

# Lipid emulsions – Guidelines on Parenteral Nutrition, Chapter 6

## Lipidemulsionen – Leitlinie Parenterale Ernährung, Kapitel 6

### Abstract

The infusion of lipid emulsions allows a high energy supply, facilitates the prevention of high glucose infusion rates and is indispensable for the supply with essential fatty acids. The administration of lipid emulsions is recommended within  $\leq 7$  days after starting PN (parenteral nutrition) to avoid deficiency of essential fatty acids. Low-fat PN with a high glucose intake increases the risk of hyperglycaemia. In parenterally fed patients with a tendency to hyperglycaemia, an increase in the lipid-glucose ratio should be considered. In critically ill patients the glucose infusion should not exceed 50% of energy intake. The use of lipid emulsions with a low phospholipid/triglyceride ratio is recommended and should be provided with the usual PN to prevent depletion of essential fatty acids, lower the risk of hyperglycaemia, and prevent hepatic steatosis. Biologically active vitamin E ( $\alpha$ -tocopherol) should continuously be administered along with lipid emulsions to reduce lipid peroxidation. Parenteral lipids should provide about 25–40% of the parenteral non-protein energy supply. In certain situations (i.e. critically ill, respiratory insufficiency) a lipid intake of up to 50 or 60% of non-protein energy may be reasonable. The recommended daily dose for parenteral lipids in adults is 0.7–1.3 g triglycerides/kg body weight. Serum triglyceride concentrations should be monitored regularly with dosage reduction at levels  $>400$  mg/dl ( $>4.6$  mmol/l) and interruption of lipid infusion at levels  $>1000$  mg/dl ( $>11.4$  mmol/l). There is little evidence at this time that the choice of different available lipid emulsions affects clinical endpoints.

**Keywords:** lipid emulsions, alpha-tocopherol, hepatic steatosis, polyunsaturated fatty acids, critically ill

### Zusammenfassung

Die Infusion von Lipidemulsionen erlaubt die Zufuhr einer hohen Energiedichte, ermöglicht die Vermeidung hoher Glukoseinfusionsraten und ist unverzichtbar für die Bedarfsdeckung mit essentiellen Fettsäuren. Zur Vermeidung eines Mangels an essentiellen Fettsäuren ist die Gabe von Lipidemulsionen innerhalb  $\leq 7$  Tage nach Beginn der PE (parenteralen Ernährung) erforderlich. Eine fettarme PE mit hoher Glukosezufuhr erhöht das Risiko für eine Hyperglykämie. Bei parenteral ernährten Patienten mit Neigung zur Hyperglykämie sollte eine Erhöhung des Verhältnisses zwischen Lipid- und Glukosezufuhr erwogen werden. Bei kritisch Kranken sollte die Glukosezufuhr auf nicht mehr als etwa 50% der Energiezufuhr begrenzt werden. Lipidemulsionen mit einer niedrigen Phospholipid/Triglyzerid-Ratio werden empfohlen und sollten mit der üblichen PE verabreicht werden, um einer Verarmung an essentiellen Fettsäuren vorzubeugen, das Risiko stark erhöhter Blutzuckerwerte zu vermindern und eine verstärkte Hepatosteatose zu vermeiden. Biologisch aktives Vitamin E ( $\alpha$ -Tocopherol) sollte regelmäßig zusammen mit Lipidemulsionen zugeführt werden, um einer Lipidperoxidation vorzubeugen. Die parenterale Lipidzufuhr sollte in der Regel etwa 25–40% der parenteralen Nicht-Protein-Energiezufuhr betragen. In bestimmten

M. Adolph<sup>1</sup>  
 A. R. Heller<sup>2</sup>  
 T. Koch<sup>2</sup>  
 B. Koletzko<sup>3</sup>  
 K. G. Kreymann<sup>4</sup>  
 K. Krohn<sup>3</sup>  
 E. Pscheidl<sup>5</sup>  
 M. Senkal<sup>6</sup>  
**Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine**

1 Dept. of Anaesthesiology and Intensive Medicine, Eberhard-Karl University, Tuebingen, Germany

2 Dept. of Anaesthesiology and Intensive Therapy, University of Dresden, Germany

3 Dept. Metabolic Diseases & Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich, Germany

4 Dept. of Medicine, Univ. of Hamburg; currently at Baxter Schweiz AG, Zuerich, Switzerland

5 Dept. of Anaesthesiology, Intensive Medicine and Special Pain Therapy, Landshut, Germany

6 Dept. Surgery I, St. Mary's Hospital Witten, Germany

Situationen (z.B. bei kritisch Kranken, respiratorisch insuffizienten Patienten) kann eine Fettzufuhr bis zu 50 oder 60% parenteraler Nicht-Protein-Energiezufuhr sinnvoll sein. Die empfohlene Tagesdosis für die parenterale Gabe von Lipidemulsionen bei Erwachsenen liegt bei 0,7–1,3 g Triglyzeride/kg KG. Die Serum Triglyzeridkonzentrationen sollten regelmäßig kontrolliert werden, um eine Dosisreduktion bei Triglyzeridkonzentrationen >400 mg/dl (>4,6 mmol/l) und eine Unterbrechung der Lipidinfusion bei >1000 mg/dl (>11,4 mmol/l) vornehmen zu können. Auswirkungen der Auswahl aus den verschiedenen verfügbaren Lipidemulsionen sind derzeit nicht eindeutig belegt.

