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Conference on 'Malnutrition matters'

Symposium 4: Hot topics in parenteral nutrition
Rationale for using new lipid emulsions in parenteral nutrition and a review of the trials performed in adults

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Lipids traditionally used in parenteral nutrition are based on *n*-6 fatty acid-rich vegetable oils such as soyabean oil. This practice may not be optimal because it may present an excessive supply of linoleic acid. Alternatives to the use of soyabean oil include its partial replacement by so-called medium-chain TAG (MCT), olive oil or fish oil, either alone or in combination. Lipid emulsions containing MCT are well established, but those containing olive oil and fish oil, although commercially available, are still undergoing trials in different patient groups. Emulsions containing olive oil or fish oil are well tolerated and without adverse effects in a wide range of adult patients. An olive oil–soyabean oil emulsion has been used in quite small studies in critically-ill patients and in patients with trauma or burns with little real evidence of advantage over soyabean oil or MCT–soyabean oil. Fish oil-containing lipid emulsions have been used in adult patients post surgery (mainly gastrointestinal). This approach has been associated with alterations in patterns of inflammatory mediators and in immune function and, in some studies, a reduction in the length of stay in the intensive care unit and in hospital. One study indicates that peri-operative administration of fish oil may be superior to post-operative administration. Fish oil has been used in critically-ill adults. Here, the influence on inflammatory processes, immune function and clinical end points is not clear, since there are too few studies and those that are available report contradictory findings. One important factor is the dose of fish oil required to influence clinical outcomes. Further studies that are properly designed and adequately powered are required in order to strengthen the evidence base relating to the use of lipid emulsions that include olive oil and fish oil in critically-ill patients and in patients post surgery.

Fish oil: Vegetable oils: Fatty acid: Surgery: Sepsis

Fatty acids

Fatty acids are hydrocarbon chains with a carboxyl group at one end and a methyl group at the other end[1]. The carboxyl group is reactive and readily forms ester links with alcohol groups, e.g. those on glycerol or cholesterol, in turn forming acylglycerols (e.g. TAG, phospholipids) and cholesteryl esters. Fatty acid chain lengths vary from 2 to ≥ 30 and the chain may contain double bonds. Fatty acids containing double bonds in the hydrocarbon chain are referred to as unsaturated fatty acids; a fatty acid containing one double bond is termed a MUFA while one containing two or more double bonds is termed a PUFA. Fatty acids have common names (Table 1) and systematic names. They are also referred to by a shorthand nomenclature that denotes the number of C in the chain, the number of double bonds and the position of the first double bond relative to the methyl-C (*n*; also termed ω; Table 1). *n*-3, *n*-6 and *n*-9 Fatty acids are so-called because the first double bond is on C-3, -6 or -9 respectively, counting the methyl-C as C-1. The simplest *n*-6 fatty acid is linoleic acid (18:2*n*-6) and the simplest *n*-3 fatty acid is α-linolenic acid (18:3*n*-3). Linoleic and α-linolenic acids cannot be synthesised in animals, including man. They are

Abbreviations: ICU, intensive care unit; MCT, medium-chain TAG.

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Table 1. Common names, shorthand nomenclature and sources of fatty acids used in parenteral lipid emulsions

Common name	Shorthand nomenclature	Typical source
Caprylic acid	8:0	Coconut oil
Capric acid	10:0	Coconut oil
Myristic acid	14:0	Coconut oil
Palmitic acid	16:0	Olive oil, soyabean oil, fish oil
Oleic acid	18:1*n*-9	Olive oil, soyabean oil
Linoleic acid	18:2*n*-6	Soyabean oil
α-Linolenic acid	18:3*n*-3	Soyabean oil
EPA	20:5*n*-3	Fish oil
DHA	22:6*n*-3	Fish oil

the classical essential fatty acids. In contrast, SFA and MUFA can be synthesised *de novo* in human subjects[2].

Although mammalian cells cannot synthesise linoleic and α-linolenic acids, they can metabolise them by further desaturation and elongation. Linoleic acid can be converted to γ-linolenic (18:3*n*-6), then to dihomo-γ-linolenic acid (20:3*n*-6) and then to arachidonic acid (20:4*n*-6). Using the same series of enzymes α-linolenic acid is converted to EPA (20:5*n*-3). A complex pathway for further conversion of EPA to DHA (22:6*n*-3) exists[1–3]. Fatty acids that are important in parenteral nutrition and their sources are listed in Table 1.

Desirable properties for lipids to be used in parenteral nutrition

Lipids used in parenteral nutrition should provide:

- a source of energy as an alternative to glucose;
- building blocks, since patients requiring parenteral nutrition will be undergoing processes involving cell replication and tissue repair;
- essential fatty acids in order that deficiency symptoms are avoided;
- a 'good' fatty acid balance, although the precise definition of this balance is still lacking;
- fatty acids with desirable biological activities.

Lipids were first introduced into parenteral nutrition formulas in the 1960s in order to provide a more balanced supply of energy, along with glucose[4–6]. The lipid typically used in parenteral nutrition is soyabean oil, in which linoleic acid comprises about 50% of the fatty acids present. Soyabean oil lipid emulsions include: Intralipid® (Fresenius Kabi, Bad Homberg, Germany); Lipovenoes® (Fresenius Kabi); Lipofundin® (B Braun, Melsugen, Germany); Ivelip® (Baxter Healthcare, Maurepas, France).

