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Lipids

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Objectives

Describe the nomenclature, route of delivery, and requirements for lipids in the diet of healthy individuals and in formulations for those who require specialized nutrition support.

Identify the lipid components in enteral and parenteral formulations.

Discuss the clinical effects and biological activity of fatty acids in specialized nutrition support.

Test Your Knowledge Questions

1. What are some of the possible ramifications of activation of the enzyme, phospholipase A2?

A. Cyclooxygenase (COX)–dependent, eicosanoid-mediated inflammatory reactions
B. Enzymatic degradation of resolvins and protectins
C. Desaturation of linoleic acid within lipids
D. Chylomicron maturation

2. How might propofol, when provided to patients within a 10% (w/v) lipid injectable emulsion (ILE), increase risk of hypertriglyceridemia? (Refer to the section on “Parenteral Delivery and Metabolism of Lipid Injectable Emulsions” for an explanation of this new terminology to replace intravenous fat emulsion [IVFE]).

A. Propofol causes acute uptake of triglycerides (TGs) by the microvilli of the small intestine.

B. Propofol is known to activate the release of TGs from adipose tissue.
C. The increased presence of liposomes in the propofol ILE may interfere with chylomicron and pseudo-chylomicron metabolism.
D. The presence of sedative in the ILE prevents phospholipid formation, which results in an increased level of TGs in the blood.

3. Which ionized form of a short-chain fatty acid (SCFA; up to 6 carbons in length) is thought to be the most important to colonic health and why?

A. Myristate
B. Caproate
C. Butyrate
D. Valerate

Test Your Knowledge Answers

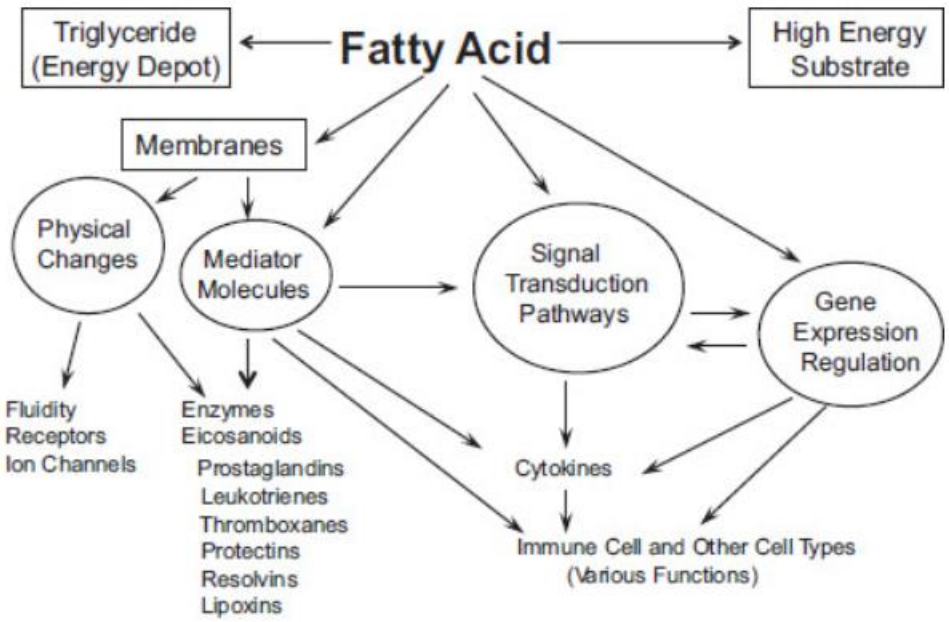
1) The correct answer is A. Arachidonic acid (AA), common to membrane phospholipids, usually occupies the sn-2 position within lipids and is almost always found at this position within the important membrane phospholipid phosphatidylinositol. During membrane cell signaling events, a possible outcome is the activation of phospholipase A2, the enzyme that acts on membrane phospholipids to release fatty acids from the sn-2 position. Release of AA sets in motion subsequent intracellular metabolic activity via the COX pathway that leads to the synthesis of the 2-series of prostaglandins, including prostaglandin E2 (PGE2), and thromboxanes, including thromboxane A2.
2) The correct answer is C. Hypertriglyceridemia may be caused by interference with chylomicron and pseudo-chylomicron metabolism as a result of the presence of liposomes within the ILE. Liposomes are formed during the emulsification process when parenteral ILE is produced. These liposomes are usually metabolized in a manner similar to the metabolism of pseudo-chylomicrons, but their presence may lead to the formation of a spherical bilayer of phospholipid and cholesterol known as lipoprotein-X. This lipoprotein inhibits both lipoprotein lipase and hepatic lipase enzymatic activity, and thus can interfere with the proper metabolism of the TGs that are part of the structure of chylomicrons and pseudo-chylomicrons. This interference and the accumulation of endogenous cholesterol can subsequently lead to an increase in circulating TGs and cholesterol. Because 10% (w/v) ILE contains a greater number of liposomes relative to 20% (w/v) ILE as a result of the relative ratio of phospholipid emulsifier to oil, the former formulation places the patient at greater risk for hypertriglyceridemia.
3) The correct answer is C. SCFAs such as acetate, propionate, and butyrate are primarily produced in the colon by bacteria and can serve as important energy sources for colonic tissue. Butyrate in particular is thought to modify inflammatory activity and promote colon health. For example, when applied directly to the colon, butyrate can attenuate the inflammatory activity seen in

ulcerative colitis. In addition, the fermentation of carbohydrate (fiber) and the production of SCFAs in the colon, especially butyrate production, appear to act as antitumorigenic stimuli.

Background

Lipids are biological substances that are soluble in organic solvents, such as methanol and chloroform, but insoluble in water. Lipids include waxes, various oils, sterols, fats, TGs, and individual components known as fatty acids. TGs, through the contribution of their fatty acid components, serve as major dietary sources of energy. Also, certain lipids provide much of the critical structural and metabolically functional components of all biological membranes. Because of these properties, lipids and the fatty acids that comprise part of their structure contribute significantly to a broad range of cellular functions needed for the maintenance and biological activity of healthy living cells (Figure 5-1). For example, the structure of membrane lipids can include the fatty acids AA, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These particular fatty acids are critically important to proper development as well as inflammatory and other physiologic processes. For example, the metabolic products of AA, EPA, and DHA include (1) inflammatory mediators (eicosanoids such as prostaglandins, leukotrienes, and thromboxanes); (2) gene regulators; (3) substances that assist in the resolution of an inflammatory response (eicosanoids such as protectins, resolvins, and lipoxins); and (4) substances that regulate overall lipid metabolism.1–5 Furthermore, AA, EPA, DHA, and other fatty acids contribute to membrane fluidity, membrane and intracellular cell signals, and modulation of apoptotic pathways.6 This chapter focuses on general lipid structure, fatty acid biochemistry and nomenclature, lipid metabolism, and the clinical aspects of lipid provision in enteral nutrition (EN) and parenteral nutrition (PN).

FIGURE 5-1 The Varied Roles of Fatty Acids in Cell Structure and Function



General Lipid Structure

The basic TG structure consists of a glycerol backbone and various fatty acids attached in ester linkage at the carbon-1 (sn-1), carbon-2 (sn-2), and carbon-3 (sn-3) positions. TGs are the most abundant lipids in the body, but they do not serve as components of membranes. Instead, these substances serve as an energy reserve for cells via the enzyme-dependent release, distribution, and oxidation of fatty acids. When stored as fat in tissues (eg, adipose), energy-dense TGs provide by weight approximately 6-fold the energy available from the same weight of stored carbohydrate such as glycogen. Compared with a gram of carbohydrate, a gram of fat stored in tissues has more recoverable energy because (1) TGs have a lower intrinsic level of oxidation than carbohydrate, and (2) the weight contribution of water common to carbohydrates and proteins is missing from lipids. TGs circulate to a limited extent within the bloodstream but are more significantly stored within adipose tissue. In contrast to circulating and stored TGs, the major constituents of the membrane lipid bilayer are compound lipids known as phosphoglycerides. Similar to TGs, 2 carbon positions on the glycerol backbone, sn-1 and sn-2, are esterified by fatty acids; however, the third available position, sn-3, is occupied by a phosphate group in phosphoester linkage (known as 1,2-diacylphosphoglycerides). The most abundant phospholipids found within membranes also have a polar group of some kind, such as ethanolamine, serine, or choline, attached to the phosphate moiety. As a consequence, membrane lipids are amphipathic (or amphiphilic ["loving both"]), meaning that they simultaneously possess both hydrophobic and hydrophilic characteristics. This amphipathic property allows lipid bilayer membrane formation. Thermodynamic forces induced by interaction of the polar aqueous environment external to and within cells with the hydrocarbon portions (tails) of the 2 fatty acids within each phospholipid results in formation of linear rows of phospholipids in opposing leaflets. The linear rows of polar groups face outward (aqueous environment outside the cell) on the external leaflet and inward (aqueous environment inside the cell) on the internal leaflet of the bilayer. Hydrophobic or other amphipathic molecules such as sterols and proteins may be embedded within the lipid bilayer. For example, cholesterol, itself an amphipathic molecule and the precursor of steroid hormones, is an integral constituent of animal cell membranes.

Fatty Acid Biochemistry and Nomenclature

Each fatty acid is comprised of several carbon, many hydrogen, and 2 oxygen atoms. All fatty acids consist of a chain of carbon atoms linked together by covalent bonds. Each carbon atom within the chain has 1 or more hydrogen atoms attached. A methyl (CH_3–) group is at one end of the chain, and, at the opposite end of the chain is an acidic carboxyl (–COOH) group. Thus, the representative overall structure for every fatty acid is CH_3–$(CH_2)_x$–COOH.

Fatty acids are classified in several ways. One classification groups fatty acids based on the number of carbon atoms within the hydrocarbon chain. A given fatty acid is classified as short chain (2 to 4 carbons), medium chain (6 to 12 carbons), long chain (14 to 18 carbons), or very long chain (20 or more carbons). For example, acetic acid, found in vinegar, CH_3–COOH, a 2-carbon fatty acid, and caprylic acid, CH_3–$(CH_2)_6$–COOH, an 8-carbon fatty acid, represent a SCFA and a medium-chain fatty acid (MCFA), respectively. The length of the hydrocarbon chain conveys unique physical and chemical properties to fatty acids, and, these properties are reflected in the lipids of which these fatty acids are a part. Because

a 2-carbon unit, acetyl-coenzyme A (acetyl-CoA), is used for fatty acid synthesis, almost all fatty acids consist of an even number of carbon atoms.

Another fatty acid classification is based on the number of hydrogen atoms present on each carbon atom within the molecule. If all hydrogen atoms that could be present are present, the fatty acid is said to be saturated. Acetic acid and caprylic acid are saturated fatty acids. Alternatively, if some hydrogen atoms are missing, the fatty acid is said to be unsaturated. The degree of unsaturation among such fatty acids varies. Some fatty acids may have 2, 4, or more hydrogen atoms missing. If adjacent carbon atoms within the chain are missing hydrogen atoms, there will be a double bond instead of a single bond at that position. Thus, for unsaturated fatty acids, 1 or more double bonds may be present within the hydrocarbon chain. The greater the number of double bonds, the greater the degree of unsaturation is. This configuration, like chain length, provides various physical and chemical properties to the "behavior" of such a fatty acid. The absence of hydrogen atoms does not occur by chance. It is generated by specific enzymatically catalyzed chemical reactions. The enzymatically catalyzed removal of hydrogen atoms occurs in pairs, with 1 hydrogen atom removed from each of 2 adjacent carbon atoms within the carbon chain. This desaturation of the molecule is an oxidation reaction that results in the subsequent formation of a double bond between the 2 adjacent carbons. The enzymes that perform the oxidation reaction that removes hydrogen atoms are known as desaturases. In humans, there are 4 desaturase enzymes. Each desaturase is identified by the numerical position of the first carbon of the pair of carbons involved in the chain, numbered from the carboxyl end, which has a hydrogen atom removed and a double bond formed by the enzyme in question. These enzymes are: Δ4-, Δ5-, Δ6-, and, Δ9-desaturases. The Greek letter Delta (Δ) followed by a superscript numeral identifies the numerical position of the first carbon of the double bond pair. For example, Δ4-desaturase acts on the fourth carbon atom in the chain, removing a hydrogen atom from and generating a double bond between carbons 4 and 5. Similarly, Δ9-desaturase removes hydrogen atoms and forms a double bond between carbons 9 and 10 in the sequence. A fatty acid that contains only 1 double bond is known as a monounsaturated fatty acid (MUFA), whereas a fatty acid with a minimum of 2 double bonds is known as a polyunsaturated fatty acid (PUFA). The most abundant fatty acid in humans, oleic acid, an 18-carbon fatty acid that has a single double bond located between carbon atoms 9 and 10, is formed by desaturation of the saturated 18-carbon fatty acid, stearic acid, by Δ9-desaturase. Similarly, the presence of 3 or more double bonds within an unsaturated fatty acid is known as a highly unsaturated fatty acid. These desaturases remove hydrogens from the same "side" of adjacent carbon atoms, forming what is known as a cis double bond.

