for preterm neonates: what will it take to change clinical practice? *Neonatology* 2014;105:64–70.
- 172 Amusquivar E, Ruperez FJ, Barbas C, et al: Low arachidonic acid rather than alpha-tocopherol is responsible for the delayed postnatal development in offspring of rats fed fish oil instead of olive oil during pregnancy and lactation. *J Nutr* 2000;130:2855–2865.
- 173 Carlson SE, Werkman SH, Peeples JM, et al: Arachidonic acid status correlates with first year growth in preterm infants. *Proc Natl Acad Sci USA* 1993;90:1073–1077.
- 174 de Meijer VE, Le HD, Meisel JA, et al: Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr* 2010;50:212–218.
- 175 Pradelli L, Mayer K, Muscaritoli M, et al: n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care* 2012;16:R184.
- 176 Mian SI, Dutta S, Le B, et al: Factors affecting survival to intestinal transplantation in the very young pediatric patient. *Transplantation* 2008;85:1287–1289.
- 177 Lacaille F, Vass N, Sauvat F, et al: Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. *Gut* 2008;57:455–461.
- 178 Lopushinsky SR, Fowler RA, Kulkarni GS, et al: The optimal timing of intestinal transplantation for children with intestinal failure: a Markov analysis. *Ann Surg* 2007;246:1092–1099.

- 179 Robinson DT, Ehrenkranz RA: Parenteral nutrition-associated cholestasis in small for gestational age infants. *J Pediatr* 2008;152:59–62.
- 180 Goulet O, Sauvat F: Short bowel syndrome and intestinal transplantation in children. *Curr Opin Clin Nutr Metab Care* 2006;9:304–313.
- 181 Nandivada P, Chang MI, Potemkin AK, et al: The natural history of cirrhosis from parenteral nutrition-associated liver disease after resolution of cholestasis with parenteral fish oil therapy. *Ann Surg* 2013; [Epub ahead of print].
- 182 Kalish BT, Le HD, Fitzgerald JM, et al: Intravenous fish oil lipid emulsion promotes a shift toward anti-inflammatory proresolving lipid mediators. *Am J Physiol Gastrointest Liver Physiol* 2013;305:G818–G828.
- 183 Barclay AR, Beattie LM, Weaver LT, et al: Systematic review: medical and nutritional interventions for the management of intestinal failure and its resultant complications in children. *Aliment Pharmacol Ther* 2011;33:175–184.

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Intravenous Lipids in Adult Surgical Patients

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Abstract

Parenteral nutrition is considered an essential element of the perioperative management of surgical patients. It is recommended in patients who require nutritional therapy but in whom the enteral route is contraindicated, not recommended or non-feasible. The new generation of lipid emulsions (LEs) based on olive and fish oils are safe and may improve clinical outcome in surgical patients. The increased provision of n-3 polyunsaturated fatty acids in fish oil-containing LEs seems to be associated with fewer infectious complications and shorter ICU and hospital stays following major abdominal surgery. Increased provision of olive oil in the absence of fish oil may also exert beneficial effects, but a clear conclusion on this is limited due to the low number of available studies. Hence, at the moment, the evidence supports the use of n-3-polyunsaturated fatty acid-enriched LEs as a part of the parenteral nutrition regimen for selected groups of patients, such as those with major surgical trauma or those undergoing extended resections or liver transplantation.

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Introduction

A surgical procedure is a specific type of partially controlled trauma that causes extensive changes within the functioning of multiple systems in the patient's body. The goal of this response is to restore homeostasis. The magnitude of the response and how well and how quickly it returns to homeostasis are dependent on many factors, such as the patient's nutritional status, the patient's genetics, the underlying disease, the presence of co-morbidities, and the type and size of the surgical intervention. Parenteral nutrition (PN) is considered an essential element of the perioperative management of surgical patients. It is recommended for patients who require nutritional therapy but in whom the enteral route is contraindicated, not recommended or non-feasible and who belong to one of the following groups [1, 2]:

- severely undernourished patients who cannot be adequately fed by the oral or enteral routes;
- patients unable to receive at least 60% of the required nutrient intake during the postoperative period via the enteral route;
- patients with postoperative complications impairing gastrointestinal function and who are unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days;
- patients with prolonged gastrointestinal failure.

Lipid Emulsions in Surgical Patients

Lipid emulsions (LEs) are an important component of PN because they are a source of energy and essential fatty acids [2, 3]. As observed recently, some fatty acids in LEs can also act as pharmaconutrients and exert immunomodulating effects [3]. For many years, soybean oil-based LEs rich in n-6 polyunsaturated fatty acids (PUFAs) were used as the lipid component of PN. There is some evidence that n-6 PUFAs may promote inflammation, which may increase surgical stress and worsen the outcome [3, 4]. As a result, new generations of LEs have been developed that contain a reduced amount of soybean oil and n-6 PUFAs [3], and this has been done by replacing soybean oil (termed long-chain triglycerides) partially with:

- medium-chain triglycerides;
- synthetic ('structured') lipids that consist of a glycerol backbone esterified with medium-chain triglycerides or long-chain triglycerides;
- olive oil, which provides the n-9 fatty acid oleic acid;
- fish oil, which provides the n-3 PUFAs eicosapentaenoic acid and docosahexaenoic acid;
- combinations of these oils.

A trial in healthy subjects showed that inclusion of n-3 fatty acids in PN blunts the physiological response to endotoxin [5]. Prolonged, regular parenteral n-3 PUFA administration results in rapid and sustained cellular uptake, increased n-3 PUFA content in cellular membranes and a reduced ratio of n-6 to n-3 PUFA [6]. The increased provision of n-3 PUFAs in fish oil-containing LEs seems to be associated with fewer infectious complications and shorter ICU and hospital stays following major abdominal surgery [7, 8]. Increased provision of olive oil, in the absence of fish oil, may also exert beneficial effects, but a clear conclusion on this is limited due to the low number of available studies. A summary of the recent clinical trials is presented in table 1, and a summary of the recent meta-analyses is shown in table 2. Recent studies reveal that including n-3-PUFAs as a component of the LE received by surgical patients may promote a number of positive clinical effects, including the following:

- improved liver function [11, 12];
- improved immunologic and inflammatory parameters [9, 17];

Table 1. Recent trials of fish oil-containing lipid emulsions in surgical patients

Author	Patients studied	Control lipid emulsion	Intervention lipid emulsion	Duration	Effect seen for intervention vs. control
Jiang et al. [9]	Colectomy and rectectomy (n = 206)	SO	SO + FO	7 days after surgery	Reduction of SIRS Shorter LOS
Umpierrez et al. [10]	Surgical ICU (n = 100)	SO	SO/Olive oil	28 days	No differences in LOS, infections, metabolic and immune function, or mortality
Wang et al. [11]	Gastrointestinal surgery (n = 64)	SO/MCT	SO/MCT/FO	5 days after surgery	Better liver function Better immune status
Han et al. [12]	Major surgery (n = 38)	SO/MCT	SO/MCT + FO	7 days after surgery	Reduction in postoperative liver dysfunction Fewer infections
Ma et al. [13]	Elective digestive surgery (n = 40)	SO/MCT	SO/MCT/ Olive oil/FO	5 days after surgery	No differences
Zhu et al. [14]	Colectomy and rectectomy (n = 57)	SO	SO + FO	7 days after surgery	Shorter LOS
Zhu et al. [15]	Liver transplantation (n = 98)	SO/MCT	SO/MCT + FO	7 days after surgery	Reduced injury of liver Shorter LOS Fewer infectious complications
Berger et al. [16]	Cardiopulmonary by-pass surgery, (n = 28)	None (saline)	FO	12 and 2 h before surgery + immediately after surgery	Increased n-3 fatty acid concentrations in platelet and atrial tissue membranes within 12 h of the first FO administration Decreased biological and clinical signs of inflammation
De Miranda Torrinhas et al. [17]	Surgery for gastrointestinal cancer (n = 63)	SO/MCT	FO	3 days preoperatively	Higher IL-10 levels on day 3 Lower IL-6 and IL-10 levels on day 6 Smaller decrease in leukocyte oxidative burst

FO = Fish oil; ICU = intensive care unit; IL = interleukin; LOS = length of stay; MCT = medium-chain triglycerides; SIRS = systemic inflammatory response syndrome; SO = soybean oil.

Lipid emulsions shown as A/B (e.g. SO/MCT) or A/B/C (e.g. SO/MCT/FO) represent pre-existing mixtures of those oils, whereas lipid emulsions shown as A/B + FO (e.g. SO/MCT + FO) represent supplementation of a pre-existing mixture with pure FO.

- shorter length of hospital stay [9, 14, 15];
- fewer complications [12, 14, 15].

Moreover, these effects are seen if n-3 PUFAs are administered for 3 days preoperatively [17], for 7 days postoperatively [9, 12, 14, 15] or perioperatively [16]. It appears that when administered for a short term (less than 5 days), n-3 PUFAs influence immune parameters and liver function and that a longer infusion (5–7 days) also reduces the complication rate and shortens the length of stay. Therefore, it seems that the duration of this intervention should be at least 5–7 days pre- or postoperatively.

Increased provision of olive oil in the absence of fish oil may also exert beneficial effects, but a clear conclusion on this is limited due to the low number of available studies.

Table 2. Recent meta-analyses of fish oil-containing lipid emulsions in surgical patients

Author	Number of RCTs included (number of patients)	Effect seen for fish oil-containing lipid emulsion vs. control (usually SO or SO/MCT)
Chen et al. [18]	13 (892)	Shorter ICU stay Shorter LOS Fewer infections Improved liver function
Li et al. [19]	21 (1,487)	Shorter LOS Fewer infections Improved liver function No difference in mortality
Tian et al. [20]	6 (306)	Improved liver function

ICU = Intensive care unit; LOS = length of stay; MCT = medium-chain triglycerides; RCT = randomized controlled trial; SO = soybean oil.

Selection of Patients

The European Society for Clinical Nutrition and Metabolism recommends the use of n-3-PUFAs in critically ill surgical patients [2]. On the other hand, the American Society for Parenteral and Enteral Nutrition, in its recently published report, emphasized the possible detrimental effect of soybean oil-based LEs but did not name fish oil as an alternative [21].

Nevertheless, based on the recent data, which are presented above, the use of specific formulas enriched in n-3-PUFAs should be considered in:

- patients undergoing major abdominal cancer surgery (esophagectomy, gastrectomy, and pancreaticoduodenectomy);
- patients undergoing liver surgery;
- patients undergoing liver transplantation;
- trauma patients.

Summary

LEs are an important component of PN because they are a source of energy and essential fatty acids. Recent studies showed that the use of non-standard emulsions, such as those providing n-3-PUFAs, might improve the outcome of surgery. However, the exact clinical effect depends on the timing of the intervention. Fish oil helps to improve immune parameters, reduce the complication rate and decrease the length of stay. For these reasons, n-3-PUFAs should replace standard formulas in some groups of surgical patients.

References

- 1 Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al: ESPEN Guidelines on Enteral Nutrition: surgery including organ transplantation. *Clin Nutr* 2006;25:224–244.
- 2 Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F: ESPEN Guidelines on Parenteral Nutrition: surgery. *Clin Nutr* 2009;28:378–386.
- 3 Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.
- 4 Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW: Total parenteral nutrition in the surgical patient: a meta-analysis. *Can J Surg* 2001;44:102–111.
- 5 Pluess TT, Hoyoz D, Berger MM, Tappy L, Revelly JP, Michaeli B, et al: Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. *Intensive Care Med* 2007;33:789–797.
- 6 Arshad A, Chung WY, Isherwood J, Mann CD, Al-Leswas D, Steward WP, et al: Cellular and plasma uptake of parenteral omega-3 rich lipid emulsion fatty acids in patients with advanced pancreatic cancer. *Clin Nutr* 2013, DOI: 10.1016/j.clnu.2013.09.017.
- 7 Heller AR, Rossler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al: Omega-3 fatty acids improve the diagnoses-related clinical outcome. *Crit Care Med* 2006;34:972–979.
- 8 Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW: Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicentre trial. *Crit Care Med* 2007;35:700–706.
- 9 Jiang ZM, Wilmore DW, Wang XR, Wei JM, Zhang ZT, Gu ZY, et al: Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. *Br J Surg* 2010;97:804–809.
- 10 Umpierrez GE, Spiegelman R, Zhao V: A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. *Crit Care Med* 2012;40:1792–1798.
- 11 Wang J, Yu JC, Kang WM, Ma ZQ: Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. *Nutrition* 2012;28:623–629.
- 12 Han YY, Lai SL, Ko WJ, Chou CH, Lai HS: Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. *Nutr Clin Pract* 2012;27:91–98.
- 13 Ma CJ, Sun LC, Chen FM, Lu CY, Shih YL, Tsai HL, et al: A double-blind randomized study comparing the efficacy and safety of a composite vs a conventional intravenous fat emulsion in postsurgical gastrointestinal tumor patients. *Nutr Clin Pract* 2012;27:410–415.
- 14 Zhu MW, Tang DN, Hou J, Wei JM, Hua B, Sun JH, et al: Impact of fish oil enriched total parenteral nutrition on elderly patients after colorectal cancer surgery. *Chin Med J (Engl)* 2012;125:178–181.
- 15 Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y: Effects of ω -3 fish oil lipid emulsion combined with parenteral nutrition on patients undergoing liver transplantation. *JPEN J Parenter Enteral Nutr* 2013;37:68–74.
- 16 Berger MM, Delodder F, Liaudet L, Tozzi P, Schlaepfer J, Chiolerio RL, et al: Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. *Am J Clin Nutr* 2013;97:246–254.
- 17 de Miranda Torrinhas RS, Santana R, Garcia T, Cury-Boaventura MF, Sales MM, Curi R, et al: Parenteral fish oil as a pharmacological agent to modulate postoperative immune response: a randomized, double-blind, and controlled clinical trial in patients with gastrointestinal cancer. *Clin Nutr* 2013;32:503–510.
- 18 Chen B, Zhou Y, Yang P, Wan HW, Wu XT: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 19 Li NN, Zhou Y, Qin XP, Chen Y, He D, Feng JY, et al: Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. *Clin Nutr* 2014;33:226–239.
- 20 Tian H, Yao X, Zeng R, Sun R, Tian H, Shi C, et al: Safety and efficacy of a new parenteral lipid emulsion (SMOF) for surgical patients: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* 2013;71:815–821.
- 21 McClave S, Martindale R, Tayler B, Gramlich L: Appropriate use of parenteral nutrition through the perioperative period. *JPEN J Parenter Enteral Nutr* 2013;37(suppl 1):73S–82S.

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Intravenous Lipids in Adult Intensive Care Unit Patients

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Abstract

Malnutrition of critically ill patients is a widespread phenomenon in intensive care units (ICUs) worldwide. Lipid emulsions (LEs) are able to provide sufficient caloric support and essential fatty acids to correct the energy deficit and improve outcome. Furthermore, components of LEs might impact cell and organ function in an ICU setting. All currently available LEs for parenteral use are effective in providing energy and possess a good safety profile. Nevertheless, soybean oil-based LEs have been associated with an elevated risk of adverse outcomes, possibly due to their high content of omega-6 fatty acids. More newly developed emulsions partially replace soybean oil with medium-chain triglycerides, fish oil or olive oil in various combinations to reduce its negative effects on immune function and inflammation. The majority of experimental studies and smaller clinical trials provide initial evidence for a beneficial impact of these modern LEs on critically ill patients. However, large, well-designed clinical trials are needed to evaluate which LE offers the greatest advantages concerning clinical outcome. Lipid emulsions (LEs) are a powerful source of energy that can help to adjust the caloric deficit of intensive care unit (ICU) patients. LEs possess various biological activities, but their subsequent impact on critically ill patients awaits further investigations.

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General Aspects of Nutritional Support for Intensive Care Patients

Although nutritional demands and metabolism vary among critically ill patients, the onset of a trauma causes a generalized host response that is characterized by dynamic changes to their metabolic activity and thus energy requirements. This so-called

stress response has been studied in detail in patients undergoing major surgery or after trauma [1]. The stress response also occurs in patients with sepsis, burn injury or onset of severe infection, although the timing and details of the reaction may differ. As the stress response has a direct impact on the nutritional regime of ICU patients, a simplified overview of the main features that are relevant for nutrition is presented in the following section.

In general, the metabolic stress reaction can be divided into three phases. The first, so-called ebb phase, starts immediately after the initial insult and lasts for 1–2 days, depending on the extent of injury/stress [1]. This phase is characterized by an overall decrease in metabolic activity and energy requirements that are often accompanied by a decline in oxygen consumption and cardiac output. Although an individual in the ebb phase has a low basal metabolic rate, the individual initiates, in preparation for the following metabolic phases, a stress-hormone driven mobilization of endogenous energy stores (such as hepatic and skeletal muscle glycogen), which clinically translates into significant hyperglycemia. The onset of the flow phase is signaled by an increase in cardiac output, restoration of respiratory rate and escalation of the energy demand to adjust to the injury and stabilize the circulation. Metabolically, the flow phase is characterized by the provision of substrates ('fuel'), which is basically achieved through catabolism and insulin resistance. The catabolic reaction encompasses protein breakdown (primarily skeletal muscle and later respiratory and gut musculature) to increase the availability of glucogenic amino acids as well as a rise in gluconeogenesis and impaired uptake of glucose in insulin-dependent tissues. Free fatty acids are provided to yield energy through lipolysis and the depletion of endogenous fat stores. The duration of the flow phase varies and might be up to weeks depending on the progress of healing and the occurrence of complications. In the final, so-called anabolic or recovery phase, restoration of lean body mass and weight is intended. Of special importance is the restoration of muscle tissue that was lost during the initial phases.

The consideration of the above-mentioned stress response has a pivotal impact on the establishment of an adequate nutritional regime for the critically ill patient. First, it is of major importance that metabolic changes are dynamic depending, amongst others, on the extent of the injury, timing and complications. Second, the metabolic stress response impacts survival and has thus been evolutionarily programmed. Some features, such as hyperglycemia, could theoretically be influenced by massive intervention (e.g. excessive insulin application), but study data show that this might cause more harm than good. Third, except in the short time period of the ebb phase, where low metabolic rates are observed, the energy demand of critically ill patients is high, leading to a mobilization of the endogenous pool of substrates, especially in situations with insufficient exogenous provision of calories. By the provision of exogenous substrates, it is possible to reduce the adverse effects of catabolism, promote recovery and finally beneficially influence survival.

Parenteral Nutrition of Intensive Care Unit Patients

Given that malnutrition is a proven prognostic factor for a fatal outcome in intensive care patients, it is of major importance to provide adequate caloric intake. Enteral nutrition (EN) is regarded as the gold standard in an ICU setting, as it promotes the integrity of the intestine and thus reduces the rate of complications [2, 3]. However, two cohorts of patients may significantly benefit from the application of parenteral nutrition (PN). In the first group, the use of EN may be (temporarily) contraindicated (due to gut ischemia, peritonitis, major abdominal surgery), and thus PN is required to avoid malnutrition. Recommendations for the use of PN in ICU patients vary extensively among the national societies, with more liberal use in European guidelines and a restricted application regime in the USA and Canada [3, 4]. The role of PN as a supplement to EN is more controversial. Recent study data indicate that in critically ill patients, EN alone tends to underfeed and might lead to an undesirable energy deficit [5]. Cahill et al. could, for instance, demonstrate that, despite the international guidelines recommending early enteral feeding of ICU patients, only about 50% of the prescribed calories were applied in the first two weeks of ICU admission [6]. The main reasons for this were frequent interruptions of the enteral applications due to high gastric residual volume, vomiting, mechanical tube problems, diagnostic procedures or surgery [7]. The concept of supplemental PN encompasses the combination of PN and EN in ICU patients who do not meet the targeted caloric intake with EN alone. A recent study by Heidegger and colleagues could demonstrate that supplemental PN in patients receiving <60% of the target energy after receiving EN was associated with a significantly reduced energy deficit and complication rate and fewer days of mechanical ventilation [8].