A meta-analysis of total parenteral nutrition has suggested that inclusion of lipids might be detrimental (lipids *v.* no lipids; $P = 0{\cdot}09$)[7], at least in very-ill patients; most of the studies included in the meta-analysis used soyabean oil-based lipid emulsions. A study in patients following major gastrointestinal surgery has identified that the amount of *n*-6 PUFA (i.e. linoleic acid) infused is one of two predictors of the length of hospital stay (increased by 1·6 d/100 g *n*-6 PUFA infused), the other being the delay in the onset of initiating nutritional support[8]. A number of *in vitro* experiments have shown that soyabean oil-based lipid emulsions can exert immunosuppressive effects (for references, see Calder *et al.*[9]), which would clearly be detrimental in patients at risk of infection and sepsis. Clinical trials with soyabean oil-based lipid emulsions provide conflicting evidence, with some showing selective immunosuppressive effects[10–12], perhaps linked to poorer patient outcomes[11]. However, other studies do not show such effects on the immune system[13–15] or on clinical outcomes[16]. Details of these studies are given in Table 2[17]. Despite the inconsistencies in the outcomes of such studies, there is a view developing that the use of lipid emulsions based entirely on soyabean oil may not be optimal or may even be harmful. The concern about potential harm, based mainly on the notion that *n*-6 PUFA might be 'pro-inflammatory, immunosuppressive and pro-coagulatory', has led to the development of alternative lipid emulsions for parenteral applications. Two alternative philosophies to reducing the amount of linoleic acid have been adopted. The first has been to simply dilute soyabean oil with another oil that is fairly inert. Examples of this strategy include the use of so-called medium-chain TAG (MCT; i.e. TAG containing predominantly medium-chain fatty acids) and the use of olive oil. The second approach has been to partially replace soyabean oil with another oil that is believed to exert benefits in its own right. An example of this strategy is the use of fish oil. Soyabean oil is often referred to as 'long-chain TAG', but this nomenclature is an incorrect use of this term since the lipids found in olive oil, fish oil and other oils not used in parenteral nutrition are also TAG containing long-chain fatty acids. The following lipid emulsions are available as alternatives to pure soyabean oil emulsions: Lipofundin MCT/LCT® (B Braun), a 50:50 (v/v) mixture of MCT (in the form of coconut oil) and soyabean oil; Lipovenoes MCT® (Fresenius Kabi), a 50:50 (v/v) mixture of MCT (in the form of coconut oil) and soyabean oil; Structolipid® (Fresenius Kabi), produced by inter-esterification of a 50:50 (v/v) mixture of MCT (in the form of coconut oil) and soyabean oil; ClinOleic® (Baxter Healthcare), an 80:20 (v/v) mixture of olive and soyabean oils; Lipoplus® (also known as Lipidem®; B Braun), a 50:40:10 (by vol.) mixture of coconut, soyabean and fish oils; SMOFLipid® (Fresenius Kabi), a 30:30:25:15 (by vol.) mixture of coconut, soyabean, olive and fish oils. In addition, the product Omegaven® (Fresenius Kabi), which is 100% fish oil, is available for use as a supplement to be diluted with another lipid emulsion of choice.

Use of medium-chain TAG in parenteral nutrition

Emulsions containing MCT mixed with soyabean oil are well established, having been introduced in the 1980s[18,19]. Medium-chain fatty acids are: more soluble than longer-chain fatty acids and readily cleared from the circulation; easily oxidised and not stored as TAG; may be protein sparing because they are ketogenic; do not impair liver function and do not interfere with pulmonary hydrodynamics or gas exchange; resistant to peroxidation[18,19].

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Table 2. Some reported immunological and clinical outcomes of studies using lipid emulsions based entirely on soyabean oil (modified from Calder[17])

