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REVIEW

Use of Intravenous Fat Emulsions in Adult Critically Ill Patients: Does omega 3 make a difference?

Veronique Donoghue,[a,c] Maryke Spruyt,[b] Renée Blaauw[c]

[a] *Fresenius Kabi, Midrand, South Africa*
[b] *Head, Clinical Department: Critical Care, Faculty of Health Sciences, University of the Free State*
c Division of Human Nutrition, Faculty of Medicine and Health Sciences, Stellenbosch University

Critical illness is a multisystem process that can result in significant morbidity and mortality. In most patients, critical illness is preceded by a physiological deterioration, characterized by a catabolic state and intense metabolic changes, resulting in malnutrition and impaired immune functions.[1] Intravenous lipid emulsions (IVLE) constitute the main source of energy and fatty acids (FA) in parenteral nutrition formulations and remain associated with the development of adverse effects. Different types of lipid emulsions (LE) have different effects on blood function tests and metabolic functions including inflammatory and immune response, coagulation and cell signalling. These effects appear to be based on complex modifications in the composition and structure of cell membranes, through eicosanoid and cytokine synthesis and by modulation of gene expression. Proinflammatory properties of omega-6 polyunsaturated fatty acids (PUFA) have been associated with poor clinical outcomes and have led to the development of newer generation IVLE. There is clinical data suggesting that omega-3 PUFA, particularly fish oil, have beneficial effects on the immune system, organ function and improves clinical outcomes in surgical and acute respiratory distress syndrome (ARDS) patients. In addition, there is some promising data on their use in septic patients.[2-4]

This literature review focuses on the administration of different lipid emulsions, in particular omega-3 PUFA via the parenteral nutrition route, in critically ill adult patients. The clinical consequences associated with critical illness as well as the administration of different intravenous lipid emulsions are addressed, focusing on how omega-3 PUFA can possibly attenuate inflammation, improve outcomes and reduce complications associated with the administration of parenteral nutrition.

1 Sepsis and the critically ill patient

Sepsis remains common in critically ill patients. The prevalence of systemic inflammatory response syndrome (SIRS) is estimated to range from 20% to 60%, with approximately 40% of patients with sepsis developing septic shock.[5] Severe sepsis and septic shock have high mortality rates and are the leading cause of death in Intensive Care Units.[6]

1.1 Metabolic Response to sepsis and critical illness

The metabolic response to stress is part of an adaptive response to survive critical illness and restore homeostasis as rapidly as possible. Sir David Cuthbertson described several phases of metabolic response over time, including the 'ebb' and 'flow' phases. More recently, the chronic or post-injury phase, frequently encountered in the Intensive Care Unit (ICU) has been added.[7] The ebb phase occurs several hours after the injury and lasts for 12–24 hours, consists of reductions in cardiac output, oxygen consumption (VO_2), the basal metabolic rate, and glucose tolerance. The flow phase lasts for 3–8 days, depending on injury severity. It is characterised by increases in cardiac output, respiratory rate, VO_2, hyperglycaemia, skeletal muscle catabolism, and a negative nitrogen balance.[8] The post injury phase lasts for some weeks, as protein and fat stores are restored and weight regained.[9]

The central nervous system partially regulates the inflammatory component via pro- and anti-inflammatory cytokines and other inflammatory mediators. These cytokines are signalling peptides produced by inflammatory cells, and released in response to injury.[10]

The pro-inflammatory cytokines released, namely, tumour necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8, impair some of the body's physiological functions and play pivotal roles in the metabolic changes associated with sepsis. They initiate the acute phase response, recruit reticuloendothelial cells (lymphocytes, macrophages and monocytes), promote wound repair and induce the production of other cytokines.[7,9] To balance and control inflammation, coexistent anti-inflammatory cytokines, IL-10 and IL-13, are produced.[10] The inflammatory response is initiated by activation of the innate immune system by pro-inflammatory stimuli such as damage-associated molecular patterns (DAMPS) and pathogen associated molecular patterns (PAMPS).[11] In addition to typical clinical signs of sepsis, like fever and lethargy, these cytokines also trigger anorexia and induce weight loss, proteolysis and lipolysis.[7]

Levels of TNF-α and IL-6 have consistently been shown to correlate with the mortality and poor outcome following severe injury and sepsis. Both TNF-α and IL-10 levels are associated with mortality.[10]

Recently, the term persistent inflammation, immunosuppression, and catabolism syndrome (PICS) is used to describe the observed phenotype of chronic multi organ failure (MOF). Patients with PICS experience prolonged low-grade inflammation and catabolism with resultant loss of lean body mass (LBM). The PICS paradigm is as follows: following a major inflammatory insult (sepsis, trauma, burns, acute pancreatitis, etc.) there are simultaneous inflammatory (SIRS) and anti-inflammatory – compensatory anti-inflammatory response syndrome (CARS) – responses. In some cases, the SIRS becomes overwhelming, leading to early MOF and death.[12,13]

Modern ICU care focusses on early recognition of shock and treatment. If patients do not die of early MOF, there are two possible pathways. Either their immunity recovers rapidly, immune homeostasis is achieved and they recover, or immunologic dysfunction persists and they enter chronic critical illness (CCI), defined as > 14 days in the ICU with organ dysfunction. These patients with CCI experience ongoing immunosuppression and inflammation associated with a persistent acute phase response (e.g. high C reactive protein) with ongoing protein catabolism. Despite aggressive nutrition intervention, there is a remarkable loss of LBM associated with a proportional decrease in functional status and poor wound healing.[12,13]

1.2 Nutritional consequences and management of critically ill patients

The metabolic response to stress has several clinical consequences from changes in metabolic rate to use of macronutrients as energy sources, stress hyperglycaemia, muscle wasting, changes in body composition and behavioural changes.[7]

Current management aims to control infection, achieve haemodynamic stabilisation and modulate the immune response to provide organ and metabolic support, by treating the source and providing adequate oxygen delivery, ensuring glucose control and initiating nutrition therapy (NT).[14]

NT is important in all critically ill patients and the goals focus on attenuating the metabolic response to stress, preventing oxidative cellular injury, and favourably modulating the immune response.[15] This includes providing adequate nutrition, preventing nutritional deficiencies, preserving lean body mass, maintaining glucose control, avoiding metabolic complications, decreasing infectious complications and improving clinical outcomes.[16] The enteral route is preferable and should be commenced once initial resuscitation and the patient is haemodynamically stable.[17] Where enteral nutrition (EN) is impossible or not tolerated, parenteral nutrition (either as total or supplementary) may safely be administered.[18]

Many critically ill patients develop muscle wasting and weakness, with an adverse outcome. This is due to the hypercatabolism of critical illness as well as anorexia, gastrointestinal dysfunction and resultant decreased nutritional intake that accompanies severe illness.[19] Recent research indicates that critically ill or major surgical patients can lose as much as a kilogram of lean body mass (LBM) a day, during the first week of ICU stay. Patients may regain weight post-ICU, but much of the weight gain is fat mass, not functional lean muscle mass.[20]

NT in general will not be discussed in the literature review.

