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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids

Alexandre Lapillonne [a, b, *], Nataša Fidler Mis [c], Olivier Goulet [d], Chris H.P. van den Akker [e], Jennifer Wu [f], Berthold Koletzko [g], the ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition[1]

[a] Department of Neonatology, APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France
[b] Department of Pediatrics, Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX, USA
[c] Department of Gastroenterology, Hepatology and Nutrition, Division of Paediatrics, University Medical Centre Ljubljana, Ljubljana, Slovenia
[d] Department of Pediatric Gastroenterology, Hepatology and Nutrition, Intestinal Failure Rehabilitation Center, National Reference Centre for Rare Digestive Diseases, APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France
[e] Department of Pediatrics – Neonatology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[f] Department of Clinical Nutrition, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
[g] Dr von Haunersches Kinderspital, Div. Metabolic and Nutritional Medicine, Ludwig Maximilian Universität, University of Munich Medical Center, Munich, Germany

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* Corresponding author. Department of Neonatology, APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France.
E-mail address: walter.mihatsch@gmx.de (A. Lapillonne).

[1] ESPGHAN/ESPEN/ESPR/CSPEN working group on Pediatric Parenteral Nutrition: BRAEGGER Christian, University Children's Hospital, Zurich, Switzerland; BRONSKY Jiri, University Hospital Motol, Prague, Czech Republic; CAI Wei, Shanghai Jiao Tong University, Shanghai, China; CAMPOY Cristina, Department of Paediatrics, School of Medicine, University of Granada, Granada, Spain; CARNIELLI Virgilio, Polytechnic University of Marche, Ancona, Italy; DARMAUN Dominique, Université de Nantes, Nantes, France; DECSI Tamás, Department of Pediatrics, University of Pécs, Pécs, Hungary; DOMELLÖF Magnus, Department of Clinical Sciences, Pediatrics, Umeå University, Sweden; EMBLETON Nicholas, Newcastle University, Newcastle upon Tyne, The United Kingdom; FEWTRELL Mary, UCL Great Ormond Street Institute of Child Health, London, UK; FIDLER MIS Nataša, University Medical Centre Ljubljana, Ljubljana, Slovenia; FRANZ Axel, University Children's Hospital, Tuebingen, Germany; GOULET Olivier, University Sordonne-Paris-Cité; Paris-Descartes Medical School, Paris, France; HARTMAN Corina, Schneider Children's Medical Center of Israel, Petach Tikva, Israel and Carmel Medical Center, Haifa Israel; HILL Susan, Great Ormond Street Hospital for Children, NHS Foundation Trust and UCL Institute of Child Health, London, United Kingdom; HOJSAK Iva, Children's Hospital Zagreb, University of Zagreb School of Medicine, University of J. J. Strossmayer School of Medicine Osijek, Croatia; IACOBELLI Silvia, CHU La Réunion, Saint Pierre, France; JOCHUM Frank, Ev. Waldkrankenhaus Spandau, Berlin, Germany; JOOSTEN, Koen, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; KOLAČEK Sanja, Children's Hospital, University of Zagreb School of Medicine, Zagreb, Croatia; KOLETZKO Berthold, k LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; KSIAZYK Janusz, Department of Pediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute. Warsaw; LAPILLONNE Alexandre, Paris-Descartes University, Paris, France; LOHNER Szimonetta, Department of Pediatrics, University of Pécs, Pécs, Hungary; MESOTTEN Dieter, KU Leuven, Leuven, Belgium; MIHÁLYI Krisztina, Department of Pediatrics, University of Pécs, Pécs, Hungary; MIHATSCH Walter A., Ulm University, Ulm, and Helios Hospital, Pforzheim, Germany; MIMOUNI Francis, Department of Pediatrics, Division of Neonatology, The Wilf Children's Hospital, the Shaare Zedek Medical Center, Jerusalem, and the Tel Aviv University, Tel Aviv, Israel; MØLGAARD Christian, Department of Nutrition, Exercise and Sports, University of Copenhagen, and Paediatric Nutrition Unit, Rigshospitalet, Copenhagen, Denmark; MOLTU Sissel J, Oslo University Hospital, Oslo, Norway; NOMAYO Antonia, Ev. Waldkrankenhaus Spandau, Berlin, Germany; PICAUD Jean Charles, Laboratoire CarMEN, Claude Bernard University Lyon 1, Hopital croix rousse, Lyon, France; PRELL Christine, LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; PUNTIS John, The General Infirmary at Leeds, Leeds, UK; RISKIN Arieh, Bnai Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel; SAENZ DE PIPAON Miguel, Department of Neonatology, La Paz University Hospital, Red de Salud Materno Infantil y Desarrollo – SAMID, Universidad Autónoma de Madrid, Madrid, Spain; SENTERRE Thibault, CHU de Liège, CHR de la Citadelle, Université de Liège, Belgium; SHAMIR Raanan, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Tel Aviv University, Tel Aviv, Israel; SIMCHOWITZ Venetia, Great Ormond Street NHS Trust, London, The United Kingdom; SZITANYI Peter, General University Hospital, First Faculty of Medicine, Charles University in Prague, Czech Republic; TABBERS Merit M., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN DEN AKKER Chris H.P., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN GOUDOEVER Johannes B., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN KEMPEN Anne, OLVG, Amsterdam, the Netherlands; VERBRUGGEN Sascha, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; WU Jiang, Xin Hua Hospital, Shanghai, China; YAN Weihui, Department of Gastroenterology and Nutrition, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

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Table: Recommendations for the use of intravenous lipid emulsions