Patient characteristics	Parenteral nutrition used	Duration	Immuno-inflammatory and clinical outcomes measured	Effects observed	Reference
Undernourished patients undergoing surgery for gastric or oesophageal cancer	No lipid *v.* Soyabean oil	Daily for 2 weeks before and then for 1 week after surgery	No. of blood granulocytes, lymphocytes, T-cells and B-cells	No. of granulocytes increased at week 3 in soyabean oil group; total lymphocytes decreased (approx 50%) at week 3 in the no-lipid group	Dionigi *et al.*[13]
			Serum IgG and IgM concentrations	None	
			Leucocyte chemotaxis	None	
			Granulocyte adherence to nylon	Decreased (approx 30%) at week 3 in the no-lipid group	
			Granulocyte phagocytosis	None	
Malnourished patients undergoing surgery for gastrointestinal cancer	Soyabean oil	For 7 d before surgery	Natural killer cell activity of PBMNC	Decreased (approx 50%) at day 7	Monson *et al.*[10]
			T-cell proliferation in response to mitogen	None	
			IL-2 production by T-cells in response to mitogen	None	
			Cytotoxicity of IL-2 activated PBMNC	Decreased (approx 50%)	
Malnourished seriously-ill patients	No lipid *v.* soyabean oil	10 d	No. of blood T-cells, helper T-cells, suppressor T-cells	Helper : suppressor cells decreased (approx 20%) in the soyabean oil group	Gogos *et al.*[14]
			No. of blood natural killer cells	Absolute no. and percentage of natural killer cells decreased (approx 5–10%) in the no-lipid group	
Malnourished patients undergoing surgery for gastrointestinal cancer	No lipid *v.* soyabean oil	For 7 d before surgery	Natural killer cell activity of PBMNC	None	Sedman *et al.*[15]
			T-cell proliferation in response to mitogen	None	
			IL-2 production by T-cells in response to mitogen	Decreased (approx 10%) in the no-lipid group; increased (approx 35%) in the soyabean oil group	
			Cytotoxicity of IL-2 activated PBMNC	Decreased (approx 35%) in the soyabean oil group	
Patients with trauma	No lipid *v.* soyabean oil	10 d	Natural killer cell activity of PBMNC	Lower (approx 65%) in the soyabean oil group	Battistella *et al.*[11]
			Period on mechanical ventilation	Greater in the soyabean oil group (27 d *v.* 15 d)	
			No. of infections	Greater in the soyabean oil group (72 *v.* 39)	
			Length of intensive care unit stay	Greater in the soyabean oil group (29 d *v.* 18)	
			Length of hospital stay	Greater in the soyabean oil group (39 d *v.* 27 d)	
Patients undergoing bone marrow transplantation	Low-dose soyabean oil *v.* standard soyabean oil	From 3 days before transplantation until oral energy intake exceeded 42 kJ/kg for two successive days	Time to first blood infection	None	Lenssen *et al.*[16]
			Types of bacteria cultured from blood	None	
			Types of fungi cultured from blood	None	
			Urinary tract infections	None	
			Lung infections	None	
Patients undergoing gastrointestinal or oesophageal surgery	No lipid *v.* soyabean oil	From 7 d before until 14 d after surgery	Serum C-reactive protein concentrations	None	Furukawa *et al.*[12]
			Serum IL-6 concentrations	None in unstressed patients, but IL-6 higher at 2 h and 1 d post surgery in stressed patients in soyabean oil group	
			T-cell proliferation in response to mitogens	None in unstressed patients, but T-cell proliferation lower at day 7 post surgery in stressed patients in the soyabean oil group	

PBMNC, peripheral blood mononuclear cells; approx, approximately.

Studies have directly compared the effects of soyabean oil and a mixture of MCT and soyabean oil on immune function[14,15]. In critically-ill patients there is no difference in numbers of various immune cells in the bloodstream but $CD4^+$:$CD8^+$ cells is maintained in the MCT–soyabean oil group whereas it declines in the soyabean oil group[14]; this finding is indicative of better maintenance of immune function in the former group. In patients post gastrointestinal surgery there are no differences in lymphocyte proliferation or IL-2 production between soyabean oil and MCT–soyabean oil groups[15]. However, natural killer cell activity is increased in the MCT–soyabean oil group. Again, this finding is suggestive of better immune function in the MCT–soyabean oil group.

Use of olive oil in parenteral nutrition

Olive oil is found in two lipid emulsions, ClinOleic and SMOFLipid. As SMOFLipid also contains fish oil, studies with this emulsion will be described in the discussion on fish oil (see later). Olive oil is an important component of the Mediterranean diet and is generally considered to be healthy[20]. Oleic acid, a major constituent of olive oil, has little impact on immune function and is fairly resistant to peroxidation. ClinOleic does not affect lymphocyte proliferation *in vitro*, while soyabean oil-based emulsions are suppressive[21]. *In vitro* and animal studies using ClinOleic have been collated and reviewed[22]. Trials of ClinOleic in home parenteral nutrition, in patients with burns and in critically-ill patients have now been conducted and are summarised in Table 3. Three trials in home parenteral nutrition have shown that ClinOleic is safe and well tolerated; ClinOleic has no effect on immune function, inflammatory markers, oxidative stress or routine laboratory variables[23–25]. A study of the use of ClinOleic in intradialytic parenteral nutrition has revealed no difference from soyabean oil in relation to markers of inflammation and oxidative stress and an absence of adverse effects[26]. A comparison has been made of a parenteral regimen of high glucose in combination with MCT–soyabean oil and low glucose in combination with ClinOleic in patients with severe trauma in the intensive care unit (ICU)[27]. The low-glucose ClinOleic group was reported to have lower blood glucose and less requirement for insulin, as would be expected, and also to exhibit a shorter duration of mechanical ventilation, fewer infections, better immune function and a shorter length of ICU stay. These findings were interpreted as being a result of the use of ClinOleic, but the study design does not allow the findings to be associated with any particular component of the nutrition. A recent study of soyabean oil *v.* ClinOleic in critically-ill patients (mainly patients post surgery in the ICU) has shown no differences in inflammatory markers, infections, ICU stay, hospital stay or mortality[28]. Similarly, in patients with severe burns in the ICU no difference was found between MCT–soyabean oil and ClinOleic in relation to inflammatory markers, number of infections, organ (including liver) dysfunction, duration of ICU stay, duration of hospital stay or mortality[29].

Thus, ClinOleic is safe to use in patients receiving home parenteral nutrition. It has been used in quite small experimental studies in critically-ill patients and in patients with trauma or burns and shown to be safe and well tolerated. However, there is little evidence at this stage of advantage over soyabean oil or MCT–soyabean oil. Further larger and well-designed studies are needed using ClinOleic in target patient groups.