1.3 Parenteral Nutrition (PN)

PN is the intravenous administration of macronutrients and micronutrients.[21] Differences in timing of initiating PN according to various guidelines are particularly due to the differences between the target populations, the levels of evidence considered, and the different types of PN products available.[22] All guidelines agree that in patients with or at high risk of malnutrition, PN should be initiated early following ICU admission if EN is impossible.

Despite numerous randomised control trials, observational studies, systematic reviews and consensus guidelines on NT in critical illness, many issues remain controversial, including the ideal method of assessing energy and protein requirements as well as optimal nutritional targets.[22]

1.4 Lipid

Intravenous lipid emulsions (LE) provide a source of essential fatty acids (EFA) and serve as a complement to carbohydrates by providing a dense source of Non Protein Energy (NPE). Addition of lipid to PN allows sufficient calories to be administered without excess fluid. LE also have a low osmolarity, thus reducing the overall osmolarity of the solution enabling some solutions to be administered peripherally (≤ 900 mOsm/L) or centrally.[28] Table 1 for published guidelines for lipid intake in critically ill patients requiring PN.

Fatty acids are classified according to their structure, carbon chain length (short, medium or long), degree of saturation (number of double bonds), and the location of double bonds (counted from the methyl carbon of the hydrocarbon chain).[3,28] They play key roles in determining the structural integrity and fluidity of cell membranes and can give rise to several important bioactive mediators. They can also regulate the expression of a variety of genes and modulate cell signalling pathways, such as those involved in apoptosis, inflammation and cell-mediated immune responses.[28,29] Changing the FA composition of cells involved in the inflammatory response influences their functions: the anti-inflammatory effects of marine ω-3 PUFA suggest that they may be useful as therapeutic agents in disorders with an inflammatory component.[30]

The metabolites of ω-3 PUFA, primarily from Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), compete with arachidonic acid (AA) for use of the same enzymes, cyclooxygenase and lipoxygenase. As a result, a higher intake of ω-3 PUFA leads to both an increase in anti-inflammatory mediators (namely prostaglandins of the 3 series and leukotrienes of the 5 series) and a decrease in pro-inflammatory mediators[31,32] (See Figure 1).

Difference between IVLE

The first LE developed in 1961 that met the criteria for safe use as part of PN in the clinical arena was 100% soybean oil (SO). This was a landmark that triggered the launch of lipid-based PN in Europe and prevented the complications of high-dose dextrose infusions that were seen with the use of lipid-free PN in the USA.[21]

Soybean Oil

SO lipid emulsions still remain the most widely used in many countries because of its proven record of safety and tolerability.[3,4] SO contains high concentrations of PUFA with a ratio of Linoleic acid (LA) to Alpha-Linolenic acid (ALA) of approximately 7:1. LA is metabolised into Arachidonic acid (AA). The eicosanoids generated from AA are prostaglandin E_2 (PGE_2), thromboxane A_2 (TXA_2) and leukotrienes including LTB_4, which are pro-inflammatory (Figure 1). The SO is naturally rich in phytosterols and has high levels of γ-tocopherol but low amounts of α-tocopherol (bioactive form of vitamin E). The phytosterols present in SO are plant sterols thought to contribute to the development of intestinal failure–associated liver disease (IFALD). The role of phytosterols in hepatocyte damage has been demonstrated by their antagonising effect on the farsenoid X nuclear receptor, which is critical in regulating the level of intrahepatic bile acids. In addition, the incorporation of phytosterols in erythrocyte membranes accelerates breakdown of these cells and increases the bilirubin load to the liver.[29]

Emulsions with a high content of ω-6 PUFA have been linked to immunosuppression.[34,35] One study evaluated the effect of lipid intake on the postoperative stress response and cell-mediated immune function of patients subjected to gastric or colorectal surgery. Higher postoperative concentrations of IL-6 and C-reactive protein were seen in patients receiving a SO LE compared with those receiving lipid free PN.[36] This is why many centres do not administer 100% SO LE to critically ill patients.[29] The emergence of this evidence has led to the development of the next-generation LE based on various oil sources.[3,4]

Coconut Oil (MCTs)

Second generation LE consisted of the addition of MCT to SO. It contains a 50/50 mixture, thus reducing the ω-6 PUFA content by 50%. MCTs are SFA 6-12 carbons long and include caprylic and capric acids. They are easily metabolised, require little carnitine for mitochondrial entry and lack pro-inflammatory properties, both characteristics unique to this fat source. MCTs are also hydrolysed and eliminated from the central circulation more quickly than LCTs, which makes them a preferred caloric source. Additionally, MCTs are resistant to peroxidation and do not accumulate in the liver. However, MCT oils are devoid of EFAs and thus cannot be used as a sole source of fat.[2,29]

Olive Oil

Olive oil (OO) is rich in ω-9 FA, (oleic acid) a type of MUFA not considered essential. OO-based emulsions were introduced in Europe in the 1990s and are classified as third generation IVLE. The relatively small amount of LA explains why this oil source requires blending with an oil containing EFA, like SO. OO has a lower content of phytosterol than pure SO and is rich in MUFAs, which are immune-neutral and are more resistant to oxidative stress injuries from free radicals.[29,32]

Fish Oil

Fish Oil (FO)based LE are the most recent development as an alternative to SO and are known as the fourth generation IVLE. They have been available in Europe and Asia for the past 10 years as a supplement to the conventional SO-based LE (Omegaven). More recently, FO has been included in a combination emulsion consisting of soybean (30%), MCT (30%), olive (25%) and fish oil (15%) (SMOFlipid). Mixing four different oils optimises the fatty acid profile and complies with current recommendations of ω-6:ω-3 PUFA ratio of 2.5:1.[37]