Lipid Emulsions in Parenteral Nutrition of Intensive Care Unit Patients

The incorporation of LEs into the nutritional regime of an ICU patient allows the provision of a high-energy supply in a reduced fluid volume. Furthermore, the use of lipids reduces the portion of glucose that is applied, leading to a lower risk of hyperglycemia [9]. As hyperglycemia is a clinical feature of the stress response that is associated with an increased incidence of complications, glucose-sparing components are advantageous [10]. In this context, patients suffering from sepsis or trauma preferentially utilize fatty acids as a caloric source when entering the hypercatabolic phases of the metabolic stress response. Some of the side effects that are described when using LEs (e.g. hepatic steatosis, hypercholesterolemia) can be reduced by monitoring serum triglyceride concentrations, which should not exceed 400 mg/dl [11].

Besides the capacity to provide caloric support, the impact of LEs on various immune functions has gained further importance and has developed into an emerging field of research. Thus, the choice of LE and its fatty acid composition is at least in part

responsible for many of the observed beneficial or adverse effects that are described in ICU patients. The first generation of parenteral LEs was introduced in the 1960s and provided a sufficient amount of non-glucose energy to the patients, as, in those days, the application of carbohydrates was state-of-the-art in the field of artificial nutrition [12]. These early LEs were based on soybean oil (SO) and delivered high concentrations of omega-6 (n-6) polyunsaturated fatty acids (PUFAs) to the patients. In the following years, published clinical, animal and in vitro studies have reported less-desirable results of this type of LE in terms of the pathophysiologic and immunologic profiles [10]. The main problematic feature was the observed immunosuppressive effects, such as apoptosis of immune cells or diminished phagocytosis of granulocytes, on the one hand and the increased generation of pro-inflammatory lipid mediators (e.g. thromboxane A₂ or leukotriene B₄) derived from n-6 fatty acids on the other hand [13]. Of note, these early formulations are still the only approved and available LEs for parenteral use in some countries (e.g. USA). The next generation of LEs was introduced in 1980 and reduced the amount of SO by partial replacement with medium-chain triglycerides (MCTs, predominantly derived from coconut oil), which are thought to act more neutrally on the immune system [14]. Although experimental data suggest advantages of these newer SO/MCT emulsions in terms of tolerance, uptake and clearance from the circulation, clinical trials fail to demonstrate uniform results. Concerning the impact on immunity/inflammation, mixtures of SO/MCTs offer slight advantages compared with SO alone in ICU patients [15]. Up to now, the latest major step in the development of parenteral LEs was the incorporation of LEs containing olive oil (OO) and/or fish oil (FO) into PN regimes in the 1990s [16]. Hence, pharmaceutical companies offer LEs with diverse combinations and quantities of SO, MCT, OO and FO. The rationale to include OO (with oleic acid as a major component) is to reduce lipid peroxidation and mitochondrial reactive oxygen species production [17]. Regarding immunological effects, OO-containing LEs display only slight beneficial effects on the generation of pro-inflammatory mediators and cellular immunity. Clinical trials that investigated the role of OO in critical care patients show an inconsistent picture. Huschak and colleagues could demonstrate beneficial effects of OO regarding infections, length of stay in the ICU and duration of mechanical ventilation in trauma patients compared to SO/MCT [18]. However, this trial is not without controversy due to the diverging quantities of glucose that are administered to the patients. In contrast to these results and in favor of OO, other trials dealing with critically ill surgical patients, burn trauma or medical-surgical ICU patients could show significant advances of OO over SO or SO/MCT [19]. While the overall role of OO can be described as immune neutral, data for the use of parenteral FO indicate a dose-dependent modulation for the inflammatory response toward the anti-inflammatory direction. FO provides the very long-chain n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [2], and increased provision of n-3 PUFAs may result in augmented incorporation of these fatty acids into the cell membrane with subsequent replacement of n-6 fatty acids and a decline in the gen-

eration of pro-inflammatory lipid mediators [2]. In addition, EPA and DHA are sources of anti-inflammatory mediators such as thromboxane A₃ and leukotriene B₅. Recently, a highly interesting, novel class of n-3 PUFA-derived lipid mediators, named resolvins, has been identified that is generated by di-oxygenation of EPA and DHA upon neutrophil-endothelial cell interaction [20]. The detailed impact of these inflammation-resolving mediators and their future therapeutic use needs further elucidation. Besides experimental animal or in vitro data supporting the favorable properties of FO in the context of inflammation, a set of clinical trials analyzing FO-containing LEs in ICU patients has been performed. Heller and colleagues examined the effect of different FO dosages in 661 intensive care patients, with a major fraction suffering from abdominal sepsis [21]. The authors could demonstrate that inclusion of FO in a PN regime exhibited a dose-dependent reduction in the length of stay in an ICU as well as in antibiotic demand. Furthermore, in patients receiving FO (0.15–0.25 g/kg/day) mortality was significantly decreased [21]. Although the study was neither controlled nor randomized, these findings demonstrated a clinical benefit from the incorporation of FO in PN regimes of critical ill patients. Further evidence for the positive effects of FO was recently provided by a randomized controlled study that applied FO-containing LEs to 40 patients with acute severe pancreatitis [22]. In contrast, Friesecke and colleagues could not find any differences in mortality, duration of mechanical ventilation, or number of infections in critically ill patients receiving FO compared to those receiving SO/MCT treatment [23]. In accordance with the above-mentioned data, a recently published meta-analysis on the use of parenteral FO in critically ill patients pointed out that FO-based LEs might decrease mortality and ventilation time [24]. A major limitation is the fact that, due to the paucity of the clinical data (6 randomized controlled trials including 390 patients), a general, evidence-based recommendation for the use of parenteral FO in ICU patients can thus far not be given [24].

Summary and Outlook

LEs are a valuable component of a nutritional regime in an ICU setting, as they provide sufficient caloric support in order to overcome the energy deficits that are often observed in critically ill patients. Although the role of (supplemental) PN is not without controversy, recent study data and personal experience indicate that the prevention or treatment of malnutrition has the highest priority and prognostic impact. Clinical studies and experimental data indicate that application of the currently available LEs is safe and efficient. As EN alone might fail to meet the caloric targets, the addition of PN might benefit the patient. For example, besides affecting the energy supply, lipids are able to exert a variety of biological and pathophysiological activities that directly impact immune function. When choosing the best LE for ICU patients with severe metabolic impairment, these immunomodulatory properties should be

considered. First-generation SO-based LEs should be handled with care due to their potential impairment of immune function and exacerbation of inflammation, especially in patients with severe infections. Newer LEs, for example, address this disadvantage by the partial replacement of SO with FO. In particular, the biological function of FO-derived lipid mediators, such as resolvins and protectins, and their possible therapeutic use in resolving inflammatory processes need further evaluation. Despite a good pathophysiological rationale, the positive experimental data and few published clinical trials on the role of modern LEs can thus far not be conclusively assessed. Large prospective, randomized and adequately controlled clinical trials investigating comparable PN regimes are needed in the future to evaluate the impact of these formulations on clinical outcome and therapeutic use.

References

- 1 Hecker M, Felbinger T, Mayer K: [Nutrition in intensive care medicine]. *Anaesthesist* 2012;61:553–564.
- 2 Mayer K, Schaefer MB, Seeger W: Fish oil in the critically ill: From experimental to clinical data. *Curr Opin Clin Nutr Metab Care* 2006;9:140–148.
- 3 McClave SA, Martindale RG, Vanek VW, et al: Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009;33:277–316.
- 4 Singer P, Berger MM, Van den Berghe G, et al: Espen guidelines on parenteral nutrition: Intensive care. *Clin Nutr* 2009;28:387–400.
- 5 Alberda C, Gramlich L, Jones N, et al: The relationship between nutritional intake and clinical outcomes in critically ill patients: Results of an international multicenter observational study. *Intensive Care Med* 2009;35:1728–1737.
- 6 Cahill NE, Dhaliwal R, Day AG, et al: Nutrition therapy in the critical care setting: What is 'Best achievable' practice? An international multicenter observational study. *Crit Care Med* 2010;38:395–401.
- 7 Cahill NE, Murch L, Cook D, et al: Barriers to feeding critically ill patients: A multicenter survey of critical care nurses. *J Crit Care* 2012;27:727–734.
- 8 Heidegger CP, Berger MM, Graf S, et al: Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: A randomised controlled clinical trial. *Lancet* 2013;381:385–393.
- 9 Jeejeebhoy KN: Parenteral nutrition in the intensive care unit. *Nutr Rev* 2012;70:623–630.
- 10 Calder PC, Jensen GL, Koletzko BV, et al: Lipid emulsions in parenteral nutrition of intensive care patients: Current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- 11 Hecker M, Felbinger TW, Mayer K: Nutrition in intensive care medicine: Part 2: Special nutritional problems. *Anaesthesist* 2013;62:233–241;quiz 242–243.
- 12 Waitzberg DL, Torrinhas RS, Jacintho TM: New parenteral lipid emulsions for clinical use. *JPEN J Parenter Enteral Nutr* 2006;30:351–367.
- 13 Mayer K, Seeger W: Fish oil in critical illness. *Curr Opin Clin Nutr Metab Care* 2008;11:121–127.
- 14 Ulrich H, Pastores SM, Katz DP, et al: Parenteral use of medium-chain triglycerides: A reappraisal. *Nutrition* 1996;12:231–238.
- 15 Grau T, Ruiz de Adana JC, Zubillaga S, et al: [Randomized study of two different fat emulsions in total parenteral nutrition of malnourished surgical patients; effect of infectious morbidity and mortality]. *Nutr Hosp* 2003;18:159–166.
- 16 Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: A multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.
- 17 Tirosh O, Ilan E, Anavi S, et al: Nutritional lipid-induced oxidative stress leads to mitochondrial dysfunction followed by necrotic death in FaO hepatocytes. *Nutrition* 2009;25:200–208.
- 18 Huschak G, Zur Nieden K, Hoell T, et al: Olive oil based nutrition in multiple trauma patients: A pilot study. *Intensive Care Med* 2005;31:1202–1208.
- 19 Mateu-de Antonio J, Grau S, Luque S, et al: Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr* 2008;99:846–854.

- 20 Serhan CN: Resolution phase of inflammation: Novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Annu Rev Immunol* 2007;25:101–137.
- 21 Heller AR, Rössler S, Litz RJ, et al: Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;34:972–979.
- 22 Wang X, Li W, Li N, et al: ω -3 Fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: A randomized and controlled study. *JPEN J Parenter Enteral Nutr* 2008;32:236–241.
- 23 Friesecke S, Lotze C, Köhler J, et al: Fish oil supplementation in the parenteral nutrition of critically ill medical patients: A randomised controlled trial. *Intensive Care Med* 2008;34:1411–1420.
- 24 Manzanares W, Dhaliwal R, Jurewitsch B, et al: Parenteral fish oil lipid emulsions in the critically ill: A systematic review and meta-analysis. *JPEN. J Parenter Enteral Nutr* 2014;38:20–28.

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Intravenous Fish Oil in Adult Intensive Care Unit Patients

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Abstract

Omega-3 fatty acids contained in fish oils have shown efficacy in the treatment of chronic and acute inflammatory diseases due to their pleiotropic effects on inflammatory cell signalling pathways. In a variety of experimental and clinical studies, omega-3 fatty acids attenuated hyperinflammatory conditions and induced faster recovery. This chapter will shed light on the effects of intravenous fish oil in adult intensive care unit (ICU) patients and will discuss clinical data and recent meta-analyses on the topic. While significant beneficial effects on infection rates and the lengths of ICU and hospital stays have concordantly been identified in three recent meta-analyses on non-ICU surgical patients, the level of evidence is not so clear for critically ill patients. Three meta-analyses published in 2012 or 2013 explored data on the ICU population. Although the present data suggest the consideration of enteral nutrition enriched with fish oil, borage oil and antioxidants in mild to severe acute respiratory distress syndrome, only one of the three meta-analyses found a trend ($p = 0.08$) of lower mortality in ICU patients receiving intravenous omega-3 fatty acids. Two of the meta-analyses indicated a significantly shorter hospital stay (5.17–9.49 days), and one meta-analysis found a significant reduction in ICU days (1.92). As a result of these effects, cost savings were postulated. Unlike in surgical patients, the effects of fish oil on infection rates were not found to be statistically significant in ICU patients, and dose-effect relationships were not established for any cohort. Thus, obvious positive secondary outcome effects with intravenous fish oil have not yet been shown to transfer to lower mortality in critically ill patients. There is a need for adequately powered, well-planned and well-conducted randomized trials to give clear recommendations on the individual utility and dosage of intravenous omega-3 fatty acids in critical illness.

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Introduction

Increased incidence and severity of sepsis [1] remains a major concern worldwide. Guideline-based therapy [2] has slightly reduced the case fatalities over the years, but the overall population-based deaths per annum from critical illness are still increasing [1]. Therefore, a clear demand exists for optimizing therapy for the critically ill. Due

to the absence of clear clinical outcome effects of immunonutrition, the 2012 sepsis guidelines suggested using '*nutrition with no specific immunomodulating supplementation in patients with severe sepsis (grade 2C)*' [2].

The use of enteral or parenteral formulas enriched with immune-enhancing substances has been termed immunonutrition. When looking for immunomodulatory effects beyond nutrition, the term pharmaconutrition has also been used. The strict separation between nutritive interventions on one hand and pharmacotherapy on the other hand is therefore increasingly disappearing [3]. Nutrients are considered substrates that maintain nutritive or metabolic processes of the organism; in contrast, drugs are substances that can improve a pathophysiological condition. Marine omega-3 fatty acids (FAs) share functions as both nutrients and drugs. By reducing the length of hospital stay and antibiotic therapy [4], even in critically ill patients, net cost savings are possible from the use of omega-3 FAs, despite the higher expenditure for the prescriptions [5].

Omega-3 FAs have shown their efficacy in the treatment of chronic and acute inflammatory diseases [6] due to their pleiotropic effects on inflammatory cell signalling pathways [7–9]. In a variety of experimental [10, 11] and clinical studies, omega-3 FAs attenuated hyperinflammatory conditions and induced faster recovery [12, 13].

Four meta-analyses in the field of intravenous fish oil were published recently. Three of the analyses dealt with critical illness [14–16], while two reflected surgical patients [16, 17], and in part, these reported different results. Although meta-analyses are regarded as a high-level of evidence, the level of robustness of these analyses is greatly affected by the included studies, and until bigger and better studies are available, a more global perspective seems attractive [18].

Specialties of the Biology of Omega-3 and Omega-6 Polyunsaturated Fatty Acids in the Critically Ill

The general nomenclature, properties and metabolism of omega-3 FAs have thoroughly been presented in the first chapters of this book. Most research on supplementation with fish oil has been done in clinical or epidemiologic settings, where the intake was observed over months or even years [19]. Cellular lipid membranes, however, represent a dynamic high-turnover barrier system. Thus, infusion of a fish oil emulsion at a clinical relevant dose of 0.2 g/kg results in rapid incorporation of omega-3 FAs into cell membranes [10] and in further metabolism [16] within a few days, even in patients under critical care conditions [12]. As inflammatory cascades are increasingly up-regulated in patients, the membrane ratio of omega-3 and omega-6 FAs will shift towards the omega-3 derivatives, e.g. leukotriene (LT) B₅ instead of LTB₄ [16]. The five series of omega-3-derived LTs are less pro-inflammatory than the four series of omega-6-derived LTs. The same applies for omega-3- and omega-6-derived prostanoids [8, 11]. In line with early experimental trials showing a limitation

of excessive LTB₄ generation after fish oil infusion [11], the oxygenation index was improved in patients with sepsis [20] and pancreatitis [21].

A decade ago, novel omega-3-derived lipid mediators with pro-resolving activities on inflammatory processes were identified in exudates from resolving inflammation; these comprised the lipoxins, resolvins, and protectins [22]. Their syntheses are favoured by the transcriptional up-regulation of neutrophil 15-lipoxygenase by PGE₂ and PGD₂, the so-called 'eicosanoid switch' [22], and they are highly stereospecific and act in the pico- to nanomolar range [9]. Furthermore, these mediators affect polymorphonuclear cell recruitment and trafficking and the expression of pro-inflammatory genes, and they reduce leukocyte-mediated tissue injury and take part in chemokine removal. Their existence and the experimental data about their effects additionally support the use of omega-3 FAs to limit the hyperinflammatory states in patients [9].

The Antihyperinflammatory Role of Omega-3 Fatty Acids in the Critically Ill

Through several positive feedback loops, early host defence induces hyperinflammatory states. Counterbalancing antagonistic systems are induced with a time delay: the early phase (0–72 h) is characterized by the predominance of pro-inflammatory eicosanoids and cytokines (e.g. TNF- α , IL-1, IL-6, IL-8), and the parts overlapping the later phase are characterized by the predominance of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-13, TGF- β). This time course of cytokine production can differ in patients with recurrent septic episodes.

Overshooting the early up-regulation of host defence induces severe tissue injury, culminating in multiple organ failure. Omega-3 FAs are capable of dampening early hyperinflammatory processes by changing cell-to-cell signal transduction, as shown in figure 1. Besides shifting eicosanoid generation and improving membrane fluidity and raft assembly, G-protein-coupled receptor transduction as well as NF κ B activation and subsequent cytokine release are blunted by fish oil-derived omega-3 FAs and their metabolites [7, 23, 24]. For ease of understanding, figure 1 only differentiates the immunomodulatory effects of omega-3 FAs on the pro-inflammatory side.

However, later features of host defence are enhanced by omega-3 FAs without inducing hyperinflammatory states. In this regard, post-traumatic metabolism was improved [25], which might, in part, be explained by resolvin E₁ activity [26]. This complex regulation is conferred by reduced release of pro-inflammatory arachidonic acid-derivatives and platelet-activating factor and, on the other hand, by the amplification of anti-inflammatory eicosapentaenoic acid-derivatives, which lower the formation of cytokines such as TNF and IL-1 [27] without inhibiting phagocytosis, burst activity, or bactericidal activity [28]. The observed modulation of inflammation by omega-3 FA, thus, cannot unequivocally be assigned to the pro- or anti-inflammatory side. While early pro-inflammatory eicosanoids are down-regulated, cellular host defence mechanisms are augmented later on (fig. 1).

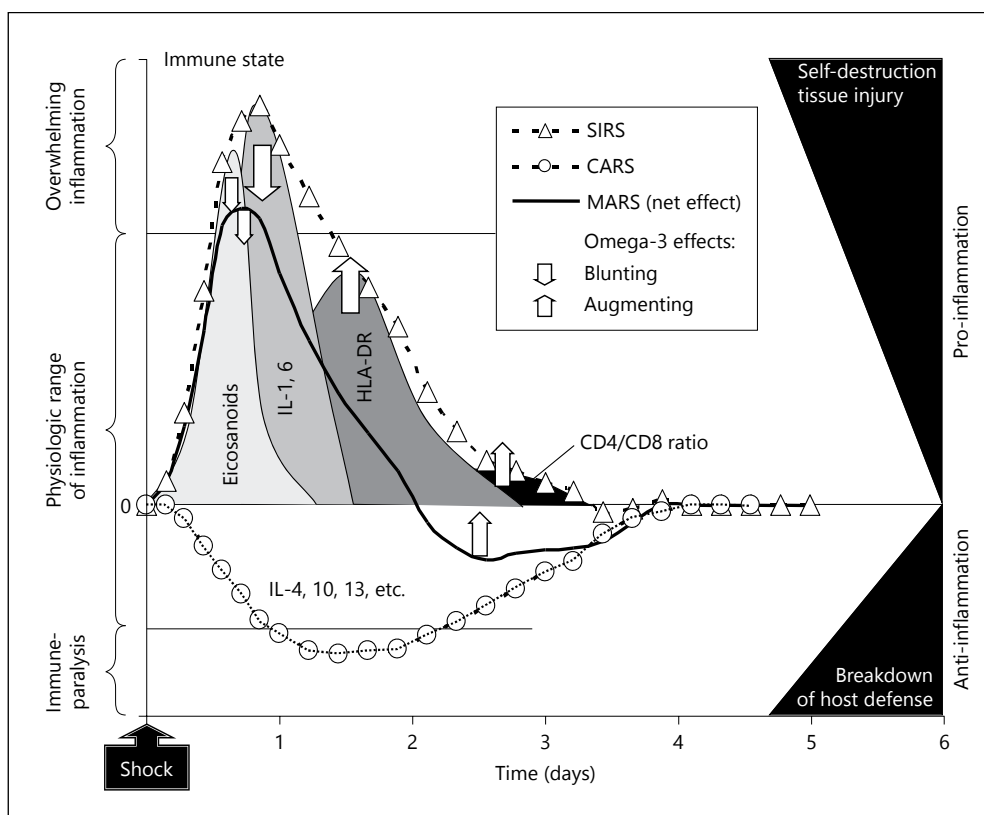


Fig. 1. Clinical targets of immunomodulation by omega-3 FAs: Overwhelming partial reactions are blunted (pro-inflammatory eicosanoids, cytokines), weak defence mechanisms are augmented (HLA-DR, CD4/CD8 ratio). Systemic inflammatory reaction syndrome (SIRS), compensatory anti-inflammatory reaction (CARS), net immunoreaction → mixed antagonistic reaction syndrome (MARS).