Fish oil in parenteral nutrition

Fish oil contains the very-long-chain *n*-3 PUFA EPA and DHA. There is strong evidence for health benefits of these fatty acids especially in relation to CVD[30–33]. They act to modify tissue and blood lipid metabolism, blood lipid concentrations, blood coagulation, immune function, inflammation and endothelial function[34–38]. EPA and DHA are readily incorporated into cells and tissues and act to modify membrane properties, eicosanoid profiles, signal transduction processes and gene expression[38]. Through these mechanisms they result in improved cell and tissue function. Thus, using fish oil to partly replace soyabean oil in parenteral nutrition offers the possibility to both decrease the amount of linoleic acid present and to increase the amount of biologically-active *n*-3 PUFA[39–42]. Obviously, this objective is not achieved with MCT or olive oil since neither of them contains substantial amounts of *n*-3 PUFA.

Three lipid emulsions that include fish oil as a component are available: Omegaven; Lipoplus; SMOFLipid. Omegaven is a pure fish oil emulsion (100 g lipid/l) that will typically contain approximately 3 g EPA + DHA/100 ml. It is recommended that Omegaven is used in combination with other emulsions (e.g. those based on soyabean oil or mixtures of MCT and soyabean oil) such that Omegaven contributes 10–20 % of the infused emulsion. Lipoplus (known as Lipidem is some countries) is an emulsion (200 g lipid/l) with the lipid being a mix (%, v/v) of 50 MCT, 40 soyabean oil and 10 fish oil. Each 100 ml Lipoplus will typically contain about 0·6 g EPA + DHA. SMOFLipid is an emulsion (200 g lipid/l) with the lipid being a mix (%, v/v) of 30 MCT, 30 soyabean oil, 25 olive oil and 15 fish oil. Each 100 ml SMOFLipid will typically contain about 1 g EPA + DHA.

Studies of fish oil in patients following surgery

Intravenous infusion of a lipid emulsion containing fish oil into patients for 5 d following gastrointestinal surgery results in an altered fatty acid composition of leucocytes; EPA content is increased 2·5-fold[43]. This outcome would be expected to impact on the profile of eicosanoids produced from arachidonic acid and EPA. Indeed, several studies have demonstrated that intravenous infusion of lipid emulsions containing fish oil into patients who had undergone major gastrointestinal surgery results in lower production of arachidonic acid-derived eicosanoids and higher production of EPA-derived eicosanoids by blood leucocytes stimulated *ex vivo*[43–46]. Plasma TNFα concentrations are lower at day 6 post surgery while plasma IL-6

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Table 3. Summary of clinical trials of ClinOleic* (an 80:20 (v/v) mixture of olive and soyabean oils) in adults

Type of patient	Parenteral nutrition used	Duration	Outcomes measured	Effects of ClinOleic observed	Comments	Reference
Home parenteral nutrition	ClinOleic (*n* 13); comparison with previous experience using soyabean oil	6 months	Routine clinical laboratory variables Adverse effects	None None	Not controlled; No statistical analysis	Thomas-Gibson *et al.*[23]
Home parenteral nutrition	ClinOleic (*n* 14)	3 months	Routine clinical laboratory variables Inflammatory and immune markers (C-reactive protein, several cytokines, neopterin) Oxidative stress marker (malondialdehyde) Adverse effects	None None None None	Not controlled	Reimund *et al.*[24]
Home parenteral nutrition	ClinOleic (*n* 6) *v.* soyabean oil (*n* 4)	3 months	Routine clinical laboratory variables Adverse effects	None None	Not controlled	Vahedi *et al.*[25]
Intradialytic	ClinOleic (*n* 21) *v.* soyabean oil (*n* 20)	5 weeks	Inflammatory markers (C-reactive protein, several cytokines) Antioxidant enzymes and oxidative stress marker (malondialdehyde) Adverse effects	None None None	–	Cano *et al.*[26]
Trauma	Low glucose + ClinOleic (*n* 18) *v.* high glucose + soyabean oil (*n* 15)		Metabolic profile (blood glucose etc.) Insulin requirement Immune function (monocyte HLA-DR expression) Duration of mechanical ventilation No. of infections Length of ICU stay	Lower blood glucose Lower Higher Shorter Fewer Shorter	Difficult to interpret	Huschak *et al.*[27]
Critically ill (mainly post-surgery ICU)	ClinOleic (*n* 16) *v.* soyabean oil (*n* 23)	>5 d	Routine clinical laboratory variables Inflammatory markers (leucocyte count, C-reactive protein, fibrinogen, albumin) No. and type of infections Length of ICU stay Length of hospital stay Mortality Adverse effects	None None None None None None None	–	Mateu-de Antonio *et al.*[28]
Severely burned	ClinOleic (*n* 11) *v.* MCT–soyabean oil (*n* 110	5–7 d	Routine clinical laboratory variables Inflammatory markers (C-reactive protein, several cytokines) Organ dysfunction Ventilation requirement No. of infections Length of ICU stay Length of hospital stay Mortality Adverse effects	None None None None None None None None None	–	García-de-Lorenzo *et al.*[29]

ICU, intensive care unit; MCT, medium-chain TAG; HLA, human leucocyte antigen.
*Baxter Healthcare, Maurepas, France.