**Schlüsselwörter:** Fettemulsionen, alpha-Tocopherol, hepatische Steatose, mehrfach ungesättigte Fettsäuren, kritisch Kranke

## Background

The infusion of lipid emulsions allows for high energy supply with iso-osmolar solutions. In addition, an adequate proportion of the energy intake as lipids facilitates the prevention of high glucose infusion rates and can, therefore, contribute to the prevention of hyperglycaemia and hepatic steatosis. Lipid emulsions are also indispensable for supplying the requirements of essential fatty acids.

The quantitatively dominant lipids in enteral and parenteral nutrition are triglycerides (triacylglycerols, neutral lipids; glycerol esterified with three fatty acids). The physical, chemical and metabolic properties of triglycerides are determined by their fatty acid contents. Based on their chain length, fatty acids are considered as short-chain (<8 carbon atoms), medium-chain (8–10 carbon atoms), intermediate-chain (12–14 carbon atoms) and long-chain ( $\geq 16$  carbon atoms) fatty acids, which can either be saturated (without double bonds) or mono- or polyunsaturated. Saturated, monounsaturated and polyunsaturated fatty acids differ in their metabolic and physiological properties. While saturated fatty acids serve primarily as an energy source, polyunsaturated fatty acids play an important role as components of structural lipids, for example in biological membranes. Polyunsaturated fatty acids of the n-6 series (linoleic acid and metabolites), and polyunsaturated fatty acids of the n-3 series ( $\alpha$ -linolenic acid and metabolites) cannot be synthesised de novo by higher organisms and are, thus, essential nutrients. For healthy adults the recommended dietary intake of linoleic acid is 2.5% and of  $\alpha$ -linolenic acid is 0.5% of the energy intake [1]. Long-chain polyunsaturated fatty acids formed from the essential fatty acids, linoleic acid and  $\alpha$ -linolenic acid, are important components of cell membrane and markedly affect numerous membrane properties such as their fluidity, transport processes, and the activity of membrane-anchored proteins and receptors. They also modify gene expression by binding to nuclear receptors like PPAR. Certain polyunsaturated fatty acids (dihomo- $\gamma$ -linolenic acid, 20:3n-6; arachidonic acid, 20:4n-6; eicosapentaenoic acid, 20:5n-3) serve as precursors in the synthesis of eicosanoids. The n-6 fatty acid arachidonic acid is a precursor of pro-inflammatory mediators (such as leukotrienes of the n-4 series), and of

prostaglandins and thromboxanes of the n-2 series, which increase the vascular tone and promote platelet aggregation. In contrast, prostaglandins and thromboxanes of the n-3 series and leukotrienes of the n-5 series, formed from the n-3 fatty acid eicosapentaenoic acid, have many antagonistic effects such as a reduction in platelet aggregation and vascular tone as well as anti-inflammatory effects.

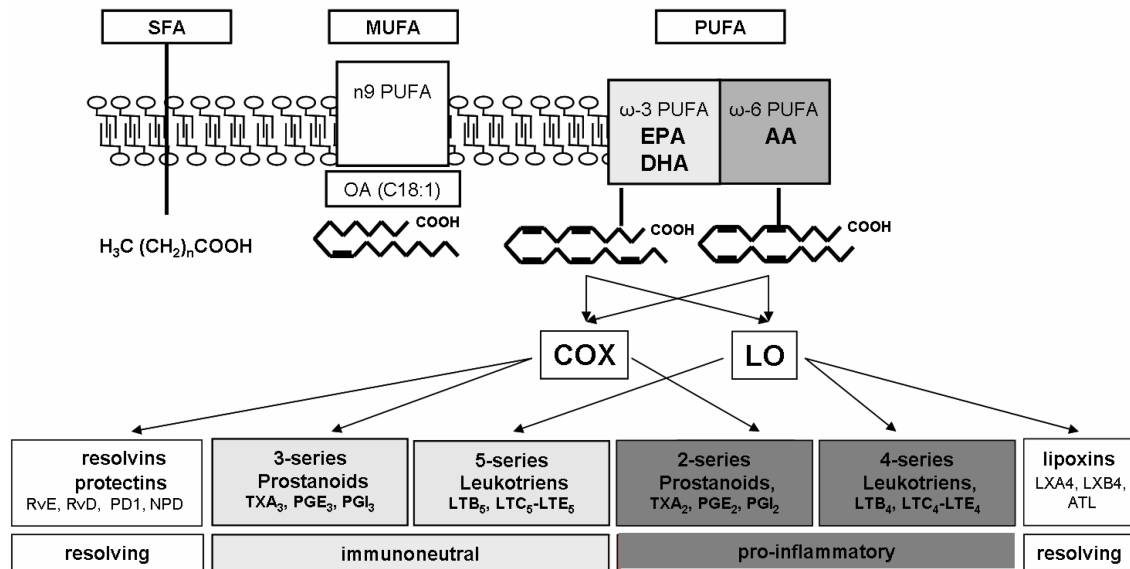
More recently novel lipid mediators derived from polyunsaturated fatty acids with pro-resolving activities on inflammatory processes have been identified. They were identified in exudates from resolving inflammation and comprise the lipoxins, resolvins, and protectins (for review see [2], [3]). Their synthesis is favored by the transcriptional up-regulation of neutrophil 15-LO by PGE<sub>2</sub> and PGD<sub>2</sub>, the so-called “eicosanoid switch” [4]. They are highly stereospecific and act in the pico- to nanomolar range [5], [6]. They affect PMN recruitment and trafficking, expression of pro-inflammatory genes, reduce leukocyte-mediated tissue injury, and take part in chemokine removal.