Due to the high concentrations of EPA and DHA, FO is thought to have anti-inflammatory potential by interfering with the AA pathway and producing the anti-inflammatory eicosanoids prostaglandins E_3 (PGE_3), thromboxanes A_3 (TXA_3) and leukotrienes B_5 (LTB_5) as well as resolvins, protectins and maresins. FO is also rich in the antioxidant α-tocopherol, which is added to prevent the oxidation of its FA.[32,38]

Despite sharing several common properties, the oil sources used and the percentages of different oils dictate the key differences between intravenous lipid emulsions (IVLE). Their differences account for their additional benefits or detriments, especially when used for prolonged periods (Table 2 for the analysis of LE). Typical IVLE are manufactured with 1 of 4 types of oil; soybean, coconut, olive or fish. Each has unique inflammatory properties and may even confer different pharmaceutical and therapeutic benefits.[29]

Omega 6: omega 3 PUFA ratio

In an experimental immunocompetence model, Grimm et al. demonstrated that IVLE show varying immunomodulatory effects dependent on the ω-6:ω-3 PUFA ratio. The optimum immune response was maintained by infusion of a lipid emulsion with a ω-6:ω-3 PUFA ratio of 2.1:1.[39] According to recommendations, new lipid emulsions should be composed of a reduced ω-6 PUFA, especially LA, counterbalanced by MCT, MUFA and long-chain ω-3 PUFA. Based on experimental and clinical studies, the most favourable ω-6:ω-3 PUFA ratio is proposed to range between 2:1 and 4:1.[4,39-41]

Various professional organisations have developed consensus guidelines for prescribing different types of lipids in PN (Table 1). These guidelines vary in their recommendations according to the types of lipids available and registered in the various countries. Until recently, FO containing lipid emulsions were not available in the US, unless under special concession. However, SO/MCT/OO/FO LE (SMOFlipid) was registered by the FDA in 2016.

1.4.1 Lipid Emulsions: Overview of Clinical Benefit

Discrepancies occur between the different clinical and experimental study results partly due to the lack of standardised criteria and because of the different PN formulations. Moreover, the clinical relevance of animal models has been largely criticised, as they invariably fail to reproduce the complexity of human illness.[1] Human studies conducted in adult patient populations, comparing FO LE to alternatives, are discussed further in this review.

1.4.1.1 Critical Illness

The biological effects associated with LE are likely to benefit a majority of patients under metabolic stress receiving PN.

Griffin highlighted the fact that reversing the negative nitrogen balance in septic patients would probably be impossible to achieve without therapeutic manipulation of cytokine or cyclooxygenase inhibitors.[45]

Numerous studies in ICU patients indicate the clinical value of ω-3 PUFA in critically ill patients (Table 3). Mayer et al. [(46,47)] showed that ω-3 PUFA infusion for 5 days increased free ω-3 PUFA and reversed the ω-6:ω-3 PUFA ratio within 24 to 48 hours to an ω-3 over ω-6 predominance. Moreover, ω-3 PUFA were incorporated into mononuclear leukocyte membranes, with significantly increased EPA and DHA content and significantly increased (EPA+DHA)/AA ratio. Serum cytokine levels (TNF-α, IL-1β, IL-6 & IL-8) decreased by 30% in patients treated with FO, whereas it doubled in those treated by LCTs (ω-6 PUFA).

Heller et al. demonstrated that IV FO administered for ≥ 3 days improved survival and reduced infection rates, antibiotic requirements and length of stay (LOS) at doses of 0.15 – 0.2g FO/kg/day.[48]

A randomised study conducted by Khor et al. comparing IV FO vs saline in 28 critically ill patients with severe sepsis showed a significant APACHE II score and serum PCT reduction on day 3, 5 and 7 in the FO group. However, serum TNF-α level, LOS of ICU and hospital stay was not significantly different.[6]

Barbosa et al. studied the effects of FO LE on 25 septic patients for 5 days. The FO group had an increase in plasma EPA level. The plasma IL-6 concentration decreased more, and IL-10 significantly less, in the FO group. There was no difference in days of mechanical ventilation (MV), ICU LOS and mortality. The FO group tended to have a shorter hospital LOS which became significant when only surviving patients were included.[49] Another study conducted in 20 patients with SIRS and 20 patients with sepsis showed an increase in TNF-α and IL-6 values on day 7, whereas IL-1 values were significantly higher on days 3, 7 and 10 in the MCT/LCT group. Conversely, IL-10 values on days 3 and 7 were significantly higher in the FO group.[50]

Grecu et al. compared LCT + FO vs LCT in 54 patients with abdominal sepsis for 5 days and showed significantly lower reoperation rates, ICU and hospital LOS. The CRP levels were also lower in the FO group on day 5, but they found no difference in mortality.[51]

However, in a study conducted in 166 medical critically ill patients, comparing MCT/LCT LE to MCT/LCT plus FO supplementation for more than 6 days, there was no significant difference in terms of IL-6 levels and clinical outcomes (infections, duration of MV, ICU LOS and 28 day mortality).[52]

Another study conducted by Hall et al. in 60 critically ill patients with sepsis studied the effects of parenteral ω-3 PUFA (0.2g FO/kg/day) administered as an independent drug and standard medical care vs standard medical care. The FO supplemented group had a significant decrease in new organ dysfunction (assessed by delta-SOFA and maximum SOFA) and maximum CRP. There was no significant reduction in LOS between cohorts and no associated reduction in 28-day or inpatient mortality; however, in the less severe sepsis group there was a statistically significant reduction in mortality.[53]

Edmunds et al. used a secondary analysis from an International Nutrition database and compared the effects of different IV LE on clinical outcomes in critically ill patients. They showed that compared to lipid-free PN, patients who received FO have faster time to ICU discharge. Compared to LCT, patients who received OO or FO had a shorter time to termination of MV alive and a shorter time to ICU discharge.[54]

All the above studies had very small numbers so their significance is uncertain. The dose of FO as well as the duration also differed.