Mayer and colleagues [29] observed a significant depression of bactericidal oxygen radical production in neutrophils after administration of omega-6 FA, as opposed to omega-3 FA, in critical illness. Moreover, they presented data from monocytes of septic patients showing reduced production of TNF- α , IL-1, IL-6, and IL-8, without effects on the anti-inflammatory IL-10 response due to fish oil administration [30]. Therefore, recent Canadian practice guidelines recommend the replacement of omega-6 FAs [31]: *Lipids that reduce the load of omega-6 fatty acids/soybean oil emulsions should be considered. However, there are insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 fatty acid/soybean oil load in critically ill patients receiving parenteral nutrition.*

Host defence is one of the most complexly regulated systems within the mammalian organism. Multitudes of back-coupling mechanisms are responsible for up-regulating the immune response and for subsequent shut down of hostile responses dur-

ing recovery, and multiple anti-inflammatory strategies to cure sepsis have failed in recent decades. The lessons learned from those studies are that the complexly regulated host defence cannot be controlled by one simple anti-inflammatory approach, which on one hand may save the organism from self-destruction but on the other hand could lead to further septic complications. Because of their pleiotropic functions, marine omega-3 FAs fulfil the role of modulators rather than the role of any simple pro- or anti-inflammatory player. Until now, it seemed that fish oil improved the best of both via different pathways, even in critical illness [3, 7].

Inflammatory Reactions in the Lung

In particular, inflammatory activation of neutrophils induces interactions with the endothelium (via selectins and β_2 -integrins) and the release of pro-inflammatory arachidonic acid derivatives in the pulmonary circulation, which result in capillary damage and consequently in increased leakage. These mechanisms are crucial pathogenic factors for the development of acute lung injury. The mortality of acute respiratory distress syndrome (ARDS) still remains high. In the last years, numerous experimental and clinical studies were conducted to evaluate new therapeutic strategies for the treatment of ARDS [32].

Administration of fish oil represents a promising adjuvant strategy because of its anti-hyperinflammatory effects combined with its lower impairment of cellular immune function, such as bacterial clearance and killing, as compared to long-chain omega-6 FAs [33, 34]. Improvement of the critically ill was encouraging after replacing arachidonic acid in cellular membranes with long-chain omega-3 FAs such as eicosapentaenoic acid and docosahexaenoic acid in fish oil [35].

Old data from experimental ARDS models [10, 11] showed a correlation between fish oil administration and the synthesis of eicosapentaenoic acid-derived LTs, while the arachidonic acid-derived LTs and thromboxanes were only detectable in small quantities. Consequently, transcapillary filtration of oedema fluid into the alveoli was controlled in the fish oil group [11].

The clinical impact of these findings were very well demonstrated in patients with respiratory failure who were on enteral fish oil supplementation with OXEPA[®], which contains omega-3 FAs from fish oil, borage oil as a source of gamma-linolenic acid and antioxidants [36–41]. Significantly lower ventilatory support, lower ICU stay and improved survival were found in a meta-analysis by the Canadian Practice Guideline Group [42]. The ARDS network published one study that set out to investigate the effects of enteral boluses of a lipid supplement twice a day in 272 patients with ARDS [43]. This study, the so-called ‘EDEN-OMEGA trial’, was stopped early for futility, but several issues were raised due to an insufficient study protocol, which caused the results to be questioned [44]. In particular, the effect of protein supplementation on survival was not equally distributed over the groups, while bolus administration of

lipids disturbed the uptake of omega-3 FAs from the intestine and caused diarrhoea. The initiation of the provision of fish oil, which took up to 48 hours before the start of administration of the supplement, may also be an issue. Considering the early mechanisms of inflammation, as depicted in figure 1, the protocol should have administered fish oil earlier and longer by the intravenous route to enable more rapid membrane uptake and subsequent metabolism, all of which the study failed to demonstrate. Taking together all of the limitations, the ARDS-network study [43] has added far more noise than signal to the discussion on the value of fish oil in ARDS. Consequently the most recent Canadian Practice Guideline [42] did two separate analyses: one with and one without the EDEN-OMEGA trial [43]. Overall, they still concluded: *Based on 2 level 1 studies and 5 level 2 studies, the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) should be considered.*

Peritonitis and Abdominal Sepsis

Although impressive data on ex vivo-stimulated cells from septic patients receiving fish oil have been reported by Mayer [29, 30], the literature is not clear on the clinical outcome, which limits definite recommendations on the use of omega-3 FAs in sepsis.

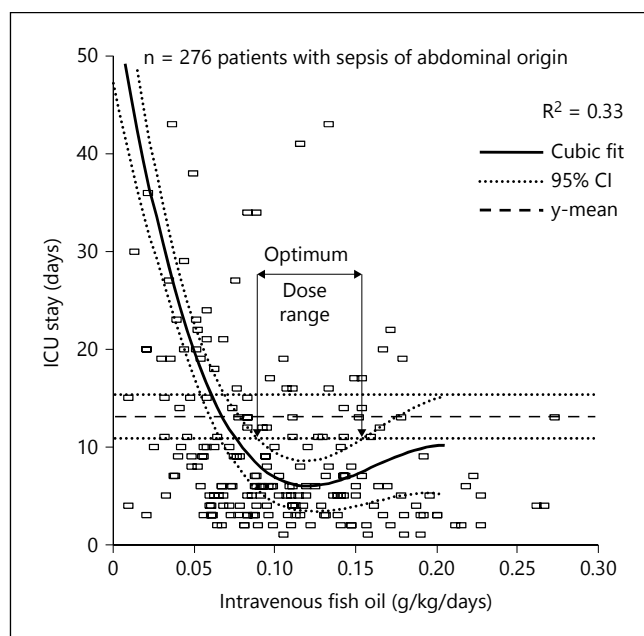
In a prospective, open label, multicentre case series in 661 patients receiving parenteral fish oil, we evaluated survival, the length of ICU and hospital stays and the use of antibiotics with respect to the primary diagnosis and extent of organ dysfunction [4]. Compared to the subgroup receiving less than 0.05 g/kg/day of fish oil, significantly more patients survived when 0.1–0.2 g/kg/day was administered.

This observation may be attributed to the lower requirement for antibiotic treatment when fish oil was given at daily doses between 0.15 and 0.2 g/kg. Figure 2 shows the relationship between fish oil dose and ICU stay in the subgroup of septic patients. The predicted mortality by the SAPS II-score was 21.7%; however, the observed mortality in this group was substantially reduced in the dose-independent analysis (mean fish oil-dose 0.10 g/kg/day) by 7.4% (CI₉₅ 3.1–11.8). Furthermore, the optimized fish oil dosage of 0.23 g/kg/day was sufficient to reduce mortality by 16.0% (CI₉₅ 5.8–26.2) in those patients.

To clarify the variety of results of the randomized controlled studies of recent years, several meta-analyses were undertaken in the field of intravenous fish oil in critical illness. Three of these analyses dealt with critical illness [14–16], while two covered surgical patients [16, 17]. The data on surgical patients are discussed earlier in this book by Klek and Waitzberg.

While significant beneficial effects on infection rates and lengths of ICU and hospital stays have concordantly been identified in three recent meta-analyses on non-ICU surgical patients, the level of evidence is not so clear for patients with critical illness. Only one of the meta-analyses found a trend ($p = 0.08$) for lower mortality in the in-

Fig. 2. Effects of fish oil dose on the length of ICU stay in surviving patients with abdominal sepsis (bivariate analysis corrected for disease severity) [4]. Optimum dose range given for minimizing the length of ICU stay in a cubic polynomial fit. Non-survivors are not included due to their bias regarding length of stay. Dotted lines indicate 95% confidence intervals.



travenously omega-3 FA-treated ICU population. Two of the meta-analyses significantly indicated a 5.17–9.49 day shorter hospital stay, and one meta-analysis found a significant reduction in ICU stay of 1.92 days. One pharmacoeconomic follow-up study based on the Pradelli data [16] showed significant cost savings for four European countries in ICU and non-ICU patients if intravenous fish oil was used [5]. Unlike the group of surgical patients, the effects of fish oil on infection rates were not statistically significant in ICU patients. Table 1 shows the key problem causing the partly different results in the three meta-analyses with regards to mortality and length of ICU stay.

Only the two original studies by Friesecke [45] and Barbosa [20] were consistently included in all three meta-analyses, representing the common data backbone with 1/5 of the available caseload. However, the largest study in the field, which was performed by Wichmann [46] on 256 patients, was only considered in the Pradelli analysis that covered 65% of all available mortality data and 75% of the caseload on ICU length of stay. Compared to the two other analyses that only included 37–47% of the available caseload, Pradelli considered the broadest cohort of patients. However, this analysis considered only full peer-reviewed papers and, therefore, dropped 115 patients from the abstract publications of uncertain quality by Grecu [47], Ignatenko [48], and Leiderman [49] (see table 1). Despite their limited overlap of studies, the agreement in the main statements of the three meta-analyses *gives some confidence to the robustness of the findings in favour of improved outcome* [18].

Standards for performing meta-analyses have been published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [50]. Com-

Table 1. Current meta-analyses on fish oil in ICU patients [14–16] and surgical patients [16, 17, 55]

Outcome/meta-analysis	ICU patients				Surgical patients		
	n	Pradelli et al. [16]	Palmer et al. [15]	Manzanares et al. [14]	Chen [55]	Pradelli et al. [16]	Li et al. [17]
Hospital stay							
Caseload patients/studies, n/n		615/8	117/3	not given	627/7	554/7	1,051/11
Mean difference, days		–5.17	–9.49		–2.98	–1.86	–2.14
95% CI		–8.35 to –1.99	–16.51 to 2.47		–4.65 to –1.31	–3.13 to –0.59	–3.02 to –1.27
p value		0.001	0.008		0.0005	0.004	<0.00001
Infection							
Caseload patients/studies, n/n		524/5	337/5	236/3	539/7	395/6	2,853/9
Odd's ratio		0.71	0.78	0.76	0.56	0.53	0.53
95% CI		0.45 to 1.12	0.43 to 1.41	0.42 to 1.36	0.32 to 0.98	0.34 to 0.82	0.35 to 0.81
p value		0.14	0.41	0.35	0.04	0.004	0.003
Mortality							
Caseload patients/studies, n/n		547/7	391/8	359/5	not given	300/3	826/6
Odd's ratio		0.94	0.83	0.71	not given	0.58	1.50
95% CI		0.61 to 1.45	0.57 to 1.20	0.49 to 1.04		0.18 to 1.84	0.54 to 4.19
p value		n.s.	0.32	0.08	n.s.	n.s.	0.44
Single studies with respective caseload	256	Wichmann et al. [46]			homogeneous signal from 3 meta-analyses		
	165	Friesecke et al. [45]	Friesecke et al. [45]	Friesecke et al. [45]			
	61			Gupta [56]			
	56		Wang [57]	Wang [57]			
	54		Greco et al. [47] ¹	Greco et al. [47] ¹			
	44	Sabater [58]					
	40	Wang et al. [21]					
	34		Ignatenko et al. [48] ¹				
	27		Leidermann et al. [49] ¹				
	24	Berger [59]					
	23	Barbosa et al. [20]	Barbosa et al. [20]	Barbosa et al. [20]			
	23	Weiss [60]					
	21		Mayer et al. [29]				
	10		Mayer et al. [30]				

Table 1. Continued

Outcome/meta-analysis	ICU patients				Surgical patients		
	n	Pradelli et al. [16]	Palmer et al. [15]	Manzanares et al. [14]	Chen [55]	Pradelli et al. [16]	Li et al. [17]
ICU stay							
Caseload patients/studies, n/n		615/8	305/6	334/5	387/5	not given	not given
Mean difference, days		−1.92	−0.57	−0.46	−1.80		
95% CI		−3.27 to −0.58	−5.05 to 3.90	−4.87 to 3.95	−3.04 to −0.56		
p value		0.005	0.8	0.84	0.004		
Single studies with respective caseload	256	<i>Wichmann et al. [46]</i>			reported only in one meta-analysis		
	165	Friesecke et al. [45]	Friesecke et al. [45]	Friesecke et al. [45]			
	61			Gupta [56]			
	54		<i>Greco et al. [47]¹</i>	<i>Greco et al. [47]¹</i>			
	44	<i>Heller et al. [25]</i>					
	40	<i>Wang et al. [21]</i>	<i>Wang et al. [21]</i>				
	40	Wachtler [61]					
	34		Ignatenko et al. [48] ¹				
	28			Khor [62]			
	27		Leidermann et al. [49] ¹				
	24	Berger [59]					
	23	Barbosa et al. [20]	Barbosa et al. [20]	Barbosa et al. [20]			
	23	<i>Weiss [60]</i>					

The underlying original references are depicted for parameters with discordant meta-analyses. Italics: statistical significance or at least a positive trend; all others: no difference detected. n.s. = Not significant.

¹ Abstract only.

pleteness of the database with high-quality research is the key claimed herein to the evidence-based practice and clinical applicability of meta-analyses. However, conflicting results from meta-analyses on the same topic are well known [51]. As already outlined, including varying trials derived from different search strategies may account for that problem. In this regard, distinct search strategies may also reflect variations in the analysts' scope on the topic, rather than different selection results being considered a systematic flaw of evidence-based methodology. Thus, it is of paramount importance to understand the exact scope of each meta-analysis when

discussing incongruent results. A further cause for a flawed systematic review is data pooling originating from different treatments, dosages, and timelines, which increase background noise rather than precision. Finally, trials with flawed methodology, uncontrolled standard treatment and general publication bias make it difficult to make the right choice when selecting trials for a meta-analysis. The meta-analyses have included the statement '*Authors were contacted to receive further information*', but I was never contacted by any meta-analyst (except for the Pradelli paper [16], which I co-authored). If that had happened, the double inclusion of trials [17] from the same group reporting on different parameters but originating from the same set of patients [25, 52, 53] would have been avoided, and it would have been possible to contribute preliminary data from another study [13]. In particular, when confidence intervals are wide, repetitive, unrecognized inclusion of a patient cohort increases the type II error of a meta-analysis, which means it becomes even more difficult to reach statistical significance when detecting an existing difference by the analysis.

An editorial on the type II error by the grandmasters of statistics Altman and Bland [54] was titled '*Absence of evidence is not evidence of absence*'. Even though the effect size of fish oil, even in critically ill patients, is measurable, an enormous background noise hampers clear detection of the signal. *The principal difficulty lies in the existence of too much evidence: the vital evidence however is obscured by erroneous information* [51]. The key determinants that provide statistical evidence for any intervention include (1) the effect size, (2) the noise-to-signal ratio, (3) and the case load. Figure 3 illustrates the problem at hand.

Grid cell A represents the present situation of fish oil supplementation in critically ill patients and the challenges that meta-analyses and guideline boards have to deal with. Moving from A to B happens if a true treatment effect occurs in a homogenous population. In regards to the current topic, this happens by selecting certain subgroups or parameters. To analyse the whole picture, one could claim that all studies must be included in the analysis. This point is crucial because the decision of whether or not to include a study with a flawed study protocol determines whether more noise than signal is added, further increasing the type II error. A typical problem study is the aforementioned EDEN-OMEGA trial [43, 44], which is highly weighted within the analysis because of its large caseload but brings noise rather than signal. Including badly planned and conducted studies as well as bias of a variable nature will end up in field C of figure 3, where it is no longer possible to significantly extract the existing signal from the noise. Thus, well-conducted trials with adequate caseloads will make it possible to detect an existing signal, even in the presence of background noise (grid cell D in fig. 3 [51]).

When discussing the outcome effects of a fish oil signal, the question of dosage is of particular interest. The dose decides if we end up within the right or left column of figure 3. The existing studies never investigated the dose-effect relationships, thus allowing for clear recommendations. The aforementioned observational study [4] sug-

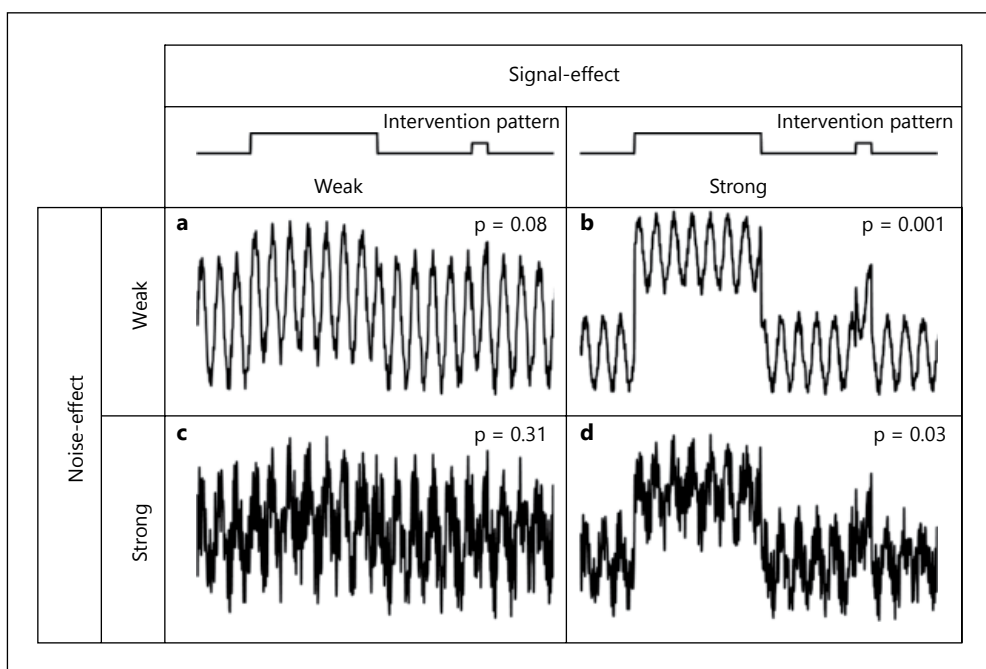


Fig. 3. Curves of any given treatment effect of fish oil over time. The curves were all generated as sine functions with variable superimposed signals (intervention pattern) and variable random-noise effects. P values for the intervention effects are given. Even though the given intervention pattern is implemented in all curves, the background noise decides whether or not the signal can be recognized again with statistical certainty in a given caseload.

gested doses of fish oil between 0.15 and 0.2 g/kg/day in septic patients, but only a few patients received more than this dose in that trial. Thus, it is uncertain if even higher dosages might improve outcome. One dose-escalating study (FOILED study Clinical-Trials.gov ID NCT01146821) that included up to 0.5 g/kg/day fish oil is underway to close this gap of knowledge.