## Lipoxins

Lipoxins are derived from AA and are generated through different biosynthetic pathways. Cells rich in 15-lipoxygenase (15-LO) like airway epithelial cells, macrophages and basophils oxidize AA to 15S-HETE that is further converted by neutrophil 5-LO to an epoxytetraene intermediate from which LXA4 and LXB4 are formed. Alternatively, these lipoxins can also be generated from LTA4 by platelet 12-LO, most preferably under conditions of hypoxia and diminished platelet glutathione content.

In addition, lipoxins can be generated from 15-HETE stored in membrane inositol-containing lipids. Upon release, 15-HETE instead of AA is processed by neighbouring leukocytes resulting in decreased leukotriene and increased lipoxin formation.

In the presence of aspirin, COX-1 is inhibited and COX-2 is acetylated. In vascular endothelial and in epithelial cells, acetylated COX-2 metabolizes AA to 15R-HETE that is then processed by neutrophil 5-LOX to the aspirin-triggered lipoxins (ATLs) 15-epi-LXA4 and 15-epi-LXB4. These epimers are more stable than the LXA4 and LXB4 due to slower enzymatic degradation.



**Figure 1: Eicosanoids synthesis pathways.** Depending on the fatty acid content of cellular membranes lipid mediators with different pro-inflammatory potency or pro-resolving properties are generated from omega-3 or omega-6 polyunsaturated fatty acids via the cyclooxygenase or lipoxygenase pathway. Pro-inflammatory arachidonic acid (AA)-derived 5-series leukotrienes, 2-series prostanoids, and thromboxane A<sub>2</sub> and eicosapentaenoic acid derived 3-series prostanoids and 5-series leukotrienes with largely reduced inflammatory properties. Pro-resolving lipoxins derive from AA while resolvins and protectins are generated from EPA.

Both LXA<sub>4</sub> and ATL bind to the ALX/FPRL1-receptor, which leads to reduced agonist-induced superoxide production of PMNs and also inhibits their migration [7]. In addition, lipoxins regulate CD11/CD18 expression and L-selectin shedding [8]. On the other hand, they increase monocyte recruitment and uptake of apoptotic PMNs by macrophages [9].

## Resolvins and protectins

The resolvins and protectins are derived from the omega-3 fatty acids EPA and DHA by different biosynthetic pathways (Figure 1). Only resolvins of the E1-series are generated from EPA through the tandem transcellular conversion of EPA by acetylated COX II in vascular endothelial and epithelial cells and LOX in activated neutrophils. Alternatively, resolvin E1 (RvE1) can be synthesized independent from aspirin by cytochrome P450 monooxygenase [10].

Resolvins of the D-series (RvD1) and protectins (PD1, NPD1) are derived from DHA by biosynthetic pathways involving LOX. In addition, via aspirin-acetylated COX II, aspirin-triggered RvD1 (AT-RvD1) can be generated.

RvE1 is a ligand of the orphan receptor ChemR23 acting and inhibits NF- $\kappa$ B activation [11]. In addition, RvE1 is a partial agonist at the LTB<sub>4</sub>-receptor BLT1 on PMNs and dampens LTB<sub>4</sub>-dependent activation of PMNs as shown by reduced mobilization of intracellular calcium by RvE1 compared to LTB<sub>4</sub> [12]. In addition, RvE1 dose-dependently inhibited LTB<sub>4</sub>-induced calcium mobilization.

RvE1 dramatically reduced neutrophil infiltration in zymosan-induced peritonitis in mice that was BLT1-dependent at low but independent at high RvE1 concentra-

tions [12]. Furthermore, RvE1 blocked PMN superoxide generation [13] and reduced the expression of proinflammatory genes.

Also, resolvins of the D-series block production of pro-inflammatory mediators as shown in the case of TNF- $\alpha$ -induced generation of IL-1 $\beta$  in microglial cells [14]. Furthermore, they regulate PMN infiltration into inflamed tissues [14], [15], [16].

Like resolvins, protectins regulate PMN infiltration as demonstrated by reduced peritoneal PMN recruitment in a mouse model [6]. PD1 exerts its actions also when administered after the initiation of inflammation and was shown to act in an additive fashion together with RvE1. Furthermore, PD1/NPD1 has profound neuroprotective actions as evidenced by the limitation of brain injury after stroke. In this context, Lukiw and coworkers demonstrated that protection by NPD1 from oxidative stress-mediated injury mainly occurs through the modulation of apoptotic signaling pathways [17].

PD1 exerts immunoregulatory effects as it blocks T-cell migration, secretion of TNF $\alpha$  and IFN- $\gamma$ , and promotes T-cell apoptosis via clustering of lipid rafts [18], [19]. Furthermore, in concert with lipoxins and resolvins, it increases CCR5 expression on apoptotic PMNs thereby promoting removal of CCR5L and termination of the inflammatory reaction [20].