Four meta-analyses have studied different LE in critically ill patients.[55-58] They found no difference in mortality, but a significant reduction in hospital LOS with IV FO LE. However, two of these meta-analyses showed significant reduction in infection rate in the group receiving FO supplemented PN.[55,57] Also, Pradelli et al. showed reduced inflammation markers in the FO group, especially IL-6, and a shift towards LTB_5 series production.[57] He conducted a cost effectiveness analysis on PN regimens containing omega-3 PUFA in ICU patients. The reduction in infection rates and overall LOS translated to a cost saving of between €3972 and €4897 per ICU patient.[59]

A recent review published found insufficient high-quality data investigating inflammatory and immune markers as well as clinical outcomes to determine the true effect of PN with FO containing LE compared to other IVLE.[60]

1.4.1.2 Lipid Emulsions in ARDS

The acute phase of ARDS can be a component of sepsis and septic shock with comparable pathogenesis and is characterised by an excessive inflammatory response with the release of pro-inflammatory cytokines and eicosanoids. The alveolar-capillary barrier is altered, resulting in vascular permeability and neutrophil leakage into the alveolar and interstitial space.[1] The main clinical features of ARDS include rapid onset of dyspnoea, severe defects in gas exchange and diffuse pulmonary infiltrates on x-rays.[62]

The role of nutrition in the management of ARDS has traditionally been supportive. Recent research demonstrated the potential of certain dietary lipids (e.g., fish oil, borage oil) to modulate pulmonary inflammation, thereby improving lung compliance and oxygenation, and reducing time on ventilator.[62]

While LE appear to be safe in patients with normal lung function or chronic obstructive pulmonary disease, soybean-based emulsions have been shown to induce several modifications in gas exchange and pulmonary inflammation in patients with acute respiratory failure.[63,64] The deleterious effects appear to be predominantly due to their high proportion of LA and to excessive or rapid LCT infusion.[65] This reduces PaO_2/FiO_2 ratio, pulmonary blood pressure and vascular resistances, through an imbalance in production of vasodilating and vasoconstricting eicosanoids.[64,66]

The effects of a fish oil containing LE as part of PN was studied in 25 septic patients, showing improved gas exchange. At Day 6, the PaO_2/FiO_2 ratio was significantly higher in the fish oil group. However, days on MV did not differ.[49] Another study[67] using the same LE in patients with ARDS showed significant short term changes in anti-inflammatory eicosanoid values. However, in an earlier study by the same group in ARDS patients, they could not demonstrate significant changes in haemodynamics and gas exchange.[68]

Similar results have been shown in studies using ω-3 PUFA as part of enteral nutrition[69-72], but as this falls beyond the scope of this review it will not be discussed.

1.4.1.3 Lipid emulsions and surgical patients

There are numerous clinical studies (Table 4) on the efficacy and safety of LE in surgical patients. LCTs were the first LE used in post-surgical patients and were found to increase proinflammatory cytokines and decrease T-cell proliferation in stressed patients, while having no effect in unstressed patients.[73]

There is data using fish oil containing LE in surgical patients showing a good safety profile, generation of ω-3 PUFA derived lipid mediators and a reduced length of stay. The use of fish oils in these patients has shown improved plasma levels of α-tocopherol and better liver tolerance.[74-81] Mayer concluded, based on a review of the available evidence, that inclusion of ω-3 PUFA in PN improves immunologic parameters and LOS in surgical patients.[82]

A meta-analysis conducted by Chen et al.[83] reviewed the safety and efficacy of fish oil enriched PN in postoperative patients undergoing major abdominal surgery. He showed that fish oil-enriched PN had a positive effect on length of hospital stay (-2.98 days), length of ICU stay (-1.8 days) and reduction in postoperative infection rate by 44%. Levels of aspartate aminotransferase and alanine aminotransferase reduced and plasma α-tocopherol increased. These results were also confirmed in the meta-analysis by Wei et al.[84] Tian et al. showed similar results in reduction in liver enzymes, triglycerides and CRP in the FO group, but no difference in hospital LOS.[85]

Recently, a more extensive meta-analysis analysed the clinical efficacy and safety of ω-3 PUFA-enriched parenteral LE in elective surgical and ICU patients. The results showed that ω-3 PUFA-enriched emulsions were associated with a clinically significant reduction in infection rate and length of stay, both in ICU (-1.92 days) and in hospital overall (-3.29 days). Other beneficial effects shown included reduced markers of inflammation, improved lung gas exchange, liver function, antioxidant status and fatty acid composition of plasma phospholipids, and a trend towards less impairment of kidney function.[57]

1.4.1.4 Lipid Emulsions and Parenteral Nutrition Associated Liver Disease (PNALD)

The administration of PN has been associated with liver changes such as steatosis, steatohepatitis, fibrosis, cirrhosis, and biliary changes such as cholestasis, cholelithiasis and cholecystitis. These changes may occur in 25–100% of adult patients who receive PN. Liver involvement may progress to cirrhosis, possibly requiring liver and bowel transplant.[100]

Diagnosis depends on bilirubin and liver enzyme levels. The correlation between changes in laboratory tests and histopathological findings in liver biopsies is low.[101]

There are various factors associated with liver changes associated with PN; namely, duration on PN, overfeeding especially with calories, lipid load, high phytosterol intake and low α-tocopherol intake. Table 2 for phytosterol and α-tocopherol content of different LE.

The effects of FO LE compared to other LE on liver dysfunction, have been studied in surgical patients. FO LE showed improvement in liver enzymes and plasma α-tocopherol levels.[74,75,78,80,86,90,93] Some studies showed no difference liver function test with FO LE.[88,92,96]

Sungurtekin et al. demonstrated an increase in liver steatosis on day 7 and 10 in patients with sepsis and SIRS on PN without FO.[50] Recently, a retrospective study was conducted in adult patients receiving FO supplementation in PN. GGT, ALP and ALT decreased with FO PN supplementation. The decrease was greater when the doses of FO were higher (0.71 g FO/kg – 5.28 g FO/kg).[102]

Two studies conducted in patients undergoing liver transplantation, compared PN with and without FO. A significant reduction in ALT and Prothrombin Time was seen in the FO group with a significant decrease in post-transplant hospital stay.[103,104]

Reduction in liver enzymes and improved antioxidant status was also shown in four meta-analyses.[57,83,85,105] The dosage of FO that showed benefit was 0.1 – 0.15 g/kg/day[57] and 0.07 – 0.225 g/kg/day[83].

Klek et al.[106] performed a study to evaluate the safety and efficacy of a soybean/MCT/olive/fish oil LE vs a soybean oil emulsion in intestinal failure patients on long-term parenteral nutrition. After four weeks on PN, the patients receiving the fish oil containing LE had significantly lower liver enzymes, increased serum α-tocopherol and a positive change in their fatty acid profile.