The removal of hydrogen atoms on the same "side" (cis) of adjacent carbon atoms and introduction of a single, cis double bond between the 2 carbon atoms, results in significant bending of the fatty acid chain, by approximately 30°. Consequently, 2 cis double bonds may result in an approximate 60° bend in the molecule. This property of unsaturated fatty acids has important ramifications with respect to individual lipid characteristics and, consequently, the physical and functional characteristics of membranes. If 2 or more saturated fatty acids are next to each another within a leaflet of a lipid bilayer, the carbon atoms in adjacent long chains within the leaflet can interact with relative ease via hydrophobic bonding and pack more closely. Conversely, the bending of unsaturated fatty acid

molecules does not allow adjacent lipids to interact so closely. As a result, membrane fluidity and responsiveness to stimuli vary relative to the amount of saturated vs unsaturated fatty acids present. As the number of unsaturated fatty acids among membrane lipids increases, the fluidity of the membrane increases, with the converse being true if more saturated fatty acids are present.

Table 5-1 presents the various nomenclatures that may be used to identify some of the more common biological fatty acids. Each of these systems may identify the total number of carbons and number of double bonds present; some classifications also denote the numerical position of any double bond that may be present.

TABLE 5-1 Fatty Acid Nomenclature

Common Name	Chemical Name	No. of Double Bonds	No. of Carbon Atoms	Scientific Δ Double Bond Numbering	*n* and ω Numbering
Butyric acid	Butanoic acid	0	4	4:0	NA
Caproic acid	Hexanoic acid	0	6	6:0	NA
Caprylic acid	Octanoic acid	0	8	8:0	NA
Capric acid	Decanoic acid	0	10	10:0	NA
Lauric acid	Dodecanoic acid	0	12	12:0	NA
Myristic acid	Tetradecanoic acid	0	14	14:0	NA
Palmitic acid	Hexadecanoic acid	0	16	16:0	NA
Palmitoleic acid	9-hexadecenoic acid	1	16	$16:1\Delta^{9}$	16:1*n*-7 ω-7
Stearic acid	Octadecanoic acid	0	18	18:0	NA
Oleic acid	9-octadecenoic acid	1	18	$18:1\Delta^{9}$	18:1*n*-9 ω-9
Vaccenic acid	11-octadecenoic acid	1	18	$18:1\Delta^{11}$	18:1*n*-7 ω-7
Linoleic acid	9,12-octadecadienoic acid	2	18	$18:2\Delta^{9,12}$	18:2*n*-6 ω-6
α-Linolenic acid	9,12,15-octadecatrienoic acid	3	18	$18:3\Delta^{9,12,15}$	18:3*n*-3 ω-3
γ-Linolenic acid	6,9,12-octadecatrienoic acid	3	18	$18:3\Delta^{6,9,12}$	18:3n-6 ω-6
Dihomo-γ-linolenic acid	8,11,14-eicosatrienoic acid	3	20	$20:3\Delta^{8,11,14}$	20:3*n*-6 ω-6
Arachidic acid	Eicosanoic acid	0	20	20:0	NA
Gadoleic acid	9-eicosenoic acid	1	20	$20:1\Delta^{9}$	20:1n-9 ω-11
"Mead" acid	5,8,11-eicosatrienoic acid	3	20	$20:3\Delta^{5,8,11}$	20:3n-9 ω-9
Arachidonic acid	5,8,11,14-eicosatetraenoic acid	4	20	$20:4\Delta^{5,8,11,14}$	20:4*n*-6 ω-6
Eicosapentaenoic acid	5,8,11,14,17-eicosapentaenoic acid	5	20	$20:5\Delta^{5,8,11,14,17}$	20:5*n*-3 ω-3
Behenic acid	Docosanoic acid	0	22	22:0	NA
Erucic acid	13-docosenoic acid	1	22	$22:1\Delta^{13}$	22:1*n*-9 ω-9
Docosahexaenoic acid	4,7,10,13,16,19-docosahexaenoic acid	6	22	$22:6\Delta^{4,7,10,13,16,19}$	22:6*n*-3 ω-3
Lignoceric acid	Tetracosanoic acid	0	24	24:0	NA

NA, not applicable.

One system uses the uppercase Greek letter Delta (Δ). In this system, the carboxyl group of each fatty acid is considered to occupy the first (numerical "1") position. For example, the polyunsaturated 18-carbon fatty acid, linoleic acid, contains 2 double bonds, 1 between the number 9 and 10 carbons, and 1 between the number 12 and 13 carbon atoms. Thus, this fatty acid is designated as 18:2Δ9,12.

Linoleic acid is known chemically as 9,12-octadecadienoic acid. "Octa" signifies 8 carbons, "deca" signifies 10 carbons (ie, 18 carbons total), and "dienoic" (or "diene") refers to the 2 double bonds within the acid. A "trienoic" (or "triene") fatty acid contains 3 double bonds.

An additional system of nomenclature used for PUFAs identifies different fatty acid families based on the last, relative to the carboxyl group, double-bond location. These fatty acid families are members of the ω (or n) series. In this system, the last double bond that occurs relative to the carboxyl group is designated with the last letter in the Greek alphabet, omega (ω). However, in this instance, the numerical position of this double bond is numbered relative to the terminal methyl (CH3) group within the molecule. Thus, linoleic acid is denoted as an ω-6 fatty acid family member because the last double-bonded carbon atom occurs 6 carbon atoms from and including the methyl terminus of the hydrocarbon chain. One may also denote these fatty acids by substituting the italicized English letter n for ω. When the n series designation is applied, a combinatorial system is used. Thus, linoleic acid is denoted as 18:2n-6 (ω-6 or n-6 family member).

Humans can synthesize all fatty acids necessary for life except for linoleic acid and α-linolenic acid. Humans cannot synthesize these 2 fatty acids because the specific desaturase enzymes that can introduce a double bond past position 9–10 within a given fatty acid are absent, which prevents the de novo synthesis of linoleic and α-linolenic fatty acids. Thus, the synthesis by elongation and subsequent desaturation of longer-chained fatty acids necessary for life is prohibited. Absence of the necessary desaturase enzymes means that all human unsaturated fatty acids are synthesized from palmitoleic (16:1Δ9 [16:1n-7]), oleic (18:1Δ9 [18:1n-9]), linoleic (18:2Δ9,12 [18:2n-6]), or α-linolenic (18:3Δ9,12,15 [18:3n-3]) acids. Consequently, both linoleic and α-linolenic acids must be obtained via the diet, and each serves as a critical precursor for the synthesis of other necessary long-chain unsaturated fatty acids, such as AA and DHA. In this regard, it is important to note that the efficiency of conversion of linoleic acid to AA, and α-linolenic acid to DHA is suboptimal in the critically ill or malnourished patient.

Enteral Delivery and Metabolism of Dietary Lipids

In the typical Western diet, about 35% of ingested food is in the form of fat and TGs comprise 90% of all ingested dietary lipids within the fat. Various oils, the animal fat in meat or dairy, and plant TGs in seeds (nuts) and vegetables contribute in varying amounts to fat intake. Depending on the source, the TGs within the lipid fraction may contain different proportions of saturated and unsaturated fatty acids of different chain lengths. The TGs in animal fat contain more saturated fatty acids, whereas certain plant TGs may contain more unsaturated fatty acids. The human diet may also contain about 2 to 3 g of the charged phosphoglyceride, phosphatidylcholine, per day. Bile, discussed later in the chapter, provides about 12 g of phosphatidylcholine per day to the intestinal lumen.7,8

Without a mechanism to “solubilize” these substances, humans could not physiologically use TGs for energy, development, or cellular structure. Sophisticated systems allow these enterally ingested substances to be broken down, absorbed, reassembled, and transported throughout the body. When TGs are exposed to the environments of the digestive system, the presence of bile acids is initially important to making them available for use. Bile is produced and secreted by the liver and stored in the gall bladder, and enters the small intestine via the bile duct into the duodenum. Bile is about 92% water and 6% bile acids (bile salts), plus a few other components, such as phosphatidylcholine, cholesterol, and some fatty acids. Bile salts are derivatives of cholesterol and contain either a glycine (glycocholic acid) or taurine (taurocholic acid) molecule conjugated to the cholesterol derivative cholic acid. Glycine is the simplest amino acid. Although often identified as an amino acid, taurine (made from the sulfur-containing amino acid cysteine), is not an amino acid (no carboxyl group); instead, it is a naturally occurring sulfonic acid.

Bile salts are amphipathic. This characteristic is important with respect to their subsequent interaction with TGs as TGs enter the digestive tract and appear within the lumen of the small intestine. Bile salts are effectively detergents, as they interact directly with TGs within the aqueous environment of the small intestine to form an emulsion (ie, a system that involves small, mostly spherical globules known as micelles, comprised of hydrophobic regions oriented internally, with polar or charged groups facing externally, which interact with the polar aqueous system). Why does the emulsion form and remain stable in aqueous systems? Briefly, in an aqueous system, there is a fair amount of thermodynamic disorder (ie, entropy). If a hydrophobic molecule is introduced into such a polar system, a possible outcome would be for water molecules to structurally surround each hydrophobic molecule. This action, were it to occur, would substantially structure the water molecules. This result is not thermodynamically favored; it requires energy input. Consequently, hydrophobic molecules in water (or any polar environment) will cluster into large droplets or regions that exclude water, with water molecules structured only around the surfaces of the large globules. This action results in a much more ultimately disordered system, which favors entropy, and is therefore more thermodynamically stable. In the presence of a detergent such as bile salts (which are not truly dissolved), the lipid molecules occupy very small regions surrounded by detergent molecules and can form a stable emulsion. Therefore, with the detergent-like activity of bile salts, amphipathic TGs form mostly spherical globules with water structured only around the surface of the globule (micelle). These micelles, then, are the form of TG and bile salt emulsions that one finds within the lumen of the small intestine.

The emulsification process and micelle formation make TGs and fatty acid esters available for hydrolysis by intestinal lipases and esterases. This activity is critical for metabolism of long-chain TGs. Ingested glycerol and individual fatty acids of up to 10 carbons in length can be absorbed directly via the villi of the intestinal mucosa and can enter the bloodstream through available capillaries. Medium-chain TG (MCT) lipid emulsions can be directly absorbed without requiring either bile salts for emulsification or energy for uptake. Such MCFAs and glycerol can be directly transported to the liver by lipid carrier proteins. However, long-chain TGs require bile salts for both enzymatic digestion and formation of micelles. Enzymatic activity at the micelle-aqueous interface by lipases preferentially releases fatty acids, first from the sn-3 position, and then, the sn-1 position, from the TGs. These actions result in a

mixture of free fatty acids, in addition to the glycerol molecule with 1 fatty acid attached (a monoglyceride) or 2 fatty acids attached (a diglyceride) in ester linkage.

The major lipase activity within the duodenum involves 2 components, colipase and pancreatic lipase (triacylglycerol lipase), which are both secreted by the pancreas. Colipase is generated from a procolipase by the action of trypsin within the duodenum. This small protein of approximately 10,000 Da specifically binds to pancreatic lipase to form a complex that, in association with the micelle, becomes enzymatically active. This complex, via colipase, binds to the lipid-water interface (polar region) of the micelle. Binding of this complex to the micelle initiates a conformational change in the lipase that alters the structure of the enzyme, allows binding to the hydrophobic region of the micelle, and allows hydrolysis of the embedded TGs to occur. Once bound, the lipase acts on the TGs at the sn-3 position, which releases the fatty acid at that position and forms a 1,2-diglyceride. Then, further enzymatic activity releases the fatty acid from the sn-1 position, which leaves a monoglyceride. In addition to this activity, the enzyme phospholipase A2, secreted by the pancreas (also activated by trypsin action on prophospholipase A2), interacts with phosphatidylcholine and removes the fatty acid at sn-2 to generate lysophosphatidylcholine (which requires bile acids for enzymatic activity). The final result of the lipid hydrolysis of the micelles is, therefore, the generation of free fatty acids released from positions 1 and 3; 1,2-diglycerides; 2-monoglycerides; and lysophosphatidylcholine molecules within the lumen.