concentrations are lower at day 10 post surgery in patients who have undergone major gastrointestinal surgery and have then received a mix of MCT, soyabean oil and fish oil (50:30:20, by vol.; a prototype version of Lipoplus) for 5 d post surgery compared with those who have received an MCT–soyabean oil mix[44]. Clinical outcomes are not reported. A more recent study has infused Omegaven, providing 10 g fish oil/d, on the day before abdominal surgery and on days 1–5 following abdominal surgery[47]. On days 4 and 5 the patients also received standard total parenteral nutrition, which included 50 g fat as soyabean oil/d. A tendency for TNFα production by endotoxin-stimulated whole blood to be lower at day 5 post surgery was reported for the fish oil group, but this effect was not significant. Serum IL-6 concentrations were found to be significantly lower at days 0, 1 and 3 post surgery in the fish oil group than in controls. Monocyte expression of human leucocyte antigen DR was shown to be preserved in the fish oil group, but to decline at days 3 and 5 in the control group. No differences in infection rates or mortality were observed. However, post-operative stay in intensive care was found to show a tendency to be shorter in the fish oil group (4·1 d *v.* 9·1 d in the control group) as did total hospital stay (17·8 d *v.* 23·5 d in the control group). Post-operative stay on medical wards was reported to be significantly shorter in the fish oil group ($P<0·05$). Another study has compared the effects of lipid-free total parenteral nutrition or parenteral nutrition including soyabean oil or a mix (%, v/v) of 83 soyabean oil and 17 fish oil from Omegaven for 5 d after large bowel surgery[48]. No differences were found between the groups in relation to the numbers of circulating lymphocytes, B lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes or natural killer cells before surgery or at days 3 and 6 post surgery, although these variables were affected by surgery itself. Also, no differences were found between groups in relation to T-lymphocyte proliferation, but IL-2 production was increased in the fish oil group and the post-surgery decline in interferon-γ production was prevented by fish oil. It has been reported that length of hospital stay in patients post gastrointestinal surgery is significantly shorter ($P=0·006$) in patients receiving fish oil (17·2 d) than in the control group (21·9 d)[49]. In another study of patients post surgery the administration of SMOFLipid for 6 d was shown to result in significantly shorter hospital stay (13·4 d *v.* 20·4 d; $P<0·05$) than soyabean oil[42]. Taken together, these studies indicate that inclusion of fish oil in parenteral nutrition regimens for patients who have undergone gastrointestinal surgery modulates generation of inflammatory eicosanoids[43–46] and cytokines[44,47] and may help to counter the surgery-induced decline in antigen-presenting-cell activity[47] and production of T-lymphocyte cytokines[48]. Importantly, these studies do not reveal any deleterious effects of fish oil infusion in these patients. Furthermore, the studies that have examined the hard end point of length of hospital stay suggest a real clinical benefit from fish oil infusion in these patients[42,47,49]. Another report from a cohort of patients receiving parenteral nutrition post surgery has also indicated the benefit of inclusion of fish oil in the regimen[50]. No differences were reported between the control group (MCT–soyabean oil) and the patients receiving fish oil (a mix of Omegaven with a 50:50 (v/v) MCT–soyabean oil mix in which a maximum of one-third of the mix was as fish oil) in relation to the percentage of patients who developed wound infections (6 *v.* 11 for the fish oil and control groups respectively) or who died (12 *v.*15 respectively) or in the length of hospital stay (25 d *v.* 29 d respectively). However, the percentage of patients in the fish oil group who were readmitted to the ICU (5) was shown to be significantly lower ($P<0·05$) than that in the control group (17). A group of patients also received the fish oil-containing emulsion for 2 d pre-operatively. Here, a number of very significant benefits were found: a significantly decreased need for mechanical ventilation (17% *v.* 31% in the control group; $P<0·05$); a significantly shorter length of hospital stay (22 d *v.* 29 d; $P<0·05$); significantly less need for readmission to intensive care (5% *v.* 17%; $P<0·05$); significantly lower mortality (3% *v.* 15%; $P<0·05$)[50]. Another study has revealed that intravenous infusion of a lipid emulsion containing (%, w/w) 80 soyabean oil and 20 Omegaven into patients for 5 d following major gastrointestinal surgery accelerates normalisation of liver and pancreatic function compared with soyabean oil alone[51]. Overall, no difference was found between the groups in relation to length of stay in the ICU or in hospital. However, in a subgroup of patients at risk of sepsis a reduced ICU stay was reported for the patients receiving fish oil (4·0 d *v.* 5·3 d for the control group; $P=0·01$)[51]. In a recently published study in which a mixed group of >650 patients, including approximately 230 patients post surgery, received parenteral nutrition including fish oil (Omegaven) for ≥3 d (mean 8·7 d) a significantly lower rate of infections ($P<0·0005$), fewer complications ($P<0·005$) and shorter length of hospital stay ($P=0·05$) were reported in the patients post-surgery receiving fish oil compared with those receiving the control emulsion[8]. Furthermore, infusion of about 0·15 g fish oil/kg per d was shown to decrease mean ICU stay from 8·7 d to 5·3 d and hospital stay from 27·4 d to 25·5 d. Thus, findings available from published studies in patients post gastrointestinal surgery clearly demonstrate clinical benefit from the inclusion of very-long-chain *n*-3 PUFA in the form of fish oil in parenteral nutrition regimens[8,42,47,49–51]. However, a greater benefit has also been demonstrated if these fatty acids are additionally provided pre-surgery, which of course is only possible in elective surgery[50]. The greater benefit of pre-operative infusion of long-chain *n*-3 PUFA most probably relates to better incorporation of the fatty acids into leucocytes and other tissues.