1.4.2 Complications associated with IV Lipid Emulsions

The IVLE component in PN can cause several metabolic and physiological adverse effects (AEs).

a. Hypertriglyceridaemia

Hypertriglyceridaemia is one of the most common AEs and can predispose patients to elevations in liver enzymes, haemolysis and respiratory distress.[29] The tolerance of lipids is monitored by measuring plasma triglyceride (TG) levels. An increase in plasma triglyceride levels indicates that the rate of lipid infusion exceeds the rate of hydrolysis. Lipoprotein lipase (LPL) is the enzyme responsible for hydrolysing triglycerides into two free fatty acids. Sepsis and steroids are two examples of factors which decrease LPL activity.[107]

LCT and LCT/MCT LE have been shown to increase plasma triglyceride levels, whereas FO containing LE have shown a significant reduction in plasma triglyceride levels in both surgical and septic patients or the ability to maintain the levels within normal ranges[74,76,78,86-88] (Tables 3 and 4).

A meta-analysis conducted by Chen et al. on the safety and efficacy of FO enriched PN in postoperative patients undergoing major surgery found no significant difference in plasma TG levels compared to PN without FO.[83] However, the meta-analysis conducted by Tian et al. found significant differences between LCT/MCT/OO/FO vs LCT and vs OO/LCT suggesting beneficial effect of FO containing LE in surgical patients.[85]

In general, IVLE should not be infused in patients with plasma triglycerides (TGs) > 3-4 mmol/l, and those with high basal (> 2-3 mmol/l) TG concentrations should be closely monitored to avoid complications.[4] The SA National Parenteral Nutrition Practice Guidelines for Adults recommend that in the case of hypertriglyceridemia, the amount of lipid infused should be reduced and/or the type of fat should be changed.[27]

b. Fat overload syndrome

Fat overload syndrome is another complication associated with rapid infusion and/or high doses of IVLE therapy. It presents with headaches, jaundice, hepatosplenomegaly, respiratory distress and spontaneous haemorrhage. Other symptoms of fat overload include anaemia, leukopenia, thrombocytopenia, low fibrinogen levels, and depressed levels of coagulation factor V. These symptoms can be reversed by stopping the IVLE infusion or prevented by administering LE as part of an all-in-one PN solution, infused at a controlled rate over 24 hours.[29] Guidelines from ESPEN recommend that IVLE be administered at a rate of 0.7 – 1.5 g/kg over 12 – 24 hours.[4] FO LE seem to reduce the risk of lipid overload by accelerating TG clearance more than SO LE. Despite being cleared more efficiently, FO LE undergo less catabolism than SO LE. The mechanism involved in the hydrolysis of FO LE and SO LE is very different. It appears that FO does not reduce the production of TG but rather enhances the clearance of emulsion particles and may not predispose patients to the complications associated with rapid infusion of SO LE.[29]

c. Hepatic abnormalities

The hepatic abnormalities induced by PN administration manifest differently depending on whether they occur in adults or children. In adults, fat accumulation more often leads to benign, asymptomatic steatosis, with mild to moderate transaminitis (ALT > 42 IU/L and AST > 40 IU/L)[100] and hyperbilirubinaemia (> 34 µmol/L).[42] Risk factors for the development of PNALD have been addressed briefly previously.

d. *Essential Fatty Acid Deficiency (EFAD)*

Linoleic acid and alpha linolenic acid are the two essential FA that cannot be synthesised by the human body. The typical ICU patient requires 9-12 g/day LA and 1-3 g/day ALA. Their importance is emphasised by their further metabolism to AA, and EPA and DHA.[25] Low essential FA intake eventually leads to EFAD, which is associated with water losses from the skin due to increased permeability, susceptibility to infections, lowered resistance to irradiation injury and impaired wound healing, hematologic disturbances, fat infiltration of the liver, impaired chylomicron synthesis, and heightened fat absorption. EFAD is a potential effect of FO LE therapy as sole FA source or a reduction of SO LE.[4] At least 2–4% of total calories should be administered as linoleic acid to prevent EFA deficiency[101] or essential FA should be provided at 7-10 g/day, equating to 14–20 g LCT or 30–40 g/day LCT from OO/LCT mix.[27]

e. *Pulmonary Complications*

Parenteral SO LE have been shown to induce inflammation of pulmonary vessels, leading to pulmonary hypertension, phagocyte activation, and the formation of granulomas.[63,64] The accumulation of lipid droplets in the microcirculation can compromise pulmonary gas exchange, by actions of lipid-derived mediators such as eicosanoids and peroxides or by the diminished availability of the vascular relaxant NO.[4,66]

The administration of FO LE has been shown to improve gas exchange and reduce pro-inflammatory eicosanoids.[49,57]

f. *Oxidative Stress*

Unsaturated FA, such as LA may lead to oxidative stress because they can undergo lipid peroxidation that involves incorporation of an oxygen molecule into the FA when breaking down the double bonds. This produces lipid peroxides, which are unstable molecules and are converted to volatile metabolites that can trigger chain reactions, resulting in inactivation of enzymes, proteins and other elements necessary for viability of cells.[32]

Vitamin E, a powerful antioxidant, can protect against peroxidation. Storage conditions, such as light exposure and temperature can also influence peroxidation. MCTs consist of saturated FA, and oleic acid in olive oil is a MUFA, both of these FA types are resistant to peroxidation.[4]

g. *Coagulation Complications*

The effect of LE on coagulation have not been extensively assessed.[28]

Currently there is no evidence of adverse effects of FO LE based on an increased bleeding risk due to their antiplatelet effects.[57] Heller et Al.[94] investigated the issue of potential coagulation disturbances associated with postoperative parenteral FO administration after major abdominal surgery. Their findings suggest that the infusion of fish oil in doses up to 0.2 g/kg BW per day is safe regarding coagulation and platelet function. Even with administration for up to four weeks, FO containing PN did not alter the haematological parameters and the INR remained unchanged.[106]

h. *Immune Function and Infections*

LE can influence immune systems, as addressed previously; there are concerns that pure SO LE might impair clinical outcomes due to their potential to promote inflammation and inhibit immune responses, especially in situations with an overproduction of proinflammatory mediators such as trauma or sepsis (Tables 3 and 4). Early clinical trials alluded to this effect; however, the clinical evidence for this is not strong. Methodologically flawed studies using hypercaloric feeding regimens and extrapolations from highly experimental approaches play an important role in this debate.[4]

Current recommendations are that new lipid emulsions should be composed of a reduced ω-6 PUFA, especially linoleic acid, counterbalanced by MCT, MUFA and long-chain ω-3 PUFA.[4,39-41]

2 Monitoring

Close monitoring of all patients receiving PN daily should include assessment of clinical, laboratory (Table 5) and nutritional indices. This guarantees that the nutrition prescription is appropriate and adequate and that the risks of complications are minimised.[21,108] Clinical evaluation includes monitoring vital signs, fluid balance, stool output and a physical examination (abdomen and line site). The PN bag should be checked for leakage, cracking or separation of content, infusion rate and nutritional prescription, and nutritional intake should be monitored. Readiness to introduce enteral or oral nutrition should be assessed daily.[21,27,108,109]

Monitoring patients on PN is necessary to determine efficacy of specialised nutrition therapy, detect and prevent complications, evaluate changes in clinical condition and document clinical outcomes.[21,108.]