The micelles that contain a mixture of free fatty acids and the different mono- and diglycerides interact with and are absorbed by the microvilli of the epithelial cells of the small intestine (intestinal mucosal enterocytes). After absorption by the microvilli, the fatty acids and glycerides within the micelles dissociate, diffuse across the epithelial cell membranes, and enter the cytoplasm. The bile salts are destined to return to the liver via the superior mesenteric and portal veins after reabsorption by the small intestine enterocytes. Inside the cytoplasm, the absorbed free fatty acids, mono- and diglycerides, and endogenous fatty acids previously synthesized by these cells are used for reesterification to form TGs. In this environment, the TGs combine with phospholipids (about 85%), cholesterol esters, and apolipoprotein B-48 (apoB-48) to form immature chylomicrons.

Immature chylomicrons are released by exocytosis from the enterocytes into the lymphatic system. After circulating through the lymphatic system, the immature chylomicrons eventually encounter the bloodstream via the emptying of the thoracic duct into the left subclavian vein. Within the blood, these immature chylomicrons mature through interaction with high-density lipoprotein (HDL), where a donation occurs. The HDL provides the apolipoproteins apoC-II and apoE to form a mature chylomicron—the largest lipoprotein particle to circulate.

Acquisition of the various apolipoproteins that occurs in the blood allows the chylomicron to interact with various tissues. The main classes of apolipoproteins include A, B, C, D, and E. The various lipoprotein classes may have subclasses, such as apoA-I and apoA-IV, apoB-48, apoC-I, or apoC-II. These proteins function in lipid transport, as a cofactor necessary for a particular lipase activity and/or as a structure necessary for a circulating lipoprotein particle to associate with a cell surface receptor. Lipids are delivered in the form of chylomicrons primarily to the liver and to cells that comprise adipose tissue. These chylomicrons also specifically deliver lipids, via appropriate lipoprotein–cell-surface receptor

binding, to the heart, skeletal muscle, and other organs. Indeed, the major energy source used continuously by the heart, resting muscle, and long-term exercised muscle tissue, is lipid.

As lipoproteins circulate through the bloodstream and interact with various tissues, the enzyme lipoprotein lipase within the membranes of the capillary endothelial cells hydrolyzes the TGs to free fatty acids and glycerol, which are absorbed by the different tissues. Over time, the hydrolysis of the chylomicron TG core results in smaller-sized circulating chylomicron enriched in cholesterol and proteins. This form of the chylomicron, known as a remnant, is eventually degraded by the liver via specific liver tissue receptors, and thus removed from the circulation. Endogenously (liver) synthesized cholesterol and TGs are converted within the liver to very low-density lipoprotein (VLDL), which is then secreted into the bloodstream. Within the blood, the gradual enzymatic degradation of VLDL, first to intermediate-density lipoprotein (IDL) and finally to low-density lipoprotein (LDL), occurs. TGs released by this process enter the tissues, and the LDL particles subsequently bind to specific membrane receptors and deliver cholesterol to the tissues. A portion of IDL may bind to the liver and, through the action of hepatic lipase, be remodeled to release LDL into the blood. A portion of LDL may also be taken up by the liver, the proteins degraded and cholesterol released. The return of cholesterol and various lipids from tissues to the liver is accomplished via HDLs. Thus, while LDL delivers cholesterol to the tissues, HDL scavenges this substance from the tissues and returns the material to the liver, where conversion of cholesterol to bile acids takes place. Loss of bile acids through intestinal transport effectively removes cholesterol from the tissues. For these reasons, LDLs are euphemistically known as “bad” cholesterol and HDLs as “good” cholesterol. Any free fatty acids in the blood that are generated by mobilization of lipid stores and conversion to fatty acids and glycerol by lipase activity bind to albumin and circulate through the bloodstream and eventually reach the tissues that demand an energy source.7,8

Parenteral Delivery and Metabolism of Lipid Injectable Emulsions

Terminology

In this edition of the Core Curriculum, the term lipid injectable emulsion (ILE) replaces the term intravenous fat emulsion (IVFE). This change in terminology has been recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) to agree with the US Pharmacopeia terminology and, for patient safety, to avoid confusion between the abbreviation IVFE and the abbreviation for intravenous iron (IVFe).

Types of Lipid Injectable Emulsions

ILEs are oil-in-water emulsions consisting of 1 or more TG–containing oils, glycerin, and a phospholipid emulsifier. Commercial parenteral ILE are provided in TG concentrations of 10%, 20%, and 30% (w/v). These emulsions may also contain other lipid-soluble substances such as vitamin E, vitamin K, phytosterols (plant cholesterol–like substances), and cholesterol. Table 5-2 lists selected oils present in commercially available parenteral emulsions.

TABLE 5-2 Fat Composition of Selected Lipid Emulsions

Emulsion Product	Lipid, %	Energy, kcal/L	Glycerol, g/L	Egg Phosphatide, g/L	Oil Content, g/L			
					Soybean Oil	Olive Oil	MCT Oil	Fish Oil
ClinOleic, Clinolipid	20	2000	22.5	12	40	160	—	—
Intralipid 30%	30	3000	17.0	12	300	—	—	—
Intralipid 20%	20	2000	22.5	12	200	—	—	—
Ivelip	20	2000	25	12	200	—	—	—
Lipofundin MCT	20	1908	25	12	100	—	100	—
Lipofundin N	20	2008	25	12	200	—	—	—
Lipoplus	20	1910	25	12	80	—	100	20
Lipovenoes	20	2000	25	12	200	—	—	—
Nutrilipid	20	2000	25	12	200	—	—	—
Omegaven	10	1120	25	12	—	—	—	100
Smoflipid	20	2000	25	12	60	50	60	30
Structolipid	20	1960	22	12	64% (w/w) LCT	—	36% (w/w) MCT	—

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Structure and Metabolism

The parenteral ILEs listed in Table 5-2 are each structurally designed such that the chylomicron-like particles (micelles) within each emulsion resemble natural chylomicrons with respect to size, core TGs, and a monolayer of phospholipid. Like natural chylomicrons, these spherical pseudo-chylomicrons are, on average, 200 to 500 nm in diameter and have a central TG core surrounded by a phospholipid (emulsifier) envelope.9 In natural chylomicrons, the types of core TGs reflect dietary intake, whereas pseudo-chylomicrons contain a TG core that consists of specific commercial oils (see Table 5-2). Also, whereas natural chylomicrons enter the circulation bearing apolipoproteins and further acquire additional apolipoproteins from HDL, pseudo-chylomicrons enter the circulation with no apolipoproteins but rapidly acquire them from HDL.10

Emulsifying agents, such as egg phosphatide, have a detergent-like action and are added to ILEs to provide a barrier that prevents coalescence of the oil droplets of the emulsion. However, the necessary addition of an emulsification agent can cause a potentially undesirable structure known as a liposome to form. Liposomes, spherical byproducts of the emulsifier used in the emulsification process, are less than 70 nm in diameter and consist primarily of a phospholipid bilayer that surrounds a trapped aqueous phase. Metabolism of each of these entities requires several stages, and the process begins immediately upon entrance into the bloodstream.

Pseudo-chylomicrons behave very similarly to natural chylomicrons with respect to their metabolism. Once in the circulation, pseudo-chylomicrons acquire apolipoproteins and endogenous cholesterol, and,

through cell membrane and other lipoprotein interactions, exchange phospholipids. These dynamically changing pseudo-chylomicrons are efficiently transported in the circulation and engage tissue cell membranes. Cellular interaction (smooth and cardiac muscle and adipose tissue) exposes the pseudo-chylomicron to lipoprotein lipase activity, the result of which is the release of fatty acids from the TG core and movement of free fatty acids into the cells. The degradation of the pseudo-chylomicrons in this manner ultimately results in the appearance of small, TG-poor pseudo-chylomicrons that are known as remnants. Like natural chylomicron remnants, pseudo-chylomicron remnants are removed by the liver. Similarly, liposomes acquire apolipoproteins and undergo, in general, metabolic consequences similar to those of pseudo-chylomicrons.

Dysfunction of this system can lead to hypercholesterolemia and/or hyperlipidemia. These conditions may involve any of the lipoproteins discussed previously. When TGs alone are involved, the condition is known as hypertriglyceridemia. For example, an abnormal lipoprotein known as lipoprotein-X can form from liposomes present in the circulation. Recall that liposomes are the product of emulsifiers that are added to the lipid emulsion. Lipoprotein-X is essentially a spherical bilayer of phospholipid and cholesterol. This abnormal protein, identified in obstructive jaundice and in congenital lecithin-cholesterol acyltransferase deficiency, inhibits lipase activity (both lipoprotein lipase and hepatic lipase) toward natural chylomicrons and pseudo-chylomicrons.11,12 Consequently, a high concentration of lipoprotein-X in the circulation can inhibit lipid metabolism and lead to hypercholesterolemia or hypertriglyceridemia.6,9 The relative number of liposomes within an ILE and, therefore, the potential for lipoprotein-X to form depend on the oil content. Thus, a 10% (w/v) emulsion will contain a larger number of liposomes than a 20% (w/v) emulsion, because of the relative ratio of phospholipid emulsifier to oil. And, although most commercial ILEs are available as 20% (w/v) formulations, ILEs used as vehicles for intravenous (IV) drug delivery (eg, propofol) are usually 10% (w/v) ILE (see Practice Scenario 5-1). Consequently, lipoprotein-X may still form under certain circumstances, and clinicians should consider this risk over the long term or when high amounts of such ILEs have been provided. In the absence of careful monitoring, hypertriglyceridemia, a condition indicated by elevated plasma TG levels, is a possible adverse effect of provision of lipids in PN. It occurs when the body cannot clear TGs from plasma lipids via oxidation and/or storage in adipose tissue, and it may be caused when the supply of lipids into the bloodstream exceeds lipoprotein lipase activity or, as described previously, when lipoprotein lipase activity is reduced.13–15

Hypertriglyceridemia is associated with various clinical and metabolic problems, such as sepsis, renal failure, and pancreatitis.16 Consequently, whenever ILEs are used, clinicians should consistently monitor patients for the threshold plasma TG level above which the exogenously administered lipids cannot be efficiently metabolized.

Fatty Acid β-Oxidation

The degradation (ie, catabolism) of fatty acids—whether saturated or unsaturated, or even-chain or odd-chain—proceeds by oxidative pathways. As previously addressed, the oxidation of fatty acids (and/or lipids) releases substantially more energy than does oxidation of carbohydrate. Cells can use this available energy to help meet the enormous energy demands required for various metabolic processes.

The oxidation of fatty acids is, therefore, critically important to meeting energy demands. The most common pathway of oxidative degradation of fatty acids is known as β-oxidation. The β-oxidation of even-chain fatty acids yields several molecules (equal to one-half the total number of carbons) of the 2-carbon compound acetyl-CoA. For example, complete β-oxidation of the 16-carbon saturated fatty acid palmitic acid would yield 8 moles of acetyl-CoA per mole of palmitic acid. Similarly, oxidation of odd-chain fatty acids yields several molecules of acetyl-CoA and 1 molecule of propionyl coenzyme A (propionyl-CoA) (last oxidation step). Acetyl-CoA can directly enter the citric acid (Krebs) cycle, whereas propionyl-CoA is first converted to succinyl coenzyme A (succinyl-CoA), which also can directly enter the citric acid cycle. An example of the substantial energy yield afforded by this oxidative process is the net synthesis of 129 moles of adenosine-5'-triphosphate per mole of palmitic acid (aerobic respiration coupled to oxidative phosphorylation) upon the complete β-oxidation of this fatty acid. For β-oxidation to proceed, free fatty acids in the cytoplasm must first be transported into the mitochondrial matrix. Generally, fatty acids of up to 10 carbons in length may simply cross the mitochondrial membranes and reach the mitochondrial matrix without the requirement for special transport mechanisms. The first step in the β-oxidation of these molecules is the thioester linkage of coenzyme A (CoA) to the fatty acid by an acyl-CoA synthetase. Acyl-CoA synthetase enzymes are classified by their chain-length specificity. In contrast to the unrestricted movement of SCFAs into the mitochondrial matrix, long-chain fatty acids (LCFAs) must be shuttled across the membranes by specific carrier and translocase mechanisms that require L-carnitine. The first step in this translocation process is the covalent connection of the fatty acids to CoA by acyl-CoA synthetases. These enzymes are located within the outer membranes of mitochondria. Once the fatty acid is activated in the mitochondrial outer membrane by addition of CoA, the acyl-CoA products enter the intermembrane space and are transported to the mitochondrial matrix by a specific L-carnitine shuttle system. When the fatty acid–CoA derivative reaches the inner membrane surface, the fatty acid is transferred from CoA in ester linkage to the hydroxyl group of carnitine and subsequently translocated across the inner membrane to the matrix region. Before release from the inner membrane, the fatty acid–carnitine derivative associates with an enzyme that transfers the fatty acid from carnitine to CoA and the fatty acid–CoA derivative is released to the matrix. Carnitine is subsequently transported back across the inner membrane to the intermembrane space, and there it can again participate in subsequent shuttles of CoA-activated fatty acids to the mitochondrial matrix. Once in the matrix, the fatty acid–CoA derivative is acted upon by several enzymes that progress down the length of the fatty acid from the carboxyl group to the last methyl group to oxidize the fatty acid by 2 carbon lengths at a time (acetyl-CoA is produced). Each round of oxidation yields a remaining fatty acid that is 2 carbons shorter than the previous molecule. This activity repeats, round after round, until the entire fatty acid has been oxidatively degraded to several molecules of acetyl-CoA (or, in the case of odd-numbered fatty acids, several molecules of acetyl-CoA and 1 molecule of propionyl-CoA). Unsaturated fatty acids undergo identical enzymatic conversion, except that additional enzymatic steps cope with a double bond. The double bond is essentially shifted in position, which allows a 2-carbon segment to be oxidized and released as acetyl-CoA.