R 4.1	In paediatric patients, intravenous lipid emulsions (ILE) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding. (LoE 1−, RG A, strong recommendation for)
R 4.2	In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation. (LoE 1−, RG A, strong recommendation for)
R 4.3	In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day. (LoE 4, GPP, conditional recommendation for)
R 4.4	In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day. (LoE 3−4, RG 0, conditional recommendation for)
R 4.5	In order to prevent essential fatty acids (EFA) deficiency in preterm infants a lipid emulsion dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/day can be given. This lipid emulsion dosage ensures an adequate intake of linolenic acid (LNA) with all lipid emulsions currently registered for paediatric use. (LoE 2−, RG 0, strong recommendation for)
R 4.6	In order to prevent EFA deficiency in term infants and in children a lipid emulsion dosage providing a minimum LA intake of 0.1 g/kg/day can be given, which also provides an adequate intake of LNA with all ILEs currently registered for paediatric use. (LoE 3−4, RG 0, conditional recommendation for)
R 4.7	In preterm infants, newborns and older children on short term PN, pure soybean oil (SO) ILEs may provide less balanced nutrition than composite ILEs. For PN lasting longer than a few days, pure SO ILEs should no longer be used and composite ILEs with or without fish oil (FO) should be the first choice treatment (LoE 1−, RG A, conditional recommendation for)
R 4.8	In preterm infants, ILEs should be protected by validated light-protected tubing. (LoE 1−, RG B, strong recommendation for)
R 4.9	In infants and children, 20% ILEs should be the first choice treatment (LoE 1−, RG B, strong recommendation for)
R 4.10	In newborns including preterm infants, routine use of ILEs should be continuous over 24 h (LoE 2++, RG B, conditional recommendation for)
R 4.11	If cyclic PN is used, for example for home PN children, ILEs should usually be given over the same duration as the other PN components. (LoE 4, GPP, strong recommendation for)
R 4.12	In paediatric patients, heparin should not be given with lipid infusion on a routine basis. (LoE 3−4, GPP, conditional recommendation for)
R 4.13	Carnitine supplementation may be considered in paediatric patients expected to receive PN for more than 4 weeks or in premature infants on an individual basis (LoE 3−4, GPP, conditional recommendation for)
R 4.14	In critically ill paediatric patients, ILE should be an integral part of PN. Composite ILEs with or without FO may be used as the first choice treatment. Available evidence raises the important question on the best timing to provide parenteral nutrition support in critically ill children, but do not allow to differentiate potential effects on outcomes of the timing of introducing parenteral lipid supply (LoE 4, GPP, conditional recommendation for)
R 4.15	In paediatric patients with sepsis, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA requirements (LoE 4, GPP, conditional recommendation for)
R 4.16	Case reports have suggested the use of ILEs as a possible antidote for the treatment of drug toxicity in children, which however is not based on well-designed trials (LoE 3−4, GPP, conditional recommendation for)
R 4.17	In patients with severe unexplained thrombocytopaenia, serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage may be considered. (LoE 3−4, GPP, conditional recommendation for)
R 4.18	As part of measures to reverse IFALD in paediatric patients, a discontinuation of SO ILE, a reduction of other ILE dosage and/or the use of composite ILE with FO, should be considered along with the treatment and management of other risk factors (LoE 2+, RG B, strong recommendation for)
R 4.19	The use of pure FO ILE is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe IFALD, based on case reports. (LoE 3−4, GPP, conditional recommendation for)
R 4.20	Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants) (LoE 2−, RG B, strong recommendation for)
R 4.21	Reduction of the dosage of ILEs can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children (LoE 4, GPP, conditional recommendation for)

1. Methods

Literature search timeframe: The references cited in the previous guidelines [1] are not repeated here, except for some relevant publications, and only the previous guidelines are cited instead. All publications published after the previous guidelines (i.e., from January 2004 to December 2014), have been considered for the first draft of this manuscript. Randomized controlled trials (RCTs), review articles, prospective studies and meta-analyses published in 2015 and 2016, during the revision process, have also been considered.

Type of publications: Original papers, meta-analyses and reviews.

R 4.1	**In paediatric patients, intravenous lipid emulsions (ILE) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding. (LoE 1−, RG A, strong recommendation for, strong consensus)**
R 4.2	**In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation. (LoE 1−, RG A, strong recommendation for, strong consensus)**
R 4.3	**In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day. (LoE 4, GPP, conditional recommendation for, strong consensus)**
R 4.4	**In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day. (LoE 3−4, RG 0, conditional recommendation for, strong consensus)**

Language: English

Key words: Parenteral nutrition, lipid/fat emulsions, paediatric, fatty acids, LC-PUFA, IFALD, PNALD, cholestasis.

2. Introduction

The rate, amount, and type of lipids provided intravenously are important aspects regarding the efficacy and safety in neonates and children [1–3]. Intravenous lipid emulsions (ILEs) are an indispensable part of paediatric parenteral nutrition (PN) as a non-carbohydrate source of energy delivered as an iso-osmolar solution in a low volume (2.0 kcal/mL with 20% ILEs, or 1.1 kcal/mL with 10% ILEs due to the higher relative content of glycerol). Generally a lipid intake of 25–50% of non-protein calories is recommended in fully parenterally fed patients (see also section on “Energy” of these guidelines). Lipids provide essential fatty acids (EFAs) and help with the delivery of the lipid soluble vitamins A, D, E, and K.

The ILE particle is metabolized following the same pathway as a natural chylomicron. The triglyceride portion is hydrolysed by the endothelial lipoprotein lipase (LPL) [4]. In the circulation, ILE particles also exchange apoproteins and cholesterol with endogenous lipoproteins, thus transforming the initial ILE particle into a so-called remnant particle. The liver rapidly removes ILE remnant particles by hydrolysing them with hepatic lipase. The released free fatty acids (FFAs) can be captured by the adjacent tissues or can circulate bound to albumin, for use in other tissues or uptake by the

liver. The rate of hydrolysis varies according to the type of the triglyceride substrate (i.e., length of the FA, degree of saturation, position of the FA on the glycerol). LPL activity is influenced by prematurity, malnutrition, hypoalbuminaemia, metabolic acidosis, high plasma lipid concentrations, and may be reduced in catabolic states. If the ILE is infused at a rate that exceeds the rate of utilisation, plasma triglyceride concentration will rise and may cause adverse effects including reticulo-endothelial system overload. If the rate of hydrolysis exceeds the rate at which the released FFAs are taken up and oxidized, the plasma concentration of FFAs will also increase and in turn may decrease the LPL activity.

3. Type of lipid emulsions

3.1. 20% Lipid emulsions (20% LEs)

Pure soybean oil (SO) based ILEs (SO ILEs) have been widely used for several decades in adults, children, and neonates. More recent ILEs were also vegetable oil-based ILEs until the newest ILEs with fish oil (FO) became available. These ILEs have marked differences in terms of oil source, FA composition, vitamin E (tocopherols) and phytosterol contents.

Pure SO ILEs are frequently studied in comparison with more recently introduced ILEs. The SO ILEs contain high concentrations of EFAs (~60% of total FAs) with a ratio of linoleic acid (LA) (18:2n-6) to alpha-linolenic acid (LNA) (18:3n-3) of approximately 8:1, but they lack appreciable amounts of any of the long-chain polyunsaturated fatty acids (LC-PUFAs) [5]. In addition, pure SO ILEs contain low amounts of α-tocopherol, the form of vitamin E with the highest *in vivo* antioxidant effect [6]. The low α-tocopherol content further enhances deleterious lipid peroxidation of the high parenteral PUFA supply [2].

The only currently available 20% olive oil/soybean oil-based ILE (OO/SO) contains 80% OO and 20% SO. It is rich in the monounsaturated oleic acid (18:1n-9) [7] and has a naturally higher vitamin E/PUFA ratio, resulting in an improved vitamin E status in recipient patients [1].

The 20% medium-chain triglycerides (MCT)/SO-based ILE (also named MCT/LCT) contains equal proportions of MCTs and long-chain triglycerides (LCTs), from coconut oil and SO, respectively. It contains less PUFAs than the pure SO ILEs and also lacks appreciable amounts of LC-PUFAs [3,5].

Two 20% composite ILEs which include FO as well as other oils have been marketed in Europe. They contain 50% MCT, 40% SO, 10% FO (MSF) or 30% SO, 30% MCT, 25% OO and 15% FO (SMOF), respectively [5]. Compared to pure SO ILEs, both of these ILEs also contain higher amounts of vitamin E and less phytosterols [8].