In a recently published study that used MCT–soyabean oil or Lipoplus in patients in the ICU who had undergone abdominal aorta aneurysm repair surgery no differences were found in glucose metabolism or in inflammatory markers[52]. Furthermore, clinical outcomes were not reported to be affected, but a trend was found towards shorter ICU stay (1·6 d *v.* 2·3 d) and shorter hospital stay (9·9 d *v.* 11·3 d).

Thus, all three available fish oil-containing lipid emulsions have been used in adult patients post surgery (mainly gastrointestinal). No adverse effects of the use of fish oil have been reported, indicating that it is safe to use for such

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patients. The use of fish oil is associated with altered patterns of inflammatory eicosanoids and cytokines in patients post gastrointestinal surgery and immune function may be better maintained by fish oil in these patients. Two studies have reported that the use of fish oil is associated with a trend towards reduced length of ICU stay and three studies have reported that fish oil significantly reduces length of hospital stay (two more studies report a trend to reduced length of hospital stay). Lack of significance in studies that report favourable trends may be a result of the small sample size of those studies. Peri-operative administration of fish oil may be superior to post-operative administration. Taken together the studies in patients post surgery present a fairly consistent and positive view of the efficacy of intravenous fish oil administration post surgery. However, in these studies patients who would not normally require parenteral nutrition have frequently been included. Furthermore, the lengths of ICU and hospital stay reported in both control and fish oil groups are frequently much longer than typically seen in many clinical settings. Thus, although the data presently available are highly supportive of the inclusion of fish oil, translation of the findings to the real clinical situation requires further studies designed to mimic current clinical practice; clearly, such studies need to be properly designed and adequately powered.

Studies of fish oil in critically-ill patients

In patients with sepsis who were intolerant of enteral nutrition and received by infusion a standard soyabean oil-based emulsion or an emulsion containing fish oil (Omegaven) for 5 d[53] or 10 d[54] it was reported that blood leucocyte counts and serum C-reactive protein concentration tend to be lower and production of leukotriene B_5 by stimulated neutrophils is much higher in patients receiving fish oil[53]. Production of TNFα, IL-1β, IL-6, IL-8 and IL-10 by endotoxin-stimulated mononuclear cells does not increase during infusion of the fish oil-containing emulsion whereas production of the four pro-inflammatory cytokines is markedly elevated during the first 2 d of soyabean oil infusion[54]. These studies establish that infusion of long-chain *n*-3 PUFA into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes. It has been demonstrated that this effect might be associated with clinical improvements. In a study of parenteral *n*-3 PUFA (in the form of Omegaven) infusion that included patients with abdominal sepsis, multiple trauma or severe head injury a significantly lower rate of infection assessed as demand for antibiotics ($P<0·001$) and shorter lengths of ICU and hospital stay (both $P<0·001$) were reported for those patients receiving >0·05 g fish oil/kg per d when compared with those receiving <0·05 g fish oil/kg per d[55]. Mortality was shown to be significantly decreased ($P<0·05$) in those patients who received >0·1 g fish oil/kg per d. The survival advantage was found to be greater in some patient groups than others (severe head injury>multiple trauma>abdominal sepsis>non-abdominal sepsis>post surgery), but small numbers of patients in some groups make the interpretation of these data difficult. Furthermore, this study was not controlled or blinded. Nevertheless, these recent data are strongly suggestive of genuine clinical benefit from the inclusion of long-chain *n*-3 PUFA in parenteral nutrition regimens given to critically-ill patients. This conclusion is in part supported by a recent study of patients with severe acute pancreatitis[56]. The patients received soyabean oil or a mixture of soyabean oil and Omegaven for 5 d. Although no differences were found between the groups in relation to inflammatory markers, number of infections or lengths of ICU (27·5 d in the control group *v.* 21·4 d in the fish oil group) and hospital stay, better gas exchange ($P<0·05$) and a reduced requirement for continuous renal replacement therapy ($P<0·05$) was reported for those patients receiving fish oil. In contrast to the generally positive findings from these studies, no differences were found between MCT–soyabean oil and MCT–soyabean oil–Omegaven given over 7 d in medical patients in the ICU in several outcomes, including immune markers, inflammatory markers, bleeding, ventilation requirement, number of infections, length of ICU stay and mortality[57].

Thus, of the three available fish oil-containing lipid emulsions only Omegaven has been used in critically-ill adults. No adverse effects of the use of fish oil have been reported in these studies, indicating that it is safe to use in such patients. The influence of fish oil on inflammatory processes and on immune function in critically-ill patients is not yet clear. Similarly, the impact of fish oil on clinical end points such as infections, length of ICU and hospital stay and mortality is not clear, since there are too few studies and those that are available[55–57] report contradictory findings or do not have a satisfactory design. One important factor, highlighted by one study of parenteral *n*-3 PUFA from fish oil[55] is the dose of fish oil required to influence clinical outcomes. Overall, the data available are suggestive of some clinical benefit from the inclusion of long-chain *n*-3 PUFA in parenteral nutrition regimens given to critically-ill patients. However, only limited studies have been published and the inconsistency of findings limits translation to the clinic. Thus, further studies are required; clearly, such studies need to be properly designed and adequately powered.