3 Conclusion

The use of omega-3 PUFA in critically ill adult patients remains controversial as there are some conflicting results from previous reviews and meta-analysis. The need for further research remains a priority, on account of study heterogeneity, few significant differences in outcomes, rates of infection and sepsis, as well as differences in the timing and dose of FO administration.

Table 1: Published guidelines for lipid intake in critically ill patients requiring PN

Society	Year	Lipids (g)
ACCP (23)	1997	No recommendations
CCCPG (24)	2015	Consider IV lipids that reduce the load of omega-6 PUFA fatty acids/soybean oil emulsions. Insufficient data to make a recommendation on the type of lipids to be used that reduce the omega-6 PUFA fatty acid/soybean oil load
ESPEN (25, 26)	2009 2017	Lipid emulsions should be an integral part of PN for energy and to ensure EFA provision in long-term ICU patients IVLE (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12 to 24 hours Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish-oil enriched lipid emulsions probably decrease length of stay in critically ill patients. **Surgery**: Consider Postoperative PN including omega-3 PUFA.
ASPEN (17)	2016	Withhold or limit SO based IVLE during the first week following initiation of PN in the critically ill patient to a maximum of 100g/week. Alternative IVLE may provide outcome benefit over soy-based IVLE; however recommendation cannot be made at this time due to lack of availability of these products in US.
SA National DOH (27)	2016	0.7-1.5 g/kg/day Essential FA: 7-10 g/day, equating to 14-20 g LCT or 30-40 g LCT from OO/LCT mix. IV FO administration: 0.1-0.2 g/kg/day FO containing LE have been shown to be anti-inflammatory and contain less hepatotoxic phytosterols

Abbreviations: ACCP: American College of Chest Physicians; CCCPG: Canadian Critical Care Practice Guidelines; ESPEN: European Society for Clinical Nutrition and Metabolism; ASPEN: American Society of Parenteral and Enteral Nutrition; SA National DOH: South African National Department of Health; ICU: Intensive Care unit; IVLE: Intravenous Lipid Emulsions; FO: Fish oil; LCT: Long chain triglycerides; MCT: Medium chain triglycerides; OO: Olive oil; FA: Fatty acids

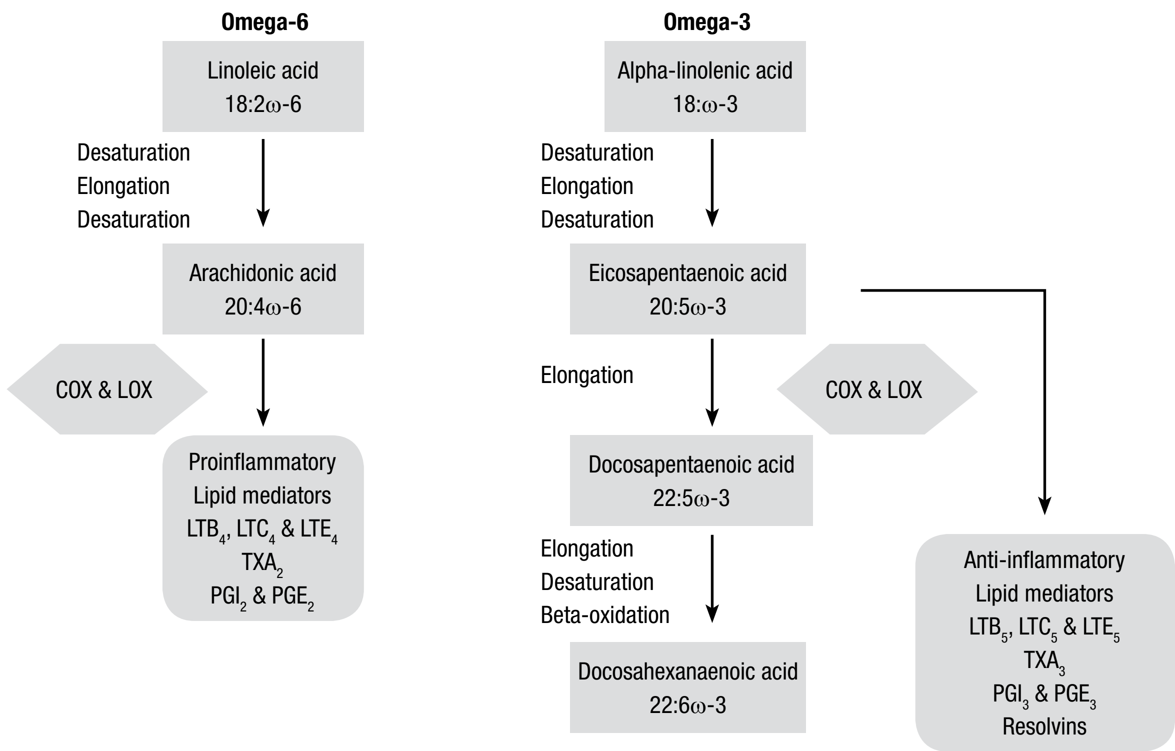

Figure 1: Metabolism of Omega-6 and Omega-3 polyunsaturated fatty acids (adapted from 31-33)
COX – Cyclooxygenase, LOX: Lipoxygenase, TXA2: Thromboxane A2 (platelet aggregator, vasoconstrictor), PGI2: Prostaglandin I2 (vasodilator, antiaggregator), PGE2: Prostaglandin E2 (Immunosuppresor)

Table 2: Characteristics of commercially available intravenous lipid emulsions used in reported randomised controlled trials (2, 28, 29, 32, 42, 43).