3.2. 10% Lipid emulsions (10% LEs)

A 10% ILE consisting of pure FO is also available. However, this is registered for use only in adult patients with the goal of supplementing n-3 FAs, while it is not intended to be used as the sole lipid source for long-term PN. Because the pure FO ILE is a 10% solution, it requires twice the volume to be infused as compared to standard 20% ILE. This might be problematic in infants who are on volume restriction. Besides, 10% ILEs have a higher phospholipid content, which can potentially increase plasma triglyceride concentrations.

4. Energy supply

Preterm infants have special nutritional needs in early life, and there is now evidence to suggest that lipids administered at this age may determine various outcomes in later life, including both physical growth and intellectual development [9,10]. Recent meta-analyses and RCTs provide evidence that the initiation of lipids within the first two days of life in very preterm infants appears to be safe and well tolerated [10–14]. No signs of increased respiratory impairment, chronic lung disease, sepsis, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhages, retinopathy of prematurity, or mortality could be demonstrated.

In terms of efficacy, most studies investigated a combination of earlier lipid intake along with early or increased amino acid intake, making it difficult to attribute which macronutrient led to a supposed improved growth [14]. However, some studies demonstrated improved neonatal growth after early initiation of ILE alone [15,16]. It appears possible that the amount of early lipids influences later neurodevelopmental outcome as suggested by observational studies [17].

Positive effects of early parenteral lipids on nitrogen balance have been shown in two studies performed in premature infants [11,18]. In the larger one, the efficacy of the introduction of a high dose of parenteral lipids (i.e., 2–3 g/kg/day) combined with 2.4 g/kg/day of amino acids from birth onwards was compared to a group receiving a similar amount of amino acids, but without lipids. In the group with parenteral lipids, the nitrogen balance on day two was significantly more positive, plasma urea concentrations were significantly lower, and albumin synthesis was enhanced [19], suggesting that administration of parenteral lipids combined with amino acids from birth onwards improves protein anabolism. On the other hand, triglycerides and glucose concentrations were significantly higher in the early lipid group compared with the control group and more infants required insulin therapy. Since there were no benefits for growth, hospital clinical outcomes, total duration of hospital stay, and long term neurodevelopment [20], the clinical benefits of such strategy remain to be proven.

To date there is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance. However, starting lipid emulsion the first day of life at a dose of 2–3 g/kg/d may induce a higher occurrence of hyperlipidaemia as indicated above [19].

The maximum amount of lipids that can be safely given in premature infants is currently not known with certainty. Bilirubin displacement from albumin binding sites by FFAs has also been mentioned as a potential risk of early use of ILE, especially in infants ≤28 weeks gestational age [21]. However, significant displacement of bilirubin does not occur until the FFA to albumin molar concentration ratios are greater than five, while infusion rates of up to 3.25 g/kg/day do not result in ratios over four [22]. Therefore, it is unlikely that lipid infusion at rates of 3–4 g/kg/day results in increased incidence of hyperbilirubinemia or kernicterus. Furthermore, questions arise on long term detrimental effects of ILEs since aortic stiffness and myocardial function in young adulthood has been associated with the exposure to SO ILEs during neonatal life [23]. However, this association does not provide evidence for a causal role of SO ILEs, rather than other associated factors, and it also does not allow generalisation of effects with respect to other ILEs. Most studies in preterm infants limit parenteral lipid intake to 3.0–4.0 g/kg/day, notably a lesser lipid supply than what would be achieved with full enteral feeding. Further well-designed and adequately powered studies are necessary to determine the optimal dose of lipid infusion and the long-term effects on morbidity, growth, and neurodevelopment.

The use of lipids as an energy source reduces the glucose infusion rate necessary to cover the total energy requirements. Since glucose infusion rate should not exceed the maximum glucose oxidation rate (17.3 g/kg/day (12 mg/kg/min) in children) (see also section on “carbohydrates”), a significant amount of lipids should be provided to cover the energy requirements. A

study in malnourished infants and young children has shown that the amount of infused lipid must also be adapted to the lipid oxidation capacity [1]. The maximal lipid oxidation rate is about 3 g/kg/day in young children and decreases with age to 1.7–2.5 g/kg/day in adults. Any lipid provided in excess of metabolic utilization will be stored primarily in adipose tissue and increases the risk of fat overload syndrome which may impair the immune response.

5. Essential and long-chain polyunsaturated fatty acid supply

R 4.5	**In order to prevent essential fatty acids (EFA) deficiency in preterm infants a lipid emulsion dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/day can be given. This lipid emulsion dosage ensures an adequate intake of linolenic acid (LNA) with all 20% ILEs currently registered for paediatric use. (LoE 2–, RG 0, strong recommendation for, strong consensus)**
R 4.6	**In order to prevent EFA deficiency in term infants and in children a lipid emulsion dosage providing a minimum LA intake of 0.1 g/kg/day can be given, which also provides an adequate intake of LNA with all 20% ILEs currently registered for paediatric use. (LoE 3–4, RG 0, conditional recommendation for, strong consensus)**

Omission of ILEs from PN may lead to biochemical evidence of EFA deficiency within few days in infants [1]. To prevent EFA deficiency, a minimum LA intake of 0.25 g/kg/day in preterm infants and 0.1 g/kg/day in term infants and older children should be given, which also supplies adequate amounts of LNA (in most ILE the LA to LNA ratio is about 8:1). It should be noted that the provision of EFAs varies with the type of ILE used, and therefore the amount of ILE needed to cover the EFA requirements differs. As an example, a supply of 0.5 g/kg/day of a SO ILE will provide the recommended minimum supply of LA to a preterm infant, whereas 1 g/kg/day will be necessary with an MCT/SO ILE or a composite ILE with FO. At maximum infusion rate, all commercially available solutions (except for the pure FO ILE) provide enough LA and LNA.

The supply of LC-PUFAs is important to consider in neonates because these FAs are conditionally essential in this population and have critical roles during early development [3,9,10]. Vegetable oil-based ILEs lack appreciable amounts of n-6 (arachidonic acid (ARA)) and n-3 LC-PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) which are only supplied in very small amounts from the egg phospholipid emulsifier. In preterm infants the use of pure SO ILEs results in high serum concentrations of LA, whereas the formation of the LC-PUFAs appears to be reduced relative to other available ILEs which have lower EFA contents [22,24,25]. Despite a significantly lower EFA content, similar or even slightly higher LC-PUFAs levels than those observed with pure SO are achieved in preterm infants receiving OO/SO ILEs, most likely because of enhanced LA conversion [22,26]. MCTs seems to enhance the incorporation of EFAs and LC-PUFAs into circulating lipids in preterm infants as the latter are probably spared from oxidation due to preferential oxidation of MCTs [2,25]. Overall, in preterm infants, ILEs providing a mixture of vegetable oils result in more favourable metabolic parameters, and a more desirable lower PUFA supply than pure SO ILEs, but LC-PUFA plasma or blood levels comparable to that of term infants cannot be achieve with any of these lipid emulsions.

In older children, all commercially available 20% ILEs contain sufficient amounts of essential LA and LNA to prevent deficiency. As a general rule, any 20% ILE can be prescribed to compose parenteral regimens or in combination with enteral nutrition to normometabolic patients who require intravenous lipids for a short duration [27].