Conclusion

In critically ill patients, positive secondary outcome effects such as shorter stay in the hospital have clearly and independently been demonstrated in all recent meta-analyses. Variable severity of diseases, unclear intervention time points, enteral routes in failing intestine, and one-size-fits-all approaches are methodological flaws of several studies that failed to show clear outcome effects and put meta-analyses at risk for type II error. Completeness of the database with high-quality research is the key to evidence-based practice and clinical applicability of meta-analyses.

Thus, there is a need for adequately powered, well-planned and well-conducted randomized trials to finally transfer the well-documented, beneficial secondary outcome effects of marine omega-3 FAs into lower mortality in critically ill patients. Only then clear recommendations on individual utility and dosage of intravenous omega-3 FAs in the critically ill will be possible.

References

- 1 Dombrovskiy VY, Martin AA, Sunderram J, Paz HL: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244–1250.
- 2 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165–228.
- 3 Calder PC: Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *Br J Clin Pharmacol* 2013;75:645–662.
- 4 Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al: Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;34:972–979.
- 5 Pradelli L, Eandi M, Povero M, Mayer K, Muscaritoli M, Heller AR, et al: Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: A discrete event simulation model. *Clin Nutr* 2013; DOI: 10.1016/j.clnu.2013.11.016.
- 6 Heller AR, Theilen HJ, Koch T: Fish or chips? *News Physiol Sci* 2003;18:50–54.
- 7 Calder PC: Mechanisms of action of (n-3) fatty acids. *J Nutr* 2012;142:592S–599S.
- 8 Heller A, Koch T, Schmeck J, van AK: Lipid mediators in inflammatory disorders. *Drugs* 1998;55:487–496.
- 9 Serhan CN, Chiang N: Resolution phase lipid mediators of inflammation: agonists of resolution. *Curr Opin Pharmacol* 2013;13:632–640.
- 10 Breil I, Koch T, Heller A, Schlotzer E, Grunert A, van AK, et al: Alteration of n-3 fatty acid composition in lung tissue after short-term infusion of fish oil emulsion attenuates inflammatory vascular reaction. *Crit Care Med* 1996;24:1893–1902.
- 11 Koch T, Heller A, Breil I, van Ackern K, Neuhof H: Alterations of pulmonary capillary filtration and leukotriene synthesis due to infusion of a lipid emulsion enriched with omega 3 fatty acids. *Clin Intens Care* 1995;6:112–120.
- 12 Berger MM, Delodder F, Liaudet L, Tozzi P, Schlaepfer J, Chiolerio RL, et al: Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. *Am J Clin Nutr* 2013;97:246–254.
- 13 Heller A, Denz A, Neidel J, Konopke R, Gottschlich B, Seifert S, et al: Effects of a metabolic optimized fasttrack concept (MOFA). *Infection* 2011;39(suppl II):S126.
- 14 Manzanares W, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK: Parenteral fish oil lipid emulsions in the critically ill: a systematic review and meta-analysis. *JPEN J Parenter Enteral Nutr* 2014;38:20–28.
- 15 Palmer AJ, Ho CK, Ajibola O, Avenell A: The role of omega-3 fatty acid supplemented parenteral nutrition in critical illness in adults: a systematic review and meta-analysis. *Crit Care Med* 2013;41:307–316.
- 16 Pradelli L, Mayer K, Muscaritoli M, Heller AR: n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care* 2012;16:R184.
- 17 Li NN, Zhou Y, Qin XP, Chen Y, He D, Feng JY, et al: Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials. *Clin Nutr* 2014;33:226–239.
- 18 Calder PC, Deckelbaum RJ: Intravenous fish oil in hospitalized adult patients: reviewing the reviews. *Curr Opin Clin Nutr Metab Care* 2013;16:119–123.
- 19 Calder PC: Fatty acids and inflammation: the cutting edge between food and pharma. *Eur J Pharmacol* 2011;668(suppl 1):S50–S58.
- 20 Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC: Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care* 2010;14:R5.
- 21 Wang X, Li W, Li N, Li J: Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *JPEN J Parenter Enteral Nutr* 2008;32:236–241.

- 22 Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN: Lipid mediator class switching during acute inflammation: signals in resolution. *Nat Immunol* 2001;2:612–619.
- 23 Wendel M, Paul R, Heller AR: Lipoproteins in inflammation and sepsis. II. Clinical aspects. *Intensive Care Med* 2007;33:25–35.
- 24 Wendel M, Heller AR: Anticancer actions of omega-3 fatty acids – current state and future perspectives. *Anticancer Agents Med Chem* 2009;9:457–470.
- 25 Heller AR, Rössel T, Gottschlich B, Tiebel O, Menschikowski M, Litz RJ, et al: Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. *Int J Cancer* 2004;111:611–616.
- 26 Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, et al: Stereochemical assignment, anti-inflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *J Exp Med* 2005;201:713–722.
- 27 Molvig J, Pociot F, Worsaae H, Wogensen LD, Baek L, Christensen P, et al: Dietary supplementation with omega-3-polyunsaturated fatty acids decreases mononuclear cell proliferation and interleukin-1 beta content but not monokine secretion in healthy and insulin-dependent diabetic individuals. *Scand J Immunol* 1991;34:399–410.
- 28 Palombo JD, DeMichele SJ, Boyce PJ, Lydon EE, Liu JW, Huang YS, et al: Effect of short-term enteral feeding with eicosapentaenoic and gamma-linolenic acids on alveolar macrophage eicosanoid synthesis and bactericidal function in rats. *Crit Care Med* 1999;27:1908–1915.
- 29 Mayer K, Fegbeutel C, Hattar K, Sibelius U, Kramer HJ, Heuer KU, et al: Omega-3 vs omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. *Intensive Care Med* 2003;29:1472–1481.
- 30 Mayer K, Gokorsch S, Fegbeutel C, Hattar K, Rosseau S, Walmrath D, et al: Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. *Am J Respir Crit Care Med* 2003;167:1321–1328.
- 31 Canadian Clinical Practice Guideline Committee: 9.2 Composition of parenteral nutrition: type of lipids. 2013. <http://www.criticalcarenutrition.com/docs/cpgs2012/9.2.pdf> (accessed Dec 23, 2013).
- 32 Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al: Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–2533.
- 33 Kelbel I, Koch T, Prechtel A, Heller A, Schlotzer E, Schiefer G, et al: Effects of parenteral application of fish oil versus soy oil emulsions on bacterial clearance functions. *Infusionsther Transfusionsmed* 1999;26:226–232.
- 34 Pscheidl E, Schywalsky M, Tschakowsky K, Boke-Prols T: Fish oil-supplemented parenteral diets normalize splanchnic blood flow and improve killing of translocated bacteria in a low-dose endotoxin rat model. *Crit Care Med* 2000;28:1489–1496.
- 35 Mayer K, Grimm H, Zimminger F, Seeger W: Parenteral nutrition with n-3 lipids in sepsis. *Br J Nutr* 2002;87(suppl 1):S69–S75.
- 36 Elamin E, Miller A, Ziad S: Immune enteral nutrition can improve outcomes in medical-surgical patients with ARDS: a prospective randomized controlled trial. *J Nutr Disorders Ther* 2012;2:109.
- 37 Theilla M, Schwartz B, Zimra Y, Shapiro H, Anbar R, Rabizadeh E, et al: Enteral n-3 fatty acids and micro-nutrients enhance percentage of positive neutrophil and lymphocyte adhesion molecules: a potential mediator of pressure ulcer healing in critically ill patients. *Br J Nutr* 2012;107:1056–1061.
- 38 Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, et al: Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. *Crit Care Med* 1999;27:1409–1420.
- 39 Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J: Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med* 2006;34:1033–1038.
- 40 Pontes-Arruda A, Aragao AM, Albuquerque JD: Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* 2006;34:2325–2333.
- 41 Grau-Carmona T, Moran-Garcia V, Garcia-de-Lorenzo A, Heras-de-la-Calle G, Quesada-Bellver B, Lopez-Martinez J, et al: Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clin Nutr* 2011;30:578–584.
- 42 Canadian Clinical Practice Guideline Committee: 4.1b(i) Composition of enteral nutrition: fish oils, borage oils and antioxidants. 2013. [http://www.criticalcarenutrition.com/docs/cpgs2012/4.1b\(i\).pdf](http://www.criticalcarenutrition.com/docs/cpgs2012/4.1b(i).pdf) (accessed Dec 23, 2013).
- 43 Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P: Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011;306:1574–1581.
- 44 Felbinger TW, Weigand MA, Mayer K: Supplementation in acute lung injury. *JAMA* 2012;307:144–146.

- 45 Friesecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P: Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. *Intensive Care Med* 2008; 34:1411–1420.
- 46 Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW: Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med* 2007;35:700–706.
- 47 Grecu I, Mirea L, Grintescu I: Parenteral fish oil supplementation in patients with abdominal sepsis. *Clin Nutr* 2003;22(suppl 1):23.
- 48 Ignatenko O, Yaroshetskiy A, Masolitin S, Protsenko D, Gelfand B: Fish oil treatment in severe trauma patients. *Intensive Care Med* 2010;36:S316.
- 49 Leiderman I, Malkova O, Levit A: Omega 3 enriched lipid emulsion decreases APACHE II and SOFA scores values in abdominal sepsis patients. *Clin Nutr Suppl* 2010;5:30.
- 50 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6:e1000100.
- 51 Petticrew M, Kennedy SC: Detecting the effects of thromboprophylaxis: the case of the rogue reviews. *BMJ* 1997;315:665–668.
- 52 Heller AR, Fischer S, Rössel T, Geiger S, Siegert G, Ragaller M, et al: Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. *Br J Nutr* 2002; 87(suppl 1):S95–S101.
- 53 Wendel M, Rössel T, Bergmann S, Otto S, Ragaller M, Zimmermann T, et al: Impact of total parenteral nutrition including omega-3 fatty acids on the regulation of plasma lipoproteins and glycemic control after major abdominal surgery. *e-ESPEN* 2007;2: e103–e110.
- 54 Altman DG, Bland JM: Absence of evidence is not evidence of absence. *BMJ* 1995;311:485.
- 55 Chen B, Zhou Y, Yang P, Wan HW, Wu XT: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 56 Gupta A, Govil D, Bhatnagar S, Gupta S, Goyal J, Patel S, et al: Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. *Indian J Crit Care Med* 2011;15:108–113.
- 57 Wang X, Li W, Zhang F, Pan L, Li N, Li J: Fish oil-supplemented parenteral nutrition in severe acute pancreatitis patients and effects on immune function and infectious risk: a randomized controlled trial. *Inflammation* 2009;32:304–309.
- 58 Sabater J, Masclans JR, Sacanell J, Chacon P, Sabin P, Planas M: Effects of an omega-3 fatty acid-enriched lipid emulsion on eicosanoid synthesis in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. *Nutr Metab (Lond)* 2011;8:22.
- 59 Berger MM, Tappy L, Revelly JP, Koletzko BV, Geyer J, Corpataux JM, et al: Fish oil after abdominal aorta aneurysm surgery. *Eur J Clin Nutr* 2008;62: 1116–1122.
- 60 Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H: Immunomodulation by perioperative administration of n-3 fatty acids. *Br J Nutr* 2002; 87(suppl 1):S89–S94.
- 61 Wachtler P, König W, Senkal M, Kemen M, Koller M: Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma* 1997;42:191–198.
- 62 Khor BS, Liaw SJ, Shih HC, Wang LS: Randomized, double blind, placebo-controlled trial of fish-oil-based lipid emulsion infusion for treatment of critically ill patients with severe sepsis. *Asian J Surg* 2011; 34:1–10.

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Intravenous Lipids in Home Parenteral Nutrition

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Abstract

Intravenous lipid emulsions (IVLEs) are an important component of the nutritional admixtures for patients on long-term home parenteral nutrition (HPN) for chronic intestinal failure (CIF). IVLEs are primarily used as a source of energy and essential fatty acids, and the content of polyunsaturated fatty acids (PUFAs) is the most important characteristic of IVLEs. IVLEs rich in n-6 PUFAs may have a pro-inflammatory effect, whereas those rich in n-3 PUFAs may exert an anti-inflammatory effect. Other components to be considered are the risk of lipid peroxidation and the contents of α -tocopherol and phytosterols. Published studies were reviewed to determine the effects of the commercially available IVLEs on essential fatty acid status, liver function tests, lipid peroxidation and inflammatory indices, and α -tocopherol status, as well as their clinical safety and efficacy in patients on HPN. Investigations on the efficacy of fish oil-based IVLEs, which are rich in n-3 PUFAs, in the treatment of parenteral nutrition-associated liver disease (PNALD) in adult patients on HPN for CIF were also analyzed. The current commercial IVLE formulations have similar clinical safety profiles and efficacies and can prevent the development of essential fatty acid deficiency in adults on HPN for CIF. IVLE with a low content of n-6 PUFAs and with or without increased n-3 PUFA content may reduce the risk of PNALD. Fish oil-based IVLE, which is rich in n-3 PUFAs, may be effective in reversing hepatic cholestasis due to PNALD.

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Intravenous lipid emulsions (IVLEs) are oil-in-water emulsions consisting of one or more triacylglycerol-containing oils, a phospholipid emulsifier, and glycerol. For clinical purposes, the fatty acid profile is the most relevant characteristic of an IVLE. Other components to be considered but that are not always reported on the product label are the contents of phospholipids, α -tocopherol, phytosterols and vitamin K (table 1). The first developed IVLE was soybean oil (SO)-based with a high content of the n-6 polyunsaturated fatty acid (PUFA) linoleic acid (18:2n-6), which could cause nutritional complications such as reticuloendothelial system dysfunction, an exaggerated systemic inflammatory response in the critically ill, and increased lipid peroxidation and liver dysfunction in acutely ill infants and in patients of any age requiring

Table 1. Composition of commercially available intravenous lipid emulsions

Oil source	Linoleic acid (18:2n-6), % by weight	α-linolenic acid (18:3n-3), % by weight	Eicosapentaenoic acid (20:5n-3), % by weight	Docosahexaenoic acid (22:6n-3), % by weight	n-6:n-3 ratio	α-tocopherol, mg/l	Phytosterols, mg/l
SO 100%	44–62	4–11	0	0	7:1	40–220	≈350
SO 50% MCT 50%	27–52	4–7	0	0	7:1	85±20	NA
SO 20% OO 80%	18.5	2	0	0	9:1	32	≈330
SO 40% MCT 50% FO 10%	24.4	3.3	3.1	2.3	2.7:1	190±30	NA
SO 30% MCT 30% OO 25% FO 15%	37.2	4.7	4.7	4.7	2.5:1	200	47

SO = Soybean oil; MCT = medium-chain triacylglycerol oil; OO = olive oil; FO = fish oil; NA = not available.
(Adapted from reference 1.)

long-term home parenteral nutrition (HPN). In order to decrease the n-6 PUFA content, the second-generation IVLEs consisted of a 50:50 (by weight) physical mixture of SO and medium-chain triacylglycerols (SO-MCT). The third generation consisted of 80% olive oil and 20% SO by weight (OO-SO), and the fourth included fish oil either alone (FO) or in combination with one or more of the oils used in previous IVLEs (SO-MCT-FO or SO-MCT-OO-FO). FO is rich in n-3 PUFAs, which have anti-inflammatory properties and may have potentially important pharmacological benefits [1–3]. The phospholipid content of IVLEs exceeds the amount needed to solubilize their triacylglycerol content (phospholipids/triacylglycerols: 10%>20%>30% IVLE). A part of phospholipids are present as liposome-resembling particles that impede lipid metabolism and may accumulate as lipoprotein X, causing hypercholesterolemia [2]. Phytosterols are plant sterols (sitosterol, campesterol, stigmasterol) that have been demonstrated to reduce bile acid excretion in animal studies. A progressive increase and accumulation of phytosterol content in cell membranes and plasma lipoproteins has been associated with cholestasis in children on long-term HPN [1, 3]. IVLEs may provoke peroxidative stress due to their content of PUFAs (both n-6 and n-3), which can act as substrates for the formation of lipid peroxides. Lipid peroxidation may occur in vitro during storage and after compounding in all-in-one admixtures, as well as in vivo after infusion. The susceptibility of IVLEs to peroxidation is directly related to the number of double bonds in their carbon chain (n-3 PUFAs > n-6 PUFAs > n-9 monounsaturated fatty acid) and is counteracted by enriching the emulsions with α-tocopherol. Comparison of the various IVLEs indicated that in vitro

lipid peroxidation is directly related to the PUFA content and inversely related to the α -tocopherol/PUFA ratio of the IVLE [1, 4]. Oxidative stress can play a role in the development of parenteral nutrition-associated liver disease (PNALD) of patients on long-term HPN [5]. The vitamin K (phyloquinone) content of an IVLE is related to the vegetable oil used in its preparation and its concentration (13.2–30.8 $\mu\text{g}/\text{dl}$ for the 10% IVLE and 27–68 $\mu\text{g}/\text{dl}$ for the 20% IVLE). The vitamin K content of IVLE is of importance for patients taking warfarin and who may have decreased prothrombin time, and on the other hand, vitamin K supplementation may contribute positively to bone metabolism [3].