## Characteristics of lipid metabolism in critically ill patients

Endogenous lipid stores are the main energy source for critically ill patients with an inadequate food intake. In

such situations, adipose tissue triglycerides are hydrolyzed to release free fatty acids and glycerol into the circulation [21]. The markedly increased mobilisation of free fatty acids results in a decrease in intracellular triglyceride storage. This increased lipid catabolism is not countered by parenteral administration of carbohydrates. Usually, the released free fatty acids are rapidly utilised in peripheral tissues. Depending on the overall metabolic situation, there is either ketone body formation or re-esterification and triglyceride formation in the liver, subsequently released into the circulation as very low density lipoproteins (VLDL). The increase in plasma levels of free fatty acids is proportional to the severity of the trauma, and the extent to which the production of free fatty acids surpasses their utilisation.

- Fat-free parenteral nutrition can result in subnormal serum levels of essential fatty acids within one week (IIb)
- Administration of lipid emulsions is required within no more than one week after starting PN (C).

## Commentary

Total PN with carbohydrate and amino acid solutions but without lipid emulsions results in a biochemically detectable deficiency of essential fatty acids, with a drop in linoleic acid and a rise in the trien/tetraen ratio, within only one week ([22]; IIb). These deficiencies can be corrected by parenteral administration of lipid emulsions [23]. In infants, not only biochemical but also clinical signs of essential fatty acid deficiency, such as scaly dermatitis, can be seen after just one week of fat-free PN ([24], [25], [26]; Ib).

- Low-fat PN with a high glucose intake increases the risk of hyperglycaemia (Ia)
- In parenterally fed patients with a tendency to hyperglycaemia, an increase in the lipid-glucose ratio should be considered (C).

## Commentary

Tappy et al. [27] randomised critically ill patients to either PN with 75% glucose, 15% amino acids and 10% lipid energy intake or PN with 70% lipid, 15% glucose and 15% amino acid energy intake. The low lipid intake was associated with increased blood glucose levels (Ia).

The typical metabolic changes resulting from the systemic inflammatory reaction is characterized by reduced carbohydrate and increased lipid oxidation. Therefore, an increased exogenous carbohydrate intake enhances the risk of hyperglycaemia.

In a randomised study of polytrauma patients, there was a significantly higher rate of infection in patients administered parenteral soybean oil emulsion with an extremely high non-protein energy intake of 28 kcal/kg compared to patients who received no intravenous lipids over the first few days [28]. However, it is noteworthy that the energy intake in patients given fat-free nutrition was 25%

lower, hence complications might also have resulted from excessive overall substrate supply. In contrast, a meta-analysis of studies in surgical patients showed no differences in the course of the illness and rate of complications with PN either with or without lipid emulsions administered [29].

## Effects of parenteral lipid administration on glucose metabolism

In healthy patients, both the plasma glucose concentration and the glucose uptake by tissues remained unaffected by simultaneous parenteral infusion of glucose (4 mg/kg/min, using the glucose-clamp technique) and lipid emulsions (20% soybean oil or 20% soybean oil/medium-chain triglycerides (MCT)) at an infusion rate of 0.07 g/kg/h). However, both lipid emulsions reduced glucose oxidation as compared to the control group ([30], IIa).

In critically ill patients, oxidative and non-oxidative glucose utilisation (continuous glucose administration, 2 mg/kg/min, plus amino acid administration, 0.15 g N/kg/day) is not influenced by the simultaneous administration of lipid emulsions (1 mg/kg/day, 20% soybean oil emulsion) (indirect calorimetry, (1-<sup>13</sup>C)-glucose, (6,6-<sup>2</sup>H<sub>2</sub>)-glucose) ([31], IIa). An increase in glucose intake (4 mg/kg/min) does not result in a decrease in endogenous glucose production or gluconeogenesis in critically ill patients. As compared to lipid-dominated PN (only 15% of the total calories are administered as glucose, rest as 20% soybean oil emulsion) no decrease in net protein loss was achieved by a glucose intake of 4 mg/kg/min. Tappy et al. [27] suggested that in critically ill patients glucose should not exceed 50% of the parenteral energy intake due to the potential detrimental effects of predominantly glucose-based PN, such as enhanced insulin secretion, potential insulin resistance, and high CO<sub>2</sub> production resulting from the stimulation of the de-novo lipogenesis.

## Liver damage

In adult patients with gastrointestinal disorders, administration of PN containing soybean oil, which provided either 2.5% or 30% of non-protein energy over a two-week period, did not result in significant differences in ALT (alanine transferase), AST (aspartate transferase) and alkaline phosphatase between the two groups ([32]; Ib). In critically ill patients, an excessive intake of glucose increases hepatic lipogenesis [33], [34], [35], [36], whereas intravenous lipids reduce the dependency on glucose as an energy source. A case study showed that intravenous lipid administration lowered hepatic steatosis [37]. Animals receiving lipid-free PN demonstrated an increase in hepatic steatosis, and in ALT and AST as compared to PN with lipids [38].

The impact of PN with or without lipids on hepatic steatosis was tested in a randomised controlled study on 37 patients (22 men). The patients received their non-protein energy intake either from glucose only or from

glucose and a lipid emulsion; a third group received an extremely high amino-acid low-carbohydrate intake [39]. Over a period of 11–13 days of PN, the liver fat content, measured in repeated biopsies, increased from 5% to 35% in the glucose group ( $p < 0.001$ ) and from 7% to 23% ( $p < 0.001$ ) in the amino acid group, whereas the group receiving lipid emulsions showed no increase in steatosis. The accumulation of fat in the liver was associated with raised levels of serum ALT and AST, but no cholestatic changes.