The smaller preterm infants who receive ILEs that do not contain FO develop an early and severe DHA deficit [28]. Those who receive composite ILEs with FO have higher circulating DHA levels in both plasma and red blood cells than those receiving any other ILEs [29]. This does not mean, however, that the DHA supply provided by ILEs containing FO covers the needs. Indeed, when the mean DHA supply by the composite ILE with FO is similar to the foetal accretion rate (i.e., 42 mg/kg/day), a decrease, not an increase, in circulating DHA levels is observed [30]. It is speculated that both oxidation and tissue uptake may occur and that higher DHA supply might be necessary to fulfil requirements.

A marked elevation of EPA in plasma and red blood cells is observed frequently when ILEs containing FO are used [29]. The estimated EPA supply with FO containing mixed LEs is about 44 mg/kg/day, which is ~10 times greater than that of preterm infants fed their mother's milk [30]. The high EPA intake in the FO group is associated with a significantly greater postnatal drop in ARA levels which suggest a reduced ARA synthesis [29]. The provision of any ILEs with FO that provide no ARA raises questions as to their suitability and biological effects particularly in young infants since low ARA blood concentrations is possibility associated with adverse effects on growth and neurocognitive development [31]. Whether or not these changes in FA profiles are beneficial for the short term and the long term requires further careful evaluation. Based on these findings, it appears prudent to provide n-6 and n-3 precursor fatty acids, as well as n-6 and n-3 LC-PUFA, in balanced amounts and ratios.

6. Choice of lipid emulsion and effects on health

The choice of ILEs is influenced by several considerations which include the composition of the ILE (i.e., fatty acid composition, phytosterols, MCTs, α-tocopherol etc.), the duration of PN, the setting (home PN vs. intensive care unit (ICU) or perioperative PN), age, disease conditions, and other factors. When prescribing ILEs, an understanding of the biological properties and of their FA components is mandatory. As the FA compositions of current ILEs cannot address specific individual clinical needs, the metabolic profiles, and the specific requirement of the patients should guide the prescription of the best-available ILEs to improve not only short term outcomes such as healing and recovery, but also long term outcomes such as growth, cognitive development and development of the immune system.

6.1. Risk of sepsis

Lipids directly support microbial growth and depending on their FA composition lipids can modulate immune functions. The effects of intravenous lipids on the immune system of paediatric patients has only be partially explored. *In vitro* studies showed adverse effects of lipids on the survival of monocytes derived from children, and binding of IL-2 to its receptors. Pure SO ILEs promote more IL-6 production than OO/SO ILEs do [32]. On the other hand, clinical studies in paediatric patients did not reveal adverse effects of ILEs on complement factors or leucocyte function [33], and normal levels of monocyte activation and complement factors have been documented in paediatric patients on long term PN [22].

There are concerns that the administration of ILEs may increase the risk of coagulase-negative staphylococcal bacteraemia in premature infants. Decreased whole blood bactericidal activity has been documented in infants on long term PN but it was not possible to differentiate between the effect of ILEs and other influencing factors such as fasting or other components of the PN solution [1]. A recent comparative study found that ILEs were not significantly associated with an increased risk of overall bacterial and

bloodstream infection rates when given in all-in-one bags [34]. Although this issue has not been settled conclusively, it appears that the nutritional benefits of intravenous lipid administration outweigh the potential risks.

A systemic review and meta-analysis in preterm infants showed a weak association of less sepsis episodes in infants receiving non-pure SO based ILEs as compared to SO ILE [13], which indicates that the source of lipids may play an important role in this situation. This result is however based on only 2 studies that compared pure SO ILE with OO/SO or MCT/SO and has not been confirmed by other meta-analyses [35]. This is, however, in accordance with decreasing DHA concentrations over time in preterm infants receiving pure SO ILEs [36] and with the observed association between low DHA and ARA concentrations and the increased incidence of sepsis [37].

In adults, large RCTs and meta-analyses have shown benefits of composite ILEs without and with FO as compared to pure SO ILE with regard to the risk of infection in ICU [38] and surgical patients [39]. Strategies of using ILEs other than SO ILEs for improving *a priori* the outcomes of older children including those admitted in paediatric ICU may be beneficial even if they have not been fully tested yet [40].

6.2. Prevention of intestinal failure associated liver disease

R 4.7	**In preterm infants, newborns and older children on short term PN, pure soybean oil (SO) ILEs may provide less balanced nutrition than composite ILEs. For PN lasting longer than a few days, pure SO ILEs should no longer be used and composite ILEs with or without fish oil (FO) should be the first-choice treatment (LoE 1−, RG A, conditional recommendation for, strong consensus)**

Intestinal failure associated liver disease (IFALD), also called parenteral nutrition associated liver disease (PNALD) or parenteral nutrition related cholestasis or reflects an heterogeneous liver injury consisting of cholestasis, steatosis, fibrosis and even cirrhosis [41,42]. The most common figure in paediatric patients is cholestasis. Cholestatic liver disease may evolve to fibrosis and cirrhosis [41].

Paediatric patients at risk of IFALD should be identified early in order to prevent, as much as possible, the occurrence of cholestasis. Patients at highest risk include premature infants, infants with long term bowel rest, loss of entero-hepatic cycle (ileal resection, enterostomy) or repeated sepsis, and infants with short bowel syndrome. These patients should be managed by promoting oral feeding as much as possible and by limiting the risk of sepsis and small intestinal bacterial overgrowth [43].

The mechanisms by which ILEs can favour IFALD have been reviewed recently by the ESPGHAN Committee on Nutrition [44] and the ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation [42]. Since ILEs are considered as one of the many risk factors [45–47], a significant reduction of the dose of ILEs (1 g/kg/d) may prevent cholestasis. Despite pilot studies were in favour of this concept [48,49], other studies including a large RCT including preterm infants born before 29 weeks of gestation failed to demonstrate that a reduced intake of ILEs reduces the risk of cholestasis [50,51]. Furthermore, this remains controversial, since it carries an increased risk of developing EFA deficiency and perhaps also altered development [17,52].

Single studies proposed potential benefits of fish oil containing ILE on indicators of disturbed liver function. One RCT performed in children on home PN showed that the mean total bilirubin concentration decreased in the group on SMOF ILE whereas it increased in the group on SO ILE [58]. Similarly, another study performed in infants with early IFALD and a conjugated bilirubin between 17 and 50 μmol/L at inclusion showed that those receiving the SMOF ILE had a lower conjugated bilirubin concentration at the end of the trial and were more likely to have a decrease of conjugated bilirubin to 0 μmol/L than those receiving a SO ILE [59]. However, a meta-analysis including RCTs and non RCTs showed of fish oil containing ILE for prevention of cholestasis [127].

The ESPGHAN Committee on Nutrition recently performed a systematic review with, where appropriate, a meta-analysis on the effect of different types of ILE on cholestasis and IFALD [44]. The objective of this work was to assess the role of different ILEs in the pathogenesis of cholestasis and IFALD in infants and in children. The primary outcome measure was the incidence of cholestasis (serum conjugated bilirubin >2 mg/dL; 34 μmol/L) and the secondary outcomes included levels of conjugated and total bilirubin, liver enzymes, alkaline phosphatase, and ɣ-glutamyl transferase.