IVLEs are an important component of the nutritional admixtures for HPN. HPN is considered the primary treatment for chronic intestinal failure (CIF) due to benign disease that results from obstruction, dysmotility, surgical resection, congenital defect or disease-associated loss of absorption, and it is characterized by the inability to maintain balance in protein energy, fluid, electrolytes or micronutrients [6]. IVLEs are used as an alternative energy source to dextrose, avoiding the complications of excessive dextrose, and they serve as a source of essential fatty acids (EFAs) to prevent essential fatty acid deficiency (EFAD) and, more recently, as pharmaconutrients [1–3]. In long-term HPN, it is generally recommended that lipids should provide 15–30% of the total intravenous calorie intake or 30–50% of non-protein calories. The infusion rates of LE should be 0.8–1.5 g/kg body weight per day (or 0.11 g/kg per hour) because side effects have been reported above this threshold [1, 2]. The effects of IVLEs on the PUFA profiles of plasma and cell-membrane phospholipids of patients on long-term HPN for CIF depends on and are consistent with the PUFA contents of the IVLE (table 2). All [7–11] but one [12] investigation on SO, which is rich in n-6 PUFAs, showed that the infusion of SO was associated with a decrease in linolenic acid (18:2n-6) and an increase in arachidonic acid (20:4n-6), suggesting a stimulation of the elongation and desaturation of linolenic acid to the pro-inflammatory arachidonic acid. The few studies on the replacement of SO with SO-MCT reported no changes in plasma or red-blood-cell-membrane PUFAs with respect to baseline [12] or in comparison to the infusion of SO alone [13, 14]. One investigation found that the only significant change following the infusion of OO-SO was a decrease in α -linolenic acid (18:3n-3) in plasma phospholipids [15], whereas two further studies observed that the infusion of OO-SO was associated with an increase in monounsaturated oleic acid (18:1n-9) and a decrease in linoleic acid in both plasma and cell-membrane phospholipids [16, 17]. Two randomized controlled studies, one in children and one in adults, on the effect of SO-MCT-OO-FO found similar results showing an increase in n-3 PUFAs (eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)) and an increased n-3:n-6 ratio of both plasma and cell-membrane phospholipids [18, 19]. Similarly, an increased concentration of n-3 PUFAs associated with a significant decrease in arachidonic acid was reported when FO was added to the ongoing parenteral nutrition admixture containing either OO-SO [20] or SO [21]. According to the European Society for Clinical Nutrition and Metabolism guidelines on HPN in adult patients, the EFA requirement

Table 2. Effect of the different intravenous lipid emulsions (IVLEs) on the fatty acid (FA) profiles of plasma and cell membrane phospholipids and on the essential fatty acid (EFA) status of patients on long-term home parenteral nutrition for chronic intestinal failure

Author, [reference], year	Type of study (age group, number of patients)	Type of IVLE	FA profile in phospholipids (Plasma = P, red blood cell membranes = RBC)	EFA status triene:tetraene ratio in plasma phospholipids (normal value <0.2)
Abushufa [7], 1995	Observational (adults, 25)	SO	RBC: ↓ 18:2n-6	NR
Pironi [8], 1996	Observational (adults, 7)	SO	RBC: ↓ 18:2n-6 and 20:4n-6 and ↑ 22:5n-6	>0.2 in 1 patient
Jeppesen [9], 1998	Observational (adults, 56)	SO	P: ↓ 18:2n-6 and ↑ 20:4n-6	>0.2 in 25% of patients
Ling [10], 2002	Observational (adults, 11)	SO	P: ↓ 18:2n-6 and 20:4n-6	<0.2
Chambrier [11], 2002	Observational (adults, 20)	SO	P: ↓ 18:2n-6 and ↑ 20:4n-6	NR
Dahlan [12], 1992	Randomized cross-over (adults, 5)	SO vs. SO-MCT	RBC: ↑ 18:2n-6 and ↓ 20:4n-6 with SO No changes from baseline with SO-MCT	NR
Goulet [13], 1992	Prospective non-randomized (children, 12)	SO-MCT after SO	P and RBC: no changes after switching from SO to SO-MCT	NR
Chambrier [14], 2004	Prospective crossover (adults, 11)	SO vs. SO-MCT	No differences between the groups	No clinical EFAD
Reimund [15], 2005	Prospective non-randomized (adults, 14)	OO-SO after SO or SO-MCT	P: ↓ 18:3n-3	<0.2
Goulet [16], 1999	RCT (children, 18)	SO vs. OO-SO	P: ↑ 18:1n-9 and ↓ 18:2n-6 and 20:5n-3 with OO RBC: ↓ 18:2n-6 with OO	<0.2 with both LEs
Vahedi [17], 2005	RCT (adults, 13)	SO vs. OO-SO	P and lymphocyte membranes: ↑ 18:3n-6 with OO P: ↑ 18:1n-9 in the OO group	<0.2 with both LEs
Goulet [18], 2010	RCT (children, 28)	SO vs. SO-MCT-OO-FO	P and RBC: ↑ 20:5n-3 and C22:6n-3; ↑ n-3:n-6 ratio with SO-MCT-OO-FO	NR
Klek [19], 2013	RCT (adults, 73)	SO vs. SO-MCT-OO-FO	P and RBC: ↑ 20:5n-3 and C22:6n-3; ↑ n-3:n-6 ratio with SO-MCT-OO-FO	NR
Pironi [20], 2010	Case report (adult, 1)	FO added to OO-SO	RBC: ↑ 20:5n-3 and 22:6n-3; ↓ 20:4n-6	NR
Xu [21], 2012	Prospective (adults, 15)	FO added to SO	P: ↑ 20:5n-3 and 22:6n-3; ↓ 20:4n-6	NR
Burns [23], 2013	Case report (adult, 1)	FO	NR	<0.2
Gura [24], 2008	Retrospective with historical control (children, 39)	FO	NR	>0.2 in one patient
Puder [25], 2009	Retrospective with historical control (children, 42)	FO	NR	>0.2 in 2 patients who had LE infusion interrupted

Table 2. Continued

Author, [reference], year	Type of study (age group, number of patients)	Type of IVLE	FA profile in phospholipids (Plasma = P, red blood cell membranes = RBC)	EFA status triene:tetraene ratio in plasma phospholipids (normal value <0.2)
de Meijer [26], 2010	Prospective open (children, 10)	FO	NR	No clinical or biochemical EFAD

SO = Soybean oil; SO-MCT = 50% soybean oil – 50% medium-chain triacylglycerol oil; OO = olive oil; FO = fish oil; triene:tetraene ratio, 20:3n-9:20:4n-6; NR = not reported; RCT = randomized controlled trial.
18:1n-9, oleic acid.
18:2n-6, linoleic acid; 18:3n-6, γ -linolenic acid; 20:4n-6, arachidonic acid; 22:5n-6, docosapentaenoic acid.
18:3n-3, α -linolenic acid; 20:5n-3, eicosapentaenoic acid; 22:6n-3, docosahexaenoic acid.
20:3n-9, eicosatrienoic acid.
22:4n-6, docosatetraenoic acid.

of 7 to 10 g/day can be satisfied by the infusion of 14–20 g of fat from SO or of 30–40 g of fat from an OO-SO IVLE [22]. Published studies have demonstrated that SO-MCT, SO-MCT-OO-FO as well as FO alone may also prevent EFAD, as assessed by the triene:tetraene ratio in plasma phospholipids (table 2) [8–10, 14–17, 23–26].

The various IVLEs may play roles in the development as well as in the treatment of PNALD. Hepatic dysfunction has been described in 15–85% of patients on HPN for benign CIF. Chronic cholestasis with associated inflammation and more rapid progression to fibrosis, portal hypertension and end-stage liver disease are the predominant features in neonates and children, whereas steatosis and steatohepatitis with a slower evolution are the principal lesions in adults. Liver failure due to PNALD is a major cause of HPN failure that requires a lifesaving combined liver-intestinal transplantation [6, 27]. The pathogenesis is multifactorial and includes parenteral nutrition, intestinal failure and system-related factors. Thus, both the definitions of PNALD and of intestinal failure-associated liver disease (IFALD) are used. HPN hyperalimentation, excess or deficiency of some nutrients, frequent surgical procedures, lack of enteral intake, presence of a short bowel, small bowel bacterial overgrowth, sepsis related to central venous catheters or to the underlying diseases, and immaturity of the liver in children have all been reported to play a role in the pathophysiology of liver disease [5, 6]. Among the IVLEs, the administration of SO at a dose of >1 g/kg body weight has been reported to favor the development of IF/PNALD, primarily through its high content of pro-inflammatory n-6 PUFAs and phytosterols [5]. The European Society for Clinical Nutrition and Metabolism guidelines on HPN in adult patients give the following recommendation to prevent the development of PNALD: all forms of over-feeding should be avoided (grade B); the fat:glucose energy ratio should not exceed 40:60, and lipids should comprise no more than 1 g/kg per day (grade B); glucose administration in excess of 7 mg/kg/min and continuous rather than cyclic infusion are also considered risk factors (grade B); and infections, in

Table 3. Effect of the different lipid emulsions (IVLEs) on liver function tests, inflammatory indices, lipoperoxidation indices, vitamin E status and clinical outcome parameters in patients on long-term home parenteral nutrition for chronic intestinal failure

Author, [reference], year	Type of study (age group, number of patients, duration of treatment)	Type of IVLE	Liver function tests	Inflammatory and peroxidation indices and α -tocopherol status	Clinical outcome
Goulet [13], 1992	Prospective non randomized (children, 12, 6 months)	SO-MCT after SO	Decrease in gamma-GT at 6 months	Moderate lipid peroxidation	Good clinical tolerance
Rubin [28], 2000	RCT (adults, 22, 4 weeks)	SO vs. SO-MCT structured	SO-MCT structured: normal SO: abnormal in 2 patients	Similar lipid peroxidation	Similar clinical safety and adverse events
Chambrier [14], 2004	Prospective crossover (adults, 11, 4 months)	SO vs. SO-MCT	Normal with both IVLE	P: ↓ vitamin K with SO-MCT	Similar clinical tolerance
Reimund [15], 2005	Prospective non randomized (adults, 14, 3 months)	OO-SO after SO or SO-MCT	No changes		Similar good clinical safety and efficacy
Goulet [16], 1999	RCT (children, 18, 2 months)	SO vs. OO-SO	No differences	P: similar α -tocopherol Lower lipid peroxidation with OO	Similar clinical safety and efficacy
Thomas-Gibson [29], 2004	Prospective cross-over with retrospective comparison (adults, 13, 6 months)	SO vs. OO-SO	No changes	NR	Similar clinical safety
Vahedi [17], 2005	RCT (adults, 13, 3 months)	SO vs. OO-SO	No differences	NR	Similar adverse events
Goulet [18], 2010	RCT (children, 28, 4 weeks)	SO vs. SO-MCT-OO-FO	Normal in both groups, but significantly smaller increase of plasma bilirubin with SO-MCT-OO-FO	P: ↑ α -tocopherol in SO-MCT-OO-FO Similar lipid peroxidation	Similar adverse events
Klek [19], 2013	RCT (adults, 73, 4 weeks)	SO vs. SO-MCT-OO-FO	Normal in both groups, but ALT, AST and total bilirubin significantly lower with SO-MCT-OO-FO	P: ↑ α -tocopherol in SO-MCT-OO-FO P: IL-6 and sTNF-RII levels did not change in either group	Serious adverse events significantly more frequent with SO

SO = Soybean oil; MCT = 50% medium chain triacylglycerol oil; OO = olive oil; FO = fish oil; RCT = randomized controlled trial; NR = not reported.

particular line sepsis, must be promptly controlled to prevent deterioration of any liver abnormalities (grade B) [22].

A few studies have compared the safety and efficacy of IVLEs as alternatives to SO in long-term HPN [13–19, 28, 29] (table 3). When only randomized controlled trials were considered [16–18, 28], no statistically significant differences in the frequencies of alterations of the liver function tests were observed between SO and the other IVLEs. Two investigations, one in children and one in adults, showed that the elevat-

Table 4. Fish oil lipid emulsion for the treatment of intestinal failure/parenteral nutrition-associated liver disease in adult patients on long-term home parenteral nutrition for chronic intestinal failure

First author, year	Type of study (age group, number of patients, duration of treatment)	Treatment		Liver histology grade	
				before	after
Pironi [20], 2010	Prospective (adult, 1, 8 months)	FO, 0.20 g/kg body weight/day added to OO-SO	Cholestasis: Steatosis: Inflammation: Fibrosis:	0 2 2 3	0 1 1 3
Jurewitsch [30], 2011	Prospective (adult, 1, 4 months)	FO, 0.25 g/kg body weight/day	Steatosis: Cholestasis: Fibrosis:	none heavy lobular and portal 2	none, portal hepatitis reactive cholangiopathy 2
Xu [21], 2012	Prospective (adults, 15, 1 month)	FO, 0.15–0.25 g/kg body weight/day added to SO	Cholestasis: Steatosis: Inflammation: Fibrosis:	1.5 2.2 2.8 1.9	1 1.5 1.5 1.7
Burns [23], 2013	Prospective (adult, 1, 16 months)	FO, 1 g/kg body weight/day	Histology not performed Serum concentration outcome: ↓ total bilirubin from 12.4 to 4.2 mg/dl ↓ C-reactive protein from 23 to 4.1 mg/dl Slight decrease of AST and ALT Initial increase and subsequent decline of alkaline phosphatase		

SO = Soybean oil; MCT = medium chain triacylglycerol oil; OO = olive oil; FO = fish oil; A = adults; C = children; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

ed values of liver function tests, which remained within the normal limits throughout the study period, was significantly lower with SO-MCT-OO-FO [18, 19]. A lower lipid peroxidation was observed for all alternative IVLEs in 3 investigations carried out by the same group [13, 16, 18], whereas a significant increase in the serum α -tocopherol concentration was reported using SO-MCT-OO-FO [17, 18], which has a higher content of this antioxidant vitamin (table 1). No change was observed for the concentrations of inflammatory cytokines [28]. Notwithstanding the significant differences in the biochemical endpoints, the studies demonstrated that the various IVLEs had similar clinical safety and efficacies (table 3).

Since 2008, several studies have reported the reversal of IF/PNALD with severe cholestasis in children when FO was used instead of or in addition to SO [5]. The therapeutic effect of FO is primarily attributed to the anti-inflammatory effect of n-3 PUFAs [5]. Alternatively, it is suggested that the effect may be due to the withdrawal of the pro-inflammatory SO that the children were receiving [5]. More recently, positive reports on adults have been published [20, 21, 23, 30] (table 4). In two cases, FO

was used as the unique source of fat [23, 30], whereas it was added to the ongoing OO-SO [20] or SO in the other two studies [21]. FO was administered at a rate of 0.20 g/kg body weight/day of infusion in three studies [20, 21, 30] and at 1 g/kg/day in one study [23]. The effect of FO was assessed by liver histology in three cases [20, 21, 30]. In all three studies, a reversal or a decrease in cholestasis, inflammation and steatosis was seen, whereas no changes were observed in liver fibrosis, which is the most important marker of progression to end-stage liver disease and would be an indication for combined liver and small bowel transplantation [6, 27].

In conclusion, in adults on long-term HPN for CIF, (a) the current commercial IVLE formulations have similar clinical safety and efficacies and can prevent the development of EFAD; (b) IVLEs, as alternatives to SO, may be useful to reduce the risk of IF/PNALD because of their lower content of pro-inflammatory n-6 PUFAs and/or their higher content of anti-inflammatory n-3 PUFAs; (c) FO alone or in addition to other IVLEs seems effective in reversing hepatic cholestasis due to IF/PNALD; and d) further studies are required to clarify if the therapeutic effect of FO is due to the anti-inflammatory effect of its high content of n-3 PUFAs alone or if the effect is also due to its high content of α -tocopherol and/or low content of phytosterols as well as to the decrease of the SO load.

References

- 1 Vanek VW, Borum P, Buchman A, et al: A.S.P.E.N. position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract* 2012; 27:440–491.
- 2 Wanten GJ, Calder PC: Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr* 2007;85: 1171–1184.
- 3 Mirtallo JM, Dasta JF, Kleinschmidt KC, et al: State of the art review: intravenous fat emulsions: current applications, safety profile, and clinical implications. *Ann Pharmacother* 2010;44:688–700.
- 4 Pironi L, Guidetti M, Zolezzi C, et al: Peroxidation potential of lipid emulsions after compounding in all-in-one solutions. *Nutrition* 2003;19:784–788.
- 5 Staun M, Pironi L, Bozzetti F, et al: Guidelines on parenteral nutrition: Home parenteral nutrition (HPN) in adult patients. *Clin Nutr* 2009;28:467–479.
- 6 Pironi L, Goulet O, Buchman A, et al: Outcome on home parenteral nutrition for benign intestinal failure: A review of the literature and benchmarking with the European prospective survey of ESPEN. *Clin Nutr* 2012;31:831–845.
- 7 Abushufa R, Reed P, Weinkove C, et al: Essential fatty acid status in patients on long-term home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1995; 19:286–290.
- 8 Pironi L, Belluzzi A, Miglioli M: Low levels of essential fatty acids in the red blood cell membrane phospholipid fraction of long-term home parenteral nutrition patients. *JPEN J Parenter Enteral Nutr* 1996; 20:377–378.
- 9 Jeppesen PB, Høy CE, Mortensen PB: Essential fatty acid deficiency in patients receiving home parenteral nutrition. *Am J Clin Nutr* 1998;68:126–133.
- 10 Ling PR, Ollero M, Khaodhiar L, et al: Disturbances in essential fatty acid metabolism in patients receiving long-term home parenteral nutrition. *Dig Dis Sci* 2002;47:1679–1685.
- 11 Chambrier C, Garcia I, Bannier E, et al: Specific changes in n-6 fatty acid metabolism in patients with chronic intestinal failure. *Clin Nutr* 2002;21:67–72.
- 12 Dahlan W, Richelle M, Kulapongse S, et al: Effects of essential fatty acid contents of lipid emulsions on erythrocyte polyunsaturated fatty acid composition in patients on long-term parenteral nutrition. *Clin Nutr* 1992;11:262–268.
- 13 Goulet O, Postaire M, De Potter S, et al: Medium-chain triglycerides and long-term parenteral nutrition in children. *Nutrition* 1992;8:333–337.

- 14 Chambrier C, Bannier E, Lauverjat M, et al: Replacement of long-chain triglyceride with medium-chain triglyceride/long-chain triglyceride lipid emulsion in patients receiving long-term parenteral nutrition: effects on essential fatty acid status and plasma vitamin K1 levels. *JPEN J Parenter Enteral Nutr* 2004;28:7–12.
- 15 Reimund JM, Rahmi G, Escalin G, et al: Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;21:445–454.
- 16 Goulet O, de Potter S, Antébi H, et al: Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *Am J Clin Nutr* 1999;70:338–345.
- 17 Vahedi K, Atlan P, Joly F, et al: A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. *Br J Nutr* 2005; 94:909–916.
- 18 Goulet O, Antebi H, Wolf C, et al: A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: A single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2010;34: 485–495.
- 19 Klek S, Chambrier C, Singer P, et al: Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid) – a double-blind, randomised, multicentre study in adults. *Clin Nutr* 2013;32:224–231.
- 20 Pironi L, Colecchia A, Guidetti M, et al: Fish oil-based emulsion for the treatment of parenteral nutrition associated liver disease in an adult patient. *E Spen Eur E J Clin Nutr Metab* 2010;5:e243–e246.
- 21 Xu Z, Li Y, Wang J, et al: Effect of omega-3 polyunsaturated fatty acids to reverse biopsy-proven parenteral nutrition-associated liver disease in adults. *Clin Nutr* 2012;31:217–223.
- 22 Rangel SJ, Calkins CM, Cowles RA, et al: Parenteral nutrition-associated cholestasis: An American Pediatric Surgical Association outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg* 2011;2012:225–240.
- 23 Burns DL, Gill BM: Reversal of parenteral nutrition-associated liver disease with a fish oil-based lipid emulsion (Omegaven) in an adult dependent on home parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2013;37:274–280.
- 24 Gura KM, Lee S, Valim C, et al: Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics* 2008;121:e678–e686.
- 25 Puder M, Valim C, Meisel JA, et al: Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg* 2009;250: 395–402.
- 26 de Meijer VE, Le HD, Meisel JA, et al: Parenteral fish oil as monotherapy prevents essential fatty acid deficiency in parenteral nutrition-dependent patients. *J Pediatr Gastroenterol Nutr* 2010;50:212–218.
- 27 Pironi L, Joly F, Forbes A, et al: Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. *Gut* 2011; 60:17–25.
- 28 Rubin M, Moser A, Vaserberg N, et al: Structured triacylglycerol emulsion, containing both medium- and long-chain fatty acids, in long-term home parenteral nutrition: a double-blind randomized cross-over study. *Nutrition* 2000;16:95–100.
- 29 Thomas-Gibson S, Jawhari A, Atlan P, et al: Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure. *Clin Nutr* 2004;23:697–703.
- 30 Jurewitsch B, Gardiner G, Naccarato M, et al: Omega-3-enriched lipid emulsion for liver salvage in parenteral nutrition-induced cholestasis in the adult patient. *JPEN J Parenter Enteral Nutr* 2011;35:386–390.

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The Complexity of Prescribing Intravenous Lipid Emulsions

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Abstract

Intravenous lipid emulsions (LEs) are relevant for patients receiving parenteral nutrition because they prevent the depletion of essential fatty acids (FAs) and, as a highly dense energy source, enable the reduction of glucose provision, thereby decreasing the risks of hyperglycemia and hepatic impairment. The prescription of LEs is complex, due mainly to their distinct FA components, which may alter the immune response in different ways and distinctly influence inflammation, oxidative stress and blood coagulation according to their biochemical properties. In addition, an excess of other LE components, such as phospholipids and phytosterols, may be associated with hepatic steatosis and dysfunction. These associations do not represent direct risks or obstacles to LE use in metabolically stable patients but can render the choice of the best LE for hypermetabolic patients difficult. The infusion of LEs according to the available guidelines provides more benefit than harm and should be part of exclusive parenteral nutrition regimens or complement enteral nutrition when appropriate. The patient's metabolic profile should guide the type of FA and amount of lipids that are provided. For critically ill hypermetabolic patients, growing evidence indicates that standard LEs based solely on soybean oil should be avoided in favor of new LEs containing medium-chain triglycerides, olive oil, or fish oil to decrease the provision of potentially oxidative, inflammatory/immunosuppressive, and prothrombotic n-6 FAs. In addition, as sources of eicosapentaenoic and docosahexaenoic acids, LEs containing fish oil may be important for critically ill patients because they allow better modulation of the immune response and likely reduce the length of intensive care unit stay. However, current evidence precludes the recommendation of a specific LE for clinical use in this patient population.