Lipid Recommendations for Individuals Requiring Specialized Nutrition Support

Patients receiving specialized nutrition support require a mixed substrate of carbohydrate and lipids to meet metabolic and energy needs, but the ideal amount of lipids to administer is unknown. Lipid recommendations usually exceed quantities necessary to prevent essential fatty acid deficiency (EFAD). Higher levels of lipids are used because (1) lipids provide the highest energy yield among fuel substrates; (2) the oxidative metabolism of lipid produces less carbon dioxide than similar glucose loads; and (3) specific fatty acids may potentially modify immune and inflammatory responses.

Patients who receive enteral or parenteral lipid formulations may be at risk for EFAD if insufficient quantities of linoleic acid and α-linolenic acid are provided. Reports have suggested that providing between 1% and 4% of total energy as linoleic acid is sufficient to prevent EFAD.17,18 The requirement for α-linolenic acid is lower (0.25% to 0.5% of total energy).18,19 A variety of plant oils have been used as the lipid source to provide essential fatty acids for patients requiring specialized nutrition support (Table 5-3).20 As shown in Table 5-3, soybean and corn oil are rich sources of linoleic acid that contain, respectively, 54% and 61% of this fatty acid. Soybean and canola oils are each good sources of α-linolenic acid that provide 7% and 10%, respectively, of this essential fatty acid (EFA).

TABLE 5-3 Comparison of Dietary Fatty Acids in Common Oils

	Breakdown of Fatty Acid Content, %[a]			
Dietary Fat	Saturated Fatty Acids	Linoleic Acid	α-Linolenic Acid	Monounsaturated Fatty Acid
Canola oil	6	22	10	62
Safflower oil	10	77	Trace	13
Sunflower oil	11	69	0	20
Corn oil	13	61	0	25
Olive oil	14	8	1	77
Soybean oil	15	54	7	24
Palm oil	45	12	1	37
Palm kernel oil	52	10	1	11
Coconut oil	92	2	0	6
Cod liver oil[b]	23	1	1	47

[a]Normalized to 100%.

bCod liver oil has approximately 27% eicosapentaenoic acid and docosahexaenoic acid.

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Enteral Nutrition Recommendations

To meet EFA requirements, commercial enteral formulas include a variety of oils, including corn, soybean, safflower, and canola oils (Table 5-4). There is no absolute recommendation for a given enteral formula's lipid content; consequently, as demonstrated by Table 5-4, the lipid content of common enteral formulas varies widely. Among commercial enteral formulas, elemental products generally provide the least amount of fat. In contrast, polymeric enteral products often provide more than 25% of energy in the form of fat, and this percentage increases as formulas are concentrated into more energy-dense solutions. Current enteral fat recommendations are driven primarily by disease state and must be considered in context with the quantity and kind(s) of lipids provided. Chapters in Part III of this book discuss disease-specific lipid recommendations.

TABLE 5-4 Fat Composition of Selected Enteral Formulas

	Fat					
Formula	% of Energy	Source	g/L	Linoleic Acid, g/L	MCTs, g/L	*n*-3 Fatty Acids, g/L
Compleat	34	Canola oil	40	8.6	0	2.6
Diabetisource AC	44	Canola oil, refined fish oil (anchovy, sardine)	58.8	10	0	6.2
Fibersource HN	29	Canola oil, MCTs	40	6.6	8.0	2.7
Glucerna 1.0 Cal	49	High-oleic safflower and canola oils	54.5	7.8	0	0.7
Glucerna 1.2 Cal	45	High-oleic safflower and canola oils	60.0	10.25	0	2.52
Glucerna 1.5 Cal	45	High-oleic safflower and canola oils	75.0	12.8	0	3.15
Glytrol	42	Canola oil, high-oleic safflower oil, MCTs	47.6	6.8	9.6	1.8
Impact	25	Palm kernel oil, refined fish oil (anchovy, sardine), high-linoleic safflower oil, high-oleic sunflower oil	28.0	3.0	0	2.5
Impact Peptide 1.5	38	MCTs, refined fish oil (anchovy, sardine), canola oil, soybean oil	63.6	8.3	31.6	6.1
Isosource 1.5 Cal	35	Canola oil, MCTs	59.2	9.7	12.0	4.0
Isosource HN	29	Canola oil, MCTs	40.0	6.5	8.0	2.7
Jevity 1 Cal	29	Canola oil, corn oil, MCTs, soy lecithin	34.7	10.0	6.6	1.5
Jevity 1.2 Cal	29	Canola oil, corn oil, MCTs, soy lecithin	39.3	11.2	7.9	2.0
Jevity 1.5 Cal	29.4	Canola oil, corn oil, MCTs, soy lecithin	49.8	13.5	9.5	2.6
Nepro with Carb Steady	48	High-oleic safflower and canola oils	95.8	14.5	0.0	2.5

Novasource Renal	45	Canola oil	100.0	20.3	0.0	8.4
Nutren 1.0	30	Canola oil, MCTs	34.0	5.8	6.8	2.4
Nutren 1.0 Fiber	30	Canola oil, MCTs	34.0	5.9	6.8	2.4
Nutren 1.5	35	Canola oil, MCTs	60.0	10.0	12.0	4.1
Nutren 2.0	41	MCTs, canola oil	92.0	9.8	46	4.0
Nutren Pulmonary	56	MCTs, canola oil, corn oil	94.8	15.8	40	3.9
NutriHep	12	MCTs, canola oil, corn oil	21.2	2.0	14.8	0.5
Osmolite 1 Cal	29	Canola oil, corn oil, MCTs, soy lecithin	34.7	9.5	6.9	1.8
Osmolite 1.2 Cal	29	Canola oil, high-oleic safflower oil, MCTs, soy lecithin	39.3	5.4	7.5	1.3
Osmolite 1.5 Cal	29	Canola oil, high-oleic safflower oil, MCTs, soy lecithin	49.1	6.7	9.8	1.5
Oxepa	55.2	Canola oil, MCTs, marine oil, borage oil, soy lecithin	93.8	15.9	23.5	11.7
Peptamen	33	MCTs, soybean oil	39.0	5.2	27.6	0.7
Peptamen with Prebio	35	MCTs, soybean oil	40	5.2	28	0.7
Peptamen 1.5	33	MCTs, soybean oil	56.0	6.6	40	0.8
Peptamen 1.5 with Prebio	34	MCTs, soybean oil	56	6.6	40	0.8
Peptamen AF	40	MCTs, refined fish oil (anchovy, sardine), soybean oil	54	6.3	28	3.8
Peptamen Intense VHP	34	MCTs, refined fish oil (anchovy, sardine), high-linoleic safflower oil, soybean oil	38.0	4.4	18	2.3
Perative	25	Canola oil, MCTs, corn oil, soy lecithin	37.3	6.8	14.9	1.2
Pivot 1.5	30	Marine oil/MCT structured lipid, soy oil, canola oil, soy lecithin	50.8	10.6	9.4	6.9
Promote	23	Soy oil, MCTs, safflower oil, soy lecithin	26.0	11.7	4.7	1.3
Promote with Fiber	25	Soy oil, MCTs, safflower oil, soy lecithin	28.2	12.2	4.7	1.3
Pulmocare	55.1	Canola oil, MCTs, corn oil, high-oleic safflower oil, soy lecithin	93.3	18.4	18.7	4.8
RenalCal	36	MCTs, canola oil, corn oil	82	6.2	60	1.4
Replete	30	Canola oil, MCTs	34.0	5.6	6.8	2.4
Replete Fiber	30	Canola oil, MCTs	34.0	5.6	6.8	2.3
Suplena with Carb Steady	48	High-oleic safflower oil, canola oil	95.8	16.1	0.0	3.1
Tolerex	2	Safflower oil	2	1.2	0.0	0.0
TwoCal HN	40.1	High-oleic safflower oil, MCTs, canola oil, soy lecithin	90.5	10.1	16.9	1.1
Vital 1.0 Cal	33	Canola oil/MCT structured lipid, canola oil, MCTs, DATEM	38.1	3.5	18	1.6
Vital 1.5 Cal	33	Canola oil/MCT structured lipid, canola oil, MCTs, DATEM	57.1	5.5	27	2.5
Vital AF 1.2 Cal	39	Marine oil/MCT structured lipid, MCTs, canola oil, soy oil, DATEM	53.9	6.3	24	7.3
Vital High Protein	20	MCTs, marine oil, corn oil	23.2	0.95	11.6	4.2
Vivonex Plus	6	Soybean oil	6.7	4	0.0	0.5
Vivonex RTF	10	Soybean oil, MCTs	11.6	3.6	4.8	0.5
Vivonex T.E.N.	3	Safflower oil	3	2.2	0.0	0.0

DATEM, diacetyl tartaric acid esters of mono- and diglycerides; MCT, medium-chain triglyceride.

Parenteral Nutrition Recommendations

Two 100% soybean oil–based emulsions are currently available in the United States for IV use. In each of these emulsions, linoleic acid provides approximately 55% to 60% of total energy and approximately 3% to 4% of total energy is from α-linolenic acid.

A newer generation alternative ILE, Smoflipid, has recently become commercially available in the United States. Like all alternative ILEs, this emulsion is designed to meet EFA requirements and is composed of a blend of soybean oil, olive oil, fish oil, and MCTs. Another blended, alternative ILE, ClinOleic/Clinolipid, composed of soybean and olive oils is approved but not commercially available in the United States. The amount of EFAs in the alternative emulsions may vary significantly when compared with soybean oil–based ILEs; consequently, the blended oils must be balanced to provide sufficient concentrations of EFAs. These newer generation ILEs reduce the soybean oil portion of the emulsion with the intention of lowering potential inflammatory mediators that may be associated with higher levels of linoleic acid. To prevent inadequate EFA dosing, the EFA content of alternative ILEs that contain significantly lower soybean oil should be identified before they are administered. Compared with soybean oil, Smoflipid and ClinOleic/Clinolipid contain approximately 67.0% to 66.2% less linoleic acid, respectively.

To meet EFA requirements in adult PN patients with 100% soybean oil–based ILEs, a variety of lipid regimens may be prescribed. Often, 500 mL of a 20% ILE may be given weekly.21 Given the lower concentration of linoleic acid found in Smoflipid and ClinOleic/Clinolipid, the lipid dosage for patients receiving either of these products should be calculated based on their energy requirements and whether any other sources of lipids are provided. The 2016 critical care guidelines from ASPEN and the Society of Critical Care Medicine (SCCM) suggest that when using soybean oil emulsion as the sole IV fat source, the ILE should be held for the first week or given at a maximum of 100 g/wk if there is a concern or risk for EFAD.22 European guidelines suggest that most patients on long-term home PN with chronic intestinal failure without ongoing metabolic complications can be safely treated with provision of no more than 1 g of IV soybean-based lipid emulsion per kg per day.23

PN lipid dosing depends on energy expenditure, the patient's clinical status, body weight, tolerance, ability to metabolize the lipid emulsion, and consideration of additional energy given to the patient.24 Before starting the infusion, clinicians should obtain the patient's serum TG levels to establish the baseline value. In adult patients requiring PN, ILEs should not exceed 2.5 g lipid per kg per day.25 In critically ill patients requiring PN, the recommendations are more consistently conservative, with some data supporting less than 1 g lipid per kg per day.25–27 These recommendations for lipid provision are based on evidence that the potential for metabolic adverse reactions associated with rapid infusion and excessive amounts of parenteral lipids may be reduced while simultaneously improving capacity for lipid clearance (see Practice Scenario 5-1).28 Additional recommendations for ILEs include limiting the infusion rate so it does not exceed 0.11 g/kg/h to prevent potential adverse reactions or toxicities associated with rapid infusion.29

Practice Scenario 5-1

Question: What strategies can prevent adverse metabolic outcomes when propofol is used concomitantly with nutrition support?