In neonates receiving an ILE for a short term, the pooled meta-analysis did not find any significant difference in any composite ILE compared to the pure SO ILE for the primary and secondary outcomes. One RCT not included in the meta-analysis showed that the group of preterm infants receiving an own-made mixture composed of 50% OO/SO ILE and 50% pure FO ILE had a significantly lower incidence of cholestasis than the group receiving solely the OO/SO ILE [53]. Since the literature search of the ESPGHAN systematic review, one large RCT did not show any significant difference in liver function tests between a group of preterm infants receiving SMOF ILE and a group receiving a SO ILE [54].

In children on short term PN, one RCT performed in children after bone marrow transplantation with no cholestasis before the ILE initiation showed no effect of the MCT/SO ILE versus the OO/SO ILE on serum bilirubin and transaminase concentrations [55].

Finally, in neonates and children on long term PN (i.e., more than 4 weeks), there is no significant effect on the appearance of cholestasis in neonates receiving the 10% pure FO ILE vs the SO ILE [56] nor there is a significant difference in liver enzyme tests and bilirubin concentrations in children receiving the OO/SO ILE or the SO ILE [57]. Other health outcomes

The use of pure SO ILE in preterm infants has been linked to increased pulmonary vascular resistance, impaired pulmonary gas exchange, enhanced oxidative stress and adverse immunologic effects such as increased rates of infection and sepsis [1,5,60].

Compared to LCTs, MCTs show faster plasma clearance, more rapid oxidation, and less dependency on carnitine for beta-oxidation [2,22]. Adult and paediatric studies suggested that MCT/LCT emulsions lead to higher net fat oxidation, reduced liver derangement, improved white blood cell function, and less effects on pulmonary haemodynamic and gas exchange than SO ILEs [22].

The effects of the OO/SO ILE on peroxidation and oxidative stress defence remain controversial, but are either positive or neutral [7,22,26,61,62]. Compared to pure SO ILEs, other advantages of the OO/SO ILE include decreased phytosterol load [63,64], a more neutral effect on immunological modulators [32], and beneficial effects on pulmonary artery pressure [65]. A stable isotope study in premature infants reported that the OO/SO ILE also have a beneficial effect on glucose homoeostasis compared to pure SO ILEs [66].

A RCT performed in children after bone marrow transplantation showed that the MCT/SO and the OO/SO ILEs were equally well tolerated, maintained EFA concentrations and did not have adverse effect on peroxidation status. No differences between MCT/SO and OO/SO ILEs were found for haematological parameters, liver

enzymes, vitamins, plasma peroxidation status, percentage and time to engraftment, but cholesterol levels were significantly lower in the OO/SO ILE group [55].

Whether or not recent composite ILEs containing FO may provide specific health benefits has only been partially investigated [60]. The effect on growth is controversial since one study showed higher weight and head circumference z-scores during hospitalization in preterm infants receiving composite ILEs containing FO compared to those receiving pure SO ILE [67] whereas another did not show any significant effects [54]. No effects of composite ILEs with FO could also be demonstrated on fat mass deposition, intrahepatocellular lipid content and insulin sensitivity assessed at expected term [54]. Other possible beneficial effects of ILEs containing FO in preterm infants include a lower incidence and/or severity of retinopathy of prematurity [53,68,69], the reduction of markers of oxidative stress [70], and a decreased risk of bronchopulmonary dysplasia [71,72]. However, recent meta-analyses comparing ILEs containing FO with other ILEs did not show a significant reduction in mortality, in infection rate or any other clinical variables (e.g., bronchopulmonary dysplasia, sepsis, retinopathy of prematurity, growth) and PN associated complications [29,35]. Also various biochemical markers such as hyperbilirubinaemia, hypertriglyceridaemia, elevated C-reactive protein were not better in the group on composite ILE with FO [29,40] nor was the cholesterol synthesis rate [73]. Finally, no effect of SMOF ILE on brain growth [54] and neurodevelopment [20] could be demonstrated.

Few RCTs were published after the meta-analyses cited above. One of them, using a 2-by-2 factorial protocol, assessed the effects of a composite ILE containing FO versus a pure SO ILE on intrahepatocellular lipid content assessed by MRI at expected term [54]. This study did show any significant effect on the primary outcome nor on growth parameters, adipose tissue deposition, triglyceride concentration and liver parameters.

ILE containing FO may modulate markers of the inflammatory response. In infants undergoing cardiopulmonary bypass composite ILEs containing FO provided prior to surgery, result in a lower inflammatory response after surgery [74]. In children after haematopoietic stem cell transplantation, composite ILEs with FO, compared to SO ILE, improve antioxidant profile but did not alter markers of inflammation at day 10 [75]. However, on prolonged PN for more than 21 days, IL-10 and TNF-α levels were reduced by the composite ILE with FO [76]. Finally, preterm infants receiving a composite ILE with FO compared to a SO ILE, had lower IL-6 and IL8 levels at day 30 of life or at the end of intervention [77]. All together these studies show that providing composite ILE with FO alter the inflammatory response and may be beneficial. However, none of these studies reported clinical outcomes and therefore the clinical relevance of these findings need to be further evaluated.

7. Mode of administration of ILEs

7.1. Photoprotection

R 4.8	**In preterm infants, ILEs should be protected by validated light-protected tubing. (LoE 1−, RG B, strong recommendation for, strong consensus)**

ILEs with high PUFA content are particularly prone to peroxidation. These radicals may be harmful, especially to premature infants in whom they have been associated with poor feeding and high serum triglyceride concentrations [78–81]. The exposure of lipid solutions to blue light irradiation (i.e., phototherapy light) may significantly increase lipid peroxidation leading to cellular damage of the retinal pigment epithelial cells or of the photoreceptors [82,83]. In vitro studies have suggested that administering multivitamins containing ascorbic acid together with ILEs via dark delivery tubing, provides the most effective way of preventing lipid peroxidation and also limiting vitamin loss. The formation of triglyceride hydroperoxides may occur even in ambient light [84–87]. A recent meta-analysis including over 800 infants from 4 RCTs showed a significant reduction of 50% in the mortality rate in the light-protected group [88].

7.2. Emulsions with 20% or 10% lipids

R 4.9	**In newborns including preterm infants, routine use of ILEs should be continuous over 24 h (LoE 2++, RG B, conditional recommendation for, strong consensus)**

ILEs consist of a lipid source and an emulsifier (egg yolk derived phospholipids) that envelopes the fat globules and keeps them soluble. Standard 20% emulsions contain a lower ratio of phospholipid (PL) emulsifier/triglycerides than standard 10% ILEs. The 20% ILEs are currently the most frequently used ILEs in neonatal intensive care units [89]. Preterm infants receiving 10% emulsion vs. 20% emulsion demonstrated various alterations in their plasma lipid profiles. Higher amounts of PL (i.e. particles rich in PL) impede the removal of triglycerides from plasma, leading to an increase in plasma triglyceride concentration and accumulation of cholesterol and phospholipids in low-density lipoproteins [22]. Of note, 10% pure FO emulsion has been used in infants and children at a low dosage of 1 g/kg/d, with no adverse observed effects [90] but further studies are needed to fully explore the safety of this ILE when given to infants or children.