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Why to Prescribe Intravenous Lipid Emulsions

Lipid emulsions (LEs) are the main sources of non-glucose energy with high caloric density (~9 kcal/g) and essential fatty acids (FAs) for patients requiring parenteral nutrition (PN). In addition to providing energy through oxidation, FAs from LEs participate in the transport of liposoluble vitamins and can be used for the synthesis of cell membrane structures, hormones, and other lipid-active biomediators, therefore

influencing cell signaling, body metabolism, and the immune response [1]. Due to these functions, FAs delivered by LEs are relevant to patients requiring PN, particularly those undergoing processes involving cell replication and tissue repair [2].

When to Prescribe Lipid Emulsions

Indications

LEs should be prescribed as exclusive PN regimens or as PN complementary to enteral nutrition (EN) when oral or EN is impossible, contraindicated, or insufficient. These indications apply to malnourished patients, those at risk of malnutrition with no gastrointestinal tract function, and those with disorders requiring complete bowel rest or who have not met their energy targets by enteral feeding after 2 days [3].

Contraindications

In addition to specific contraindications to PN, such as hypokalemia, hyperhydration, hypotonic dehydration, metabolic acidosis, and hemodynamic instability, general contraindications to LE infusion include hypersensitivity to LE ingredients or excipients, severe hyperlipidemia, severe blood coagulation disorder, acute shock, and unstable conditions, such as severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, and severe sepsis (specifications of products and manufacturers). Although isolated organ failure per se is not a contraindication to the parenteral application of LEs, severe liver or renal insufficiency in patients with no access to hemofiltration or dialysis may also contraindicate LE infusion, mainly when associated with impaired tissue blood flow and peripheral oxygen deficiency [4].

Why Different Lipid Emulsions were Designed for Clinical Practice

The biochemical characteristics of FAs influence their biological properties. We currently understand the individual properties of FAs, mainly their influences on the immune response, but their optimal balance in intravenous fat emulsions remains a major point of discussion.

Soybean oil (SO) was the main lipid component of LEs developed in the 1960s and 1970s. Since that time, alternative LEs aiming to offer a better balance of FAs through partial substitution of SO with medium-chain triglycerides (MCTs), olive oil (OO), and/or fish oil (FO) have been available in clinical practice. These new LEs were developed mainly to reduce the content of potentially oxidative, inflammatory, and immunosuppressive omega-6 (n-6) FAs, which are found in SO [1].

Thus, LEs currently available for clinical use are composed of different fat sources and provide distinct kinds and proportions of n-6, MCTs, n-9, and n-3 FAs (table 1).

Table 1. Characteristics of lipid emulsions designed for clinical use, adapted from [1]

Commercial name	Composition	Main characteristics
Intralipid ^{®a} Lipovenoes ^{®b} Lipofundin ^{®c} Ivelip ^{®d}	100% SO	Effective source of energy and essential fatty acids (~50% linoleic acid, 7% alpha-linolenic acid). The high n-6 PUFA content has been associated experimentally with immunosuppressive effects, mainly because these acids are sources of arachidonic acid, which can be used as a substrate for the synthesis of potential inflammatory and immunosuppressive eicosanoids.
Lipovenoes MCT ^{®a} Lipofundin MCT/LCT ^{®b}	Physical mixture: 50% SO + 50% MCTs	Effective source of energy and essential fatty acids, although mixtures of SO and MCTs provide half the amount of essential fatty acids provided by SO-based LEs. MCTs are transferred more readily into mitochondria, are largely independent of carnitine, and are oxidized more rapidly and to a greater extent than long-chain fatty acids, but they may contribute to acidosis. MCTs do not participate in eicosanoid synthesis and are less susceptible to oxidation than n-6 PUFAs from SO-based LEs.
Structolipid ^{®a}	Randomly inter-esterified mixture: 50% SO + 50% MCTs	Same characteristics as LEs composed of physical mixtures of 50% SO and 50% MCTs from coconut oil.
Clinoleic ^{®c}	~20% SO + ~80% OO	Rich in n-9 MUFAs, which do not participate in eicosanoid synthesis and are less susceptible to oxidation than n-6 PUFAs from SO-based LEs; also rich in alpha-tocopherol.
Omegaven ^{®a}	100% FO	Rich source of the n-3 PUFAs EPA and DHA; EPA acts as a substrate for the synthesis of potentially less inflammatory eicosanoids than n-6 PUFAs. In addition, both n-3 PUFAs are associated with anti-inflammatory properties and health benefits, especially with regard to CVD.
Lipoplus ^{®b/} Lipidem ^{®b}	40% SO + 50% MCTs + 10% FO	Latest generation of LEs, aiming to improve the balance of the parenteral fatty acid supply by reducing the n-6 PUFA content with the addition of MCTs and by the inclusion of n-3 PUFAs from FO.
SMOFlipid ^{®a}	30% SO + 30% MCTs + 25% OO + 15% FO	Latest generation of LEs, most closely approximating habitual lipid intake by offering all oils regularly found in the human diet.

SO = Soybean oil; PUFA = polyunsaturated fatty acid; MCTs = medium-chain triglycerides (from coconut oil); LCT = long-chain triglyceride; LE = lipid emulsion; OO = olive oil; MUFA = monounsaturated fatty acid; FO = fish oil; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; CVD = cardiovascular disease.

^a Fresenius-Kabi; ^b B. Braun; ^c Baxter Health Care; ^d Clintec Nutrition Clinique.

SO-based and MCT-rich LEs are conventionally infused worldwide, whereas those based on OO and containing FO are currently available only in Europe, Asia, and South America [1].

How to Choose the Best Lipid Emulsion Prescription for Your Patient

When prescribing the available parenteral LEs, an understanding of the biological properties of their FA components is mandatory. When possible, an LE containing FAs with properties that do not favor inappropriate cellular responses but contribute to a favorable patient outcome should be selected [2]. As the FA compositions of cur-

rent LEs cannot address specific individual clinical needs, the metabolic profiles of patients should guide the prescription of the best-available LEs to improve healing and recovery [5].

Metabolically Stable Patients

All commercially available LEs contain sufficient amounts of essential linoleic acid and alpha-linolenic acid to prevent deficiency. As a general rule, any LE can be prescribed to compose parenteral regimens or in combination with EN to normometabolic patients. In patients who have undergone gastrointestinal surgery, conflicting evidence has linked SO-based LEs to immune impairment and possible poorer clinical outcomes, but whether the stressed conditions of these patients contribute to these undesirable effects remains unclear. Furukawa et al. [6] reported that the infusion of an SO-based LE increased postoperative plasma interleukin-6 levels and impaired T lymphocyte function in severely but not moderately stressed patients who were classified according to the nature of the surgical procedures. In addition, a randomized clinical trial determined that MCT-rich and SO-based LEs showed similar metabolic safety and served as equally effective energy sources in non-severely stressed patients without renal or hepatic impairment or major trauma [7]. Thus, SO-based LEs may be prescribed to stable patients, and they offer the potential advantages of higher essential FA content than MCT-rich LEs and lower cost than alternative LEs, such as those based on OO or containing FO.

Hypermetabolic Patients

Metabolic distress is often observed in clinical practice, mainly in critically ill patients. It involves increased metabolic and oxidative rates, insulin resistance, and alterations in substrate utilization, which, in turn, can result in hyperglycemia and hepatic impairment [8].

FAs from available LEs provide more energy-dense sources of calories than amino acids (4 kcal/g) or dextrose monohydrate (3.4 kcal/g). Parenteral regimens including LEs may help to avoid hyperglycemia-related complications by allowing the infusion of reduced volumes to achieve adequate energy intake [8]. The replacement of one-third of the calories from conventional glucose-amino acid PN formulations by LEs was shown to effectively achieve an anabolic state and was associated with reduced glucose- and hepatic-related metabolic complications [9–11].

As effective non-glucose energy sources, all LEs can benefit hypermetabolic patients. However, metabolic distress increases a patient's susceptibility to complications such as oxidative stress, alterations in cell-mediated immunity, inflammation, and thrombosis [8]. These clinical intercurrents may be attenuated or aggravated by the kinds of FAs provided by LEs.

Oxidative Stress

Several disease processes favor the release of large amounts of reactive oxygen species, which may not be neutralized by the body's antioxidant defenses, allowing the occur-

rence of oxidative stress [12]. In critical illnesses, oxidative stress may exacerbate organ damage and is associated with tissue ischemia-reperfusion injury and an intense systemic inflammatory response [13]. Oxidative stress may thus play an important role in the development of multiple organ failure and sepsis, among other complications.

When using parenteral LEs in critically ill patients, the strong propensity of unsaturated FAs to react with reactive oxygen species and undergo peroxidation must be considered. FAs with higher grades of unsaturation (numbers of double bonds) are more susceptible to peroxidation. Thus, LEs that are very rich in n-6 and n-3 polyunsaturated fatty acids (PUFAs) are targets for lipid peroxidation and may increase the risk or intensity of oxidative stress in critically ill patients [14]. To minimize the risk of peroxidation, LEs with high PUFA contents include adequate doses of the powerful antioxidant alpha-tocopherol.

The administration of conventional SO-based LEs increases serum PUFA concentrations, which is of particular concern for critically ill patients [5]. LEs in which half of the SO content has been replaced by MCTs contain less PUFA (linoleic acid; 27 vs. 54%) as a percentage of the total FA content, but also less alpha-tocopherol (6.5 vs. 12 mg/l emulsion) [15]. In adult patients requiring PN, the infusion of a LE containing a 1:1 ratio of SO and MCT with 100 mg/day alpha-tocopherol was associated with less in vitro peroxidation of low- and very-low-density lipoprotein particles compared with a conventional SO-based LE [15].

Alternatively, OO-based LEs (80% OO and 20% SO) have less PUFA content than SO-based LEs and are a rich source of n-9 monounsaturated FAs and alpha-tocopherol. Compared with SO-based LEs, OO-based LEs do not change the oxidative stress markers in medical-surgical intensive care unit (ICU) patients, in healthy volunteers, or during intradialytic PN. The OO-based LEs are associated with reduced low-density lipoprotein peroxidation and improved vitamin E status in pediatric patients requiring long-term PN [16–20].

New mixed LEs containing FO are supplemented with high amounts of alpha-tocopherol (Lipoplus[®]/Lipidem[®], 190 ± 30 mg and SMOflipid[®], 163–225 mg) to reduce the risk of lipid peroxidation due to their higher content of n-3 PUFAs. Patients with stable intestinal failure and those who had undergone major abdominal surgery had increased antioxidant concentrations after the infusion of PN with mixed LEs compared with SO-based LEs, but no improvement in antioxidant status was observed in ICU patients [21–24].

Immune Dysfunction

Critically ill patients are susceptible to alterations in their immune response that may have detrimental effects *via* pro-inflammatory and immunosuppressive pathways [8]. PUFAs provided by LEs can directly influence the immune response, as they act as substrates for the synthesis of immune-function mediators. Overall, products derived from n-6 PUFAs are typically more potent mediators of inflammation and/or are more immunosuppressive than those formed from n-3 PUFAs (fig. 1) [1].

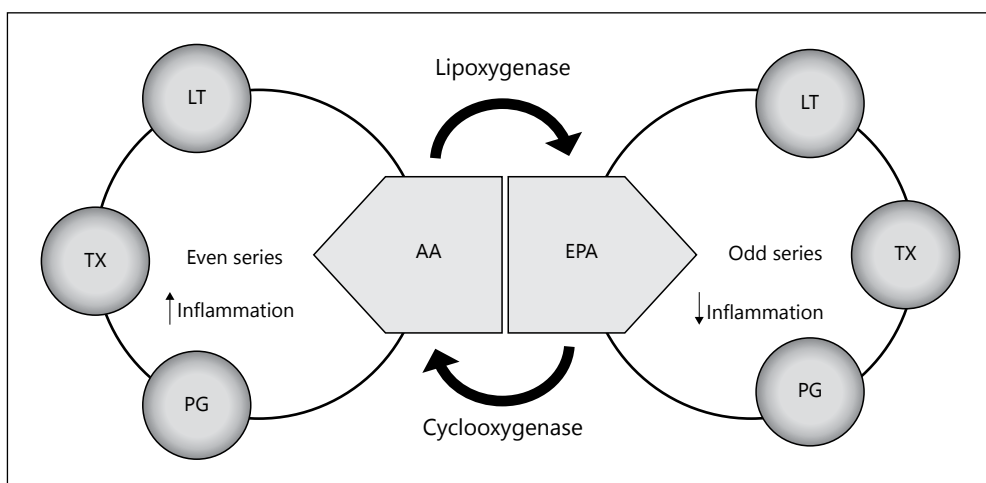


Fig. 1. Synthesis of eicosanoids from omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids. Omega-6 (n-6) arachidonic acid (AA) and omega-3 (n-3) eicosapentaenoic acid (EPA) compete for the same enzymatic pathways to synthesize immune-response mediators called eicosanoids (leukotrienes [LT], thromboxanes [TX], and prostaglandins [PG]). Eicosanoids formed from AA (the even series) are more potent mediators of inflammation and/or more immunosuppressive; they are also more prothrombotic than those formed from EPA (the odd series). In addition to shifting eicosanoid production toward those with low pro-inflammatory and immunosuppressive potential, EPA and docosahexaenoic acid from the n-3 polyunsaturated fatty acid family participate in the synthesis of anti-inflammatory resolvins and protectins and may also suppress inflammation by decreasing inflammatory cytokine release through mechanisms involving structural changes in membrane lipid rafts and the modulation of transcriptional factors, adapted from [1].

N-6 PUFAs have been associated with the impairment of leukocyte function and antibody-dependent cellular cytotoxicity, which may have serious impacts in the ICU setting [25–27]. The use of SO-based LEs, which are rich sources of n-6 PUFAs, should be avoided in the treatment of critically ill patients, particularly those with systemic inflammatory response syndrome and sepsis or septic shock. Compared with lipid-free PN, the incorporation of SO-based LEs in parenteral regimens for trauma patients was associated with higher rates of infection, longer requirement for mechanical ventilation, and longer ICU and hospital stays [28].

SO/MCT- or OO-based LEs can be used as alternative lipid sources for critically ill patients with impaired immune function because MCTs and n-9 monounsaturated FAs from OO do not participate in eicosanoid synthesis and have neutral effects on the immune response. Parenteral regimens in which fat components are provided by SO/MCT-based LEs have had better impacts on immune functions and inflammatory markers than those incorporating SO-based LEs in various clinical settings enrolling or not enrolling critically ill patients [29–32]. Only one study has documented the superior performance of an SO-based LE, compared with SO/MCT-based LEs, that is characterized by reduced durations of febrile neutropenia and an-

tibiotic administration in patients with hematological malignancies undergoing peripheral blood stem-cell transplantation [33]. OO-based LEs have been found to affect inflammatory and immune markers similarly to SO-based LEs in adult medical-surgical ICU patients requiring PN and in those undergoing dialysis, as well as during the postoperative period in patients with cancer and in home PN administration [16, 18, 34–36]. Only one study has documented higher leukocyte counts in ICU patients receiving PN containing an OO-based LE compared with SO-based LEs [37].

In the immunological setting, LEs based on or containing FO claim anti-inflammatory potential due to their high eicosapentaenoic acid (EPA) and docosahexaenoic acid contents, which may be of great interest when managing the treatment of critically ill patients, especially those with sepsis [38]. In surgical and critically ill patients, the infusion of such LEs has been associated with the preservation or improvement of leukocyte function and the attenuation of inflammatory response markers compared with SO-based LEs and even with less immune-reactive SO/MCT- or OO-based LEs [39–42]. These immunological benefits seem to positively impact clinical outcomes, as they are frequently accompanied by reduced infectious and non-infectious complication rates as well as reduced ICU and hospital stays [38, 43, 44].

Thrombosis

Several conditions that are often observed in critically ill patients can disturb circulating blood and tip the hemostatic balance toward thrombosis [8]. Eicosanoids produced from n-6 PUFAs, mainly thromboxane A₂, stimulate platelet aggregation and vasoconstriction, whereas those originating from n-3 PUFAs may have antiaggregatory and less proaggregatory effects. These observations suggest that SO-based and FO-containing LEs distinctly influence a patient's propensity for thrombosis.

Substantial data characterizing the effects of different LEs on blood coagulation markers are lacking. In one study, after an intravenous injection of endotoxin, plasma levels of the prothrombin fragment F1 + 2 and thrombin-antithrombin III complexes were higher in healthy men who received an SO-based LE than in those who received dextrose [45]. However, platelet function was not affected by the administration of SO- or SO/MCT-based LEs to critically ill, non-septic adult patients requiring PN for at least 7 days [46].

In relation to LEs with low SO content, no change in coagulation parameters or platelet aggregation was observed in patients undergoing peripheral blood stem cell transplantation or in critically ill patients who received SO- or SO/MCT-based LEs, respectively [29, 46]. However, one study documented a reduced requirement for hemofilter replacement due to blood coagulation in patients undergoing hemodialysis and who received PN with OO-based LE compared with SO-based LE [47]. LEs containing FO have shown modest benefits compared with SO-based LEs due to the transient inhibition of platelet aggregation immediately after intravenous infusion in

healthy volunteers and have shown reduced latency to collagen-induced platelet aggregation and time to maximal platelet aggregation in surgical patients with no change in bleeding time [48, 49].

How to Prescribe Lipid Emulsions

When to Start Lipid Emulsion Infusion

When PN is indicated, LEs should be infused after the achievement of hemodynamic stability and at no more than 1 week after starting PN [4]. In metabolically stressed patients, PN should be initiated within 24–48 h. The initiation of LE infusion requires adequate albumin, lipase, and carnitine levels to allow fat transport, degradation, and oxidation, respectively.

How Much Lipid Emulsion to Infuse

The recommended daily-infused doses of LEs for adults range from 0.7 to 1.3 g fat/kg body weight. For long-term (>6 months) home PN treatment, the LE dose should not exceed 1 g/kg/day; this dose can be increased to 1.5 g fat/kg body weight for shorter treatment periods when high-energy supply is required [50]. The energy requirement (and thus the parenteral LE dose) depends on the patient's metabolic profile.

In metabolically stable patients, LEs should provide about 25–40% of the parenteral non-protein energy supply according to the individual's carbohydrate and lipid tolerance. In hypermetabolic patients, a lipid intake of up to 50% of non-protein calories may be advisable, and in rare cases, an increase of up to 60% of non-protein energy is appropriate in patients with good lipid tolerance in the acute phase of respiratory insufficiency, with the aim of reducing the intensity of mechanical ventilation due to diminished carbon dioxide production [4]. In both situations, lipid infusion doses should not exceed the maximum rate of lipid oxidation (~1.2–1.7 mg/kg/min in adults) to avoid fat overload syndrome, which may impair the immune response [4].

In metabolically stressed patients, LEs can be administered safely at a rate of 0.7–1.5 g/kg over a 12–24-h period [50]. The discontinuous administration of LEs at high daily doses may contribute to fat overload and should be avoided in this clinical population. Thus, lipid infusion should be performed at least 12 h/day in acutely ill patients, and the rate of infusion should be slower (e.g., continuous pump infusion for ~24 h) in patients with critical metabolic status [4]. Shorter infusion durations may be used in stable patients, particularly those receiving long-term or home PN [4].

Hypertriglyceridemia must be avoided before and during the infusion of parenteral LEs. Serum triglyceride concentrations >400 mg/dl (>4.6 mmol/l) should prompt dosage reduction, and concentrations >1,000 mg/dl (>11.4 mmol/l) should

lead to the interruption of lipid infusion. Thus, plasma triglyceride levels should be monitored frequently during LE infusion, and the dose should be modified if necessary [4].