Summary and conclusions

Lipids traditionally used in parenteral nutrition are based on *n*-6 PUFA-rich vegetable oils such as soyabean oil. This practice may not be optimal because it may present an excessive supply of linoleic acid. Alternatives to the use of soyabean oil include its partial replacement by MCT, olive oil or fish oil, either alone or in combination. MCT-containing lipid emulsions are well established, but those containing olive oil and fish oil, although commercially available, are still undergoing trials in different patient groups. It is clear that emulsions containing olive oil or fish oil are well tolerated and without adverse effects in a wide range of adult patients. An olive oil–soyabean oil emulsion has been used in quite small experimental studies of critically-ill patients and patients with trauma or burns with little evidence at this stage of advantage over soyabean oil or MCT–soyabean oil. Fish oil-containing lipid emulsions

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have been used in adult patients post surgery (mainly gastrointestinal). This regimen has been associated with alterations in patterns of inflammatory mediators and in immune function and, in some studies, a reduction in length of ICU and hospital stay. Peri-operative administration of fish oil may be superior to post-operative administration. Fish oil has been used in critically-ill adults. Here, the influence on inflammatory processes, immune function and clinical end points is not clear, since there are too few studies and those that are available report contradictory findings. One important factor is the dose of fish oil required to influence clinical outcomes. Further studies that are properly designed and adequately powered are required in order to strengthen the evidence base relating to the use of lipid emulsions that include olive oil and fish oil in critically-ill patients and post surgery.

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References

1. Calder PC & Burdge GC (2004) Fatty acids. In *Bioactive Lipids*, pp. 1–36 [A Nicolaou and G Kafatos, editors]. Bridgwater, Somerset: The Oily Press.
2. Gurr MI, Harwood JL & Frayn KN (2002) *Lipid Biochemistry: An Introduction*, 5th ed. Oxford: Wiley-Blackwell.
3. Sprecher H (2002) The roles of anabolic and catabolic reactions in the synthesis and recycling of polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **67**, 79–83.
4. Edgren B & Wrtelind A (1963) The theoretical background of the intravenous nutrition with fat emulsions. *Nutr Dieta Eur Rev Nutr Diet* **13**, 364–386.
5. Hallberg D, Schuberth O & Wretlind A (1966) Experimental and clinical studies with fat emulsion for intravenous nutrition. *Nutr Dieta Eur Rev Nutr Diet* **8**, 245–281.
6. Wretlind A (1972) Complete intravenous nutrition. Theoretical and experimental background. *Nutr Metab (Lond)* **14**, Suppl., 1–57.
7. Heyland DK, MacDonald S, Keefe L *et al.* (1998) Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA* **280**, 2013–2019.
8. Koch T & Heller AR (2005) Auswirkungen einer parenteralen ernahrung mit n-3-fettsauren auf das therapieergebnis – eine multizentrische analyse bei 661 patienten (Effects of parenteral nutrition with n-3-fatty acids on the result of therapy – a multicentre analysis with 661 patients). *Akt Ernahrungs* **30**, 15–22.
9. Calder PC, Sherrington EJ, Askanazi J *et al.* (1994) Inhibition of lymphocyte proliferation in vitro by two lipid emulsions with different fatty acid compositions. *Clin Nutr* **13**, 69–74.
10. Monson JRT, Sedman PC, Ramsden CW *et al.* (1988) Total parenteral nutrition adversely influences tumour-directed cellular cytotoxic responses in patients with gastrointestinal cancer. *Eur J Surg Oncol* **14**, 435–443.
11. Battistella FD, Widergren JT, Anderson JT *et al.* (1997) A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma* **43**, 52–58.
12. Furukawa K, Yamamori H, Takagi K *et al.* (2002) Influences of soybean oil emulsion on stress response and cell-mediated immune function in moderately or severely stressed patients. *Nutrition* **18**, 235–240.
13. Dionigi P, Dionigi R, Prati U *et al.* (1985) Effect of Intralipid® on some immunological parameters and leukocyte functions in patients with esophageal and gastric cancer. *Clin Nutr* **4**, 229–234.
14. Gogos CA, Kalfarentzos FE & Zoumbos NC (1990) Effect of different types of total parenteral nutrition on T-lymphocyte subpopulations and NK cells. *Am J Clin Nutr* **51**, 119–122.
15. Sedman PC, Somers SS, Ramsden CW *et al.* (1991) Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. *Br J Surg* **78**, 1396–1399.
16. Lenssen P, Bruemmer BA, Bowden RA *et al.* (1998) Intravenous lipid dose and incidence of bacteremia and fungemia in patients undergoing bone marrow transplantation. *Am J Clin Nutr* **67**, 927–933.
17. Calder PC (2006) Use of fish oil in parenteral nutrition: rationale and reality. *Proc Nutr Soc* **65**, 264–277.
18. Ulrich H, McCarthy Pastores S, Katz DP *et al.* (1996) Parenteral use of medium-chain triglycerides: a reappraisal. *Nutrition* **12**, 231–238.
19. Adolph M (1999) Lipid emulsions in parenteral nutrition. *Ann Nutr Metab* **43**, 1–13.
20. Quiles JL, Ramirez-Tortosa MC & Yaqoob P (2006) *Olive Oil and Health*. Wallingford, Oxon.: CABI.
21. Granato D, Blum S, Rössle C *et al.* (2000) Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro. *JPEN J Parenter Enteral Nutr* **24**, 113–118.
22. Sala-Vila A, Barbosa VM & Calder PC (2007) Olive oil in parenteral nutrition. *Curr Opin Clin Nutr Metab Care* **10**, 165–174.
23. Thomas-Gibson S, Jawhari A, Atlan P *et al.* (2004) Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure. *Clin Nutr* **23**, 697–703.
24. Reimund JM, Rahmi G, Escalin G *et al.* (2005) Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. *Aliment Pharmacol Ther* **21**, 445–454.
25. Vahedi K, Atlan P, Joly F *et al.* (2005) A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. *Br J Nutr* **94**, 909–916.
26. Cano NJ, Saingra Y, Dupuy AM *et al.* (2006) Intradialytic parenteral nutrition: comparison of olive oil versus soybean oil-based lipid emulsions. *Br J Nutr* **95**, 152–159.
27. Huschak G, Zur Nieden K, Hoell T *et al.* (2005) Olive oil based nutrition in multiple trauma patients: a pilot study. *Intensive Care Med* **31**, 1202–1208.
28. Mateu-de Antonio J, Grau S, Luque S *et al.* (2008) Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. *Br J Nutr* **99**, 846–854.
29. García-de-Lorenzo A, Denia R, Atlan P *et al.* (2005) Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion *v.* medium/long-chain triacylglycerols. *Br J Nutr* **94**, 221–230.
30. Calder PC (2004) N-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin Sci (Lond)* **107**, 1–11.