7.3. Continuous vs. discontinuous

R 4.10	**In newborns including preterm infants, ILEs should be administered as continuous infusions over 24 h (LoE 2++, RG B, conditional recommendation for, strong consensus)**
R 4.11	**If cyclic PN is used, for example for home PN children, ILEs should usually be given over the same duration as the other PN components. (LoE 4, GPP, strong recommendation for, strong consensus)**

There is no clear evidence that a lipid free interval allows the lipids to 'clear' from the plasma or allows 'hepatic rest' to improve tolerance [22]. Short-term lipid tolerance is best when infused continuously at steady rate, as several plasma lipid concentrations correspond best with the hourly infusion rate. This is especially the case with lower gestational ages or at higher infusion rates. Besides, interruption of PN in neonates could result in higher infection rate, possibly due to increased line handling [91,92]. A retrospective analysis of PN cycling in both preterm and term neonates with gastrointestinal disorders requiring surgical intervention showed that prophylactic daily discontinuous PN infusion could not prevent a rise in conjugated bilirubin concentrations [93]. In another retrospective analysis of PN treated neonates with gastroschisis, prophylactic cycling of all PN components was associated with reduced cholestasis but the association disappeared after adjusting for confounders [92]. In both previous retrospective studies, there was no mention of the total lipid dose in both groups, so that a reduced daily lipid dose could also be responsible for a supposed difference. In a recent RCT in preterm infants comparing cycled or continuous amino acid infusion together with interrupted lipid infusion for 6 h per day in both groups, no effect on cholestasis has

been demonstrated [91]. In adults and children receiving long-term or home PN, there is a favourable risk-benefit profile of cyclic PN infusion [94]. However, infants under age 2 years are at risk for the development of hypoglycaemia after interrupting PN, and thus blood glucose concentrations should be monitored.

The clearance of the ILEs varies according to the FA composition of the ILEs and is longer for LCT infusions than MCT infusions [95]. Therefore, mixing oils of varying chain lengths can favourably influence the plasma clearance of lipid infusions.

In metabolically stressed children, ILEs can be administered safely at a low dosage over a 12–24 h period. The discontinuous administration of ILEs at higher daily doses may contribute to fat overload syndrome and should be avoided in critically ill children.

7.4. Heparin

R 4.12	**In paediatric patients, heparin should not be given with lipid infusion on a routine basis. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

The stability of the ILEs may be compromised (flocculation and creaming) by adding components that lower the pH or impose ionic stress. The size of the ILE droplets should remain well below the diameter of capillaries to avoid vascular occlusion. The stability of the ILEs is also threatened because of an interaction between heparin and calcium. This destabilization will depend on proportions of amino acids, multivitamins and ILEs [96], and has been described to occur in ternary admixtures for paediatric PN [97]. It is more likely to occur when the heparin is used at high concentrations and when intravenous lipids are used undiluted, and less likely to occur for ranges of lipid-to-nutrient ratios normally administered to premature infants [98].

Clearance of ILEs from the blood depends on the activity of LPL. LPL activity can be increased by relatively high doses of heparin [22]. However, the increase in LPL activity by heparin leads to an increase in FFAs, which may exceed the infant's ability to clear the products of lipolysis and may weaken the binding of LPL to the endothelium [22].

Overall, since heparin does not improve utilization of intravenous lipids and might compromise the stability of ILEs, it should not be given with lipid infusions on a routine basis, unless indicated for other reasons.

7.5. Carnitine

R 4.13	**Carnitine supplementation may be considered in paediatric patients expected to receive PN for more than 4 weeks or in premature infants on an individual basis (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

Carnitine facilitates the transport of long-chain FAs across the mitochondrial membrane, and thus makes them available for beta-oxidation [22,99]. Carnitine is present in human milk and cows' milk formulae, but PN solutions do not usually contain carnitine.

Carnitine is synthesized in the liver and kidney from lysine and methionine. Thus patients with renal or hepatic insufficiency may be at risk of carnitine deficiency [99]. Tissue carnitine stores of infants aged less than 24 h show a positive correlation with gestational age. Infants and preterm infants have much more limited carnitine stores and synthesis rates compared with adults [22]. In clinical practice, it is difficult to assess the carnitine status because the circulating carnitine levels poorly reflect tissue carnitine stores.

Low carnitine concentrations have been reported in patients on carnitine-free PN, especially in infants with body weight less than 5 kg [22,100]. Parenteral carnitine supplementation increases the plasma levels of total, free and acyl-carnitine, but results on metabolic nutrition and clinical outcomes are inconsistent [101–103]. A meta-analysis showed no benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain in neonates requiring PN [22].

Given that some patients have both limited carnitine stores and biosynthesis, monitoring of plasma carnitine concentrations and carnitine supplementation (e.g. 20–30 mg/kg/d) may be considered on an individual basis in premature infants or those on exclusively PN for more than 4 weeks [99,104].

8. Lipid emulsions in special disease conditions

8.1. Critically ill children

R 4.14	**In critically ill paediatric patients, ILE should be an integral part of PN. Composite ILEs with or without FO may be used as the first choice treatment. Available evidence raises the important question on the best timing to provide parenteral nutrition support in critically ill children, but do not allow to differentiate potential effects on outcomes of the timing of introducing parenteral lipid supply (LoE 4, GPP, conditional recommendation for, strong consensus)**
R 4.15	**In paediatric patients with sepsis, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA requirements (LoE 4, GPP, conditional recommendation for, strong consensus)**

Nutritional support in critically ill infants and children has not been fully studied and remains a controversial topic. A Cochrane review did not identify any RCT assessing the best timing for introducing a PN support in paediatric patients [105]. As a consequence, there are no clear recommendations on the best form or timing of nutrition in critically ill children. In one very recent large RCT, 1440 paediatric patients admitted to 3 different PICUs were randomized to receive PN support, in addition to enteral nutrition, either starting within the first 24 h of ICU treatment or on day 8. Both groups, however, received intravenous minerals, trace elements, and vitamins. As a consequence, parenteral and total energy, lipid and amino acid supply during the first week were significantly different between the 2 groups. Compared with the early PN group, the late PN group showed significantly less new infections and a shorter PICU stay, which leads to the conclusion that routine administration of PN in all pediatric ICU patients on the first day of treatment may not be advisable [106]. The study raises the important question on the best timing to provide PN support in critically ill children, but it does not allow to differentiate potential effects of different PN components, or whether the timing of introducing parenteral lipid supply may affect outcomes. Whether or not withholding lipid emulsion during the first week of critical illness in malnourished children or in children risk of becoming malnourished is beneficial or not has also not been extensively studied and is a matter of debate. On one hand, in one large RCT, children with the highest risk of becoming malnourished benefited of withholding PN (and in turn of withholding parenteral lipid) [106], on the other hand, an observational study suggested that withholding PN in malnourished children may further increase mortality and morbidity [107]. A more careful evaluation of the effect of withholding ILEs in critically ill infants and children is therefore needed.