Composition Abbreviation	Intralipid 20% SO	Lipofundin 20% MCT/LCT	ClinOleic 20% OO/SO	SMOFlipid 20% SMOF	Omegaven 10% FO Not available in SA	Lipoplus 20% MCT/LCT/FO Not available in SA
Oil source %						
Soy bean	100	50	20	30	0	40
MCT	0	50	0	30	0	50
Olive	0	0	80	25	0	0
Fish	0	0	0	15	100	10
% Fatty acids						
Linoleic	53	50	18.7	21.4	4.4	25.7
Arachidonic	0.1	0.2	0.5	1.0	2.1	NA
α-Linolenic	8	7	2.3	2.5	1.8	3.4
EPA	0	0	0	4.7	19.2	3.7
DHA	0	0	0	4.4	12.1	2.5
ω6 – ω3 ratio	7:1	7:1	9:1	2.5:1	1:8	2.7:1
Phytosterols (mg/l)	348 ± 33	NA	327 ± 8	47.6	0	NA
Phytosterols (mg/l) (44)	439 ± 5.7	278 ± 5.09	274 ± 2.6	207	NA	NA
α-tocopherol (mg/l)	38	85 ± 20	32 or 180	200	150-296	190 ± 30
Osmolarity (mOsm/L)	260	380	270	380	308-376	NA

Abbreviations: SO: Soybean oil; MCT: Medium Chain Triglycerides; OO: Olive Oil; FO: Fish oil; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic acid

Table 3: Clinical Studies in Septic patients

Study	Patients	Duration	Lipid Emulsion	Effects
Barbosa (49)	25 septic pts	5 days	LCT/MCT/FO vs MCT/LCT	**FO grp**: ↑ EPA, IL-6 ↓ significantly, IL-10 ↓ significantly less. D6: PaO_2/FiO_2 ratio was significantly higher. No difference in days on ventilator, ICU & hospital LOS. No difference in laboratory measurements
Sungurtekin (50)	20 sepsis & 20 SIRS pts	7 Days	MCT/LCT + FO vs MCT/LCT	**LCT/MCT grp**: ↑ liver steatosis on D7 & D10. No difference in AST, ALT, GGT or CRP. IL-6 & TNF-α ↑ on D7, IL-1 ↑ on D3, 7 & 10 in sepsis grp. IL-10 significantly ↑ on D3 & D7 in SIRS grp. Serum LDH & TG significantly ↑ on D7 & D10 for SIRS grp 7 only ↑ on D7 in sepsis grp.
Friesecke (52)	116 ICU pts	≥7 days	MCT/LCT+FO vs MCT/LCT	**FO grp:** No effect on inflammation (IL-6) & clinical outcome (infections, MV, ICU LOS & 28 day mortality)
Hall (53)	60 critically ill pts with sepsis	14 days or until discharge	FO supplement	**FO grp**: significant ↓ in new organ dysfunction & max CRP. No significant ↓ in LOS.
Edmunds (54)	451 critically ill pts	12 day or death	LCT vs MCT/LCT vs OO/LCT vs FO vs LCT/MCT/OO/FO	**FO or OO grp vs LCT** had shorter time to termination of MV & shorter time to ICU discharge.
Khor (6)	28 critically ill pts with severe sepsis	5 days	FO vs Saline	**FO grp**: Significant ↓ in APACHE score & PCT on D3, D5 & D7. No difference in TNF-α, ICU & hospital LOS and mortality.
Mayer (46)	21 Septic pts	5 days	LCT vs LCT + FO	**FO grp**: ↓ cytokine secretion. No effect on length of MV & mortality.
Mayer (47)	10 Septic pts	10 days	LCT vs LCT + FO	**FO grp**: ↑ EPA & DHA over AA. ↑ LTB_5. Improved neutrophil function. No effect on length of MV & mortality.
Heller (48)	661 ICU pts Multicentre	≥3 days	FO at different doses	**FO grp** at 0.1 – 0.2g/kg showed favourable effects on survival, infection rate & LOS. ↓ Antibiotics at 0.15 - 0.2g/kg.
Grecu (51)	54 pts with abdominal sepsis	5 days	LCT + FO vs LCT	Significant ↓ reoperation rates, ICU and hospital LOS. CRP lower in FO group on day 5. No difference in mortality.
Grau-Carmona (61)	159 ICU pts	≥ 5days	MCT/LCT vs LCT/MCT/FO	FO grp: Fewer instances of nosocomial infections. Similar clinical outcomes (mortality, hospital LOS, day on MV)

Abbreviations: Pts: patients; MV: Mechanical Ventilation; PCT: procalcitonin; ICU: Intensive Care Unit; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; AA: Arachidonic Acid; CRP: C-reactive protein; FO: Fish Oil; LCT: Long chain Triglyceride; MCT: Medium Chain Triglyceride; OO: Olive Oil; LTB_5: Leukotriene B5; AST: Aspartate aminotransferase; ALT: Alanine amino transferase; GGT: Gamma-Glutamyl transferase; IL-6: Interleukin-6; IL-1β: Interleukin-1β; TNF-α: Tumor-necrosis Factor-alpha; LDH: Lactate dehydrogenase; PaO2/FiO2: partial pressure arterial oxygen and fraction of inspired oxygen ratio.