Development of cholestatic liver disease associated with PN has been frequently observed in premature infants with septic infections [38]. Case studies suggest that PN-associated cholestasis in children receiving long-term PN can be improved by reducing or interrupting the parenteral lipid intake [40]. However, in adults receiving long-term nutrition (>6 months) the degree of cholestasis correlated with the energy supply, and not with the proportion of fat to energy provided ([41], IIb). In a pilot study carried out on 14 patients, a slight increase in liver size, and in the sonographically detected echodensity of the liver was detected in patients receiving soybean oil emulsion for one week, whilst no significant changes were observed in patients given soybean oil/MCT emulsion. General conclusions can not be deduced as there were methodological limitations of this study.

The occurrence of cholestasis has been associated with increased serum concentrations of phytosterols that are found in vegetable oils and in lipid emulsions [42], [43]. In newborn pigs, phytosterols reduced bile flow [44]. However, it remains controversial whether the increased phytosterol serum levels in cholestatic PN patients are a cause or an effect of cholestasis [42], [43].

## Osmolarity/peripheral venous application

- Lipid emulsions can be infused via peripheral veins over a number of days (C).

## Commentary

Due to their low osmolarity (20% lipid emulsions: 270–345 mosm/l; 350–410 mosm/kg), lipid emulsions can be infused via peripheral venous access if needed.

- The infusion of lipid emulsions presents no independent, clinically relevant risk of infection (IV).

## Commentary

*In vitro* studies suggested that the infusion only of 10% lipid emulsions resulted in significantly larger bacterial proliferation within 6–24 hours than the use of mixed PN solutions with or without lipids, after experimental inoculation with *Staph. aureus*, *Strept. pyogenes*, *Str. faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* [45], [46], [47], [48]. In contrast, a clinical study in newborns found bacterial contamination of the

infusion solution to occur after 24 or 48 hours, irrespective of whether mixtures contain lipids or not [49]. Although the *in vitro* multiplication of *Candida albicans* was similar in all infusion solutions [45], [46], in a clinical study contamination in lipid emulsions was higher after 24 hours than after 48 hours ([49]; IIb). A case-control study, however, showed that post-operative infections or febrile episodes associated with the infusion of lipid-based hypnotic propofol were due to insufficient aseptic techniques during the administration of the infusion [50]. A lower risk of contamination has been reported in complete mixtures used for PN than in the infusion of individual components with added lipid solutions [46], [51]. A meta-analysis of studies in surgical patients showed no association of infectious complications with the administration of parenteral lipid emulsions [29].

## Lipid infusion, lipid peroxidation and anti-oxidants

- Biologically active vitamin E ( $\alpha$ -tocopherol) should continuously be administered along with parenteral lipid emulsions (B).

## Commentary

Administration of polyunsaturated fatty acids results in an increase in lipid peroxidation markers (malonyldialdehyde, TBARS), with a corresponding drop in the concentration of  $\alpha$ -tocopherol in patients receiving PN containing soybean oil emulsion ([52]; IIb; [53]; Ib). In patients receiving home PN, an administration of 500 ml of 20% soybean oil emulsion plus 10 IU  $\alpha$ -tocopherol (two to three times a week) resulted in stable plasma  $\alpha$ -tocopherol levels, whereas tissue levels of  $\alpha$ -tocopherol dropped steadily ([54], IIa). Daily supplementation of PN containing a soybean oil/MCT mixed emulsion with 100 mg DL- $\alpha$ -tocopherol resulted in higher vitamin E serum concentrations and lower *in vitro* peroxidation of VLDL and LDL particles ([55]; Ib). Current soybean oil/MCT emulsions contain 0.85 mg  $\alpha$ -tocopherol/g triglyceride. PN with an olive oil/soybean oil emulsion resulted in lower concentrations of lipid peroxidation markers and higher vitamin E serum levels than with a soybean oil emulsion ([56]; Ib; [53]; Ib).

- Intravenous lipids should usually be provided with PN (C).

## Commentary

A lipid emulsion should usually be provided with PN to prevent depletion of essential fatty acids, lower the risk of hyperglycaemia, and prevent hepatic steatosis. If PN is indicated, lipid emulsions should commence after hemodynamic stability has been established or achieved.

- Parenteral lipids should provide about 25–40% of the parenteral non-protein energy supply (C).

## Commentary

Based on the recommendations of food intake for healthy persons [1] and by clinical experience, it is recommended that parenteral lipids should usually provide about 25–40% of non-protein calories, depending on the individual patient's tolerance to carbohydrates and lipids. In critically ill patients, a higher lipid intake of up to 50% of the non-protein calories may be advisable, in view of frequently altering metabolic state and glucose intolerance. In intensive care patients with respiratory insufficiency, up to 60% of non-protein energy is administered as lipid to patients with good lipid tolerance during the acute phase, with the objective to reduce the intensity of mechanical ventilation caused by diminished carbon dioxide production ( $RQ < 0.8$ ).

Huschak et al. [57] observed a significant reduction in  $CO_2$  production, and in the duration of mechanical ventilation in mechanically ventilated poly-trauma patients, when given 60% of overall energy intake as intravenous lipids as compared to the control group that received only 30% of energy as lipids (Ib).

- The recommended daily dose for parenteral lipids in adults is between 0.7 and 1.3 g triglycerides/kg body weight, but this can be increased to 1.5 g/kg body weight in case of high energy requirements (C).