Where to Infuse Lipid Emulsions

As part of PN, LEs are usually administered into a large-diameter vessel, frequently the superior vena cava or right atrium, which are accessed *via* the jugular or subclavian vein. For longer-term access, a tunneled catheter or implanted chamber is occasionally used. Nevertheless, due to the low osmolality of LEs (20% LEs: 270–345 mOsm/l, 350–410 mOsm/kg), the parenteral formulations incorporating them may have sufficient energy in a reduced fluid volume to allow infusion *via* a peripheral vein, if needed. Peripheral venous access is usually achieved in veins of the hand or forearm, but veins of the lower limb are occasionally used when those of the upper limb are not accessible [50].

Peripheral PN may, however, fail to fulfill overall macro- and micronutrient requirements, as the amounts that are given may be limited by venous intolerance to the osmolality of the admixture and by limited flow rates into a smaller vessel. The European Society for Clinical Nutrition and Metabolism guidelines state that ‘a central venous access device is often required to administer the high osmolality PN mixture designed to cover the nutritional needs fully, but peripheral venous access devices may be considered for low osmolality (<850 mOsmol/l) mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance. If peripherally administered PN does not allow full provision of the patient’s needs, then PN should be centrally administered’ [50].

Final Considerations

Despite the potential benefits of LE administration, the prescription of these products is complex, due mainly to their FA components, which may alter metabolic and immune functions in various ways according to their biochemical properties. In addition, excesses of other LE components, such as phospholipids and phytosterols, may promote hypercholesterolemia and hyperlipidemia and lead to liver steatosis and hepatic dysfunction. Although liver impairment is most common in patients receiving long-term PN, critically ill patients are also at risk because metabolic distress increases plasma FA levels; thus, parenteral LEs should be administered to such patients with caution.

No consensus currently exists with regard to the best LEs for hypermetabolic patients, due mainly to the limited number of well-controlled clinical trials examining this complex issue. Some results have been inconsistent due to the heterogeneity of study designs and patient populations. Figure 2 provides a schematic guide for the selection of parenteral LE prescription based on the available scientific evidence and

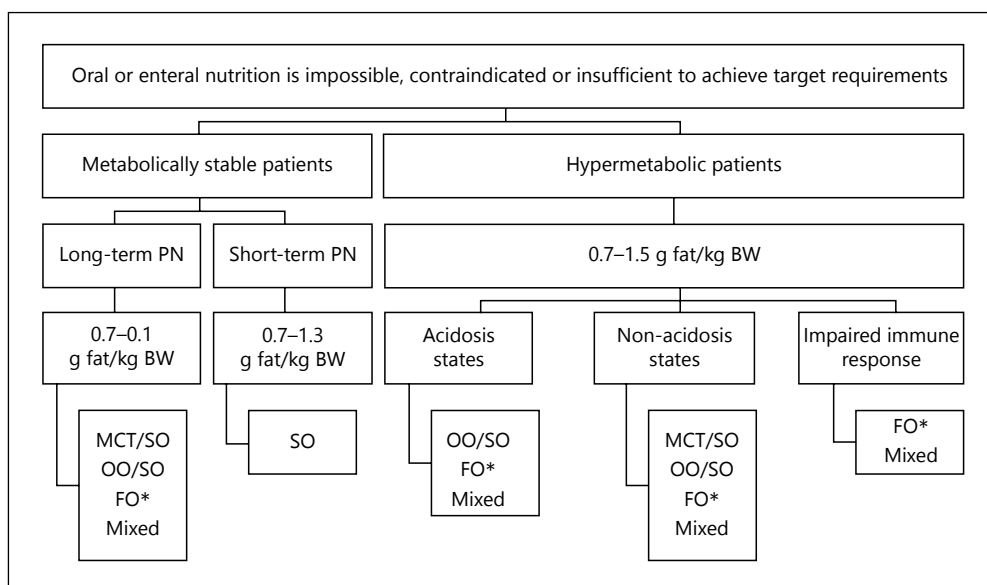


Fig. 2. Schematic guide for the prescription of parenteral lipid emulsions according to the available scientific evidence and current guidelines. PN = Parenteral nutrition; BW = body weight; MCT/SO = lipid emulsion based on 50% medium-chain triglycerides and 50% soybean oil; OO/SO = lipid emulsion based on 80% olive oil and 20% soybean oil; FO = lipid emulsion containing fish oil (* used as a supplement to standard lipid emulsions); Mixed LE = lipid emulsion based on a mixture of soybean oil, medium-chain triglycerides, and fish oil (may also contain olive oil), SO = lipid emulsion based on soybean oil.

current guidelines. Although the current European Society for Clinical Nutrition and Metabolism guidelines state that the infusion of SO-based LEs at adequate rates is safe for the treatment of critically ill patients, growing evidence indicates that these LEs should be avoided in favor of emulsions in which the linoleic and alpha-linolenic acid contents are partially replaced by MCTs, OO, or FO [8].

The recently published Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients state that ‘when parenteral nutrition with intravenous lipids is indicated, IV lipids that reduce the load of n-6 FAs/SO emulsions should be considered’ [51]. However, the authors of these guidelines also emphasized that ‘there are insufficient data to make a recommendation on the type of lipids to be used that reduce the n-6 FA/SO load in critically ill patients receiving parenteral nutrition’ [51]. This observation is in agreement with the results of a recent systematic review, which found that different SO-sparing parenteral strategies were associated with clinically important reductions in mortality, duration of ventilation, and length of ICU stay, although none of these differences was statistically significant [52].

As sources of EPA and docosahexaenoic acid, LEs containing FO may be considered for critically ill patients because they allow better modulation of the immune re-

sponse and likely decrease the length of ICU stay. A recent systematic review also suggested that FO-containing LEs could reduce mortality and the duration of ventilation in critically ill patients, but this review included only six randomized controlled trials [53]. Thus, the scarcity of clinical data precludes recommendation of the routine use of PN with FO-containing LEs. Alternative oil-based LEs may be associated with clinically important benefits in critically ill patients, but further research is warranted to confirm the preliminary evidence and allow the development of specific clinical recommendations.

References

- 1 Waitzberg DL, Torrinhas RS, Jacintho TM: New parenteral lipid emulsions for clinical use. *JPEN J Parenter Enteral Nutr* 2006;30:351–367.
- 2 Calder PC: Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options. *Proc Nutr Soc* 2013;72:263–276.
- 3 Singer P, Shapiro H, Bendavid I: Behind the ESPEN guidelines on parenteral nutrition in the ICU. *Minerva Anesthesiol* 2011;77:1115–1120.
- 4 Adolph M, Heller AR, Koch T, et al; Working group for developing the guidelines for parenteral nutrition of the German Association for Nutritional Medicine: Lipid emulsions – guidelines on parenteral nutrition, chapter 6. *Ger Med Sci* 2009;7:Doc22.
- 5 Laviano A, Rossi Fanelli F: Lipid emulsions in parenteral nutrition: does one size fits all? *S Afr J Clin Nutr* 2010;23(suppl):S08–S10.
- 6 Furukawa K, Yamamori H, Takagi K, et al: Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition* 2002;18:235–240.
- 7 Clarke PJ, Ball MJ, Hands LJ, et al: Use of a lipid containing medium chain triglycerides in patients receiving TPN: A randomized prospective trial. *Br J Surg* 1987;74:701–704.
- 8 Calder PC, Jensen GL, Koletzko BV, et al: Lipid emulsions in parenteral nutrition of intensive care patients: Current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- 9 Paluzzi M, Meguid MM: A prospective randomized study of the optimal source of nonprotein calories in total parenteral nutrition. *Surgery* 1987;102:711–717.
- 10 Meguid MM, Schimmel E, Johnson WC, et al: Reduced metabolic complications in total parenteral nutrition: pilot study using fat to replace one-third of glucose calories. *JPEN J Parenter Enteral Nutr* 1982;6:304–307.
- 11 Meguid MM, Akahoshi MP, Jeffers S, et al: Amelioration of metabolic complications of conventional total parenteral nutrition. A prospective randomized study. *Arch Surg* 1984;119:1294–1298.
- 12 Trachootham D, Lu W, Ogasawara MA, et al: Redox regulation of cell survival. *Antioxid Redox Signal* 2008;10:1343–1374.
- 13 Crimi E, Sica V, Williams-Ignarro S, et al: The role of oxidative stress in adult critical care. *Free Radic Biol Med* 2006;40:398–406.
- 14 Hardy G, Allwood MC: Oxidation of intravenous lipid emulsions. *Nutrition* 1997;13:230.
- 15 Manuel-y-Keenoy B, Nonneman L, De Bosscher H, et al: Effects of intravenous supplementation with alpha-tocopherol in patients receiving total parenteral nutrition containing medium- and long-chain triglycerides. *Eur J Clin Nutr* 2002;56:121–128.
- 16 Umpierrez GE, Spiegelman R, Zhao V, et al: A double-blind, randomized clinical trial comparing soybean oil-based versus olive oil-based lipid emulsions in adult medical-surgical intensive care unit patients requiring parenteral nutrition. *Crit Care Med* 2012;40:1792–1798.
- 17 Siqueira J, Smiley D, Newton C, et al: Substitution of standard soybean oil with olive oil-based lipid emulsion in parenteral nutrition: Comparison of vascular, metabolic, and inflammatory effects. *J Clin Endocrinol Metab* 2011;96:3207–3216.
- 18 Cano NJ, Saingra Y, Dupuy AM, et al: Intradialytic parenteral nutrition: Comparison of olive oil versus soybean oil-based lipid emulsions. *Br J Nutr* 2006;95:152–159.
- 19 Goulet O, de Potter S, Antébi H, et al: Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *Am J Clin Nutr* 1999;70:338–345.
- 20 Göbel Y, Koletzko B, Böhles HJ, et al: Parenteral fat emulsions based on olive and soybean oils: a randomized clinical trial in preterm infants. *J Pediatr Gastroenterol Nutr* 2003;37:161–167.

- 21 Wichmann MW, Thul P, Czarnetzki HD, et al: Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med* 2007;35:700–706.
- 22 Klek S, Chambrier C, Singer P, et al: Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid) – a double-blind, randomised, multicentre study in adults. *Clin Nutr* 2013;32:224–223.
- 23 Grimm H, Mertes N, Goeters C, et al: Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* 2006;45:55–60.
- 24 Antebi H, Mansoor O, Ferrier C, et al: Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: Comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr* 2004;28:142–148.
- 25 Jarstrand C, Berghem L, Lahnborg G: Human granulocyte and reticuloendothelial system function during intralipid infusion. *JPEN J Parenter Enteral Nutr* 1978;2:663–670.
- 26 Nordenström J, Jarstrand C, Wiernik A: Decreased chemotactic and random migration of leukocytes during intralipid infusion. *Am J Clin Nutr* 1979;32:2416–2422.
- 27 Loo LS, Tang JP, Kohl S: Inhibition of cellular cytotoxicity of leukocytes for herpes simplex virus-infected cells in vitro and in vivo by intralipid. *J Infect Dis* 1982;146:64–70.
- 28 Battistella FD, Widergren JT, Anderson JT, et al: A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* 1997;43:52–58.
- 29 Gogos CA, Zoumbos N, Makri M, et al: Medium- and long-chain triglycerides have different effects on the synthesis of tumor necrosis factor by human mononuclear cells in patients under total parenteral nutrition. *J Am Coll Nutr* 1994;13:40–44.
- 30 Gelas P, Cotte L, Poitevin-Later F: Effect of parenteral medium- and long-chain triglycerides on lymphocytes subpopulations and functions in patients with acquired immunodeficiency syndrome: a prospective study. *JPEN J Parenter Enteral Nutr* 1998;22:67–71.
- 31 Kuse ER, Kotzerke J, Müller S, et al: Hepatic reticuloendothelial function during parenteral nutrition including an MCT/LCT or LCT emulsion after liver transplantation – a double-blind study. *Transpl Int* 2002;15:272–277.
- 32 Sedman PC, Somers SS, Ramsden CW, et al: Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. *Br J Surg* 1991;78:1396–1399.
- 33 Demire S, Aydinuğ S, Ustün C, et al: Comparison of the efficacy of medium chain triglycerides with long chain triglycerides in total parenteral nutrition in patients with hematologic malignancies undergoing peripheral blood stem cell transplantation. *Clin Nutr* 2000;19:253–258.
- 34 Onar P, Yildiz BD, Yildiz EA, et al: Olive oil-based fat emulsion versus soy oil-based fat emulsion in abdominal oncologic surgery. *Nutr Clin Pract* 2011;26:61–65.
- 35 Reimund JM, Rahmi G, Escalin G, et al: Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;21:445–454.
- 36 Thomas-Gibson S, Jawhari A, Atlan P, et al: Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure. *Clin Nutr* 2004;23:697–703.
- 37 Mateu-de Antonio J, Grau S, Luque S, et al: Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr* 2008;99:846–854.
- 38 Waitzberg DL, Torrinhas RS: Fish oil lipid emulsions and immune response: What clinicians need to know. *Nutr Clin Pract* 2009;24:487–499.
- 39 Han YY, Lai SL, Ko WJ, et al: Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. *Nutr Clin Pract* 2012;27:91–98.
- 40 Wang J, Yu JC, Kang WM, et al: Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. *Nutrition* 2012;28:623–629.
- 41 Schade I, Röhm KD, Schellhaass A, et al: Inflammatory response in patients requiring parenteral nutrition: comparison of a new fish-oil-containing emulsion (SMOF*) versus an olive/soybean oil-based formula. *Crit Care* 2008;12:s56–s57.
- 42 Barbosa VM, Miles EA, Calhau C, et al: Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: A randomized, controlled clinical trial. *Crit Care* 2010;14:R5.
- 43 Chen B, Zhou Y, Yang P, et al: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: A meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 44 Pradelli L, Mayer K, Muscaritoli M, et al: n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care* 2012;16:R184.
- 45 van der Poll T, Coyle SM, Levi M, et al: Fat emulsion infusion potentiates coagulation activation during human endotoxemia. *Thromb Haemost* 1996;75:83–86.

- 46 Porta I, Planas M, Padró JB, et al: Effect of two lipid emulsions on platelet function. *Infusionsmed* 1994;21:316–321.
- 47 Verdier P, Mellot-Verdier I, Chausset R: Émulsions lipidiques et durée d'efficacité des hémofiltres dans l'hémodiafiltration continue [Lipid emulsions and hemofilter duration in continuous hemodiafiltration]. *Nutr Clin Metabol* 2002;16:85–90.
- 48 Elmadfa I, Stroh S, Brandt K, et al: Influence of a single parenteral application of a 10% fish oil emulsion on plasma fatty acid pattern and the function of thrombocytes in young adult men. *Ann Nutr Metab* 1993;37:8–13.
- 49 Roulet M, Frascarolo P, Pilet M, et al: Effects of intravenously infused fish oil on platelet fatty acid phospholipid composition and on platelet function in postoperative trauma. *JPEN J Parenter Enteral Nutr* 1997;21:296–301.
- 50 Staun M, Pironi L, Bozzetti F, et al: ESPEN guidelines on parenteral nutrition: Home parenteral nutrition (HPN) in adult patients. *Clin Nutr* 2009;28: 467–479.
- 51 Dhaliwal R, Cahill N, Lemieux M, et al: The Canadian critical care nutrition guidelines in 2013: An update on current recommendations and implementation strategies. *Nutr Clin Pract* 2014, DOI: 10.1177/0884533613510948 .
- 52 Manzanares W, Dhaliwal R, Jurewitsch B, et al: Alternative lipid emulsions in the critically ill: a systematic review of the evidence. *Intensive Care Med* 2013;39:1683–1694.
- 53 Manzanares W, Dhaliwal R, Jurewitsch B, et al.: Parenteral fish oil lipid emulsions in the critically ill: A systematic review and Meta-analysis. *JPEN J Parenter Enteral Nutr* 2014;38:20–28.

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Use of Intravenous Lipids: What Do the Guidelines Say?

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Abstract

The use of intravenous lipids is very frequent in most parenteral nutrition (PN) prescriptions. In this chapter, a systematic review of the literature was performed to compare the position of the various scientific societies (mainly the European Society for Clinical Nutrition and Metabolism, the American Society for Parenteral and Enteral Nutrition, and the German and Canadian Nutrition Societies) in terms of recommendations of when intravenous lipids should be prescribed for different clinical conditions. These recommendations may be supported by strong evidence or, if not available, by expert opinion. These recommendations help the physician in his daily prescription of PN in the hospital and help the patient requiring home PN.

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Introduction

Intravenous lipid emulsions (IVLEs) have been included in parenteral nutrition (PN) regimens for more than 40 years [1], mainly to serve as a source of essential fatty acids and to decrease the carbohydrate calorie load. IVLEs have been the subject of numerous clinical and experimental studies for various conditions, such as post-surgery care, multiple trauma, short bowel syndrome and sepsis. The traditionally used IVLEs are based on soybean oil as the sole lipid source. Such IVLEs are often referred to as long-chain triglycerides (LCTs). Alternative IVLEs have been developed and reduce the amount of provided n-6 polyunsaturated fatty acids (PUFAs) compared with soybean oil. Alternative IVLEs include medium-chain triglycerides (MCTs), n-9 mono-unsaturated fatty acids (MUFAs) and n-3 PUFAs in a mixture with n-6 fatty acids from soybean oil [2].

In this article, the recent literature and current guidelines and recommendations for the use of IVLEs in common clinical conditions will be discussed. Amongst the organisations making these guidelines are the European Society for Clinical Nutrition

and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN). In a recent position paper issued by ASPEN, it was concluded that IVLEs are an essential component of PN that help to prevent essential fatty acid deficiency [3], and it was found that no studies showed worse outcomes for alternative IVLEs compared with soybean oil-based IVLEs. In addition, it was noted that, while soybean oil-based IVLEs are adequate based on biochemical and clinical evidence, there appears to be several benefits of alternative IVLEs [3], including the potential for less pro-inflammatory effects, less immune suppression and improved antioxidant defences. The conclusion was that alternative IVLEs are safe and effective and should be made available in the United States of America [3]. However, until very recently, alternative IVLEs have not been available for routine clinical use in the United States of America and Canada, and only very recently has an 80:20 mix of olive and soybean oils been approved by the US Food and Drug Administration.

Intravenous Lipids in Surgical Patients

European Society for Clinical Nutrition and Metabolism Guidelines

'The optimal parenteral nutrition regimen for critically ill surgical patients should probably include supplemental n-3 fatty acids. The evidence-base for such recommendations requires further input from prospective randomised trials.' (Grade C) [4].

Comment

In order to reduce the overall carbohydrate load and osmolality of total PN solutions, lipid calories can replace glucose-derived calories. The soybean oil-based emulsions rich in n-6 PUFAs potentially have a pro-inflammatory effect, and trials have suggested lower complication rates with fewer immunological effects in patients receiving PN containing less than n-6 PUFAs [5, 6]. In comparison to n-6 PUFAs, n-3 PUFAs have a relative anti-inflammatory effect, and intravenous n-3 fatty acids have been shown to blunt the physiological response to endotoxin in healthy subjects [7]. In an open-label cohort study, increasing the dosage of n-3 PUFAs was associated with reduced ICU stay following major abdominal surgery [8], and in a randomised trial, inclusion of n-3 PUFAs in PN was associated with shorter duration of hospital stay [9]. Chen et al. meta-analysed the trials including surgical patients receiving IVLEs enriched in n-3 fatty acids and showed a decrease in the postoperative infection rate, a decrease in the length of stay and an improvement in liver-function markers [10]. These findings were confirmed in another meta-analysis of the same group of patients [11]. These meta-analyses report no difference in mortality when n-3 PUFAs are used compared with their absence in PN [10, 11], but mortality is usually very low in such patients. A recent meta-analysis by Pradelli et al. that included surgical and ICU patients came to similar conclusions, namely, a reduction in infectious complications and in length of stay but no change in mortality [12]. Thus, at present, there is

some evidence that the inclusion of n-3 fatty acids in PN may benefit organ function and reduce the length of stay of patients undergoing major surgery or admitted to the surgical ICU. Updating the current ESPEN guidelines therefore seems appropriate. The Enhanced Recovery After Surgery guidelines [13] do not mention lipid use, and updated German guidelines on surgery patients are pending.