https://doi.org/10.1017/S0029665109001268 Published online by Cambridge University Press

31. Kris-Etherton PM, Harris WS & Appel LJ for the American Heart Association Nutrition Committee (2002) Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* **106**, 2747–2757.
32. Bucher HC, Hengstler P, Schindler C *et al.* (2002) N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* **112**, 298–304.
33. Studer M, Briel M, Leimenstoll B *et al.* (2005) Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* **165**, 725–730.
34. Wang C, Harris WS, Chung M *et al.* (2006) n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* **84**, 5–17.
35. Calder PC (2006) N-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* **83**, 1505S–1519S.
36. Tagawa H, Shimokawa H, Tagawa T *et al.* (1999) Long-term treatment with eicosapentaenoic acid augments both nitric oxide-mediated and non-nitric oxide-mediated endothelium-dependent forearm vasodilatation in patients with coronary artery disease. *J Cardiovasc Pharmacol* **33**, 633–640.
37. Calder PC (2007) Immunomodulation by omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* **77**, 327–335.
38. Calder PC (2008) *Danone Chair Monograph: Omega-3 Fatty Acids – The Good Oil?* Brussels: Institut Danone.
39. Furst P & Kuhn KS (2000) Fish oil emulsions: what benefits can they bring? *Clin Nutr* **19**, 7–14.
40. Adolph M (2001) Lipid emulsions in total parenteral nutrition – state of the art and future perspectives. *Clin Nutr* **20**, Suppl. 4, 11–14.
41. Grimble R (2005) Fatty acid profile of modern lipid emulsions: scientific considerations for creating the ideal composition. *Clin Nutr Suppl* **1**, 9–15.
42. Grimm H (2005) A balanced lipid emulsion – a new concept in parenteral nutrition. *Clin Nutr Suppl* **1**, 25–30.
43. Morlion BJ, Torwesten E, Lessire A *et al.* (1996) The effect of parenteral fish oil on leukocyte membrane fatty acid composition and leukotriene-synthesizing capacity in postoperative trauma. *Metabolism* **45**, 1208–1213.
44. Wachtler P, Konig W, Senkal M *et al.* (1997) Influence of a total parenteral nutrition enriched with ω-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. *J Trauma* **42**, 191–198.
45. Koller M, Senkal M, Kemen M *et al.* (2003) Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. *Clin Nutr* **22**, 59–64.
46. Grimm H, Mertes N, Goeters C *et al.* (2006) Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr* **45**, 55–60.
47. Weiss G, Meyer F, Matthies B *et al.* (2002) Immunomodulation by perioperative administration of n-3 fatty acids. *Br J Nutr* **87**, S89–S94.
48. Schauder P, Rohn U, Schafer G *et al.* (2002) Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. *Br J Nutr* **87**, S103–S110.
49. Wichmann MW, Thul P, Czarnetzki HD *et al.* (2007) Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): data from a prospective, randomized, multicenter trial. *Crit Care Med* **35**, 700–706.
50. Tsekos E, Reuter C, Stehle P *et al.* (2004) Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. *Clin Nutr* **23**, 325–330.
51. Heller AR, Rossel T, Gottschlich B *et al.* (2004) Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. *Int J Cancer* **111**, 611–616.
52. Berger MM, Tappy L, Revelly JP *et al.* (2008) Fish oil after abdominal aorta aneurysm surgery. *Eur J Clin Nutr* **62**, 1116–1122.
53. Mayer K, Fegbeutel C, Hattar K *et al.* (2003) W-3 vs. W-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. *Intensive Care Med* **29**, 1472–1481.
54. Mayer K, Gokorsch S, Fegbeutel C *et al.* (2003) Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. *Am J Respir Crit Care Med* **167**, 1321–1328.
55. Heller AR, Rössler S, Litz RJ *et al.* (2006) Omega-3 fatty acids improve the diagnosis-related clinical outcome. *Crit Care Med* **34**, 972–979.
56. Wang X, Li W, Li N *et al.* (2008) Omega-3 fatty acids-supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *JPEN J Parenter Enteral Nutr* **32**, 236–241.
57. Friesecke S, Lotze C, Köhler J *et al.* (2008) Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. *Intensive Care Med* **34**, 1411–1420.

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