Scenario: A 62-year-old woman (height, 157 cm; weight, 50 kg; body mass index, 20.3) with a past medical history of alcohol abuse and chronic obstructive pulmonary disease was involved in a motor vehicle collision. After being admitted to the hospital, the patient underwent an exploratory laparotomy, which found blunt hepatic trauma and mesentery injuries. The nutrition assessment provided a Nutrition Risk in Critically ill (NUTRIC) score (without the interleukin-6 value) of 6, and indirect calorimetry was used to determine that the patient's resting energy expenditure was 1550 kcal/d, with a respiratory quotient of 0.79. The initial diet order was for trophic enteral feeding (polymeric formula 30% lipid). On postoperative Day 3, the patient's clinical condition declined. She required vasopressor administration and was in respiratory failure. Physical examination showed that her abdomen was firm and distended. A kidney, ureter, and bladder x-ray was consistent with postoperative ileus. Since admission, the patient received a continuous infusion of propofol (Diprivan 1%, Fresenius Kabi, USA) for sedation. Sedation was problematic because the patient was experiencing alcohol withdrawal, and the propofol dose was subsequently increased to a relatively constant 15 mL/h (30 mg/kg/h), providing 36 g of fat (396 kcal) per 24 hours. The patient's serum electrolytes were within normal limits. Her serum triglyceride (TG) level was 331 mg/dL on Day 5 and 550 mg/dL on Day 7.

Intervention: On Day 4 of admission, clinicians determined that the patient had failed trophic enteral feedings, and her diet order was changed to a 3-in-1 parenteral nutrition (PN) prescription containing 20 g of a 20% lipid injectable emulsion (ILE).

Answer: Propofol alone was providing 26% of the patient's energy requirements (0.72 g lipid per kg body weight). Current propofol administration alone provided an acceptable level of lipid dose for this patient (less than 1 g/kg/d). With the addition of 20 g of a 20% ILE as part of the PN prescription, this patient would receive 1.12 g fat per kg per day. Because of the elevated serum TG level and potential variation in propofol administration, clinicians should monitor the patient's serum TG concentration frequently (eg, twice per week). To lower the total fat dose and possibly improve TG clearance, lipids should be removed from the PN solution. Recommendations for acceptable serum TG levels are less than 250 mg/dL 4 hours after ILE infusion for "piggy-backed" lipids and less than 400 mg/dL for continuous ILE infusion.50 The patient should be started on hypocaloric PN (equal to or less than 20 kcal/kg/d) because her nutrition risk is high (NUTRIC score = 6).

Rationale: The patient was at significant risk for hypertriglyceridemia and/or fat overload syndrome because of her critical illness and propofol infusion. Fat overload syndrome, a rare complication of ILE infusion, may occur when the dose or rate of lipid infusion exceeds the body's lipid clearance capacity. The presence of the higher concentration of phospholipids in 10% ILE (used as the drug vehicle for propofol) may result in an increase in lipoprotein-X particles that compete with TG-rich particles for lipoprotein lipase. This competition for lipase activity may lead to decreased TG hydrolysis, with the concomitant result of an increase in circulating TGs.

Manifestations of Essential Fatty Acid Deficiency in Patients Receiving Specialized Nutrition Support

In 1929, Burr and Burr documented EFAD in animals,30 but it was not identified in humans until the development of PN 4 decades later. In the early 1970s and 1980s, biochemical and clinical manifestations of deficiencies of both linoleic and α-linolenic fatty acids were observed in patients requiring PN for extended periods of time (2 to 4 weeks).31–34 The most notable clinical change associated with linoleic acid deficiency is a dry, scaly skin rash. However, other clinical symptoms have been noted, including increased susceptibility to infection, impaired wound healing, and immune dysfunction.35–37 Biochemical changes that occur in response to linoleic acid deficiency are manifested by a decrease in linoleic acid and AA (tetraenoic acid) levels and an increase in the mead acid (triene acid, 20:3n-9) level. Mead acid is primarily produced in humans in the absence of EFAs. A triene:tetraene ratio greater than 0.2 (Holman index) has been used to identify the presence of EFAD.38 The time required to exhibit an EFAD in adults varies depending on the individual's underlying disease and nutrition status. EFAD may occur rapidly in patients receiving continuous fat-free PN administration because of elevated insulin levels that prevent adipose tissue lipolysis. EFAD may typically be seen in patients after 4 weeks of fat-free PN, although clinical signs may be detected earlier (eg, between 10 and 20 days).24,32,39 Hypocaloric fat-free PN or a cyclic feeding schedule of fat-free PN may extend the period of time before the patient exhibits EFAD. It is thought that when PN is cycled or hypocaloric PN is provided, EFAs are mobilized and enter the circulation as a result of increased lipolysis of endogenous fat stores in response to a reduction in serum insulin concentration. In addition, hypocaloric feeding prevents the risk of hepatic dysfunction that may occur if the energy deficit (caused by the removal of lipids) is corrected by increasing the energy from dextrose or protein to maintain energy requirements. When ILEs are contraindicated, short-term hypocaloric, fat-free PN has been shown to be safe and appropriate for the critically ill patient (see Practice Scenario 5-2).22,40,41

Practice Scenario 5-2

Question: How can essential fatty acid deficiency (EFAD) be prevented when a lipid-free parenteral nutrition (PN) regimen is initiated in the intensive care unit (ICU)?

Scenario: A 57-year-old woman (height, 167 cm; weight, 82 kg; body mass index, 29.4) was admitted to the ICU of a regional hospital with respiratory failure related to pneumonia. Patient had a history of type 1 diabetes and hypertriglyceridemia. Her estimated energy requirement was 2100 kcal/d and her estimated protein requirement was 110 g/d. On hospital Day 2, polymeric enteral feeding was started at 15 mL/h. On hospital Day 3, the patient exhibited clinical signs of feeding intolerance, which was confirmed by x-ray as an ileus. Enteral feeding was discontinued, but the patient's condition worsened as the day progressed, and severe sepsis was diagnosed. On hospital Day 7, the patient's condition had stabilized, and her organ systems and metabolic parameters were improving. The following laboratory data were documented:

Serum glucose: 167 to 255 mg/dL (range during hospitalization)

Serum triglycerides (TGs): Day 3: 499 mg/dL; Day 4: 563 mg/dL; Day 7: 479 mg/dL

Intervention: On hospital Day 7, a fat-free, hypocaloric PN prescription formula (1700 kcal, 90 g protein) was initiated.

Answer: A decision to hold PN during the acute phase of severe sepsis was made for this patient.22 In this case, in light of elevated TGs, to prevent excessive glucose administration, and to improve the possibility of mobilizing essential fatty acids (EFAs) from endogenous lipid stores, a fat-free hypocaloric feeding regimen was initiated at 80% of estimated needs.41 After approximately 14 days of not receiving any lipid, or when clinical signs and symptoms indicate the possibility of EFAD, plasma fatty acid profiles should be obtained (Holman index) to assess the patient for EFAD.

Rationale: Patients should be monitored for EFAD if all sources of lipids are removed from the diet for more than 2 to 4 weeks. The dosing of lipid injectable emulsions (ILEs) depends on energy expenditure, the patient's clinical status, body weight, tolerance, and ability to metabolize lipids. Providing 2% to 4% of the energy requirement as linoleic acid may correct EFA insufficiency. Clinicians should calculate the linoleic acid dose from 100% soybean ILE or an alternative ILE to ensure adequate dosing of EFAs. Initiation of low-dose or trophic enteral feeding may also be used to offset risk of EFAD. A polymeric enteral formula containing soybean oil and a mixture of other high-linoleic oils may be used. Generally, a polymeric enteral formula that provides 10% to 15% of the patient's total energy requirements will supply adequate EFAs. However, when the patient is at high risk for fat malabsorption, or when enteral feeding is interrupted or stopped for a significant period (14 days) with no other lipid source provided, the linoleic acid dose and EFAD risk should be evaluated.

When the diet is deficient of only α-linolenic acid, eicosatrienoic acid levels remain within normal range, and no rash is detectable. Clear evidence of α-linolenic acid deficiency was first reported in a 1982 case study by Holman and colleagues of a 6-year-old girl who had been maintained on PN solution lacking α-linolenic acid.31 The observed symptoms of deficiency were primarily neurological abnormalities, including numbness, paresthesia, blurred vision, and difficulties in walking.

Several years later, α-linolenic acid deficiency was reported in elderly nursing home residents who were receiving intragastric feeding of an elemental formula that did not contain α-linolenic acid.42 With the addition of α-linolenic acid to these elderly patients' nutrition regimen, clinical symptoms disappeared.

Interestingly, Heird and Lapillonne43 reported that the metabolites of either linoleic acid metabolism (ie, γ-linolenic acid [GLA], dihomo-γ-linolenic acid [DGLA], and AA) or α-linolenic acid metabolism (ie, EPA and DHA) may correct the clinical symptoms of EFAD. Also, more recent data suggest that fish oil lipid emulsion alone may satisfy the EFA requirements for humans. In studies of children who received fish oil monotherapy, none of the patients expressed biochemical parameters or other indications of EFAD after 3 years or more of treatment.44 However, it is unknown whether linoleic acid and α-linolenic

acid, per se, have specific functional properties that cannot be met by provision of their fatty acid metabolites.

Evidence suggests that the risk of EFAD is increased in some patients who require home PN solutions.45–47 Evaluation of the EFA status of home PN patients has revealed alterations in fatty acid profiles (decreases in linoleic acid plasma levels, increases in AA plasma levels, and an increase in the AA:linoleic acid ratio) and biochemical signs associated with EFAD.46–49 ILEs may not be required or provided for all patients receiving home PN, and data are insufficient to recommend the optimal amount of EFAs required for these patients. Home PN patients may be at risk for adverse events because of the amount of dietary fat consumed, the degree of intestinal inefficiency, the frequency of ILE provided in the PN solution, and the availability of endogenous lipid stores. Ling and colleagues48 have demonstrated that linoleic acid provided at 3.2% of total energy with a daily average of 0.24 ± 0.13 g fat per kg is sufficient to prevent the development of EFAD in home PN patients. Others have reported that a weekly minimum of 1.0 g fat per kg of body weight or 500 mL of 20% ILE weekly may be necessary to correct or avoid biochemical alterations associated with EFAD.46,50

Recently, Gramlich and associates51 described 3 cases in which EFAD was suspected in patients on alternative ILEs to be a potential cause of abnormal liver enzymes. The fatty acid profiles revealed reduced linoleic acid and elevated mead acid levels, which may suggest EFAD; however, when the patients were further examined using the triene:tetrane ratio, this index remained well below the level that would indicate EFAD. In these case reports, it is important to note that the diagnosis of EFAD was made by the observation of reduced linoleic acid levels and elevated mead acid levels. With alternate ILEs in which the amount of linoleic acid may be reduced, the fatty acid profile should be interpreted cautiously. ILEs with high concentrations of ω-9 fatty acids may result in higher conversion of mead acid. Serum fatty acid profiles may reflect linoleic acid levels that are low but remain adequate for prevention of EFAD. Reduced linoleic acid composition of alternative ILEs could result in false-positives for EFAD if the definitive diagnosis of a triene:tetraene ratio greater than 0.2 is not used. The 3 patient cases demonstrated daily averages of (1) 11.4 g linoleic acid (4.7% of total energy); (2) 13 g linoleic acid (7% of total energy); and (3) 7.54 g linoleic acid (3.7% of total energy); the reported energy values were based on energy intake or calculated requirements.51

Eicosanoid Biosynthesis: ω-6 and ω-3 Fatty Acids

Fatty acids are indirectly involved as metabolic precursors for eicosanoids, lipid substances that can profoundly affect platelet aggregation, neurotransmitter release, vascular function, infection responses, inflammatory activity, and immune system activity.52–54 Eicosanoids contain 20 carbons and include prostaglandins, leukotrienes, thromboxanes, prostacyclins, lipoxins, resolvins, and protectins (neuroprotectins). Consequently, under certain conditions, these byproducts of fatty acid metabolism can have far-ranging and potentially detrimental effects. Members of the ω-6 and ω-3 series of fatty acids (AA and EPA, respectively) are the precursors for the intracellular synthesis of inflammatory eicosanoids. The most common dietary sources of ω-6 fatty acids are plants such as soybean, safflower, and corn. Plant dietary sources of ω-3 fatty acids are found in canola oil, flax seed, and leafy vegetables. Fish such as tuna, sardines, and salmon are also sources of ω-3 fatty acids. AA may be ingested in the

diet via intake of meat or organ tissue. This lipid is also synthesized when dietary linoleic acid is desaturated by the enzyme Δ6-desaturase to form GLA (18:3n-6), which in turn is converted by elongation enzyme 2-carbon addition to form DGLA (20:3n-6). This compound is desaturated by Δ5-desaturase to form, in the final reaction of this pathway, AA. The ω-3 fatty acid, α-linolenic acid (18:3n-3), is the EFA that is the precursor of EPA and DHA, although the enzymatic conversion of α-linolenic acid to EPA and DHA is inefficient. Although EPA and DHA may be somewhat enzymatically interconvertible (alternate pathways may exist), the most efficient source of EPA and DHA is via the diet. Both EPA and DHA are critical to development of proper eyesight and brain function, and EPA is the precursor of the less biologically active inflammatory mediators of the 3-series prostaglandins and 5-series leukotrienes eicosanoid series. Other anti-inflammatory prostaglandins and clot-inhibiting thromboxanes of the 1-series, however, may be synthesized from DGLA (ω-6), one of the intermediates in the AA synthesis pathway.