Concerns have been raised regarding the possible adverse effects of intravenous lipids on pulmonary function. ILEs have been considered toxic in acute respiratory failure since they may induce or intensify gas exchange abnormalities. The SO ILEs induce an increase in pulmonary blood pressure and vascular resistance [108]. In neonates, this is of particular importance because respiratory failure is frequently associated with pulmonary hypertension. Previous studies suggested that ILEs (mainly pure SO) may increase the pulmonary artery pressure in newborns with respiratory failure. There is now some evidence from experimental studies that n-3 PUFA may be beneficial in conditions associated with pulmonary hypertension through production of epoxides [109]. The clinical relevance of these findings has however not yet been proven in neonates [110].

There are also conflicting data about lipid clearance during sepsis. Some studies found that lipid clearance is reduced whilst others found no association between hypertriglyceridaemia and infection. In septic premature infants, triglyceride concentrations tend to be higher, because of decreased activity of lipoprotein lipase, and fatty acid oxidation is lower than in non-septic patients but it is difficult to define an upper limit of lipid intake based on these data [22]. In critically ill and in septic patients, close monitoring of plasma triglycerides and adjustment of lipid infusion rate if necessary is recommended.

Composite ILEs could have less pro-inflammatory effects, less immune suppression, and more antioxidant effects than the pure SO ILEs. This would make them more suitable for critically ill patients. Patients receiving composite ILEs with FO have rapid incorporation of EPA and DHA into leucocyte and monocyte cell membranes thereby decreasing their ability to produce TNF-α, IL-1b, IL-6, and IL-8 when stimulated by endotoxin [22]. FAs from FO may attenuate the initial injurious hyperinflammatory state in severe sepsis and in patients with acute lung injury [111]. The bronchoalveolar lavages of adult patients with acute respiratory distress syndrome receiving n-3 FAs and gamma-linoleic acid show an important decrease in global cell count, in polymorphonuclear cell percentage, IL-8 and leukotriene B_4 concentrations which were associated with an improvement of the PaO_2/FiO_2 ratio, a reduction in mechanical ventilation need and duration, a decreased risk of complications, and a decreased length of stay in the ICU [112]. Pretreatment with a composite ILE with FO downregulates TNF-α, leukotrienes B_4, procalcitonin and lymphocyte concentrations after open heart surgery in infants [74,113]. Several recent reviews in adults agreed that there is inadequate evidence to recommend the routine use of FO-containing emulsions in patients with sepsis because a reduction in overall mortality could not be found [108,114,115]. In paediatric patients with sepsis, there is also a lack of data to determine the optimal composition of the parenteral lipid intake and finally, in neonates, the effects of the use of composite LEs, including those containing FO on neonatal morbidity has not yet been confirmed with certainty [35].

There are several reasons to provide intravenous lipids in the critically ill child. Critical illness and the associated inflammation and tissue injury alter metabolism by inducing a catabolic state, which may exacerbate pre-existing malnutrition. Lipid metabolism and turnover are increased in critical illness as fatty acids are used as a primary fuel source [116]. Excessive carbohydrates are converted to lipids but generate carbon dioxide in the process. Administration of lipids to critically ill patients decreases *de novo* lipogenesis from glucose and CO_2 production associated with a high carbohydrate intake [22]. Infants and children generally have limited fat stores and are susceptible to the development of essential fatty acid deficiencies as early as a few days if not receiving sufficient lipids [1].

To date, and although there are no studies in children with acute respiratory failure, it might be prudent to limit lipid intake during the acute phase of respiratory failure especially when pure SO ILEs are used. Despite encouraging results with composite ILEs containing FO, large randomised studies are lacking especially in critically ill children.

8.2. Treatment of drug toxicity

R 4.16	**Case reports have suggested the use of ILEs as a possible antidote for the treatment of drug toxicity in children, which however is not based on well-designed trials (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

ILEs have been proposed as a possible antidote for the treatment of drug toxicity in adults. Initial efficacy of ILEs was shown in the setting of local anaesthetic systemic toxicity, but recent case reports suggest its consideration in a variety of other drug toxicities including beta-blockers, calcium-channel blockers, and tricyclic antidepressants [117,118]. Despite the ever-increasing case report literature of the use of ILE therapy in poisoning, the indications for its use in adults remain limited to severe cardiovascular instability resulting from lipophilic toxin poisoning, in particular if this does not respond to conventional measures [117].

Clinical cases have been reported in paediatric patients despite there are no published recommendations for ILE dosage in children [119]. A review reported the use of ILEs as Pediatric Lipid Rescue in 16 occasions, in 9 cases related to local anaesthetics and 7 cases to other drugs [120]. All of them had a positive response except one, probably due to infra-dosing. One patient developed pancreatitis and another one generated respiratory distress, likely not exclusively related to lipid emulsion but also to cardiac arrest and resuscitation efforts. Given the severity and poor prognosis of cardiac arrest and post cardiac arrest syndrome, as well as the low incidence of fat overload syndrome, one may consider lipid rescue in such severe toxicity cases in the PICU or emergency department.

8.3. Thrombocytopaenia

R 4.17	**In patients with severe unexplained thrombocytopaenia, serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage may be considered. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

ILEs do not seem to affect platelet number or function [22]. However, some concerns were raised regarding the effect of ILEs on platelet aggregation. Long-term administration of PN with pure SO derived ILEs induced hyperactivation of the monocyte-macrophage system with haematological abnormalities, including recurrent thrombocytopaenia due to reduced platelet lifespan and haemophagocytosis in bone marrow [22].

Fat overload syndrome (FOS) is a well-known complication of intravenous ILE therapy in high dosages or excessive rate of infusion [1]. It is characterized by headaches, fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous haemorrhage. Other symptoms include anaemia, leukopenia, thrombocytopaenia, low fibrinogen levels, and coagulopathy. Several reports in the literature describe fat overload syndrome caused by rapid infusion of ILE overwhelming LPL capacity and orienting lipid plasma clearance to the reticuloendothelial system

(RES) which becomes overload with fat. In cases of infection this RES fat overload may result in clinical-biological FOS with the symptoms described. FOS has been described mostly with SO ILEs but recently also with ILEs containing FO suggesting that the rate of infusion, not the type of the ILE, is responsible for the syndrome [121].

A supply of EFAs meeting minimal requirements is necessary to maintain normal platelet function [22]. Specifically, in children who have thrombocytopaenia after bone marrow transplantation, it seems logical to provide sufficient amounts of EFA to support cell membrane synthesis.

Nevertheless, it seems advisable to monitor serum triglyceride concentrations, and consider decreasing parenteral lipid intake in conditions of severe thrombocytopenia or coagulopathy (e.g. sepsis, disseminated intravascular coagulopathy).

8.4. Management of intestinal failure associated liver disease

R 4.18	**As part of measures to reverse IFALD in paediatric patients, a discontinuation of SO ILE, a reduction of other ILE dosage and/or the use of composite ILE with FO, should be considered along with the treatment and management of other risk factors (LoE 2+, RG B, strong recommendation for)**
R 4.19	**The use of pure FO ILE is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe IFALD, based on case reports. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

Reversal of IFALD by modulating the dose or the type of ILEs has been assessed by several observational studies but data from RCTs are limited. When switching the historical SO ILE to a composite ILE with or without FO, several changes occur that include a reduction in n-6 FAs, a dramatic reduction of phytosterol supply, and the provision of a large amount of alpha-tocopherol and anti-inflammatory n-3 FAs. All these may affect the course of IFALD.