Table 4: Clinical Studies in post-surgery patients

Study	Patients	Duration	Lipid Emulsion	Effects
Antebi (74)	20 pts undergoing major surgery	≥5 days	LCT/MCT/OO/FO vs LCT	**LCT grp**: significant ↑ in TG, ALT, ALP & GGT and ↑ in CRP **FO grp:**↑ in α-tocopherol & better liver function
Mertes (78)	199 postop patients	5 days	LCT/MCT/OO/FO vs LCT	**FO grp**: no effect on TG & AST, ALT & GGT & clinical outcome **LCT grp**: AST, ALT & ALP levels were above normal range on D6
Piper (86)	44 postop patient	5 days	LCT/MCT/OO/FO vs OO/LCT	**LCT/MCT/OO/FO grp** : improved liver function
Berger (87)	20 pts with AAA surgery	4 days	LCT/MCT/FO vs MCT/LCT	**LCT/MCT/FO grp:** no difference on Inflammatory marker & clinical outcome
Han (76)	30 post op Patients	7 days	MCT/LCT vs LCT/MCT +FO	**LCT/MCT grp**: had significant ↑ in TG on D4, no difference on D7. Trend for ↑ in AST, ALT & bilirubin, not significant. **LCT/MCT +FO grp**: ↓ in IL-1. IL-8, IFN-γ, TNF-α & significant ↓ in IL-6.
Wu (88)	40 GI surgery patients	5 days	LCT/MCT/OO/FO vs MCT/LCT	**MCT/LCT grp**: significant ↑ in TG on D2 & D6. No difference in other laboratory parameters (LFTs). No difference in inflammatory markers.
Tsekos (89)	249 ICU pts Major Abdominal surgery	2 yr database	MCT/LCT grp 1 MCT/LCT + FO grp 2 MCT/LCT + FO preop grp 3	Significant ↓ in mortality in grp 3 vs grp 1. No. of pts requiring MV lower in grp 3. No difference in ICU LOS. Hospital LOS was significantly ↓ in grp 3.
Zhu (90)	76 pancreatico-duodenectomy patients	5 days	MCT/LCT vs MCT/LCT + FO	**FO grp**: less ↓ in total protein & prealbumin. Significant ↓ in ALT, AST & LDH on D6. Significant ↓ in infectious complications & post op hospital LOS. No difference in mortality.
Badia-Tahull (91)	27 elective GI Surgery patients	5 days	FO + OO/LCT vs OO/LCT	**FO grp**: Significant ↓ in infections. CRP, prealbumin & leukocytes not significantly different. No difference in safety parameters.
Wang (80)	64 GI surgery patients	5 days	MCT/LCT vs MCT/LCT/FO	No difference in infectious complications. **FO grp**: ↓ in total bilirubin vs ↑ in control grp. No difference in CRP, IL-1, IL-8, IL-10. Significant ↑in LTB5:LTB4 ratio & ↓ in IL-6, TNF-α & NFκB. No difference in LFTs or TG.
Jiang (77)	206 GI cancer surgical patients	7 days	LCT vs LCT/FO	**FO grp**: Less infectious complications & significantly ↓ SIRS. Hospital LOS significantly ↓
Wei (92)	48 GI Cancer surgery patients	6 days	LCT vs LCT + FO	No significant difference in LFTs & renal function. **FO grp**: Post op WBC, IL-6, IL-1β & TNF-α significantly ↓ Rate of complications ↓.
Llop-Talaveron (93)	52 PN patients	14-31.8 days	MCT/LCT or OO/LCT for 1st wk FO-LE added 2nd wk	GGT, ALP & total Bilirubin ↑ Significantly in 1st wk. After FO added GGT, ALP & ALT ↓.
Grimm (75)	33 major abdominal Surgical patients	5 days	LCT vs LCT/MCT/OO/FO	TG, phospholipids & total cholesterol similar in both grps. **FO grp**: On D6 α-tocopherol significantly ↑. ↓ LOS .
Heller (94)	44 major abdominal surgical patients	5 days	LCT vs LCT + FO	No differences were observed in terms of coagulation & platelet function at 0.2g/kg FO.
Heller (95)	661 post-op & Septic pts	≥ 3 days	Different ω-6:ω-3 PUFA ratio	ω-6:ω-3 PUFA ratio 2:1 ↓ ICU LOS. No difference in mortality.
Genton (96)	32 post op patients	7-14 days	LCT vs LCT/MCT/OO/FO	No difference in TG, total cholesterol and liver functions
Ma (97)	99 gastrointestinal cancer surgery patient	1 day before & 7 days post-op	MCT/LCT/FO vs MCT/LCT	FO: Improved lipid metabolism. No effect on metabolic parameters, proinflammatory cytokine levels, adverse events and clinical outcomes
Metry (98)	83 post-op ICU patients	7 days	LCT/MCT/OO/FO vs LCT	No significant differences in laboratory profiles of cholesterol, TG and liver enzymes. IL-6 levels were significantly different between 2 group and IL-6 was significantly lower in FO group on D4 & D7.
Senkal (99)	40 colorectal surgery patients	5 days	MCT/LCT vs LCT/MCT/FO	FO: significant increase in EPA and DHA levels. Increase in ω-6:ω-3 PUFA ratio. AA not significantly different in both groups

Abbreviations: AAA: abdominal aortic aneurysm; TG: Triglycerides; LOS: Length of Stay; FO: Fish Oil; LCT: Long chain Triglyceride; MCT: Medium Chain Triglyceride; OO: Olive Oil; MV: Mechanical Ventilation; WBC: White Blood count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-Glutamyl Transferase; IL-6: Interleukin-6; IL-1β: Interleukin-1β; IL-8: Interleukin-8; TNF-α: Tumour-necrosis Factor-alpha; IFN-γ: Interferon – gamma; LDH: Lactate dehydrogenase; LFTs: Liver Function Tests; ICU: Intensive Care Unit; grp: group; CRP: C-reactive protein; NFκB: Nuclear factor kappa-light-chain-enhancer of activated B cells; SIRS: Systemic Inflammatory response syndrome; pts: patients; GI: Gastrointestinal; post-op: Post-operative; LTB_5: Leukotriene B_5; LTB_4: Leukotriene B_4

Table 5: Biochemical monitoring during PN administration (21, 27, 108)

Parameter	Frequency	Rationale
Na, K, Urea, Creatinine	• Baseline • Daily until stable • 1-2 times/week	Assessment of renal function, Na & K status and fluid status
Magnesium, Phosphate, Calcium	• Baseline • Daily if refeeding risk • 3 times/week until stable • Weekly once stable	Depletion is common and under recognised
Albumin, CRP	• Baseline • 2 -3 times/week • Weekly once stable	Hypoalbuminaemia Provide information on level of inflammation and severity of disease
Total bilirubin, ALT, AST & ALP, including INR	• Baseline • 2 times/week • Weekly once stable	Complex, may be due to sepsis, drug toxicity, overfeeding, glucose intake, IVLE
Triglycerides & cholesterol	• Baseline • 2 times/week • Weekly once stable	↑ could be due to non-nutritional fat intake, IVLE, sepsis.
Glucose	• Baseline • 4-6 hourly while on PN	↑: suspect overfeeding or infections ↓: improving condition
Full Blood Count	• Baseline • 1-2 times/week • Weekly once stable	Sepsis and immunosuppression, anaemia
Zn, Se, Mn, Cu, Cr	• As clinically indicated	In at risk-patients (CRRT, intestinal fistulae, prolonged feeding)
Folate & Vit B12	• As clinically indicated	Interpret with full blood count

Na: Sodium; K: Potassium; CRP: C-reactive protein; CRRT: Continuous renal replacement therapy; Zn: Zinc; Se: Selenium; Mn: Manganese; Cu: Copper; Cr: Chromium; IVLE: Intravenous Lipid emulsion; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase AST: ALP: Alkaline Phosphatase; INR: International normalized ratio; Vit: Vitamin

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