## Commentary

Fatty acids are oxidised in hepatocytes, myocardium, skeletal muscles, and other tissues. A lipid supply greater than the maximum rate of lipid oxidation, estimated between 1.2 and 1.7 mg/kg/min in adults, is not recommended. 'Fat Overload Syndrome' may result when lipid infusion rate is too high relative to the rate of utilisation. Non-utilised lipid particles can be taken up by the mononuclear phagocyte system (MPS), and the immune defence might deteriorate, as a result of inadequate chronic activation of the MPS [58], [59]. The clinical symptoms of 'Fat Overload Syndrome' are similar to systemic inflammatory response syndrome (SIRS) or sepsis: fever, hepatosplenomegaly, icterus, acute lung injury (ALI/ARDS), thrombocytopenia, bleeding, disseminated intravascular coagulation, metabolic acidosis and hypocalcaemia.

- In patients receiving parenteral lipids, a serum triglyceride concentration  $>400$  mg/dl ( $>4.6$  mmol/l) should result in a dosage reduction, and a serum triglyceride concentration  $>1000$  mg/dl ( $>11.4$  mmol/l) should lead to an interruption of lipid infusion (C).

## Commentary

While a fasting serum triglycerides  $<200$  mg/dl is desirable in healthy individuals, serum triglyceride levels of approximately 4.6 mmol/l (400 mg/dl) can be reached postprandially and are considered acceptable during infusion of lipid emulsions (C).

Hypertriglyceridemia induced by lipid infusion can usually be controlled by reducing the dose [60]; (Ib). If hypertriglyceridemia (TG  $>4.6$  mmol/l or  $>400$  mg/dl) occurs with continuous infusion, the lipid emulsion dose should be reduced, and in cases of severe hypertriglyceridemia (TG  $>11.4$  mmol/l or  $>1000$  mg/dl) the dose should be interrupted [61], [62]. During the first days of infusion, plasma triglyceride levels should be monitored so that the dose can be modified, if necessary. When lipid utilisation is impaired, e.g. in severe illness, insulin resistance or liver failure, the lipid dose should be adapted based on plasma triglyceride concentrations. Determination of serum opacity in the supernatant after centrifugation of whole blood is not considered useful.

- Lipid infusion with PN is not indicated in severe hyperlipidemia (e.g. hereditary or acquired disorders of triglyceride hydrolysis), in severe metabolic acidosis with impaired lipid utilisation, and in severe coagulopathy (DIC stage III or higher) (C).

## Commentary

Organ failure, disturbances in microcirculation after blood transfusions, or disturbances in coagulation present no absolute contraindication for parenteral lipid administration. Parenteral supply of 20% soybean oil emulsions (35% of an overall energy supply of 35–40 kcal/kg/day) resulted in no impairment in pulmonary hemodynamics, gas exchange and diffusion capacity in patients after major upper abdominal surgery ([63]; Ib).

- In acutely ill patients, lipid infusion should be administered over at least 12 hours/day. With a more critical metabolic situation, slower infusion rates such as continuous infusion over approximately 24 hours are recommended. Shorter infusion times may be chosen in stable patients, particularly those receiving long-term or home PN (C).

## Commentary

In ARDS patients, a randomised study comparing intake of 1.3 g lipid emulsion/kg body weight over either 6 or 24 hours showed a disadvantage with the rapid infusion rate as evaluated by pulmonary prostaglandin metabolism, pulmonary shunt and oxygenation index ([64]; Ib).

- The use of lipid emulsions with a low phospholipid/triglyceride ratio is recommended (B).

## Commentary

Emulsions with low a phospholipid/triglyceride ratio, usually in 20% lipid emulsions, result in less hyperlipidemia than emulsions with a higher phospholipid/triglyceride ratio (classic 10% emulsions) ([65], [66], [67], [68]; Ib)

## Available lipid emulsions

### Soybean oil emulsions

Parenteral lipid emulsions based on soybean oil have been widely used for several decades. Soybean oil contains high concentrations of polyunsaturated fatty acids (PUFA, around 60% of the total fatty acids; ratio of linoleic acid (n-6) to  $\alpha$ -linolenic acid (n-3) approximately 8:1). The administration of soybean oil emulsions resulted in high serum PUFA concentrations. However, due to the low content of biologically active vitamin E ( $\alpha$ -tocopherol), serum vitamin E levels are lower without added supplements than with an olive oil-based emulsion, which has a higher vitamin E/PUFA ratio ([56]; Ib; [53]; Ib).

Clinical, ex-vivo and animal studies suggested that the type of parenterally administered fatty acids may influence immune functions, and high PUFA containing lipid emulsions are associated with immunosuppressive effects ([69], [70], [71], [72]; Ib). Higher post-operative concentrations of IL6 and CRP were seen after administration of soybean oil emulsion (20% of the energy intake in extremely high NPE intake of 40 kcal/kg daily) as compared to lipid-free PN, in patients after resection of gastric colorectal tumours ([73]; IIa). Many authors advise not to administer 100% soybean oil emulsions to critically ill patients [64], [73], [74], [75].