Several case studies reported the efficacy of the pure FO ILE as monotherapy in the treatment of IFALD in infants and children [44]. In most of these studies, a high dose of pure SO emulsion was replaced by 1 g/kg/d of pure FO ILE. Therefore, it is still not clear whether reversal of cholestasis was due to the effect of stopping the SO load or the effect of FO itself (including the high α-tocopherol load) or both. The largest of these studies, using a before and after study design, reported that a dose of 1 g/kg/d of pure FO ILE appears to be sufficient to significantly reduce the combined risk of death and liver transplantation compared to a dose of 1–4 g/kg/d of SO ILEs. Furthermore, 50% of the patients in the pure FO ILE group and who survived and were not transplanted, reached bilirubin levels ≤2 mg/dL compared to 5.6% in the SO ILE group [122]. Another study using a retrospective design showed that the addition of pure FO ILE to the pure SO ILE (ratio 1:1) combined with a small reduction in the total lipid intake (2 g/kg/d vs. 2–3 g/kg/d) was able to reduce cholestasis in nine of the twelve PN-dependent included children [123]. Finally, a retrospective study of children with cholestasis compared changes in serum bilirubin levels while receiving SMOF ILE or remaining on SO ILE [124]. After 6 months, the median bilirubin level felt by 99 μmol/L in the SMOF ILE group but increased by 79 μmol/L in the SO ILE group ($p = 0.02$). Overall, these observational studies suggest that the use of a low-dose of pure FO ILE or alternatively of a composite ILE with FO over several months in IFALD patients might have benefits.

Beside these observational studies, two RCTs have now been published on the effects of composite ILEs or pure FO ILEs in patients with IFALD in comparison to SO ILE. In children after abdominal or oesophageal surgery who had cholestasis before the intervention the use of the MCT/SO ILE decreased bilirubin levels whereas this was not the case with the use of a SO ILE [125]. In infants less than 2 years on long term PN and who have evidence of early hepatic dysfunction, those receiving the pure FO ILE at 1.5 g/kg/d recovered more frequently from cholestasis during PN than those on the SO ILE also provided at 1.5 g/kg/d [126]. A meta-analysis which included RCTs and non RCTs concluded that the use of ILEs containing FO is effective for reversing cholestasis in neonates, while there was no benefit for prevention [127]. Similar beneficial effects on liver function tests have been reported in adult surgical or ICU patients with cholestasis [128,129].

If there is evidence suggesting that cholestasis, the early stage of IFALD, may be reversed by using ILEs containing FO, although there is also evidence that liver fibrosis or cirrhosis may not [130,131]. A study in adults showed that scores for steatosis, inflammation, and cholestasis improved in serial biopsies taken after switching from pure SO ILE to pure FO ILE, but that quantification of fibrosis was unchanged [132].

If the published studies suggest that short term administration of pure FO ILEs may be attempted as rescue treatment, they do not provide evidence that long term use (e.g., >15 days) of pure FO in fully parenterally fed children is safe. Of note, in the USA, the pure FO ILE is currently only available on a compassionate basis in a maximum dose of 1 g/kg/day for infants and children suffering IFALD to serve as rescue treatment [133,134]. In Europe, pure FO ILE is not registered for paediatric use. Pure FO ILEs provide insufficient n-6 FA supply and thereby increase the risk of EFA deficiency. Besides, decreased ARA and exceedingly increased EPA concentrations in plasma and cell membranes have been found but long term effects of these changes particularly on neurodevelopment is unknown [56,135,136]. There is also a concern that long-term administration of pure FO ILEs as a sole lipid source could alter coagulation [137,138]. A case-report was published on the development of Burr cell anaemia from haemolysis in an infant after receiving pure FO ILE for over 5 months [139]. Finally, it should be noted that the efficacy of composite ILEs with FO and pure FO ILE monotherapy has not yet been directly compared.

9. Monitoring

R 4.20	**Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants) (LoE 2–, RG B, strong recommendation for, strong consensus)**
R 4.21	**Reduction of the dosage of ILEs can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children (LoE 4, GPP, conditional recommendation for, strong consensus)**

Tolerance of lipid administration is generally monitored by biochemical parameters. Plasma clearance of infused triglycerides can be assessed by measurement of plasma triglyceride concentrations. However, normal plasma triglyceride concentration does not mean optimal oxidation of lipids and it is unclear at what serum level of triglycerides adverse effects may occur [5]. Besides, results should also be interpreted according to whether samples were taken after concomitant oral feeding, or during intermittent rather than continuous lipid infusions; for example, in home PN children, plasma clearance of infused triglycerides is better assessed 12 h after the discontinuation of ILEs.

Hypertriglyceridaemia might occur because of lipogenesis due to providing too much glucose. In this case, glucose intake rather than lipid infusion should be reduced first. Hypertriglyceridaemia may also occur in patients with sepsis (see above). Preterm infants may be at a higher risk of hypertriglyceridaemia than older infants due to their relatively limited muscle and fat mass and therefore decreased hydrolytic capacity [22]. In infants fed human milk or formula, fasting triglyceride concentrations of 1.7–2.3 mmol/L (150–200 mg/dL) are frequently encountered. However, it seems reasonable to accept slightly higher triglyceride concentrations during lipid infusion as the upper limit in premature and term infants. In a recent study on early lipid administration to VLBW infants, the occurrence of hypertriglyceridaemia defined as >3 mmol/L (265 mg/dL), a level when intake was reduced, was not associated with a higher prevalence of neonatal morbidities such as necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, and intraventricular haemorrhage [11]. In the absence of other evidence it seems advisable to reduce lipid infusions when concentrations exceed 3.0 mmol/L (265 mg/dL).

For older children, serum triglycerides concentrations of 3.4–4.5 mmol/L (300–400 mg/dL) may be acceptable based on the fact that lipoprotein lipase is saturated at around 4.5 mmol/L (400 mg/dL). Hypertriglyceridaemia is most likely to occur 4 h after an infusion is initiated. In malnourished patients, tolerance of intravenous ILEs might need to be monitored more frequently than suggested since these patients have slower rates of clearance that those who are not malnourished.

Checking serum triglyceride levels may be considered within approximately 1–2 days after initiation or adjustment of lipid infusion. Monitoring of serum triglycerides may thereafter be performed from weekly to monthly depending on the stability and history of the patient. In high risk patients (e.g. patients with high lipid or glucose dosage, sepsis, malnourishment, catabolism, extremely low birth weight infants, malnourished patients) there is a risk of hyperlipidaemia and more frequent monitoring is warranted. If plasma levels of triglycerides are above the limits defined according to age, lowering, not stopping the dosage is recommended.

Abnormal liver function has been reported in patients receiving PN both with and without ILEs. The relationship between cholestasis and ILEs has been described and manipulation of lipid dosages or switching between different lipids types have been among the most frequent strategies used in infants or children on PN with liver dysfunction. To guide treatment strategies, it is recommended to monitor liver enzymes and direct bilirubin concentrations two weeks after initiation of PN and weekly to monthly thereafter.

Conflict of interest

None declared.

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