Intravenous Lipids in Intensive Care

European Society for Clinical Nutrition and Metabolism Guidelines

‘Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients.’ (Grade B) [14].

Comment

According to the ESPEN guidelines, intravenous lipids should be considered an integral part of PN for the provision of energy and essential fatty acids in long-term ICU patients [14]. Soybean oil lipid emulsions (also known as LCTs), a 50:50 mixture of LCTs and MCTs, or other mixed lipid emulsions may be safely administered over 12–24 h at a rate of 0.7–1.5 g/kg body weight. The tolerance of mixed LCT/MCT-, n-9 MUFA- or n-3 PUFA-enriched lipid emulsions in standard use is well documented. Several studies have shown specific clinical advantages of alternative lipid emulsions over soybean oil LCTs alone, but these require confirmation by larger, prospective, controlled studies. A recent meta-analysis on alternative lipid emulsions did not find any significant advantage in terms of morbidity or mortality in a general ICU population [15]. Fish oil-enriched lipid emulsions may decrease the length of stay in critically ill patients, but this effect appears more dominant in post-surgical patients [12].

American Society for Parenteral and Enteral Nutrition Recommendations

These are more cautious than those of ESPEN, since, as mentioned earlier, alternative IVLEs containing n-9 MUFAs or n-3 PUFAs are not yet available in the United States of America [5]. ASPEN recognises the ability of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to displace n-6 fatty acids from the cell membranes of immune cells [16]. This effect reduces systemic inflammation through the production of alternative, biologically less active prostaglandins and leukotrienes. EPA and DHA have also been shown to down-regulate the expression of nuclear factor-kappa B, intracellular adhesion molecule 1, and E-selectin, which in effect decrease neutrophil attachment and transepithelial migration, thus modulating systemic and local inflammation. In addition, EPA and DHA help to stabilise the myocardium and lower the incidence of cardiac arrhythmias, decrease the incidence of acute respiratory distress syndrome (ARDS) and reduce the likelihood of sepsis. It is clear to ASPEN that rapid infusion of fat emulsions (especially those that are soybean oil-

based), regardless of the total amount, should be avoided in patients suffering from severe pulmonary failure [16]. However, ASPEN does not address the issue of administration of specific lipid emulsions.

The German Guidelines

These address the topic of IVLEs in a special article [17]. The guidelines are related to a general approach of the use of lipid emulsions in the total PN prescription but do not make any recommendations regarding specific lipid formulas. Their summarised statements, with their grade of recommendation (A to C) and level of evidence (Ia, Ib, IIa, IIb, III and IV), are as follows:

- (a) Fat-free PN can result in subnormal serum levels of essential fatty acids within one week (IIb).
- (b) Low-fat PN with high-glucose intake increases the risk of hyperglycaemia (Ia).
- (c) In parenterally fed patients with a tendency for hyperglycaemia, an increase in the lipid-glucose ratio should be considered (C).
- (d) Administration of lipid emulsions is required within no more than one week after starting PN (C).
- (e) Lipid emulsions can be infused via peripheral veins over a number of days (C).
- (f) Biologically active vitamin E (α -tocopherol) should be administered continuously along with the parenteral lipid emulsions (B).
- (g) The infusion of lipid emulsions presents no independent, clinically relevant risk of infection (IV).
- (h) Intravenous lipids should usually be provided with PN (C). Parenteral lipids should provide about 25–40% of the parenteral non-protein energy supply (C). The recommended daily dose of parenteral lipids in adults is between 0.7 and 1.3 g triglycerides/kg body weight, but this can be increased to 1.5 g/kg body weight in cases of high-energy requirements (C).
- (i) Lipid infusion with PN is not indicated for severe hyperlipidaemia (e.g. hereditary or acquired disorders of triglyceride hydrolysis), for severe metabolic acidosis with impaired lipid utilisation, or for severe coagulopathy (DIC stage III or higher) (C).
- (j) In patients receiving parenteral lipids, a serum triglyceride concentration >400 mg/dl (>4.6 mmol/l) should result in a dosage reduction, and a serum triglyceride concentration >1,000 mg/dl (>11.4 mmol/l) should lead to the interruption of lipid infusion (C).
- (k) The use of lipid emulsions with a low phospholipid/triglyceride ratio is recommended (B).

The Canadian Clinical Practice guidelines have been reluctant to support the inclusion of IVLEs in PN regimens [18]. This is partly related to the fact that most of the IVLEs available in Canada are enriched with n-6 fatty acids (i.e. soybean oil-based). They stipulate that 'based on two level 2 studies in critically ill patients who are not malnourished, are tolerating some EN, or when PN is indicated for short term use

(<10 days), withholding lipids high in soybean oil should be considered. There are insufficient data to make a recommendation about withholding lipids high in soybean oil in critically ill patients who are malnourished or those requiring PN for long term (>10 days). Practitioners will have to weigh the safety and benefits of withholding lipids high in soybean oil on an individual case-by-case basis in these latter patient populations.'

Comment

As discussed earlier, recent articles examining the effects of n-3 fatty acid-enriched lipid emulsions in critically ill surgical patients reached the conclusion that these lipid emulsions improve the length of stay and infection complications [8, 10, 12], although no specific guidelines regarding this topic are yet available [19].

Intravenous Lipids in Oncology and Haematology

The ESPEN guidelines suggest that using a higher-than-usual percentage of lipids in the admixture (e.g. 50% of non-protein energy) is beneficial (Grade C) [20]. This is based on the fact that fat is efficiently mobilised and utilised as a fuel source in cancer patients. It is recommended that no more than 1 g lipid/kg/day be given. However, not enough data are available regarding LCT/MCT admixtures to recommend these over LCT alone.

Comment

Shaw and Holdaway [21] reported that the infusion of a soybean oil-based lipid emulsion was able to significantly decrease net protein catabolism in patients with lower but not upper gastrointestinal (GI) tumours. A study in patients undergoing allogeneic bone marrow transplantation for hematologic malignancies showed reduced rates of lethal acute graft-versus-host diseases when patients received high-LCT PN regimens [22]. In conclusion, a one-to-one fat-to-glucose energy ratio might be a sensible, standard approach in cancer patients.

In a recent ESPEN analysis of the literature, morbidity was analysed in the context of IVLE use [23]. In 3 studies [24–26] of patients following GI cancer surgery, no differences in the rates of complication or infection were observed between patients receiving n-3 PUFA and control groups. One additional small study [27] showed a lower incidence of infections in post-GI cancer surgery patients receiving intravenous n-3 PUFA compared to the control group (23.1% compared with 78.6%; $p = 0.007$).

One high-quality study [28] observed a tendency for a lower incidence of infections (4 compared with 12 on day 8; $p = 0.066$) and a lower incidence of the systemic inflammatory response syndrome in post-GI cancer surgery patients receiving parenteral n-3 PUFA (4 compared with 13; $p = 0.03$).

Patients who received parenteral n-3 PUFAs had a significantly shorter length of hospital stay (mean $\pm$ SD 15 ± 5 compared with 17 ± 8 days; $p = 0.041$) [27] or a tendency for a shorter length of stay (mean $\pm$ SD: 17.5 ± 4.8 compared with 19.6 ± 5.6 days; $p = 0.19$) [24]. In 3 studies, the effects on mortality were investigated, and none showed any differences in mortality between the parenteral n-3 FA or control groups [27, 28]. From these studies, it appears that short-term (i.e. 5–7 days) perioperative parenteral administration of n-3 PUFA might result in a shortened length of ICU or hospital stay but does not improve other clinical outcome variables in surgical oncology patients. The ESPEN guidelines on this topic are pending.

The ASPEN guidelines regarding haematological and oncological patients do not mention the use of n-3 fatty acid-containing lipid emulsions [29].

Intravenous Lipids and Gastroenterology, Hepatology, Pancreatic Disease

Inflammatory Bowel Disease

The ESPEN PN in gastroenterology guidelines concluded that there are ‘no data on the efficacy of n-3 fatty acid enriched parenteral lipid emulsions in inflammatory bowel disease (IV)’ [30]. New ESPEN guidelines on this topic are in preparation.

Liver Disease

The 2009 ESPEN guidelines recommend that ‘when the patient is considered unlikely to resume normal oral nutrition within the next 5–7 days irrespective of current nutritional state’, PN should be instituted according to the ESPEN guidelines. The main goals are to ensure the adequate provision of energy, to ensure euglycaemia by giving glucose, lipids, vitamins and trace elements and to ensure optimal rates of protein synthesis by providing an adequate intake of protein or amino acids. Regarding IVFE, the use of lipids may be especially advantageous in the presence of insulin resistance. Glucose and lipid (0.8–1.2 g/kg/day) may be given simultaneously.

Unfortunately, no systematic data on the role of lipids as nutrients in this context are available, but exogenously applied lipid seems to be well tolerated by most patients [31, 32]. Most hepatology centres give parenteral lipids to patients with acute liver failure, and the majority opt for an LCT/MCT emulsion [33]. Adequate metabolic monitoring is necessary to adapt nutrient provision to substrate utilisation in order to prevent substrate overload due to inadequate intake. Strict control of the plasma levels of triglycerides (with a target <3.0 mmol/l) is necessary for this purpose [34].

Acute Pancreatitis

The ESPEN guidelines [35] suggest that ‘the use of intravenous lipids in pancreatitis is safe if hypertriglyceridemia is avoided. Triglyceride values below 12 mmol/l are recommended, but serum levels should be kept within normal ranges. Current best prac-

tice recommendations are to ensure appropriate infusion rates for fat emulsions (from 0.8 to 1.5 g/kg per day) and temporarily to discontinue the infusion if persistent (>72 h) hypertriglyceridemia occurs (>12 mmol/l) (grade C). From a pathophysiological point of view, very few reports link the infusion of lipid emulsions with the onset of acute pancreatitis; indeed, only three cases have been reported in which pancreatitis occurred upon infusion of lipid emulsions. However, the co-morbidity of these patients and the use of concomitant therapy (e.g. corticosteroids) preclude any firm conclusions being drawn. The recommendations are to administer IVLE except if the pancreatitis appears to be associated with hypertriglyceridemia or cannot be controlled within the safe range.

At present, there are no strong data to suggest that infusion of alternative parenteral lipids, such as n-3 fatty acids, olive oil, MCT or structured lipids, has major clinical advantages compared to soybean-oil emulsion. One randomised, double-blind trial by Wang et al. showed that subjects receiving fish oil emulsion had a reduced inflammatory response and reduced need for renal replacement therapy compared to those receiving soybean oil [36].

Intravenous Lipids in Home Parenteral Nutrition

Almost all HPN patients should be provided with lipid, particularly if there is no oral intake of fat. The ESPEN guidelines [37] recommend administering energy and protein such that two-thirds of the non-protein calories are provided by glucose and one-third are provided from lipid. Greater amounts of lipid have proven to be a significant independent factor for chronic cholestasis and progression from liver fibrosis to cirrhosis. Thus, even in the optimal case of 'normonutrition', no more than 1 g/kg per day of IVLE should be used for long-term HPN treatment (>6 months). In a 5-year follow-up of 90 HPN patients [38], the authors described chronic cholestasis and liver disease when 20% intravenous lipid was provided at doses higher than 1 g/kg bodyweight per day. Essential fatty acid deficiency will develop in 2–6 months with a completely fat-free intravenous regimen, and this can be normalised by providing 1.2–2.4 g soybean oil per kilogram body weight twice weekly. Patients who have existing serological essential fatty acid deficiency may require up to 2.4 g/kg twice weekly for correction [39]. Clinical experience indicates that essential fatty acid deficiency may be prevented with about 500–1,000 ml of 20% soybean oil-based lipid emulsions given on a weekly basis. If patients maintain some oral intake of fat, essential fatty acid deficiency is rarely a problem. Lipid emulsion based on olive oil appears to be equally safe as those based on soybean oil [40, 41]. Emulsions with MCTs/LCTs and fish oil have also proven safe, although data for long-term use in HPN patients are more limited [42]. However, prospective clinical studies on the long-term use of alternative lipids use are still scarce, and more data are needed.

Conclusion

The addition of IVLE to PN is recommended in almost all conditions where PN is indicated, except in cases of severe liver dysfunction. In this case, the addition of n-3 fatty acids seems to be beneficial, but well-designed and adequately powered, randomised controlled trials of alternative IVLEs are required in the fields of surgery and critical care in order to update the available guidelines.

References

- 1 Wretling A: Development of fat emulsions. *JPEN J Parenter Enteral Nutr* 1981;5:230–235.
- 2 Calder PC, Jensen GL, Koletzko BV, et al: Lipid emulsions in parenteral nutrition of intensive care patients: Current thinking and future directions. *Intensive Care Med* 2010;36:735–749.
- 3 Vanek VW, Seidner DL, Allen P, et al: A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract* 2012;27:150–192.
- 4 Braga M, Ljungqvist O, Soeters P, et al: ESPEN guidelines on parenteral nutrition: Surgery. *Clin Nutr* 2009;28:378–386.
- 5 Heyland DK, Montalvo M, MacDonald S, et al: Total parenteral nutrition in the surgical patient: A meta-analysis. *Can J Surg* 2001;44:102–111.
- 6 Wanten G: An update on parenteral lipids and immune function: only smoke, or is there any fire? *Curr Opin Clin Nutr Metab Care* 2006;9:79–83.
- 7 Pluess TT, Hayoz D, Berger MM, et al: Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. *Intensive Care Med* 2007;33:789–797.
- 8 Heller AR, Rössler S, Litz RJ, et al: Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* 2006;34:972–979.
- 9 Wichmann MW, Thul P, Czarnetzki HD, et al: Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): Data from a prospective, randomized, multicenter trial. *Crit Care Med* 2007;35:700–706.
- 10 Chen B, Zhou Y, Yang P, et al: Safety and efficacy of fish oil-enriched parenteral nutrition regimen on postoperative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* 2010;34:387–394.
- 11 Wei C, Hua J, Bin C, et al: Impact of lipid emulsion containing fish oil on outcomes of surgical patients: Systematic review of randomized controlled trials from Europe and Asia. *Nutrition* 2010;26:474–481.
- 12 Pradelli L, Mayer K, Muscaritoli M, et al: Correction: n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: A meta-analysis. *Crit Care* 2013;17:405.
- 13 Gustafsson UO, Scott MJ, Schwenk W, et al: Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr* 2012;31:783–800.
- 14 Singer P, Berger MM, Van den Berghe G, et al: ESPEN guidelines on parenteral nutrition: Intensive care. *Clin Nutr* 2009;28:387–400.
- 15 Manzanares W, Dhaliwal R, Jurewitsch B, et al: Alternative lipid emulsions in the critically ill: A systematic review of the evidence. *Intensive Care Med* 2013;39:1683–1694.
- 16 McClave SA, Martindale RG, Vanek VW, et al: Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009;33:277–316.
- 17 Adolph M, Heller AR, Koch T, et al: Lipid emulsions – guidelines on parenteral nutrition. *Ger Med Sci* 2009;7:1–13.
- 18 Canadian Critical Care Nutrition Clinical Guidelines: Summary of topics and recommendations. [<http://www.criticalcarenutrition.com/docs/cpg/srrev.pdf>] (accessed May 28, 2009).
- 19 Singer P, Doig G, Pichard C: The truth about nutrition in the ICU. *Intensive Care Med* 2014;40:252–255.
- 20 Bozzetti F, Arends J, Lundholm K, et al: ESPEN guidelines on parenteral nutrition: non-surgical oncology. *Clin Nutr* 2009;28:445–454.
- 21 Shaw JH, Holdaway CM: Protein-sparing effect of substrate infusion in surgical patients is governed by the clinical state, and not by the individual substrate infused. *JPEN J Parenter Enteral Nutr* 1988;12:433–440.

- 22 Muscaritoli M, Conversano L, Torelli GF, et al: Clinical and metabolic effects of different parenteral nutrition regimens in patients undergoing allogeneic bone marrow transplantation. *Transplantation* 1998;66:610–616.
- 23 ESPEN, 2014: Cancer: Guidelines (in preparation).
- 24 Heller AR, Rössel TR, Gottschlich B, et al: Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. *Int J Cancer* 2004; 111:611–616.
- 25 Liang B, Wang S, Ye YJ, et al: Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients. *World J Gastroenterol* 2008;14:2434–2439.
- 26 Wachtler P, König W, Senkal M, et al: Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma* 1997;42:191–198.
- 27 Jiang ZM, Wilmore DW, Wang XR, et al: Randomized clinical trial of intravenous soybean oil alone versus soybean oil plus fish oil emulsion after gastrointestinal cancer surgery. *Br J Surg* 2010;97:804–809.
- 28 Badía-Tahull MB, Llop-Talaverón JM, Leiva-Badosa E, et al: A randomised study on the clinical progress of high-risk elective major gastrointestinal surgery patients treated with olive oil-based parenteral nutrition with or without a fish oil supplement. *Br J Nutr* 2010;104:737–741.
- 29 August DA, Huhmann MB; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors: A.S.P.E.N. clinical guidelines: Nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation *JPEN J Parenter Enteral Nutr.* 2009;33:472–500.
- 30 Van Gossum A, Cabre E, Hébuterne X, et al: ESPEN guidelines on parenteral nutrition: Gastroenterology. *Clin Nutr* 2009;28:415–427.
- 31 Plauth M, Cabré E, Campillo B, et al: ESPEN guidelines on parenteral nutrition: Hepatology. *Clin Nutr* 2009;28:436–444.
- 32 Forbes A, Wicks C, Marshall W, et al: Nutritional support in fulminant hepatic failure: The safety of lipid solutions. *Gut* 1987;28:1347–1349.
- 33 Kleinberger G: Parenteral nutrition in liver insufficiency. *Schweiz Med Wochenschr* 1986;116:545–549.
- 34 Schütz T, Bechstein WO, Neuhaus P, et al: Clinical practice of nutrition in acute liver failure – a European survey. *Clin Nutr* 2004;23:975–982.
- 35 Gianotti L, Meier R, Lobo DN, et al: ESPEN guidelines on parenteral nutrition: Pancreas. *Clin Nutr* 2009;28:428–435.
- 36 Wang X, Li W, Zhang F, et al: Fish oil-supplemented parenteral nutrition in severe acute pancreatitis patients and effects on immune function and infectious risk: A randomized controlled trial. *Inflammation* 2009;32:304–309.
- 37 Staun M, Pironi L, Bozzetti F, et al: ESPEN guidelines on parenteral nutrition: Home parenteral nutrition (HPN) in adult patients. *Clin Nutr* 2009;28:467–479.
- 38 Cavicchi M, Beau P, Crenn P, et al: Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;132:525–532.
- 39 Chambrier C, Bannier E, Lauverjat M, et al: Replacement of long-chain triglyceride with medium-chain triglyceride/long-chain triglyceride lipid emulsion in patients receiving long-term parenteral nutrition: Effects on essential fatty acid status and plasma vitamin K1 levels. *JPEN J Parenter Enteral Nutr* 2004; 28:7–12.
- 40 Vahedi K, Atlan P, Joly F, et al: A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. *Br J Nutr* 2005; 94:909–916.
- 41 Reimund JM, Rahmi G, Escalin G, et al: Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* 2005;21:445–454.
- 42 Rubin M, Moser A, Vaserberg N, et al: Structured triacylglycerol emulsion, containing both medium- and long-chain fatty acids, in long-term home parenteral nutrition: a double-blind randomized crossover study. *Nutrition* 2000;16:95–100.

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