### Emulsions based on a physical mix of soybean oil and medium-chain triglycerides (MCT)

An emulsion based on a physical mix of equal parts of soybean oil and MCT-oil (from coconut oil) supplies only half the PUFA as compared to 100% soybean oil emulsions, with a similar ratio of linoleic acid (n-6) to  $\alpha$ -linolenic acid (n-3) of approximately 8:1. This lower essential fatty acid supply is adequate for meeting the needs of adults and infants [22], [76], [77], [78] (Ib). Although *in vitro* hydrolysis of medium-chain triglycerides by lipoprotein lipase is faster than that of long-chain triglycerides, clinical studies do not demonstrate uniform results. Some studies also report slower plasma elimination or increased serum triglycerides with soybean/MCT than with 100% soybean oil emulsions [79], [80], probably due to differences in rate of lipid particle clearance *in vivo* [81]. Compared to LCT, MCT are rapidly taken up by mitochondria, largely independent of carnitine, and are oxidised faster and to a greater proportion, but the energy content per g MCT fat is lower than of LCT. In an ex vivo test with cross-over design, neutrophils showed reduced bactericidal activity after infusion of soybean oil emulsions but not after a mixed soybean oil/MCT emulsion [71]. The administration of mixed soybean oil/MCT emulsion led to a slight improvement in nitrogen balance of intensive care patients after 6 and 9 days of PN ([82]; IIb), and in septic patients after 10 days of PN ([83]; Ib) as compared to 100% soybean oil emulsion. In patients after stem cell

transplantations for malignant haematological disorders, the use of the mixed soybean oil/MCT emulsion (n=18) resulted in a higher number of days with pyrexia (10 versus 7, p=0.01), and days on antibiotics (12 versus 8, p=0.04) as compared to a 100% soybean oil emulsion (n=18). Other end points, such as the occurrence of Graft versus Host Disease (GVHD) and mortality, were not different ([84]; Ib). The use of an experimental soybean oil/MCT emulsion in a 25/75 ratio resulted in significantly higher resting energy consumption, oxygen consumption and carbon dioxide production, as a result of higher thermogenetic effect of MCT as compared to a 100% soybean oil emulsion [85]. The MCT/LCT emulsion available for clinical use has a lower proportion of MCT and thus a lower thermogenic effect is expected.

### Randomly interesterified MCT/soybean oil emulsions

These emulsions contain triglyceride particles with re-esterification of medium-chain fatty acids (made of coconut oil) and long-chain fatty acids (made of soybean oil) in random distribution within the molecule. The fatty acid composition is comparable to that of the physical mix of soybean oil and MCT. These randomly interesterified emulsions are often called “structured lipids”, although they actually do not contain true structured lipids with defined positions of specific fatty acids in the triglyceride molecule [86]. Lindgren et al. [87], reported a slightly higher positive nitrogen balance in intensive care patients within the first three days of receiving an infusion of a randomly interesterified MCT/soybean oil emulsion as compared to a 100% soybean oil emulsion (II). Randomly interesterified lipids (1.0 or 1.5 g/kg/day) resulted in a higher overall lipid oxidation rate (indirect calorimetry) in post-operative patients without an increase in ketogenesis or a difference in serum triglyceride levels when compared to a soybean oil emulsion ([88], Ib). Although Chambrier et al. [89] found no difference in nitrogen balance and 3-methyl histidine excretion in post-operative patients who received the physical mix or the randomly interesterified mix of soybean oil and MCT, Kruiemel et al. [90] reported an improved nitrogen balance over the first 5 post-operative days and a slight increase in the serum triglycerides and non-esterified fatty acids in patients who were operated for an aortic aneurysm. Rubin et al. [91] reported similar safety and compatibility parameters, but with faster normalisation of raised transaminases with randomly interesterified soybean oil/MCT emulsion in patients receiving home PN (Ib).

### Olive oil/soybean oil

The available olive oil based lipid emulsion contains olive oil and soybean oil in a ratio of 4:1, and shows a high content of the monounsaturated oleic acid and of biologically active vitamin E ( $\alpha$ -tocopherol). The ratio between linoleic acid (n-6) and  $\alpha$ -linolenic acid (n-3) is 9:1.

The olive oil/soybean oil emulsion is comparable to soybean oil emulsion in terms of observed numbers of catheter infections, thromboses, and unplanned stays in hospital during long-term administration of over 6 months ([92]; IIb). In an *in vitro* test of peripheral white blood cells from healthy persons, olive oil showed less influence on the proliferation of lymphocyte subpopulations and their receptor expression than soybean oil emulsions [93], and similar effects were shown in monocytes and neutrophils [94], [95]. A small group of 2x11 burns patients showed an improvement in liver function when given parenteral olive oil emulsions as compared to a soybean oil/MCT group ([96]; Ib). In randomised controlled studies in children and infants, the olive oil based emulsion showed comparable tolerance and safety to a soybean oil emulsion, but resulted in more favourable fatty acid levels in serum, reduced markers of lipid peroxidation, and higher serum vitamin E levels ([56]; Ib; [53]; Ib).