AA, common to membrane phospholipids, usually occupies the sn-2 position and is almost always found at this position within the important membrane phospholipid phosphatidylinositol. During membrane cell signaling events, a possible outcome is the activation of phospholipase A2, the enzyme that acts on membrane phospholipids to release fatty acids from the sn-2 position.55 Release of AA sets in motion subsequent intracellular metabolic activity via the COX pathway that leads to the synthesis of the 2-series of prostaglandins, including PGE2, and thromboxanes, including thromboxane A2. AA is initially converted to prostaglandin H2 by the enzymes COX-1 and COX-2. Subsequently, prostaglandin H2, as substrate for prostaglandin synthesis, is converted to the various prostaglandins that include PGD2, PGE2, PGF2α, PGI2, and 15-d-PGJ2. The enzyme COX-1 is generally thought to be constitutively expressed in almost all bodily tissues and is involved in many bodily “housekeeping” activities. The enzyme COX-2, on the other hand, is an inducible enzyme that is directly involved in inflammation.56,57 Entrance of AA into the lipoxygenase pathway leads to the synthesis of the 4-series leukotrienes that include LTB4. The 2-series of prostaglandins and thromboxanes are powerful inflammatory mediators that can induce significantly detrimental inflammatory effects. For example, PGE2 has been extensively studied and is a known immunosuppressant.58–60 In contrast, ω-6 fatty acid–derived 1-series prostaglandins and thromboxanes and ω-3 fatty acid–derived 3-series prostaglandins and thromboxanes and 5-series leukotrienes (via COX-1 and COX-2 and lipoxygenases) are less immunosuppressive and less inflammatory. For example, thromboxane A2 strongly stimulates platelet aggregation and vasoconstriction. In contrast, platelets fail to aggregate and vasoconstriction is mild at best in the presence of thromboxane A3.61,62

Additionally, ω-3 fatty acids are competitive inhibitors of 2- and 4-series eicosanoid formation from AA, and thus their physiological availability directly influences synthesis of these substances.63 Because of these desirable consequences, provision of ω-6 fatty acids such as GLA and DGLA in addition to the ω-3 fatty acid EPA in the diet may serve to attenuate inflammatory events.64 For example, dietary supplementation with fish oil can result in a lower chemotactic activity displayed by neutrophils and monocytes, and in vitro exposure of endothelial cells, macrophages, or lymphocytes to fish oil ω-3 fatty acids can lower adhesion molecule expression by these cells.65

AA, EPA, and DHA are also the precursors of novel anti-inflammatory eicosanoids (ie, lipoxins, resolvins, and protectins) that contribute to the active resolution of an inflammatory response. Lipoxins are metabolic derivatives of AA that are generated during an inflammatory response and serve as powerful anti-inflammatory mediators. For example, lipoxin A4 inhibits LTB4-stimulated neutrophil chemotaxis through specific receptor signaling, and simultaneously attracts monocytes to apoptotic cells generated as a result of inflammation.66–68 Resolvins of the E-series, generated from EPA, modify inflammation by, for example, inhibiting polymorphonuclear leukocyte transmigration and protecting the large bowel in colitis. Among other activities, resolvins of the D-series, generated from DHA, protect kidney tissue from ischemic injury. Protectins such as PD1 are substances derived from DHA that also play an active role in resolution of an inflammatory response. When these same substances are produced in neural tissue, they are known as neuroprotectins (eg, NPD1) to denote the tissue of origin. These substances, like lipoxin A4, inhibit neutrophil migration. In addition, protectins reduce the tissue damage caused by stroke and, among several other inflammation-resolution activities, help to protect the liver from inflammatory damage.69 Although these substances are clearly critical to physiological processes, their specific role(s) in the clinical aspects of EN and PN remain to be determined.

The Clinical Impact of Specific Fatty Acids in Enteral Nutrition

ω-3 Fatty Acids

Research on Cardiovascular and Cerebrovascular Disease Risk

Considerable research has been done on the potential cardiovascular and cerebrovascular benefits of supplementation with ω-3 fatty acids. Earlier studies suggested that dietary supplementation with both EPA and DHA may reduce cardiac-associated mortality.70,71 In addition, initial evidence indicated that the levels of all-cause mortality, stroke, and cardiovascular disease (CVD) among individuals examined throughout the world were inversely related to the level of long-chain ω-3 fatty acid dietary intake.72 However, more recent data offer significantly different conclusions with respect to the effect of EPA and DHA dietary supplementation on CVD. Although increased dietary intake of these ω-3 fatty acids effectively lowers circulating TG levels, a known risk factor for CVD, DHA supplementation increased LDL cholesterol levels.73,74 Also, even when ω-3 supplementation has been associated with improvements in CVD risk factors, it has failed to demonstrate benefit relative to CVD reduction. Indeed, examination and analysis of over 20 years of randomized trials and other studies of ω-3 dietary supplementation (total N = more than 83,000 participants), the overall conclusion is that ω-3 supplementation does not lower time to death from cardiovascular causes, hospital admission related to cardiovascular causes, cardiovascular endpoints, postoperative atrial fibrillation, all-cause mortality, sudden death, myocardial infarction, or stroke.75–80

When considering the implications of the research on ω-3 fatty acid supplementation described here, clinicians should be aware that treatment guidelines have recently been revised to reflect evolving views of serum cholesterol levels as risk factors for disease. In November 2013, a joint task force for the American College of Cardiology and American Heart Association81 released new guidelines for the treatment of blood cholesterol that no longer recommend treatment target goals for LDL cholesterol

and non-HDL cholesterol, factors that have historically been evaluated in studies of ω-3 fatty acids and disease risk, including some of the research noted here. These new treatment guidelines are controversial.82

A systematic review and meta-analysis of data that represented almost 800,000 individuals found that fish consumption, although moderate in effect, was significantly associated with reduced cerebrovascular events. In contrast, long-chain ω-3 fatty acids measured as circulating biomarkers in observational studies or as supplements in primary and secondary prevention trials were not statistically associated with cerebrovascular events.83 Consequently, fish may offer cardiovascular benefits beyond that assumed for the ω-3 fatty acids the fish provide.

Supplementation in Critical Illness

The 2016 ASPEN/SCCM guidelines for nutrition support therapy in critical illness recommend that clinicians avoid the routine use of (1) all specialty formulas in critically ill patients in a medical ICU and (2) all disease-specific formulas in the surgical ICU.22 Specifically, the guidelines state that immune-modulating enteral formulations of arginine with other agents—including EPA, DHA, glutamine, and nucleic acid—should not be used routinely in the medical ICU; furthermore, these products and other similar formulations (eg, fish oil with or without arginine) should not be administered to severely septic patients.22

The ASPEN/SCCM guidelines further state that a recommendation cannot currently be made regarding the routine use of an enteral formulation characterized by an anti-inflammatory lipid profile (eg, ω-3 fish oils, borage oil) and antioxidants in patients with acute respiratory distress syndrome (ARDS) or severe acute lung injury, given the significant amount of conflicting data.22 Other recent investigations, reviews, and meta-analyses reiterate the lack of consistent evidence regarding the routine use of these enteral formulations in patients with ARDS and support the current lack of recommendation.84–86

The ASPEN/SCCM guidelines recommend formulations that contain fish oil and arginine be considered in severe trauma patients and further recommend the use of either arginine-containing immune-modulating formulations or EPA/DHA supplementation with standard enteral formula in patients with traumatic brain injury (TBI).22 In a 2016 review of experimental animal studies, Trépanier and colleagues concluded that provision of ω-3 PUFA in the form of DHA ameliorates inflammatory mediators in TBI.87 In a retrospective analysis of 240 patients with isolated TBI, Painter et al showed that tube-fed patients who received enteral immune-enhancing formula (with arginine, glutamine, EPA, and DHA), when compared with those receiving a standard enteral formula, had fewer cases of bacteremia ($P < 0.05$) and higher posttreatment prealbumin levels in Weeks 2 and 3 of treatment ($P = 0.006$ and $P = 0.04$, respectively).88 However, patients who received the immune-enhancing formula remained longer in the ICU ($P = 0.02$) and spent more days on mechanical ventilation ($P = 0.001$). The hospital length of stay and mortality were not significantly different between the 2 groups.88

The ASPEN/SCCM guidelines recommend that an immune-modulating formula (containing both arginine and fish oils) be routinely used in the surgical ICU for postoperative patients who require EN.22 Recent studies and analyses support the use of such formulas.89,90 In summary, there is support for the

consideration (severe trauma) or routine use (TBI and surgical ICU) of enteral regimens that use immune-enhancing formulations.

ω-9 Fatty Acids

Diets containing oils high in ω-9 fatty acids (primarily, oleic acid within olive oil) have been reported to be beneficial for health because they lower cholesterol and TG levels without the negative effects of lipid peroxidation.91 A recent study with more than 7000 subjects showed that the risk of stroke may be significantly reduced when a diet high in olive oil is used intensively.92 Because high-oleic oils are stable and have a favorable fatty acid profile, they are often used in enteral formulas (Table 5-4). Enteral formulas using engineered sunflower and safflower oils may have an average oleic acid content greater than 70%, which is comparable to the oleic acid content in olive oil.93 Historically, polymeric formulas with high to moderate oleic acid content have been examined in research studies of Crohn's disease with mixed results, which may be partially explained by the source and amount of oleic acid used (synthetic trioleate vs olive oil) and the contribution of other fatty acids, such as high linoleic content, in the enteral formulations.94,95

Short-Chain Fatty Acids

SCFAs play an integral role in colonic health. These fatty acids occur naturally in foods (butter, milk) but only in modest concentrations. The primary source of SCFAs is the large intestine via bacterial anaerobic fermentation of nondigestible dietary carbohydrates and fiber polysaccharides. Fermentation of these carbohydrate compounds produces the following SCFAs: acetate (2C), propionate (3C), and butyrate (4C). SCFAs are absorbed and metabolized primarily by the colon and, to a lesser degree, by liver, muscle, and brain tissue. The functions of SCFAs are diverse and include (1) a primary energy source for colonocytes, (2) stimulation of water and sodium absorption in the colon, and (3) trophic effects to the intestinal mucosa.96,97 Butyrate has been shown to be the most important SCFA in regulation and maintenance of colonic tissue. An important role of butyrate may be to modify inflammatory activity by inhibiting the release of the transcription factor, nuclear factor κ–light-chain-enhancer, of activated B cells.98 In addition, butyrate has been shown to exhibit antitumorigenic effects on cancer cell lines and has been identified with gene regulation involving processes of cellular apoptosis, proliferation, and differentiation.99,100 Daly and colleagues101 demonstrated that many of the butyrate-responsive genes are deregulated in colon carcinoma tissue as an apparent result of downregulation of cellular expression of the butyrate transporter. The data suggest that a reduction in transport of butyrate into the luminal membrane may contribute to sequential genetic alterations that lead to initiation of colorectal cancer.

More recent research has additionally established that levels of butyrate-producing bacteria are reduced in patients with type 2 diabetes, and concentrations of fecal SCFAs are also reduced in patients with severe systematic inflammatory response syndrome (SIRS) when compared with heathy controls.101,102 Further studies of butyrate and other SCFAs may provide important insights into how gut microbes may contribute to or attenuate disease progression and offer additional approaches for therapeutic intervention. (See Chapter 4 for additional information on gut microbiota.)

Medium-Chain Triglycerides

MCTs are saturated and are 6 to 12 carbons in length. These fatty acids were developed commercially in the 1950s and are among the first medical foods derived as an alternative to plant oils and other conventional fats. This lipid product is isolated primarily from plants high in MCTs, such as palm kernel and coconut oils. The MCT product does not provide EFAs and has an energy density of 8.3 kcal/g. Compared with long-chain TGs (LCTs), MCTs are significantly different with respect to absorption, metabolism, and physiological functions. Ingestion of saturated LCTs from palm kernel and coconut oils is thought to contribute to coronary heart disease via an increase in LDL cholesterol,103,104 but the effect of saturated MCTs from the same sources on LDL cholesterol levels is not clear—in some reports, LDL cholesterol levels increased105 and in others, they decreased.106 In many of these studies, the contributions and specific effects of MCTs alone are difficult to separate from other confounders.107–109

MCTs are smaller and more water soluble than LCTs. Liberation of fatty acids through hydrolysis of MCTs in the intestinal lumen is significantly faster relative to LCTs, and absorption of MCFAs is more rapid when compared with LCFAs. The absorptive rate of MCTs may be faster because they do not require the presence of bile or pancreatic lipases for absorption and are transported directly to the liver via the portal vein (bypassing the traditional LCT pathway). Once in the liver, MCTs are used primarily as an energy source. In comparison to LCTs, MCTs are not stored to any significant degree in adipose tissue, nor do they affect the reticuloendothelial system. Because MCTs are ketogenic, these TGs may provide a useful energy source for enterocytes, lymphocytes, and cells of other tissues in hypermetabolically stressed patients. Oxidation of MCTs is less affected by glucose and insulin than LCTs.110 In addition, oxidation of LCTs can be impaired by slow elimination rates from the plasma or by the requirement of carnitine for intracellular transport. In contrast, the metabolism of MCTs is a carnitine-independent system for transport into the mitochondria.111 Because of these metabolic differences, MCTs may be beneficial in attenuating inflammatory stress conditions. The metabolic characteristics of MCTs increase their role as an important lipid source for individuals with impaired and dysfunctional gastrointestinal tracts. For example, MCTs may be beneficial for individuals who have defects of fat digestion and absorption (eg, patients with pancreatitis), as well as those individuals with malabsorption secondary to intestinal resections, inflammatory bowel disease, chylous ascites, or autoimmune enteropathies.

Many enteral products have been designed with MCTs as a significant lipid component to maximize the absorption, metabolism, and tolerance of these products for use in various disease and metabolic conditions (Table 5-4).

Structured Lipids

First developed in the mid-1980s,112–115 structured lipids are “designer” TG molecules that are specifically synthesized in the laboratory via chemical and/or enzymatic methodology or, more recently, via genetic engineering.116 The resulting TG mixture contains a randomly esterified pattern of MCTs and LCTs that can contain within the same TG molecule both MCFAs and LCFAs. In structured lipids, the MCFAs are predominantly 8 or 10 carbons in length and usually are esterified at the sn-1 and sn-3

positions, and the LCFA usually is esterified at the sn-2 position on the glycerol backbone of the structured lipid. Usually, the LCFAs are predominantly members of the ω-3 family, such as GLA, EPA, or DHA. As previously stated, the enzymatic activities of gastric and pancreatic lipases predominantly catalyze the release of fatty acids at the sn-1 and sn-3 positions from the glycerol backbone of the structured lipid. This catalysis results in formation of 2-LCFA-monoacylglycerols and, for sn-2 MCFA structured lipids, free MCFAs. In physical mixtures of LCTs and MCTs, this activity results in 2-monoacylglycerols and a mixture of MCFAs and LCFAs.

Unlike pancreatic lipase, gastric lipase does not require bile salts for enzymatic activity and is more efficiently catalytic against the acyl-MCFA in MCFA-esterified TGs.117 As previously discussed, these more rapidly liberated MCFAs do not require bile salts for absorption, readily enter the portal system for transport, and enter mitochondria independently of the carnitine membrane transport pathway. Consequently, structured lipids offer a defined mechanism to rapidly deliver MCFAs and to provide a more rapid availability of EPA and DHA with, as one result, the entire attendant array of nutritionally positive aspects of these substances. Investigators have demonstrated that fatty acids located at the sn-2 position on the glycerol backbone are preferentially absorbed,118,119 and, in structured lipids, both EPA and DHA esterified at the sn-2 position are, indeed, more readily absorbed.120 Furthermore, in experimental animal studies of intestinally injured rats, structured lipids prepared with MCTs and fish oils (containing a range of LCFAs from 18:3n-3 to 22:n-6) infused gastrically were absorbed more quickly in comparison to the physical mixture of the fish oil and MCTs emulsion.121 Selected human122,123 and experimental animal EN studies124–126 have demonstrated various physiological benefits associated with the use of structured lipids, including better fatty acid absorption, lower infection rates, and improved hepatic, renal, and immune function.

Structured lipids are approved for inclusion in certain enteral formulas used in the United States and elsewhere. In addition, PN formulas that contain structured lipids are approved for use in Europe.

The Clinical Impact of Specific Fatty Acids in Parenteral Nutrition

ω-6 Fatty Acids

In the United States, two 100% soybean oil–based lipid emulsions are currently available for use in PN. Soybean oil–based ILEs contain large quantities of linoleic acid. Exclusive provision of soybean oil–based ILEs may therefore greatly exceed dietary recommendations (ie, Dietary Reference Intakes) for ω-6 fatty acids. Fatty acids of the ω-6 family influence the immune system by alteration of membrane structure and function, by modulation of immune function through AA metabolites, and by stimulation of inflammatory cytokines. IV soybean oil emulsions have been shown to depress immune function in both in vitro and ex vivo studies. These types of emulsions have been shown to decrease the cellular immune response in several in vitro studies at varying lipid concentrations. Depression of immunoglobulin M and immunoglobulin A levels, decreases in lymphocyte proliferation, depression of natural killer cell activity, and depression of neutrophil chemotactic motility have been reported with use of soybean oil–based emulsions.127–131 However, the most significant factor of these in vitro studies seems to be a dose-related response associated with increased immunosuppression in response to increased lipid

concentrations. Well-designed, prospective, randomized clinical trials (RCTs) evaluating the effects of soybean oil–based ILEs upon infections and other clinical outcomes are needed.

In a small, prospective, randomized study (N = 57) by Battistella et al,132 trauma patients who received PN with soybean ILE had more infections, longer ventilation time, and a longer hospital stay compared with patients receiving lipid-free PN. Unfortunately, this study did not administer equivalent amounts of energy to the patients. McCowen and associates133 performed a randomized study of PN with and without soybean ILE in 40 critically ill patients and found that while infections were more common in the group receiving soybean ILE, the difference was not statistically significant (53% vs 29%; P = 0.2). However, the nutrition regimens used in this study were not isocaloric. Another randomized study by Muller and colleagues134 followed patients administered PN for 10 days prior to surgery for gastrointestinal cancer. In this study, 46 patients received soybean ILE plus glucose and 66 patients received glucose only; all patients received similar amounts of amino acids.134 Mortality and major complications affecting the site of operation were significantly higher in the group receiving ILE-containing PN compared with the lipid-free PN group (P <0.05). The study results are, however, confounded by the high energy intake and large amount of lipid (50% of energy) administered to the patients. The quantity of energy and amount of lipid within the ILE used in the study exceeded 2016 ASPEN/SCCM guidelines recommendations. The largest trial to evaluate soybean ILE and infection was performed in patients who had bone marrow transplants.135 Patients were randomly assigned to low-dose (6% to 8% of energy; n = 259) or standard-dose (25% to 30% of energy; n = 253) ILE-based PN. Investigators found no association between lipid dose within the ILE and first infection. Similar numbers of patients in each group developed bacterial and fungal infections. Data also showed no difference between groups for engraftment or graft-vs-host disease, relapse, or survival. In another, very small study, 15 malnourished patients with advanced gastric or esophageal cancer received 2 weeks of preoperative and 1 week of postoperative isocaloric and isonitrogenous PN with and without soybean-based ILE.136 Postoperative infections (13 vs 15; 87.5% vs 85.7%) and hospital length of stay (21 vs 23.7 days) were similar between groups. Overall, the clinical data regarding soybean oil–based ILE and infections are contradictory and no clear relationship between the use of soybean oil–based ILE and infections has been established.

The 2016 ASPEN/SCCM guidelines suggest withholding or limiting 100% soybean oil–based ILE during the first week following initiation of PN in the critically ill patient to a maximum of 100 g/wk, if EFAD is a concern. The ASPEN/SCCM task force deemed the quality of the evidence for this recommendation to be very low, and task force members were relatively divided (64% agreement) whether the recommendation should be (1) simply to withhold 100% soybean oil–based ILE or (2) to withhold or limit it to 100 g/wk.22

ω-3 Fatty Acids

A number of earlier clinical trials and studies investigated the impact of ILEs that contain fish oil on clinical outcomes among adult patients.137–156 A few of these studies showed that perioperative ω-3 fatty acid treatment seemed to improve outcomes.153,156 However, many other investigations of various outcomes among hospitalized patients had inconsistent findings. The lack of consistent results

may potentially be explained by analysis limitations,139 study design limitations,142 and/or the heterogeneity and complexity of the patient populations in the studies with respect to types of illness, trauma, and/or surgery.

Recent studies suggest use of fish oil and/or other ω-3 fatty acid–containing emulsions may improve outcomes and may lower inflammation as assessed by liver function. In an investigation that included 451 patients distributed among several groups that received either soybean oil–based, olive oil–based, or fish oil PN emulsion, clinical outcomes were significantly improved in the ω-3 and ω-9 groups. When the soybean oil–based ILE group was compared to the fish oil–based ILE group, the times to discontinuation of mechanical ventilation ($P = 0.05$) and to ICU discharge alive ($P = 0.001$) were significantly shorter in the fish oil group. Comparison of patients receiving olive oil–based and soybean oil–based ILEs led to a similar result. The olive oil–based ILE group were terminated from mechanical ventilation sooner ($P = 0.02$), and had a shorter time to ICU discharge alive ($P <0.001$).157 In a small (60 patients) RCT, Hall and colleagues158 showed that, based on a sequential organ failure assessment (SOFA) score,159 parenteral ω-3 treatment via fish oil administration significantly reduced new organ dysfunction in septic patients.158 Furthermore, a prospective, double-blind RCT compared the efficacy and safety of an ω-3 fatty acid–enriched MCT/LCT ILE and an MCT/LCT ILE in 99 elective surgery patients with gastric and colorectal cancer.160 Although no differences were observed between groups in proinflammatory markers, the ω-3–enriched group had significantly lower TG, free fatty acid, and HDL levels. Gong and associates161 demonstrated a significant decrease 7 days postsurgery in white blood cell count, alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin, and prothrombin time in hepatectomy patients who received 100 mL of a 10% fish oil emulsion per day, for 5 days. Another RCT that examined 63 hepatectomy patients with hepatitis type B virus–associated hepatocellular carcinoma, found that fish oil supplementation led to significantly better liver function as well as significantly fewer infectious complications and shorter length of hospital stay.162 Lastly, a randomized, double-blind, multicenter investigation of 73 intestinal failure patients receiving long-term PN compared a completely soybean-based ILE to an alternative soybean oil–MCT–olive oil–fish oil blend ILE. After 4 weeks of treatment, the latter ILE led to significantly lower ALT, AST, and total bilirubin values.163

However, the results of several recent systematic reviews and meta-analyses are substantially less definitive with respect to the influence of ω-3 fatty acid–enriched alternative ILEs on clinical outcomes. A meta-analysis of 6 RCTs that involved 306 patients compared ILEs with soybean oil only, a soybean oil–MCT–olive oil–fish oil blend, and a soybean oil–olive oil blend. It found no significant differences in adverse events and lengths of hospital stay among the trials, whereas both soybean oil–MCT–olive oil–fish oil blend and soybean oil–olive oil blend ILEs similarly lowered liver enzymes relative to soybean oil alone. However, the quality of evidence from the trials that evaluated these ILEs was considered to be moderate to low.164

A systematic review of statistically aggregated results from 12 RCTs showed that when alternative lipid ILEs were used to spare soybean oil exposure, trends to lower mortality ($P = 0.20$), duration of mechanical ventilation ($P = 0.09$), and ICU length of stay ($P = 0.13$) were observed.165 However,

compared with soybean oil alone, alternative lipid emulsions had no effect on infectious complications (P = 0.35).165

Manzanares and colleagues published a systematic review and meta-analysis of parenteral fish oil lipid emulsion studies in critically ill patients that involved statistically aggregated results from 6 RCTs and 390 patients.166 This analysis found that emulsions that contained fish oil led to a trend toward reduced mortality (P =0.08) and shorter duration of mechanical ventilation (P = 0.17), but, as found in the previous analysis,165 the fish oil emulsions had no effect upon infections (P = 0.35).166 In contrast to the previous analysis, no significant effect on ICU length of stay was found (P = 0.84).166

A systematic review and meta-analysis of statistically aggregated results from 10 RCTs that examined the effect of fish oil lipid emulsion treatment among 733 patients also led predominantly to only trends, at best, in positive outcomes. There were no significant reductions in mortality (P = 0.46); days on mechanical ventilation (P = 0.14); hospital length of stay (P = 0.19); or ICU length of stay (P = 0.37).167 However, a significant reduction in infectious complications among patients treated with fish oil–containing ILE was found (P = 0.02).167

Although the evidence discussed here is inconclusive, both the US and Canadian guidelines currently suggest that clinicians can consider the use of non–soybean oil–based ILEs in critical illness. The 2016 ASPEN/SCCM guidelines22 state that alternative ILEs may provide outcome benefit over soybean oil–based ILEs; however, a recommendation was not made at the time because of the lack of availability of these products in the United States. Members of the ASPEN/SCCM task force suggested that if such ILE formulations become available in the United States, their use be considered in critically ill patients who are appropriate candidates for PN.22

Since the publication of the ASPEN/SCCM guidelines, an alternative ILE (Smoflipid; a soybean oil, MCT, olive oil, and fish oil emulsion) has become commercially available in the United States, and another alternative ILE (Clinolipid; a soybean oil and olive oil emulsion) has been approved for use. Clinicians should note that the package inserts for these emulsions provide qualifying statements about their effects upon clinical outcomes. The package insert for the ILE with the soybean oil–MCT–olive oil–fish oil blend states that “the omega-6:omega-3 fatty acid ratio and medium chain triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.” Similarly, the package insert for the ILE with the soybean oil–olive oil blend states that “the omega-3:omega-6 fatty acid ratio in Clinolipid has not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.”