## Fish-oil based emulsions

In critically ill patients, the generation of pro-inflammatory lipid mediators can be reduced with the use of fish oil emulsions, which may prevent the escalation of SIRS to sepsis or even septic shock [97], [98]. An infusion of fish oil emulsion in healthy volunteers resulted in a reduction in the *in vitro* release of endotoxin-induced pro-inflammatory mediators like TNF- $\alpha$ , IL1, IL6 and IL8 from monocytes ([75]; Ib). Morlion et al. [99] and Koeller et al. [100] found a lower ratio of leukotriene B<sub>5</sub> to leukotriene B<sub>4</sub> in post-operative patients a fish oil emulsion, with possible anti-inflammatory effects (Ib). Schauder et al. [101] reported no immunosuppressive effects but an increase in IFN- $\gamma$ , TNF- $\alpha$  and IL-2 synthesis (Ib) after 0.2 g/kg/day of parenteral fish oil in the post-operative phase (Ib). Parenteral supplementation with fish oil emulsion in post-operative patients results in a rapid increase in the ratio of eicosapentaenoic acid (20:5n-3; EPA) to arachidonic acid (20:4n-6; AA) in thrombocyte phospholipids ([102], Ib). A delay in collagen-induced, but not ADP-induced platelet aggregation did not result in altered bleeding times or bleeding complications following oesophagus resections. Patients after major abdominal surgery, who received either a soybean oil emulsion or a mixture of 20% fish oil emulsion and 80% soybean oil emulsion, showed no clinically significant difference in coagulation or bleeding times ([103]; Ib). Lower mortality, shorter mechanical ventilation times, and shorter stays in intensive care units and hospitals were reported in post-operative patients, especially if the fish oil infusion had been administered prior to surgery ([104]; Ib). The stable HLA-DR expression patterns observed when receiving fish oil were associated with less severe infections [104]. Lower levels of ALT/AST, bilirubin, LDH and lipase were also reported in cancer patients after elective abdominal surgery when a mixture of 20% fish oil emulsion and 80% soybean oil emulsion was used as compared to 100% soybean oil emulsion ([105]; Ib).

The use of fish oil emulsion in 56 patients with abdominal sepsis was associated with lower rates of re-operation and shorter length of stay in the intensive care units and total hospital stay ([106], abstract only). In an open case analysis of 661 patients, increasing fish oil dosage was advantageous for survival in 276 patients with sepsis and 118, 80 and 17 patients with either 1, 2 or 3 organ failures respectively ([107]; IIb). Parenteral fish-oil enriched lipid emulsion did not effect platelet function in critically ill patients ([108]; Ib).

The high unsaturated fatty acid content in fish oil tends undergo peroxidation, both during storage and in the patient after infusion. Apart from the direct effects of released oxygen radicals, lipid peroxidation products have a pro-inflammatory effect. Peroxidation of the high unsaturated fatty acids in the fish oil emulsions should be prevented by addition of vitamin E (15–29.6 mg/100ml).

## MCT, soybean and fish oil based emulsion

An emulsion of MCT-oil (coconut)/soybean oil/fish oil (weight ratio 5:4:1) administered to patients after elective major abdominal surgery for a 5-day duration reduced the ratio of leukotriene B<sub>4</sub>/B<sub>5</sub> in leukocytes stimulated *ex vivo* as compared to a soybean oil emulsion [100]. A post-hoc analysis on a subgroup of 256 patients after abdominal surgery in a multicentre trial reported a 5-day reduction in the postoperative length of hospital stay with MCT/soybean/fish oil (5:4:1) as compared to soybean oil emulsion, although the rate of clinically relevant complications were similar [109]. In a very small group of 8 kidney donors and transplant recipients, infusion of this lipid emulsion induced no differences in coagulation, liver or renal functions or serum creatinine in transplant recipients [110]. The currently available published clinical data on the use of this emulsion is still limited.

## Emulsion of soybean oil, MCT, olive oil and fish oil

A soybean/MCT/olive/fish oil emulsion in a weight ratio of 30:30:25:15 in healthy volunteers (20% emulsion, 0.125 g/kg/h), after 6 hours of parenteral infusion, resulted in a slight rise in serum triglycerides and respectively quicker clearance after discontinuing the appropriate lipid emulsion as compared to a 20% soybean oil emulsion [111]. A published study of 249 postoperative patients showed that the rise in serum triglyceride levels, when receiving this mixed lipid emulsion, is the same as with a soybean oil emulsion [112]. In an interim evaluation of a small number of surgical patients who received 5-days of postoperative PN, a reduction in hospital stay of 7 days was recorded in patients after a mixed emulsion (13.4 $\pm$ 2.0 days, n=19) than after a soybean oil emulsion (20.4 $\pm$ 10 days, n=14) [113]. Recent publication of the data of all 249 patients in this study, however, did not show any significant difference in the biochemical and



clinical parameters or in LOS (length of stay), in either the intention-to-treat analysis or the per-protocol analysis [112]. Furthermore, there was an increased ex vivo release of leukotriene B<sub>5</sub> and reduced leukotriene B<sub>4</sub>-release from leukocytes [114]. In a small group of intensive care patients (a total of 20 patients), it was found that there was an increase in ALT in both groups after 5 days of PN in a comparison between mixed emulsions and soybean oil emulsions. There was, however, less tendency towards an increase in the mixed emulsion group (n.s.) ([115]; lb). The currently available published clinical data on the use of this emulsion is still limited.

## Conclusions

Soybean oil-based emulsions meet energy and essential fatty acid requirements. There are indications that mixture of soybean oil with other oils such as MCT or olive oil result in more favourable metabolic parameters and a more desirable, lower PUFA supply. Emulsions containing fish-oil may provide anti-inflammatory effects and offer the potential for a targeted approach in specific disease states. Further research is needed on relevant clinical end points, and clear recommendations on clinical use of different emulsions cannot be given at this time.

## Notes

This article is part of the publication of the Guidelines on Parenteral Nutrition from the German Society for Nutritional Medicine (overview and corresponding address under <http://www.egms.de/en/gms/2009-7/000086.shtml>).

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