ω-9 Fatty Acids

Commercial ILEs with high olive oil content have been developed to reduce ω-6 fatty acid content and thus the risk associated with in vivo oxidative stress and the potential for a proinflammatory environment. When compared with soybean oil–based ILEs, olive oil–based ILEs are less inhibitory of various neutrophil responses, including human neutrophil viability,168 phagocytic activity,169,170 inflammatory cytokine production,169,171 and oxidative burst induction.169,172 Studies generally demonstrate a greater immune-neutral effect of olive oil–based emulsions when compared with

soybean oil–based ILEs. However, well-designed RCTs are needed to examine the effect of olive oil–based ILEs on clinical outcomes.

Observational survey studies and meta-analysis subgroup examinations have demonstrated clinical benefits of olive oil–based vs soybean oil–based ILEs.157,165 However, in a double-blind RCT of 100 ICU patients, Umpierrez and associates173 found no differences in clinical outcomes, including rates of infectious and noninfectious complications, between olive oil–based ILE and soybean oil–based ILE.

Recently, Jia and colleagues compared olive oil–based and soybean oil–based ILEs in the largest prospective, randomized, open-label multicenter study to date (N = 458).174 In this study of surgical patients, the safety and efficacy of a PN regimen including olive oil–based ILE in a multichamber bag and a soybean oil–based ILE PN compounded regimen were compared. The olive oil–based ILE regimen was proven to be effective (noninferior to soybean oil ILE regimen), was well tolerated, and resulted in a significant decrease in infections relative to the soybean oil–based PN ($P < 0.01$).174 It should be noted that, in studies comparing compounded PN with multichamber PN, rates of bloodstream infections are higher in the compounded group.175 However, in the trial by Jia et al,174 there were no differences in bloodstream infections between groups, and most of the infections identified were from pulmonary, incision site, and urinary tract infections.

In a double-blind, prospective RCT, 94 esophageal cancer surgical patients who received either an MCT/LCT or olive oil–based ILE in combination with EN were examined for clinical outcomes.176 In this study, no differences were observed between groups with respect to ICU length of stay ($P = 0.619$), hospital length of stay ($P = 0.544$), total infectious complications ($P = 0.533$), or, hospital mortality ($P = 0.613$).

Short-Chain Fatty Acids

Much of the recent nutrition support research has focused on the role of butyrate to alter the gut lumen environment and influence intestinal adaptation in short bowel syndrome. In investigational animal models of PN, the addition of butyrate has been shown to prevent PN-associated mucosal atrophy and improve epithelial surface proliferation.177 Similarly, in a study that examined calorically matched mice allowed to feed ad libitum (controls), treated with standard PN (amino acids, glucose, micronutrients), or treated with standard PN with added butyrate, the addition of butyrate significantly restored the number of Peyer's patch lymphocytes and immunoglobulin A levels that were reduced in standard PN mice ($P < 0.05$); also, the PN with butyrate treatment restored gut morphology with respect to recovery of crypt and villous height lost as a result of standard PN treatment ($P < 0.05$).178 Tappenden and colleagues179,180 have shown that incorporation of SCFA in PN solutions may modulate the transport capacity of glucose and other nutrients and may further improve intestinal adaptation by the upregulation of glucagon-like peptide 2. Notably, levels of butyrate-producing bacteria are reduced in patients with type 2 diabetes and, as previously discussed, concentrations of fecal SCFAs are also reduced in patients with severe SIRS when compared with heathy controls.102,181 Greater understanding of alterations of the gut microbiota associated with butyrate, and perhaps other SCFAs, may provide insights into how the gut microbiota contribute to disease progression and whether this

area may become an important focus for therapeutic intervention. (See Chapter 4 for additional information on gut microbiota.)

Medium- and Long-Chain Triglycerides

Although MCTs are more commonly added to enteral formulas, they have been used in PN mixtures. LCTs and MCTs may be physically mixed to generate an emulsion that simultaneously provides both LCTs and MCTs in varying ratios and percentages, or LCTs may be interesterified either chemically or enzymatically with MCTs to create structured lipids (as discussed earlier in the chapter). Physical mixtures of LCTs and MCTs (50:50 w/w mixture) have been used in PN solutions for years in Europe and other nations outside of the United States. These ILEs may provide benefit by (1) providing a better oxidized energy source, (2) improving nitrogen balance (attenuating protein catabolism in stress), and (3) providing rapid clearance of lipid from the blood. In addition, patients who receive MCT-LCT emulsions have been shown to have a fatty acid profile (extracted from cellular phospholipids) that is closer to normal when compared with individuals who receive soybean oil–based ILEs.182 Additionally, emulsions that contain MCTs may provide a more stable lipid emulsion relative to LCT emulsions, because MCT emulsions have decreased susceptibility to peroxidation. However, the use of MCTs in PN may increase the risk of metabolic acidosis and may lead to a lower level of glucose oxidation relative to LCTs alone6—possibilities that are particularly important to consider when treating critically ill patients. Nonetheless, the use of MCTs in nutrition seems to be a viable alternative for some patients.

In 2016, Wu and coauthors published a systematic review and meta-analysis of 21 clinical trials that examined the use of structured lipids in 1135 intent-to-treat surgical or critically ill patients.183 The trials investigated various clinical parameters and clinical outcomes in patients who received either a structured lipid, MCT-LCT PN emulsion (structured lipid group), or a physically mixed, MCT-LCT PN emulsion (MCT/LCT group). The analysis revealed significantly better protein management ($P < 0.00001$) and higher values for prealbumin ($P < 0.000001$) and albumin ($P < 0.0001$) in the structured lipid group. However, plasma TGs values were significantly lower in the structured lipid group relative to the MCT/LCT group ($P < 0.0001$). A trend that almost achieved significance was shorter hospital length of stay in the structured lipid group ($P = 0.05$). The authors of the analysis concluded that administration of the structured lipid PN emulsion improved nitrogen balance, was more protective of the liver, more efficiently eliminated TGs, and resulted in a strong trend toward a shorter hospital length of stay.183

Phytosterols and Vitamin E in Parenteral Nutrition

Plant-based ILEs provide EFAs and a rich energy source to hospitalized and home PN patients. However, prolonged use of these ILEs can carry risks, including the risk for parenteral nutrition–associated liver disease (PNALD), particularly among infants.184 PNALD encompasses many liver dysfunctions, such as cholestasis (the most common in children), steatosis (the most common in adults), and cirrhosis, that may progress in rare instances to complete liver failure. One possible explanation for these liver disorders is the presence of phytosterols within the lipid emulsion. Phytosterols, the most common of which are campesterol, sitosterol, and stigmasterol, are plant analogues of cholesterol and are found in all currently available plant-based ILE formulations.185 There is evidence that these compounds,

because of their structural similarity to cholesterol, interfere with bile synthesis and transport and thus interfere with bile acid homeostasis. This effect, coupled with the high concentrations of peroxidation-sensitive PUFAs in plant-based ILE that could lead to free radical damage of liver cells, may possibly explain subsequent liver dysfunction.

In animal studies, soybean oil–based emulsions and purified individual phytosterols, particularly stigmasterol, seem to be dominant contributors to the disruption of bile synthesis and secretion, with the subsequent induction of cholestasis.186 Investigators have explored the possibility that the suspected harmful effects of phytosterols could be ameliorated (1) through use of fish oil that does not contain phytosterols or (2) by adding an antioxidant such as vitamin E (specifically α-tocopherol) to plant-based ILE. To date, the data are conflicting. A mouse study by El Kasmi et al187 clearly showed that, in contrast to mice that received a soy-based PN emulsion, mice that were given fish oil–based PN did not exhibit PNALD. Furthermore, liver damage and cholestasis were dependent on the presence of phytosterols (stigmasterol in particular) and occurred when phytosterols were added to a fish oil–based PN emulsion. In this instance, the presence of high concentrations of ω-3 fatty acids in the fish oil emulsion did not protect the animals from the effect(s) of added stigmasterol. A more recent examination of the effect of phytosterols in mice by Harris et al188 suggests that gut microbiota may contribute to, in the authors' terminology, parenteral nutrition–associated liver injury (PNALI), perhaps through interactions of the microbiome with phytosterols. Harris and associates188 showed that the mouse gut microbiome was altered in mice demonstrating PNALI. Specifically, use of soybean-based PN resulted in PNALI and additionally led to increased appearance of the Erysipelotrichaceae taxa of bacteria in the colonic microbiota. Removal of soybean-based PN attenuated PNALI and significantly reduced the level of Erysipelotrichaceae bacteria. Addition of stigmasterol to fish oil–based PN resulted in the reappearance of Erysipelotrichaceae bacteria at a rate equivalent to that for soybean-based PN animals and again resulted in PNALI.188 In contrast to these data, Ng et al found no evidence for PNALD in preterm piglets similarly treated with soybean-based ILE–equivalent phytosterols concentrations added to a fish oil emulsion.189

In addition to the possible effects of phytosterols on liver function, PUFAs may be involved in lipid peroxidation that in turn causes liver cell damage and, ultimately, aberrant liver function. To counter this problem, antioxidants, such as vitamin E, may be important. A form of vitamin E may be added to fish oil emulsions; additionally, vitamin E can be found naturally in plant oils used in various ILE formulations.190,191 The 8 isoforms of vitamin E are α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol, all of which are fat soluble and all of which can act equivalently as an antioxidant. For humans, however, only α-tocopherol is biologically active. The enzymatically synthesized natural form of α-tocopherol present in plants, and, therefore, within the oil derived from them, is known as RRR-α-tocopherol. The RRR designation refers to the R orientation of the attached methyl group at each of the 3 chiral centers at carbons 2 (ring), 4', and 8' (side chain) of the molecule. One may also use synthetic vitamin E, which is known as all-rac-α-tocopherol (all-racemic-α-tocopherol). Because of chemical instead of enzymatic synthesis, all-rac-α-tocopherol has 8 stereoisomers of α-tocopherol (RRR, RRS RSR, RSS, SRR, SRS, SSR, SSS); only the 4 with R chirality at the 2 (ring) position, known as 2R-α-tocopherol,

have biological activity in humans (2, 4', and 8' positions yield: RRR, RRS, RSR, RSS). All 8 of the stereoisomers, however, have equivalent antioxidant activity.

Studies that examined the influence of vitamin E on the occurrence of PNALD have led to conflicting results. In addition to studying the effect of phytosterols on PNALD, Ng et al189 examined the effect of α-tocopherol on the occurrence of PNALD through addition of RRR-α-tocopherol to soybean-based ILE at a concentration that matched the biological equivalents of RRR-α-tocopherol concentration already present in the fish oil emulsion. Under this condition, addition of vitamin E ameliorated PNALD in preterm piglets. However, a similar study by Muto and coauthors192 found that addition of vitamin E—in this instance all-rac-α-tocopherol acetate—to soybean-based ILE, had no effect upon cholestasis, level of inflammation, or level of oxidative stress in neonatal, term piglets.

Although data are conflicting regarding the ameliorating effect of vitamin E on PNALD, the many animal studies and human data extensively reviewed by Zaloga186 are consistent with the hypothesis that higher phytosterol exposure is associated with PNALD and, reduction of soybean-based ILE and/or use of fish oil that does not contain any phytosterols can reduce the incidence of PNALD. Appropriately designed and powered RCTs to investigate this critically important area are needed.

Conclusion

Various enteral and ILE formulations provide numerous options for treating critically ill patients, but data are insufficient to recommend specific enteral or ILE formulations for many conditions (eg SIRS, ARDS), situations (eg, surgery, trauma), or patient populations (eg, adults, preterm or term infants). Because the appropriate selection of enteral and ILE formulations can save lives, it is critical that well-designed and adequately powered studies of the use of these formulations remain a goal of the medical and scientific community.